KUWAIT MEDICAL JOURNAL
KMJ
Est. 1967

KMJ

KUWAIT MEDICAL JOURNAL

The Official Journal of The Kuwait Medical Association

REVIEW ARTICLES

ORIGINAL ARTICLES

CASE REPORTS

KU ISSN 0023-5776

Continued inside

Open access for articles at

http: www.kmj.org.kw

Indexed and abstracted in:

SCOPUS

EMBASE

(*The Excerpta Medica Database*)

Science Citation Index Expanded

(also known as **SciSearch®)**

Journal Citation Reports/Science Edition

IMEMR Current Contents

(*Index Medicus* for the Eastern Mediterranean Region)

available online at: www.emro.who.int/EMRJorList/online.aspx

Vol. 54 No. 1 MARCH 2022

KUWAIT MEDICAL JOURNAL

CONTENTS

Continued from cover

***

PUBLISHER: The Kuwait Medical Journal (KU ISSN-0023-5776) is a quarterly publication of THE KUWAIT MEDICAL ASSOCIATION. Address: P.O. Box 1202, 13013 Safat, State of Kuwait; Telephone: 1881181 Fax: 25317972, 25333276. E-mail : kmj@kma.org.kw

INSTRUCTIONS FOR AUTHORS: Authors may submit manuscripts prepared in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. These Requirements are published in each issue of the Kuwait Medical Journal.

CHANGE OF ADDRESS: Notice should be sent to the Publisher six weeks in advance of the effective date. Include old and new addresses with mail codes.

KUWAIT MEDICAL JOURNAL (previously The Journal of the Kuwait Medical Association) is added to the list of journals adhering to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", American College of Physicians, Independence Mall West, Sixth Street at Race, Philadelphia, PA 19106-1572, USA, and can be located at http://www.icmje.org/jrnlist.html

Kuwait Medical Journal

Published by the Kuwait Medical Association
Previously known as The Journal of the Kuwait Medical Association (Est. 1967)

EDITORIAL OFFICE

Editorial Manager : Vineetha Elizabeth Mammen

EDITORIAL ADDRESS

P.O. Box: 1202, 13013-Safat, Kuwait
Telephone: (00-965) 1881181(Ext. 114, 115) - Fax: (00-965) 25317972, 25333276
E-mail: kmj@kma.org.kw
Website: www.kmj.org.kw

Guidelines for Authors

Formerly known as 'The Journal of the Kuwait Medical Association', the Kuwait Medical Journal (KMJ) was established in the year 1967. It is the official publication of the Kuwait Medical Association and is published quarterly and regularly every March, June, September and December.

KMJ aims to publish peer-reviewed manuscripts of international interest. Submissions on clinical, scientific or laboratory investigations of relevance to medicine and health science come within the scope of its publication. Original articles, case reports, brief communications, book reviews, insights and letters to the editor are all considered. Review articles are solicited. Basic medical science articles are published under the section 'Experimental Medicine'.

The Kuwait Medical Journal follows the guidelines set down in "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" developed by the International Committee of Medical Journal Editors (ICMJE). The official and most recent version of the recommendations are available at *www.icmje.org*.

Journal Policies

Ethics in Publishing

Where human investigations are part of the study, the research must be conducted ethically in accordance with the Declaration of Helsinki, and the design of the work has to be approved by a local ethics committee and informed written consent must be obtained from all subjects. Documented review and approval from the Institutional Review Board or Ethics Committee must be submitted along with any studies involving people, medical records and human tissues. A relevant statement of approval should be added in the 'Subjects and Methods' section of the manuscript.

Authors should also consult guidelines for the reporting of specific study types (*e.g.*, the CONSORT guidelines for the reporting of randomized trials); see *http://equator-network.org*.

Copyright

The publisher reserves copyright on the Journal's contents. No part may be reproduced, translated or transmitted in any form by any means, electronic or mechanical, including scanning, photocopying, recording or any other information storage and retrieval system without prior permission from the publisher. The publisher shall not be held responsible for any inaccuracy of the information contained therein.

Conflict of Interest

Potential conflicts of interest for all authors must be identified in a 'Conflict of interest' statement at the end of the manuscript. An electronic cover letter from the corresponding author is acceptable. Authors of research articles should disclose any affiliation with any organization with a financial interest, direct or indirect, in the subject matter or materials discussed in the manuscript (*e.g.*, consultancies, employment, expert testimony, honoraria, retainers, stock) that may affect the conduct or reporting of the work submitted. If uncertain as to what might be considered a potential conflict of interest, authors should err on the side of full disclosure. Because reviews and editorials are based on selection and interpretation of the literature, the Journal expects that authors of such articles will not have any financial interest in a company (or its competitor) that makes a product discussed in the article. Information about potential conflict of interest will be made available to reviewers and will be published with the manuscript at the discretion of the editors. If there is no conflict of interest, please state: "The authors declare no conflicts of interest."

Peer Review

All submitted manuscripts are reviewed by the editorial staff to ensure adherence to the guidelines of the Journal. Manuscripts that are considered suitable for review are sent to a peer in the relevant field of study as part of a double- blinded peer review. The reviewer may recommend the manuscript be accepted as is, undergo revision, or be rejected. If a reviewer recommends revision of a manuscript, the revised version must be re-submitted to the Journal within 3 months from the date when the review report is sent to the corresponding author.

Authors

To be named as an author on a submission, the following 4 criteria are followed:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. Authors should also have confidence in the integrity of the contributions of their co-authors. Specific contributions made by each author to the article must be clearly stated at the end of the document. Those who do not meet all four criteria should be mentioned in the Acknowledgment section of the submission.

Once a paper has been accepted, the Journal does not consider requests to add, delete or rearrange the sequence of the authors. If the corresponding author requests to add, remove or rearrange the authors' names after manuscript submission, the journal will seek justification for the requested change. Written confirmation signed by all authors, attesting that they agree to the addition, removal, or rearrangement of names is required. In the case of the addition or removal of authors, the author being added or removed must confirm assent. Requests that are not sent by the corresponding author will not be considered.

The corresponding author is responsible for communication with the journal during the manuscript submission, peer review, and publication process, and must ensure that all the journal's administrative requirements are properly completed. He/she should also be available throught out the submission and peer review process to respond to editorial queries in a timely manner. It is also the corresponding authors responsibility to ensure all the co-authors are made aware of the most recent status of their submission.

Fees

Publication in the Kuwait Medical Journal is free of charge.

Plagiarism

The Journal defines plagiarism as the use of others' published and unpublished ideas or words without prior consent, and presenting them as new and original, whether intentional or not. If an accepted or published paper is found to

be plagiarised, the manuscript will be retracted and the author will be blacklisted from submitting to the journal.

Preparing your manuscript

Article types

Original Articles: Original Articles include laboratory and clinical investigations as well as research not previously published or being considered for publication elsewhere. The text should contain a Title page, Abstract (in structured format) of not more than 250 words, Key Words (no more than five), Introduction, Subjects (or Materials) and Methods, Results, Discussion, Conclusion, Acknowledgment/s (if any) and References, Figure Legends, Tables, and Figures in this order. Details of the section contents are explained below for further adherence.

Review Articles (solicited only): Review articles should contain separate sections such as Title Page, Abstract (preferably in structured format) of no more than 250 words, Key Words (no more than five), Introduction, Methods/History (if applicable), Literature Review, Conclusion, Acknowledgment/s (if any) and References followed by (if relevant), Legends to figures, Tables, and Figures.

Case Reports: These should contain separate sections such as Title page, Abstract (a short summary of not more than 200 words), Key Words (no more than five), Introduction, Case history/report, Discussion, Conclusion, Acknowledgment/s (if any) and References followed by (if relevant), Legends to figures, Tables, and Figures.

Short Communications: Short communications are concise articles that aim to report new ideas, significant improvements to existing methods, a new practical application, or a new tool or resource. Short communications do not cover in detail background information about the problems treated, rather they provide key pointers to the reader. The work reported needs to be technically sound, innovative and significantly unique, advancing the state of the art. Short communication is not intended to publish preliminary results. Short communications should be similar to a research article, but with briefer Materials and Methods and Discussion.

Letters to the Editor: Letters may comment on recently published KMJ articles, novel cases or topics of current interest to the public. They should be concise and to the point, with a maximum of 1000 words and 2 authors. Letters commenting on previously published articles must be received within 6 months of publication of the relevant article.

Title Page

The title page of the submitted manuscript should provide a clear title of the study followed by full names of all authors, the highest academic degree and affiliations if any, the name and address of the institution(s) where the work was done including the department, the name and complete address of the corresponding author to whom proofs and correspondences shall be sent, duly supported with contacts such as telephone, mobile and the e-mail address. This page must also contain any disclaimers, sources of support and a conflict of interest declaration.

Structured abstract

A structured abstract (no more than 250 words) is required for studies under the section "Original Articles". It must provide an overview of the entire paper, and should contain succinct statements on the following, where appropriate: Objective(s), Design, Setting, Subjects, Intervention(s), Main Outcome Measure(s), Result(s), and Conclusion(s). (See: Haynes RB, Mulrow CD, Huth AJ, Altman DG, Gardner MJ. More informative abstracts revisited. Annals of Internal Medicine 1990; 113:69-76). Abstracts for all other category of submissions shall be a short summary followed by Key words and the report or review.

Preparation of the manuscript

The manuscript should be typed as 'normal text' with no hyphenation and no hard-returns within paragraphs (use automatic wordwrap) on A4 size (29.7 x 21 cm) paper in single column format, preferably in font size 12. Cell format for paragraphs, artwork and/or special effects for the text and/or table(s) are not acceptable. Italics shall be used only for foreign/ Latin expressions and/or special terminologies such as names of micro-organisms. Maintain a minimum of 2 cm margin on both sides of the text and a 3 cm margin at the top and bottom of each page. No part of the manuscript other than abbreviations and/or subtitles should be written in upper case. Header/foot notes, end notes, lines drawn to separate the paragraphs or pages *etc*. are not acceptable. Do not submit articles written/saved in 'Track-change' mode.

More than six authors are not appreciated for a research article and if listed, the authors may be asked to justify the contribution of each individual author. For case reports, not more than three authors are acceptable. Regarding contributions of authors over the limit mentioned above, please read the 'Acknowledgment' section.

Key words

Key Words (maximum five) should be preferably MeSH terms, and shall not duplicate words already in the manuscript title. MeSH terms can be checked at: http://www.nlm.nih.gov/mesh/.

Tables

Tables typed on separate pages using table format (MS Word or Excel) should follow the list of references. Tables must be numbered consecutively using Arabic numerals and provided with appropriate titles. Contents of the table should be simple, and information therein not duplicated, but duly referred to, in the main text. Tables recording only a few values are not appreciated, since such information can be more accurately, usefully and concisely presented in a sentence or two in the manuscript.

Design of the work

This should be stated clearly. The rationale behind the choice of sample size should be given. Those about to begin randomized controlled studies may wish to study the CONSORT statement (JAMA 1996; 276:637-639).

Illustrations

All illustrations including figures should be numbered as Fig 1, Fig 2, *etc* in running sequence and submitted as separate attachments along with the manuscript. Photographs should fit within a print area of 164 x 235 mm. In the case of figures where patient's identity is not concealed, authors need to submit a written consent of the patient or of the patient's guardian, in case of minors. Figure legends should be listed separately after the 'References' section. If any of the tables, illustrations or photomicrographs have been published elsewhere previously, a written consent for re-production is required from the copyright holder along with the manuscript. When charts are submitted, the numerical data on which they were based should be supplied.

Abbreviations

Except for units of measurement, abbreviations should be defined on their first use in the abstract and in the text and then applied consistently throughout the article. Non-standard abbreviations or those appearing fewer than three times are not accepted. Use abbreviated units of measure, only when used with numbers. Abbreviations used as legends in Tables and/or figures should be duly defined below the respective item.

Numbers and units

Measurements of length, height, weight and volume must be reported in metric units (meter, kilogram, liter *etc.*) or their decimal multiples. Temperature should be given in degrees Celsius, Blood pressure in mmHg, and hematological and biochemical measurements in Système International (SI) units. For decimal values, use a point, and not a comma, *e.g.*, 5.7. Use a comma for numbers > 10,000 (*i.e.*, 10^3) and do not use a comma for numbers < 9999, (*e.g.*, 6542).

Drug names

Non-proprietary (generic) names of product should be employed. If a brand name for a drug is used, the British or international non-proprietary (approved) name should be given in parentheses. The source of any new or experimental preparation should also be given.

Acknowledgment

Contributors who meet fewer than all 4 of the aforementioned criteria for authorship should only be listed in this section. Contributions of others who have involved in the study, such as statisticians, radiologists *etc*. and/or those who have assisted in the preparation of the manuscript being submitted could also be included in this section. The corresponding author must obtain written permission to be acknowledged from all acknowledged individuals.

References

Indicate references in the text in sequence using Arabic numerals within square brackets and as superscripts (*e.g.*,[1, 3-5] *etc*). Do not quote additional data (like part of the title, year of publication *etc*.) from the references, with citations in the text, unless very important. In the References section, list them in the same sequence as they appeared in the text. Include the names and initials of all authors if not more than six (< 6). Write the last name of authors followed by the initials with no punctuation other than a comma to separate the names. In references where authorship exceeds six, use *et al* after six author names. Do not use automatic numbering, end notes or footnotes for references. References to manuscripts either in preparation or submitted for publication, personal communications, unpublished data, *etc*. are not acceptable.

References should be limited to those relating directly to the contents of the paper and should be set out in the style outlined by the International Committee of Medical Journal Editors (ICMJE), as shown in the examples below. Additional examples are in the ICMJE sample references. *https://www.nlm.nih.gov/bsd/uniform_requirements.html*

Examples

Article: Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, ***et al***. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Book: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Book chapter: Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Weblinks: eatright.org [Internet]. Chicago: Academy of Nutrition and Dietetics; c2016 [cited 2016 Dec 27]. Available from: http://www.eatright.org/.

Manuscript submission

To present your original work for consideration, one complete set of the manuscript written in English, accompanied by tables and one set of figures (if applicable) should be submitted to the Editor by e-mail to "kmj@kma.org.kw" as attachment files.

The manuscript submitted by e-mail should be in MS Word document (.doc) format, together with a scanned copy or PDF version of the signed consent letter of the author(s) (see the section 'Authorship and Consent Form' for details). Figures or photographs, if any, need to be presented as separate attachments in JPG or BMP format with a resolution of 300 dpi and illustrations such as graphs, charts *etc*., as Excel format files. Incomplete/improper submissions will not be processed, and will be returned. Author(s) will receive a formal acknowledgment letter with a permanent reference number towards each successful submission.

Following a peer review process, the corresponding author will be advised of the status; acceptance or recommendation for revision or rejection of the paper, in a formal letter sent through e-mail. A galley proof will be forwarded to the corresponding author by e-mail at the time of publication of the accepted paper, which must be returned to the journal office within 48 hours with specific comments or corrections, if any. Such corrections in the galley proof must be limited to typographical errors or missing contents from the finally accepted version.

Authorship and consent form

All authors must give their signed consent for publication in a letter of submission, which should accompany the manuscript. This letter should contain the following statement:

"This manuscript (write the title) is an unpublished work which is not under consideration elsewhere and the results contained in this paper have not been published previously in whole or part, except in abstract form. In consideration of the KMJ accepting my/our submission for publication, the author(s) undersigned hereby assign all copyrights ownership to the KMJ and shall have no right to withdraw its publication. It is expressly certified that I/we, have done/actively participated in this study and agree to the accuracy of contents of this manuscript. It was conducted in accordance with current ethical considerations and meets with the committee's approval. I/all of us agree to its publication in KMJ and to the authorship as expressed in this declaration and in the title page of our manuscript".

The consent form must also contain the names of all authors, along with their signatures.

Manuscripts should be submitted to:
The Editor,
Kuwait Medical Journal
P.O. Box: 1202
Code-13013-Safat
Kuwait.
Telephone: (965) 1881181, 25333920 extn. 114
E-mail: kmj@kma.org.kw
Website: www.kma.org.kw/KMJ

Review Article

Novel coronavirus disease (COVID-19): Guidelines and protocols of the pandemic

Hatem A Hejaz, Bara'a Shalaldeh, Taima Alnatsheh, Ameera Zalloum
College of Pharmacy & Medical Sciences, Hebron University, P.O. Box 40, Hebron, Palestine

Kuwait Medical Journal 2022; 54 (1): 1 - 26

ABSTRACT

Coronavirus has been a significant threat since November 2019. Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections can experience a range of clinical manifestations, from no symptoms to critical illness.

A comprehensive search of databases and other sources to identify literature on COVID-19 was carried out. Literature review was conducted using different search engines such as Google Scholar, Medline via PubMed, Web of Science and Science Direct, with the terms "COVID-19", "SARS-CoV-2", "novel coronavirus 2019 (nCoV-2019)", "Wuhan coronavirus", "Wuhan virus" or "Middle East respiratory syndrome coronavirus (MERS-CoV)".

The collected data could be helpful to researchers and decision-makers (social and economic) to understand the disease and the different responses to this virus. This could prevent future outbreaks, improve clinical practice guidelines and public health policies, and find immune-based therapeutics and/or traditional medicines. By June 1st, 2020, there were about six million cases worldwide and the number is rising sharply every day. By 14th July, the number of cases reported were more than 13 million (13,266,241), and by 19th August, there were 22,610,862 cases diagnosed, with ~ 41% increase in 40 days. The actual and accurate causes and effective treatment of COVID-19 are still unknown or unavailable, and the number of active cases of the infection is rising every day, with rising panic and concern about public health worldwide.

A variety of helpful resources related to COVID-19 were collected and summarized. These are important to health providers on how to make informed health decisions.

KEY WORDS: coronavirus, MERS-CoV, nCoV-2019, pandemic, SARS-CoV

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a serious public health crisis threatening the world with extremely fast spread and mortality. The disease is transmitted by inhalation or contact with infected droplets, and the incubation period ranges from 2 to 14 days or even more. The most common symptoms are fever, dry cough and tiredness, while the serious symptoms are difficulty breathing or shortness of breath, chest pain or pressure, and loss of speech or movement. There are less common symptoms as well, such as aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on the skin, or discoloration of fingers or toes. The disease may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction, especially in elderly people and those with comorbidities. However, symptoms of coronavirus usually go away on their own and many people are asymptomatic. The virus is diagnosed in respiratory secretions by special molecular tests. In some cases, self-isolation to prevent the spread of infection is preferred and advisable. There is no specific treatment for the disease caused by a coronavirus. However, many of the symptoms can be treated and therefore, treatment is based on the patients' clinical conditions.

The disease was noticed after a group of pneumonia cases of unidentified etiology was stated in Wuhan, Hubei Province, China, on 31st December 2019.

Address correspondence to:
Dr. Hatem A Hejaz, College of Pharmacy & Medical Sciences, Hebron University, P.O. Box 40, Hebron, Palestine. Tel: +970 599132862; E-mail: hhejaz@hebron.edu

Afterwards, China reported a novel coronavirus on 9th January 2020, and this was the contributing agent of the outbreak. COVID-19, which is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel strain of coronavirus that has not been previously recognized in humans. As of 15th April 2020, the emerging coronavirus had spread nearly all over the world, with differences in disease severity among different countries and different patients[1,2]. In general, coronaviruses are among the family of enveloped positive-sense ribonucleic acid (RNA) viruses fluctuating between 60 nm to 140 nm in diameter, with spike-like projections giving it a crown-like appearance under the electron microscope; hence the name coronavirus. All ages are vulnerable and the infection majorly spreads and is transmitted through large droplets, as in coughing and sneezing by symptomatic patients. Patients can be infectious for as long as the signs last, and even on clinical recovery. Some people may act as super transmitters. The virus can persist and be viable on planes for days in favorable atmospheric conditions; however, it is damaged in less than a minute by communal disinfectants like sodium hypochlorite, hydrogen peroxide, *etc*. The infection is mainly attained both via inhalation of these droplets or by touching polluted surfaces and then touching the nose, mouth and eyes. Infection in neonates, infants and children has also been described to be significantly milder than their adult counterparts. The most popular symptoms were fever (50%) and cough (38%)[3-11].

On May 28th, 2020, the number of COVID-19 cases were 5,868,922 and 360,476 deaths worldwide with a 6.14% mortality rate, and in Palestine, the confirmed pandemic cases were 570 with four deaths only. The disease spread extremely fast, as by the end of June (within only one month), the cases had nearly doubled with 10,690,566 confirmed coronavirus cases, 516,393 deaths (8%) and 5,856,464 recoveries worldwide. The highest incidence rates and cases were in the USA (2,751,571), followed by Brazil (1,426,913), Russia (654,405), India, UK, Spain, Peru, Chile, Italy and Iran (230,211) respectively. At the same time, the number of reported cases in Palestine increased very sharply by about six times, as more than 3,095 cases were reported (including 337 cases from East Jerusalem), with 11 deaths. The highest number of cases (1947 cases) were in Hebron Governorate. With these confirmed cases, Palestine ranked 97 among the 215 countries that had coronavirus infections, with the highest outbreak rate in the world when compared to population.

The global outbreak of the disease continued to rise very sharply, as by 14th July 2020 (15:03 GMT), the coronaviruses cases reported was 13,280,070 and the number of deaths were 576,675; the increase rate of the new cases was ~24% and the death rate increased by 1.125% within a two-week period only, which are considered to be high rates. The highest incidences by this time were in the USA with 3,481,689 reported cases, followed by Brazil (1,888,889), India (916,368), Russia (739,947) and Peru (330,123)[12]. In terms of the outbreak of the disease, the ranking of the countries changed daily, but USA and Brazil remained first and second respectively for a while. By 13th July 2020, the confirmed cases in Palestine were 7441 and the number of deaths were 42, with an increase rate of 240% within only two weeks, which is extremely high and considered the highest worldwide. The highest cases were in Hebron Governorate (4980 cases), consisting of about 67% of the total reported cases. By 19th August, there were 22,610,862 cases diagnosed, with ~41% increase in 40 days only; the recovered cases were 15,326,490, and the number of deaths were 791,674, with an increase of ~27%. The highest global incidence at this time were in the USA with 5,701,390 (~39% increase) reported cases, then Brazil (3,460,413, ~45% increase), India (2,841,400, ~68% increase), Russia (942,106, ~21% increase), South Africa (596,060, ~52% increase) and Peru (558,420, ~41% increase), *etc*. as shown in Table 1. South Africa, which ranked 10 on 14th July, now ranked fifth after 40 days, with an increase of more than 50% in this short period of time, while Palestine recorded 23,427 confirmed cases on 19 August, with ~68% increase, which is extremely high. The number of confirmed cases, deaths and recovered cases in Palestine were shown in the geographical location of confirmed cases (Figure 1). With these confirmed cases, Palestine ranked 71 among 215 countries that had coronavirus.

It is worth mentioning that on 1st July 2020 and 13th July, Palestine ranked 97 and 85 respectively among the 215 countries that had coronavirus, with the highest outbreak rate in the world compared to population. Within only a seven-week period, the Palestine rank changed from 97 to 71; however, if the outbreak in Palestine continued to rise at the same rate, within a short period, Palestine would be one of the top countries having the disease, especially if real and serious precautions were not taken to apply the health recommendations of isolation and maintaining social distance. According to Palestinian Ministry of Health officials, the high outbreak of the disease in the Hebron Governorate (90% of infections) was caused by people meeting up with their families, attending wedding parties or funerals, and failing to follow health recommendations and maintain social distancing. Figure 1 shows the prevalence of COVID-19 in occupied Palestinian territory by 19th August 2020, cumulative confirmed, recovered and death cases, confirmed cases per day (April - August 2020), confirmed cases by gender (5th March - 19th August

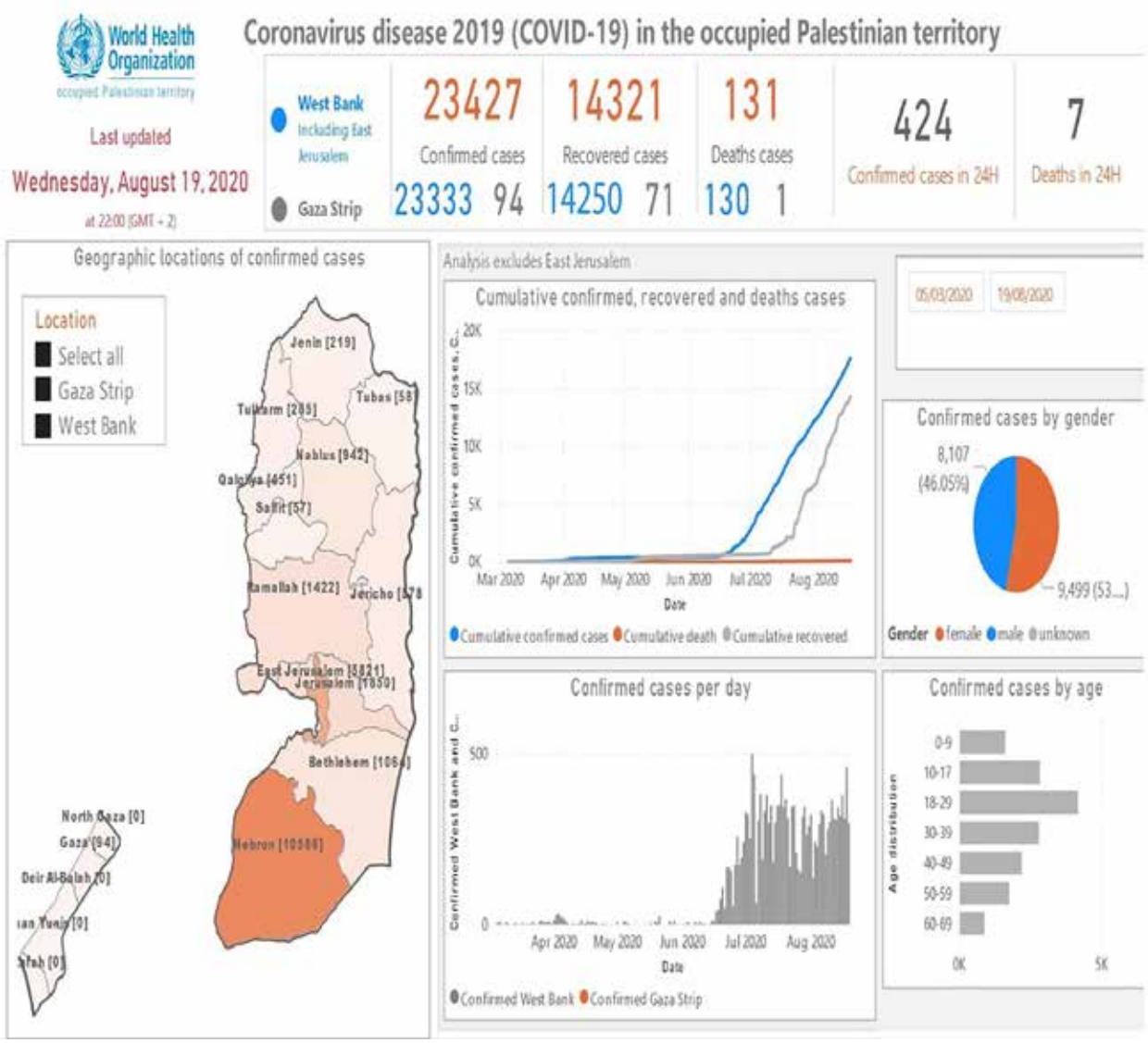


Fig 1: Coronavirus disease (2019) in Palestine[15]

2020), and confirmed cases by age in Palestine. Some data reports included and some excluded East Jerusalem[13].

Kuwait ranked 34 among 215 countries worldwide by 14th July, as the reported cases were 56, 174 and 396 death cases. By 19th August 2020, Kuwait had 78,145 (~28% increase) cases and 507 deaths (~22% increase) as shown in Table 1[12]. Kuwait, by this time, ranked 38 among the countries that had the disease. The decrease in Kuwait's ranking from 35 to 38 does not imply that the disease had been controlled or the outbreak decreased, but that the outbreak of the disease was more severe in other countries. Table 1[12] also shows the number of cases for the top 41 countries, including other information such as daily new cases, total death, total recovered, total tests done in each country, *etc*. While the actual and accurate causes and effective treatment of COVID-19 are still unknown or unavailable, and the number of active cases of the infection is rising every day as mentioned, panic and public health concerns are rising worldwide. Prevention is still the best strategy to face this pandemic. In addition, these numbers are possibly an underestimation of the actual number of infected and dead due to limitations in surveillance and testing. It is thought that the SARS-CoV-2 originated from bats, but the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects[12].

Treatment of the disease is essentially supportive; the role of antiviral agents is yet to be established. Prevention entails home isolation of suspected cases and those with mild illnesses, and strict infection control measures at hospitals that include contact and

droplet precautions. The virus spreads faster than its two ancestors, the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but has lower fatality till now. The global impact of this new pandemic is still uncertain. Treatment is mainly supportive since no antiviral has been approved yet. Efforts are being made to find effective treatment and to reduce the virus outbreak. However, not much information is known about the causes of the virus, its survival period, methods of its spreading, biochemical and hematological disorders, its complications, its prevention and treatments. Therefore, this review is focused on the latest treatment methods and precautions against COVID-19.

Slow and stop transmission, provision of optimized care for all patients, minimize the impact of the epidemic on health systems, social services, and economic activity are the main objectives for the management of the disease. More than 150 different drugs are being researched around the world. Most are existing drugs that are being tested against the virus. Here, we highlight the most important drugs, including herbal medicines, used or tested for the treatment of the disease and disease complications. In Palestine, the treatment and management protocols of COVID-19 are like the strategies and protocols in the other countries which follow the guidelines of the World Health Organization (WHO). However, the pandemic by COVID-19 is a very dangerous issue affecting people worldwide. Without fundamental therapeutic

Table 1: Reported cases and deaths by country as 19th August 2020[12]

No	Country, Other	Total Cases	Total Deaths	Total Recovered	Active Cases	Serious, Critical	Total Cases/ 1M pop	Deaths/ 1M pop	Total Tests	Population
	World	22,610,862	791,674	15,326,490	6,492,698	61,719	2,901	101.6	73,118,341	331,266,944
1	USA	5,701,390	176,365	3,063,213	2,461,812	16,875	17,211	532	13,729,872	212,764,278
2	Brazil	3,460,413	111,189	2,615,254	733,970	8,318	16,264	523	32,661,252	1,381,826,521
3	India	2,841,400	54,017	2,097,766	689,617	8,944	2,056	39	33,500,000	145,943,139
4	Russia	942,106	16,099	755,513	170,494	2,300	6,455	110	3,455,671	59,408,124
5	South Africa	596,060	12,423	491,441	92,196	539	10,033	209	2,852,011	33,032,637
6	Peru	558,420	26,834	377,453	154,133	1,516	16,905	812	1,211,552	129,114,244
7	Mexico	537,031	58,481	367,537	111,013	3,480	4,159	453	2,337,241	50,955,514
8	Colombia	502,178	15,979	326,298	159,901	1,493	9,855	314	2,087,354	19,138,335
9	Chile	390,037	10,578	364,285	15,174	1,120	20,380	553	7,955,615	46,757,289
10	Spain	387,985	28,797	N/A	N/A	617	8,298	616	2,939,840	84,135,807
11	Iran	352,558	20,264	304,236	28,058	3,869	4,190	241	14,988,134	67,934,669
12	UK	321,098	41,397	N/A	N/A	73	4,727	609	1,012,979	45,251,601
13	Argentina	312,659	6,330	228,725	77,604	1,795	6,909	140	4,378,417	34,885,189
14	Saudi Arabia	302,686	3,506	274,091	25,089	1,725	8,677	101	2,363,752	221,448,449
15	Pakistan	290,958	6,209	272,804	11,945	725	1,314	28	1,407,556	164,909,635
16	Bangladesh	287,959	3,822	168,991	115,146		1,746	23	7,713,154	60,449,422
17	Italy	255,278	35,412	204,506	15,360	66	4,223	586	5,969,629	84,460,548
18	Turkey	253,108	6,039	233,915	13,154	719	2,997	72	10,197,366	83,820,751
19	Germany	229,700	9,314	203,900	16,486	224	2,740	111	6,000,000	65,293,421
20	France	225,043	30,468	84,065	110,510	384	3,447	467	1,345,459	40,338,162
21	Iraq	188,802	6,121	134,369	48,312	582	4,680	152	2,163,050	109,774,529
22	Philippines	178,022	2,883	114,114	61,025	489	1,622	26	1,969,941	273,911,035
23	Indonesia	147,211	6,418	100,674	40,119		537	23	4,925,446	37,786,763
24	Canada	123,490	9,049	109,822	4,619	61	3,268	239	566,013	2,807,805
25	Qatar	115,956	193	112,658	3,105	66	41,298	69	222,251	11,694,115
26	Bolivia	105,050	4,233	39,965	60,852	71	8,983	362	293,066	17,678,345
27	Ecuador	104,475	6,146	87,277	11,052	365	5,910	348	2,291,327	18,806,642
28	Kazakhstan	103,815	1,415	86,450	15,950	221	5,520	75	2,180,096	9,197,590
29	Israel	98,550	789	73,848	23,913	403	10,715	86	1,356,698	43,696,575
30	Ukraine	98,537	2,184	50,441	45,912	177	2,255	50	135,000	102,585,185
31	Egypt	96,914	5,197	62,553	29,164	41	945	51	331,160	10,862,509
32	Dominican	88,127	1,501	56,760	29,866	288	8,113	138	973,523	10,107,829
33	Republic	85,411	5,802	N/A	N/A	29	8,450	574	90,410,000	1,439,323,776
34	Sweden	84,895	4,634	79,745	516	24	59	3	309,212	5,123,074
35	China	83,769	609	78,386	4,774	151	16,351	119	282,232	4,323,696
36	Oman	83,754	1,827	58,274	23,653	157	19,371	423	2,023,900	11,596,526
37	Panama	79,479	9,969	18,078	51,432	83	6,854	860	573,251	4,278,903
38	Belgium	78,145	507	69,771	7,867	96	18,263	118	1,591,015	19,219,490
39	Kuwait	74,963	3,154	34,196	37,613	489	3,900	164	1,437,110	9,448,891
40	Romania	69,801	622	67,647	1,532		7,387	66	6,193,635	9,906,322
41	Belarus	65,341	367	58,022	6,952		6,596	37		

interventions, current management is to reduce the virus spread and provide supportive care for diseased patients.

There is an urgent need to develop targeted therapies. Understanding the disease and the different responses to this virus could help to find immune-based therapeutics and/or traditional medicines. It is important to have the latest information, but we must ensure that information is coming from trustworthy sources. We have collected a variety of helpful resources related to COVID-19. We also have several initiatives to get the public involved in our work and educated on how to make informed health decisions. The global impact of this new pandemic is yet uncertain. Thus, we conducted a literature review of publicly available information to summarize knowledge about the pathogen and the current pandemic. These are also important to health providers on how to make informed health decisions for patients[1].

METHODS

Literature and guidelines among different databases were searched. A comprehensive search of databases and other sources to identify literature on COVID-19 was carried out. Literature review was conducted using different search engines such as Google Scholar, Medline via PubMed, PubMed, Web of Science and Science Direct with the terms "COVID-19", "SARS-CoV-2", "novel coronavirus 2019 (nCoV-2019)", "Wuhan coronavirus", "Wuhan virus", "Middle East respiratory syndrome coronavirus (MERS-CoV)", "Novel coronavirus pneumonia" to match with the article title, abstract or topic. Additionally, further search words with above keywords as "SARS", "SARS-CoV", "severe acute respiratory syndrome", "MERS", "MERS-CoV" or "middle east respiratory syndrome", in combination with "spike protein", "genome", "reproductive number", "incubation period", "fatality rate", "clinical characteristics", "pathology", "autopsy", "treatment" or "prevention" were used. Moreover, the already released official documents of the WHO were accessed for searching and keeping up to date data on COVID-19. Only English versions of articles were used and included in this literature review. The review includes publicly available information about the knowledge of the diseases that were discussed. The limitations of this review are that the numbers are possibly an underestimation of the actual number of infected and dead, and based on the available information published. Besides the accuracy of the information about the disease and the virus, including the origin of the virus, the symptoms are varied and changing from time to time. For example, it is thought that the SARS-CoV-2 originated from bats, but the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects. The importance of this review, as in the ever-changing situation that we are in, is to have the latest information, but we must ensure that information is coming from trustworthy sources. We have collected a variety of helpful resources related to COVID-19. We also have several initiatives to get the public involved in our work and educated on how to make informed health decisions.

RESULTS

Pathological changes caused by coronavirus

The virus can cause a range of symptoms, from mild illness to pneumonia. Symptoms of the disease are fever, cough, sore throat and headaches. In severe cases, difficulty in breathing and deaths can occur. Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. All patients had elevated white blood cell counts, with a significant rise towards the end, and all had lymphocytopenia except for patients with leukemia. Histologically, the main findings are in the lungs, including injury to the alveolar epithelial cells, hyaline membrane formation and hyperplasia of type II pneumocytes, all components of diffuse alveolar damage. The liver exhibits mild lobular infiltration by small lymphocytes and centrilobular sinusoidal dilation. Patchy necrosis is also seen. The heart shows only focal mild fibrosis and mild myocardial hypertrophy, changes likely related to the underlying conditions. Many studies on COVID-19 epidemiology and clinical characteristics have been published, but pathological data for this disease is still scarce. The pathological changes from postmortems and biopsies are described below[14].

Lungs

Among the lungs, pulmonary consolidation of variable degrees such as intra-alveolar serous fluids, fibrinous exudates and hyaline-membrane development are present. Exudate contains primarily mononuclear macrophages, and multinucleated giant cells are communal. Moreover, inclusion bodies can be found within type II pneumocytes and macrophages. Alveolar congestion and edema can be realized; the formation of hyaline thrombus in blood vessels is evident[14-16].

Spleen, hilar lymph node and bone marrow

The size of the spleen is significantly decreased and the number of lymphocytes is considerably reduced.

Table 2: Definition of a patient with COVID-19[2, 17]

SARI	An ARI with a history of fever or measured temperature ≥38 C° and cough start within the last ten days and necessitating hospitalization.
Surveillance case definitions for SARI	• SARI is a person, with history of fever and cough necessitating admittance to the hospital, with no other etiology that completely describes the clinical presentation (clinicians should also be attentive to the probability of unusual presentations in immune-compromised patients)AND any of the following: A. A history of international travel in fourteen days before symptom onset; or B. the disease happens in a health care worker who has beenworking in an environment where patients with severe acuterespiratory infections are being cared for, without regard tothe place of residence or history of travel; or C. the person develops an unusual or unexpected clinical course,especially sudden deterioration despite appropriate treatment,without regard to the place of residence or history of travel, even ifanother etiology has been identified that fully explains theclinical presentation • A person with acute respiratory illness of any degree of severity who, within 14 days before the onset of illness, had any of the following exposures: A. close physical contact [4]with a confirmed case of COVID – 19infections, while that patient was symptomatic; or B. a healthcare facility in a country where hospital-associatedCOVID - 19 infections have been reported;

SARI:Severe acute respiratory infection

Focal hemorrhage and necrosis do exist. Macrophage hyperplasia and phagocytosis can be detected in the spleen. In the lymph nodes, the count of lymphocytes is decreased and some necrosis can be found. A decline of CD4+ T cells and CD8+ T cells can be noticed in both the spleen and the lymph nodes by immunohistochemistry. Trilineage hematopoiesis is decreased in the bone marrow[16].

Heart and blood vessel

Deterioration and necrosis can be found in cardiomyocytes. Interstitial infiltration of a slight number of monocytes, lymphocytes and/or neutrophils can be realized. Endothelial inflammation and thrombus were detected in specific vessels[16].

Kidney

Exudate full of proteins can be found within the glomerular capsule. Degeneration and desquamation of renal tubular epithelium are existent. Hyaline casts can be realized. Interstitial congestion, microthrombi and focal fibrosis can be found[16].

Seasonality of COVID-19 and survival in the environment

The seasonality of coronaviruses might be determined, in part, by environmental circumstances and host vulnerability because coronaviruses are more stable under low and midrange relative moisture (20-50%), when defense mechanisms of the airways are also inhibited[12]. Current studies of the continuing outbreaks appear to point out that infection transmission is in part a role of temperature and moisture, and spread strength appears to decline with a rise in temperature and relative moisture. Initial analyses of the COVID-19 burst in China shows the high reproductive numbers which are elucidated not only in dry, cold regions but also in tropical regions with high absolute moisture, like in Guangxi and Singapore. Recently, there is only conditional confirmation that SARS-CoV-2 will exhibit noticeable winter seasonality in the Northern hemisphere, comparable to other human coronaviruses[7,12]. The environmental stability of viable SARS-CoV-2 is up to three hours in the air after the aerosolization process, up to four hours on copper, up to one day on paper and wood, and up to two-three days on plastic and stainless steel. A recent publication indicated that the virus was more stable on flat surfaces, with the discovery of infectious virus on medical mask material for up to seven days. At 4 °C, the virus was stable up to fourteen days, but deactivated after five minutes at 70 °C. The virus was identified most frequently on gloves, but infrequently on eye safety devices[11,12].

Screening and triage: early recognition of patients with Severe Acute Respiratory Infection (SARI) related to COVID-19

The purpose of triage is to recognize and separate all patients with assumed COVID-19 at the initial point of connection within the health care system (*i.e.*, emergency department or outpatient health center). Considering COVID-19 as a probable etiology of patients with an acute respiratory infection under definite circumstances is shown in Table 2[2,17]. Triage patients consume uniform triage tools and begin emergency therapy based on disease severity as follows[18]:

- Testing should be consistent with local guidance for the management of community-acquired pneumonia. Samples of other etiologies involve *Streptococcus pneumonia, Haemophilus influenza type B, Legionella pneumophila*, other familiar principal bacterial pneumonia, influenza viruses and respiratory syncytial virus.
- Close contact is defined as:

- Healthcare-related contact, involving the provision of direct care for COVID-19 patients, working with health care workers diseased with COVID-19, visiting patients or staying in close location to the COVID-19 patients.
- Working together nearby or using the same classroom environment with a COVID-19 patient.
- Traveling together with COVID-19 patients in any sort of transportation.
- Living in the same home with COVID-19 patients.

The majority of patients are older than fifty years of age with a mean age that is much older than patients diseased with H1N1 or with MERS[10]. Approximately 30-50% of COVID-19 patients had long-lasting co-morbidities. The interval from the first symptom to respiratory failure in most patients is greater than one week, which is more extended than H1N1[11]. Moreover, a lot of patients who go on to suffer from respiratory failure had hypoxemia but lacked signs of respiratory distress, particularly in old patients ("silent hypoxemia"). Besides, only a smaller number of patients have additional organ dysfunction (*e.g.,* shock, acute kidney injury) before the emergence of respiratory failure. These features are presumably because old-fashioned approaches (*i.e.*, quick sequential organ failure assessment score, new early warning score) may not aid in the prediction of those patients who will go on to suffer from respiratory failure. Consequently, it is critical to institute an expectation or primary recognition model of patients expected to fail[7,11]. In patients with mild disease, introducing them to the hospital may not be necessary if there is no concern about quick worsening or an inability to quickly return to the hospital, but the quarantine to prevent virus transmission should be arranged. All patients taking care outside the hospitals should be educated on how to isolate themselves properly according to the public health practices for home quarantine, and further sent back to a selected COVID-19 hospital if they get worse[19].

If care is to be delivered at home, an expert health care worker (HCW) should conduct a valuation to confirm that the residential situation is appropriate for giving care; therefore HCWs need to well evaluate whether the patient and the family can follow the precautions that are suggested as part of home care quarantine (*e.g.*, hand sanitization, respiratory sterility, environmental hygiene, restrictions on movement around or from the home) and shall be able to report safety concerns (*e.g.*, accidental consumption of and fire dangers related to consuming alcohol-based hand wipes)[19,20]. The patient and other house members should be provided with continuing support and instruction, and monitoring should continue for the period of house care. Home members should follow the following recommendations[19].

- Firstly, the patient shall be put in a well-ventilated single room (open the windows frequently).
- Restrict the movement of the patient in the home and reduce shared space like the bathroom and kitchen.
- Family members should remain in a different room or keep a remoteness of at least one meter from the patient.
- Allow only one caregiver to provide care to the patient. Ideally, one who is in good health and has no underlying, long-lasting or immune-compromising circumstances.
- While cleaning hands with soap and water, it is desirable to use throwaway paper wipes to dry hands.
- Caregivers must use a medical mask and shall protect their mouth and nose while taking care of the patient in the same room, and the patient should always be provided a medical mask to wear as much as possible[20].

Table 3 shows the clinical syndromes associated with COVID-19 infections in children and the clinical management of SARI when COVID-19 disease is suspected[2,17-19].

Immediate implementation of suitable infection prevention and control (IPC) measures

IPC is a critical and essential part of the clinical control of patients and WHO guidance is existing. To accomplish the peak level of success in response to COVID-19 and occurrence using the policies and practices recommended, an IPC program with a committed and qualified team, or at least an IPC important point should be in place and reinforced by the national and facility senior organization. In countries where IPC is incomplete or non-existent, it is essential to begin by confirming that at least minimum necessities for IPC are in place and to progressively move to complete achievement of all necessities of the IPC central components according to local priorities[21].

IPC approaches to stop or restrict spread in health care settings include the following:

1. Ensuring triage, initial recognition and source control (quarantining patients with predicted COVID-19).
2. Applying standard precautions and protection rules for all patients.
3. Realizing empiric extra precautions (droplet,

Table 3: Clinical syndromes associated with COVID - 19 infections the child[2, 17-19]

Severity	Symptoms
Uncomplicated illness	• Patients with uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, and headache. The elderly and immune-suppressed may present with atypical symptoms. These patients do not have any signs of dehydration, sepsis, or shortness of breath.
Mild pneumonia	• Patient with pneumonia and no signs of severe pneumonia. A child with non-severe pneumonia has cough or difficulty in breathing/ fast breathing: (fast breathing-in breaths/min).
Severe pneumonia	• Adolescent or adult: fever or suspected respiratory infection, plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 <90% on room air. • The child with cough or difficulty in breathing, plus at least one of the following: ▪ central cyanosis or SpO2 <90%; severe respiratory distress (e.g. grunting, chest indrawing); signs of pneumonia with any of the following danger signs: ▪ Inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest in drawing, fast breathing (in breaths/min): <2 ▪ Month's ≥60; 2–11 months ≥50; 1–5 years ≥40. The diagnosis is clinical; chest ▪ Imaging can exclude complications.
Acute Respiratory Distress Syndrome	• Onset: new or worsening respiratory symptoms within one week of known clinical insult. • Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. • Origin of edema: respiratory failure not fully explained by cardiac failure or fluid overload. • Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of edema if no risk factor present. Oxygenation (adults): • Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cm H2O, or non-ventilated) • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤200 mmHg with PEEP ≥5 cm H2O, or non-ventilated) • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg with PEEP ≥5 cm H2O, or no ventilated) • When PaO2 is not available, SpO2/FiO2 ≤315 suggests ARDS (including in non-ventilated patients) Oxygenation (children; note OI = Oxygenation Index and OSI = Oxygenation Index using SpO2) • Bi-level NIV or CPAP ≥5 cm H2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3

ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure

contact and, at any time appropriate, airborne precautions) for assumed cases of COVID-19.
4. Implementing administrative and organizational controls.
5. Using environmental and engineering panels.

Ensuring triage, initial recognition and source control (quarantining patients with predicted COVID)[22]

Clinical triage involves a system for evaluating all patients at admittance, allowing for initial recognition of probable COVID-19, and instant quarantine of patients with assumed illness in a region isolated from other patients (source control)[23]. To enable the initial identification of cases of predicted COVID-19, health care facilities should:

- Inspire HCWs to have a high level of clinical doubt.
- Create a well-resourced triage location at the entrance to the facility, reinforced by skilled staff.
- Introduce the usage of screening surveys according to rationalized case definition.
- Post signs in public regions prompting symptomatic patients to alert HCWs.
- Hand sanitation and respiratory hygiene are crucial preventive methods[21].

Applying standard precautions and protection rules for all patients

Standard precautions involve hand and respiratory sanitization, the use of suitable personal protective equipment (PPE) according to a risk evaluation, injection safety approaches, safe waste disposal, appropriate linens, environmental hygiene and sterilization of patient-care apparatus. Respiratory hygiene measures include[22]:

- Make sure that all patients shield their nose and mouth with a tissue or elbow when coughing or sneezing.
- Give a medical mask to patients with predicted COVID-19 while they are in waiting zones or cohorts' housings.
- Achieve hand hygiene after interaction with respiratory discharges.

Hand hygiene approaches should be performed by

HCW's before contact with a patient, before any hygienic or aseptic technique is achieved, after contact with body fluid, after touching a patient and after contact with the patient's surroundings.

- Hand hygiene involves both washing hands with an alcohol-based hand wipe and cleaning them with soap and water.

- Alcohol-based hand wipes are favored if hands are not dirty.
- Rinse hands with soap and water when they are dirty[22].

Realizing empiric extra precautions (droplet, contact and, at any time appropriate, airborne precautions) for assumed cases of COVID-19

Contact and droplet precautions

Droplet and contact precautions avoid direct or indirect spread from interaction with polluted surfaces or apparatus (contact with contaminated oxygen tubes). Put PPE (triple layer medical mask, eye protection, gloves and robe) when arriving in a room and get rid of PPE when leaving. If possible, use either throwaway or dedicated apparatus (*e.g.* stethoscopes, blood pressure cuffs and thermometers). If the apparatus needs to be mutual among patients, sterilize and disinfect after each patient use. Make sure that HCWs abstain from dabbing their eyes, nose and mouth with possibly polluted gloved or ungloved hands. Avert contaminating environmental planes that are not directly connected to patient care (*e.g.* doorknobs and light bottoms). Make sure that room ventilation is enough. Avert movement of patients or transport.

Airborne precautions

Some aerosol-generating actions, such as tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before the intubation and bronchoscopy have been linked to an elevated risk of spread of coronaviruses.

- Make sure that HCWs performing aerosol-generating actions wear PPE. At any time possible, use sufficiently ventilated single places when performing aerosol-generating actions, meaning negative pressure rooms with a minimum of twelve air alterations per hour or at least 160 liters/second/patient in facilities with normal ventilation.
- Evade the existence of needless individuals in the room. Care for the patient in a similar kind of room after automatic ventilation commences.
- Restrict the number of persons existing in the room to the absolute minimum essential for the patient's care and maintenance[24].

Implementing administrative and organizational controls

Organizational controls and policies for the prevention and control of transmission of COVID-19 within the health care setting include: creating maintainable IPC infrastructures and activities, instructing patients' caregivers, improving policies on the early recognition of acute respiratory infection possibly triggered by COVID-19 virus, confirming entrance to prompt laboratory testing for the identification of the etiologic agent, avoiding overcrowding, particularly in an emergency setting, providing devoted waiting zones for patients with symptoms, properly separating hospitalized patients, ensuring enough materials, and ensuring commitment to IPC strategies and procedures for all sides of health care[22].

Using environmental and engineering panels

These controls report the basic infrastructure of the health care capability, and its purpose is to make sure that ventilation in all areas in the health care facility is adequate, in addition to adequate environmental sanitization. Also, a distance of at least one meter should be kept between all patients[24]. Both spatial detachment and enough ventilation can assist to reduce the diffuse of many pathogens in the health care setting. Guarantee that cleaning and disinfection measures are followed regularly and appropriately. Washing environmental surfaces with water and detergent and frequent use of hospital disinfectants (like sodium hypochlorite) is effective and adequate. Ensure laundry, food service implements and medical instruments are discarded in agreement with harmless routine procedures and actions[25].

Early supportive therapy and monitoring

A. Provide supplementary oxygen therapy instantly to patients with SARI and respiratory distress, hypoxemia or shock. Start oxygen therapy at five L/min and titrate flow rates to achieve target oxygen saturation (SpO_2) ≥90% in non-pregnant patients and SpO_2 ≥92-95% in pregnant women. Children with emergency signs (obstructed or lack of breath, severe respiratory distress, central cyanosis, shock, coma or seizures/convulsions) have to receive oxygen therapy while resuscitating them to target SpO_2 ≥94%, then, the target SpO_2 is ≥90%.
B. The most important equipments that should be found in patients caring rooms include pulse oximeters, effective oxygen systems and throwaway, single-use, oxygen-delivering interfaces (nasal cannula, simple face mask and mask with reservoir bag). Use interaction safety measures when holding contaminated oxygen interfaces of COVID-19 patients[26].
C. Use conservative fluid management in patients with SARI when the shock is not evident. Patients with SARI should be treated carefully with intravenous fluids, because violent fluid resuscitation may deteriorate oxygenation, particularly in situations where there is restricted accessibility of mechanical ventilation[27].

D. Provide empiric antimicrobials to treat all expected microbes causing SARI. Offer antimicrobials within one hour of primary patient assessment for patients with sepsis. Initial antibiotic treatment should be established based on the clinical diagnosis (community-acquired pneumonia, healthcare-associated pneumonia, local epidemiology and vulnerability data) and therapy procedures. Empirical treatment involves a neuraminidase inhibitor for the cure of influenza when there is local circulation or other risk factors, including transportation history or exposure to animal influenza viruses. Initial therapy has to be scaled down based on microbiology outcomes and clinical decisions[28].
E. Systemic corticosteroids should not be given regularly for the treatment of viral pneumonia or ARDS except for clinical trials unless they are designated for another reason. This is because corticosteroids ordered to patients with SARS stated no survival assistance and probable harms (avascular necrosis, psychosis, diabetes and delayed viral clearance). Besides, a greater risk of mortality and secondary infections with corticosteroids was established[29].
F. Strictly observe patients with SARI for signs of clinical worsening, such as quickly progressive respiratory failure and sepsis, and use supportive care interventions straightaway[26].
G. Recognize the patient's co-morbid circumstances to adjust the management of serious illness and appreciate the prognosis[26].

Collection of specimens for laboratory diagnosis

Precise diagnosis is by specific molecular trials on respiratory samples (throat swab/ nasopharyngeal swab/ sputum/ endotracheal aspirates and bronchoalveolar lavage). The virus may also be noticed in the stool and in severe cases, the blood. It is essential to remember that the multiplex polymerase chain reaction plates presently existing exclude the COVID-19. Commercial tests are also not accessible at present. Additional laboratory examinations are frequently nonspecific. The white cell count is generally normal or low. There may be lymphopenia; a lymphocyte count of less than one thousand has been related to the severe disease. The platelet count is commonly normal or slightly low. The C-reactive protein and erythrocyte sedimentation rate are usually high, but procalcitonin levels are frequently normal. A high procalcitonin level may point to a bacterial co-infection. The alanine aminotransferase/aspartate transaminase, prothrombin time, creatinine, D-dimer, creatine phosphokinase and lactate dehydrogenase may be raised, and high levels are linked to severe disease[30].

The chest X-ray typically demonstrates bilateral infiltrates, but may be normal in the early stages of infection. Computerized tomography (CT) is more sensitive and precise. CT imaging commonly indicates infiltrates, ground-glass opacities and subsegmental consolidation. It is also irregular in asymptomatic patients or patients with no clinical suggestion of lower respiratory tract association. Abnormal CT scans have been employed to identify COVID-19 in uncertain cases with negative molecular diagnosis; many of these patients had positive molecular tests on duplication of testing[31]. Fast gathering and testing of suitable samples from patients meeting the supposed case definition for COVID-19 is important for clinical management and outbreak control and need to be directed by a laboratory expert. Supposed cases should be checked for the virus with nucleic acid amplification tests (NAAT), like reverse transcription-polymerase chain reaction (RT-PCR.)

Safety procedure during specimen collection

Make sure that adequate standard operating procedures are in use, and that the team is skilled for correct specimen assembly, storage, packing and transportation. All samples collected for laboratory examinations should be considered as possibly infectious and transmittable. Make sure that HCWs who gather samples comply strictly with IPC procedures[32].

The specimen to be collected

At least, respiratory material should be sampled:

- Upper respiratory samplings: nasopharyngeal and/or pharyngeal swab or wash in ambulatory patients.
- And/or lower respiratory samplings: sputum (if formed) and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory illness.

Further clinical samples may be collected as COVID-19 virus has been distinguished in blood and stool, as had the coronaviruses responsible for SARS and MERS. The interval and incidence of shedding of COVID-19 virus in stool and possibly in urine is unidentified. In the case of patients who are dead, consider post-mortem material as well as lung tissue. In living patients, combined serum (acute and convalescent) can be valuable to retrospectively define cases as serological analysis become prominent[33].

Packaging and shipment of clinical samples

Samples for virus recognition should reach the laboratory immediately after collection. The right holding of specimens during shipping is critical. Specimens that can be transported rapidly to the laboratory can be put in storage and shipped at 2-8 °C.

If there is any suspected delay in specimen transportation to the laboratory, the use of a viral transportation medium is powerfully suggested. Samples may be frozen to -20 °C or ideally -70 °C and transported on dry ice if additional delays are probable. It is essential to evade frequent freezing and melting of samples[33].

NAAT for the COVID-19 virus

Routine validation of cases of COVID-19 is established on recognition of distinctive sequences of virus RNA by NAAT, such as real-time RT-PCR, with approval by nucleic acid sequencing when essential. The viral genes directed until now contain the N, E, S and RdRP genes. RNA extraction ought to be done in a bio-safety cabinet in a BSL-2 or the same facility. Heat treatment of specimens before RNA extraction is not suggested[28]. In hospitalized patients with established COVID-19 infections, repeat upper respiratory tract samples should be gathered to prove viral clearance. The frequency of sample assembly will be influenced by the local conditions, but should be completed at least every two to four days until there are two consecutive negative results (of upper respiratory tract samples) in a clinically improved patient for at least one day.

Coronavirus statistics and charts

There are 2,395,636 confirmed cases and 164,565 deaths from the coronavirus COVID-19 outbreak as of April 19, 2020 (19:37 GMT). However, by the end of 28th June 2020, there were more than 10,088,576, cases confirmed and more than 501,442 deaths. The greatest number of new cases and deaths of COVID-19 are now being reported in the USA, Brazil, Russia, Spain, the UK, Italy, Germany and France, and this growing number of cases is due to person-to-person transmission. As represented in Figure 1, country-wise case distribution has been reported to be the highest in USA, Brazil and Russia with 25.74%, 13.04% and 6.22% respectively. This may be contributed to the large population size in USA and Russia, or the low treatment facilities in Brazil, in contrast to better approaches in medical services which are used in European countries, which have shown a moderate distribution (UK-3.08%, Italy-2.38%, India-5.25%, Peru-2.74% and Spain-2.93%)[34]. On 3rd April, the French Government reported 17,827 additional cases and 532 additional deaths from nursing homes that had not been reported previously. On 2nd April, it had reported 884 additional deaths. On 12th February, China reported 51,152 additional new cases due to a change in how cases were diagnosed and reported[12]. Figure 2 also shows the number of cases, deaths and recovery for some countries as on 13th July and 19th August 2020[34]. Comparing the data between these periods, it is shown that the number of cases, deaths and recovery in these countries had increased by significant values[34].

There are four main gaps between stated cases and real cases:

1. **Inadequate testing:** Countries that lack the systems or capacity to test appropriately.
2. **Yet to be stated cases:** People who have the virus but are either yet to present with symptoms, yet to be tested, or had a test that revealed a false negative.
3. **Asymptomatic cases:** Approximations are that about half of all persons who get the virus will never present with symptoms.
4. **Purposely under-reported**: Some countries appear to be deliberately under-reporting cases.

Among all cases. Hospitalization happened in 32% (48,755 of 152,375) of cases stated from 26 countries (median country detailed estimation, inter-quartile range (IQR), 28%, 14-63%). Severe illness (needing intensive care or respiratory support) accounted for 2,859 of 120,788 (2.4%) cases informed from 16 countries (median, IQR: 1.4%, 0-33%).

Among hospitalized cases. The severe illness was stated in 9.2% (3,567 of 38,960) of hospitalized cases from 19 countries (median, IQR: 15%, 3.8-35%). Death occured in 1,005 of 9,368 (11%) hospitalized cases from 21 countries (median, IQR: 3.9%, 0-13%). Figure 2 summarizes the number of cases, deaths and recovery for some countries as on 13thJuly 2020[34].

Aggregating or comparing COVID-19 case counts is futile. The net result is the number of global cases is likely to be significantly different from reported statistics. Some estimates are that global infections are as much as 500% to 1000% higher than reported, which makes any aggregated reported numbers useless. The analysis started in January by excluding Wuhan data, and then all Chinese data. Following this, Iranian data looked suspect. Italy then changed definitions to under-report cases. After that, they gave up on aggregates and focused on individual countries. At least that way, changes would be based on a relatively consistent methodology. Ideally, testing would be randomized, significant in size, and from a trustworthy source. Iceland, Norway, Australia, Germany and South Korea (in green, Figure 3) rate the best. Switzerland, Italy, Japan, the US and the Netherlands (in red) rank poorly. Dashed lines are countries with widespread facemask use as shown in Figure 3. However, the chart in Figure 3 is misleading. For example, Iceland rates at the top, but not because it has the greatest number of severe cases. Instead, Iceland ranks highly as it has been doing far more testing – including random sampling[34].

as of July 13, 5:20 GMT	Total infections	Active infections	Recoveries	Deaths
Total (worldwide)	13,041,698	4,881,944	7,588,094	571,660
USA	3,413,995	1,759,129	1,517,084	137,782
Brazil	1,866,176	580,513	1,213,512	72,151
India	879,466	301,850	554,429	23,187
Russia	727,162	214,766	501,061	11,335
Peru	326,326	97,345	217,111	11,870
Chile	315,041	24,160	283,902	6,979
Spain	300,988	N/A	N/A	28,403
Mexico	299,750	79,980	184,764	35,006
United Kingdom	289,603	N/A	N/A	44,819
South Africa	276,242	137,289	134,874	4,079

as of August 19, 8:12 GMT	Total infections	Active infections	Recoveries	Deaths
Total (worldwide)	22,322,068	6,474,486	15,062,931	784,651
USA	5,656,204	2,469,540	3,011,577	175,087
Brazil	3,411,872	747,674	2,554,179	110,019
India	2,768,670	677,059	2,038,585	53,026
Russia	937,321	171,909	749,423	15,989
South Africa	592,144	94,412	485,468	12,264
Peru	549,321	148,644	374,019	26,658
Mexico	531,239	110,158	363,307	57,774
Colombia	489,122	161,180	312,323	15,619
Chile	388,855	15,869	362,440	10,546
Spain	384,270	N/A	N/A	28,670

Fig 2: The number of cases, deaths and recovery for some countries as on 13th July and 19th August 2020[34] .

DISCUSSION

Management of mild cases of patients with confirmed COVID-19 disease

Mild cases are asymptomatic patients or patients with mild fever (37.5 °C), cough, cold symptoms, nasal congestion, malaise and without dyspnea. Most patients have mild or no symptoms. The most important step in care is the isolation of patients to prevent transmission of the virus to other relatives or healthcare providers[35]. Mild cases need supportive care and symptomatic treatment with antipyretic agents, if needed only. Paracetamol is the first line of treatment and nonsteroidal anti-inflammatory drugs have caution in use. Hydration and nutrition supplements should be taken and adequate calorie intake must be ensured, along with frequent cough and fever monitoring. The organ function should be routinely monitored, and any secondary infection should be prevented. All management is in the house unless there are severe symptoms. If there is any development in the disease, patient must refer to the healthcare center[36].

Management of severe cases of patients with confirmed COVID-19 disease

Oxygen therapy

Patients that develop severe symptoms such as respiratory distress (less than 30 breath/min), SpO_2

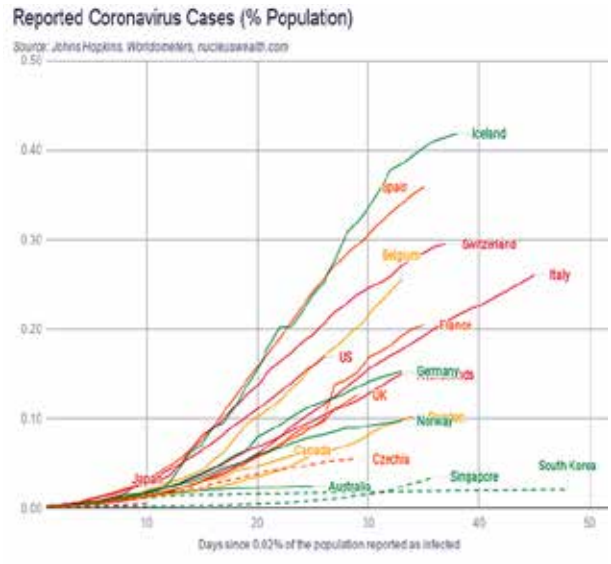


Fig 3: Reported coronavirus cases (% population)[34].

<90%, cyanosis and shock must receive oxygen therapy by including nasal catheter and mask oxygenation and nasal high-flow oxygen therapy. If possible, inhalation of mixed hydrogen and oxygen (H_2/O_2: 66.6%/33.3%) can be applied to target more than 91% of SpO_2 in non-pregnant adults and 92-95% to pregnant ones at room air[37]. The nasal cannula is preferred for children with respiratory distress because it is better to tolerate. High flow nasal catheter or non-invasive mechanical ventilation is used when respiratory distress is not relieved after standard oxygen therapy. High flow nasal catheters are considered to be safer than non-invasive ventilation because many scientists suggest that it may be associated with the nosocomial transmission of the disease. About one third or two-third of critically ill-patients need them. If the patient doesn't improve in time (nearly 1-2 hours), invasive mechanical ventilation should be considered. Invasive mechanical ventilation is used to avoid ventilator-induced lung injury while facilitating gas exchange via lung-protective ventilation[38]. Patients with severe symptoms should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, nasal prongs, simple face mask and mask with reservoir bag), and should have regular monitoring of vital signs[7]. In the case series of 99 hospitalized patients with COVID-19 infection from Wuhan, oxygen was given to 76%, non-invasive ventilation in 13%, mechanical ventilation in 4% and extracorporeal membrane oxygenation in 3%[7].

Treatment with therapeutic agents

No pharmaceutical products have yet been shown to be safe and effective for the treatment of COVID-19. However, several medicines have been suggested as potential investigational therapies, many of which are now being or will soon be studied in clinical trials, including the solidarity trial co-sponsored by WHO and participating countries. The following therapeutic agents were used in the treatment and management of COVID-19.

Chloroquine and hydroxychloroquine

Chloroquine and its analogs were employed for the treatment and prevention of malaria in the 1900s. In addition to that, they possess immunomodulatory effects for the treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. They also have antiviral properties, especially for viruses that induced inflammation like Ebola, HIV and SARS[39]. These agents are non-protonated; when they are introduced intracellularly, they become protonated and increase the pH of the corresponding cell. The pH changes inhibit viral infusion with the cell membrane of the host. They can also inhibit nucleic acid replication and appear to interfere with the terminal glycosylation of ACE2 receptor expression, which should prevent SARS-CoV-2 receptor binding and subsequent spread of infection[40]. Studies have shown that chloroquine has a potent cytotoxic response with 99% inhibition of viral replication. Moreover, in-vivo models show high inhibition of viral spread before viral exposure, in which it concludes that they may be used as a prophylactic agent. The working group is against the possible use of chloroquine and hydroxychloroquine in prophylaxis for COVID-19. At present, there is no evidence of the efficacy of this drug in the prevention of COVID-19.

Savarino *et al*[39] hypothesized that chloroquine might block the production of pro-inflammatory cytokines (such as interleukin-6); thereby blocking the pathway that subsequently leads to ARDS. Based on this finding, experts and organizers of clinical trials suggested that chloroquine is a promising antiviral agent against SARS-CoV-2. Hydroxychloroquine showed a safety profile and is three times more potent than chloroquine in cytotoxic response, hence a lesser dose of hydroxychloroquine is used[30]. It must be taken into account that therapy would most likely be required in older patients and/or in case of severe disease (at least for the moment). This study, which has meanwhile been published, suggests that SARS-CoV-2 positivity in nasopharyngeal secretions (measured by RT-PCR) is significantly decreased at day 6 after inclusion (*i.e.* day 10 after symptom onset) in hydroxychloroquine-treated COVID-19 patients (n=26) versus patients who received supportive care only (n=16 external controls). However, the study has a limitation of small size and the non-homogeneous

group they consider as the first line for severely ill patients. In the same line, it is not recommended for out-patients because there is no sufficient study for efficacy and cost benefits[41]. Current in vitro pharmacokinetic models suggest a loading dose of hydroxychloroquine 400 mg orally twice daily on day one, followed by 200 mg orally twice daily for four days. The panel recommends the use of the drug at a dose of 500 mg b.i.d for 10 days. Alternatively, if chloroquine is not available, you can use hydroxychloroquine 200 mg b.i.d. These agents have mostly been tolerated by patients, but it has adverse gastrointestinal effects. It can cause toxicity leading to neuropathy, retinopathy and cardiomyopathy, albeit with long time use and not in the short term. Concurrent administration of QTc prolonging agents and strong 2D6 inhibitors (chloroquine only) should be avoided to minimize cardiac adverse effects. Although the manufacturer's labeling of chloroquine and hydroxychloroquine caution against their use in patients with glucose-6-phosphate dehydrogenase, there is limited data to support this risk and no incidence of hemolytic anemia has been seen in patients with glucose-6-phosphate dehydrogenase in 30 years of drug exposure[42].

Remdesivir

Remdesivir is a pro-drug which contains 1'-cyano-substituted adenosine nucleotide analog to metabolize the cell and tissue so as to activate the nucleoside triphosphate (GS-443902), which inhibits the viral RNA-dependent RNA polymerases in the viral infectious cycle cascade. The second action is adenosine analog, which may involve lethal mutagenesis and chain termination. It was initially developed for the treatment of Ebola hemorrhagic fever, but it has no approval for any indications till date[43]. Nucleotide analogs are used in RNA viral for inhibition of viral replication by suppression of polymerases enzyme; however, many viruses have resistance to these agents and result in exo-ribonuclease proofreading and removal. Remdesivir has the potential to avoid this proofreading.

An in vitro study showed its activity in human lung epithelial cells against coronaviruses. In China, two phase 3 randomized, open-label trials, NCT04292899 and NCT04292730, were initiated by the manufacturer (Gilead) to evaluate the safety and antiviral activity of 5- and 10-day regimens of Remdesivir, in conjunction with the standard of care in patients with severe and moderate COVID-19, and are estimated to finalize patient recruitment by May 2020. In the United States, remdesivir has been used for 4-10 days until the respiratory symptoms improve[44]. It is used as 200 mg IV loading dose within 30 minutes, followed by 100 mg OD for 2-10 days. Some adverse effects appear while using Remdesivir such as nausea, vomiting, rectal bleeding and elevated aminotransferase level. However, it is still not clear whether these effects are generally from the disease or the drug itself. No clinical study has been carried out to elucidate the usage of the drug for pregnant women and drug-drug interaction is still not reported [45].

Lopinavir/Ritonavir

Lopinavir is an aspartic acid protease inhibitor. Proteases are essential enzymes for replication and maturation of viruses, and lopinavir inhibits the spread of the virus in the host cell. Ritonavir is combined to boost the half life of lopinavir by inhibition of CYP450. The drug has been approved for use in the treatment of HIV. A recent study showed that lopinavir/ritonavir affects the inhibition of 3-chymotrypsin like protease which was found to be a novel coronavirus[46]. In a recent study Bin Cao *et al*[42] that randomized a total of 199 patients with laboratory-confirmed SARS-CoV-2 infection, 99 patients were treated with lopinavir/ritonavir and 100 patients were treated with standard care. The lopinavir/ritonavir group was not associated with any development and treatment effects. Subsequently, the number of deaths after 28 days was the same in the two groups, which elucidates that there is no benefit associated with its usage in severely ill patients[47]. However, there are still trials that suggest that lopinavir/ritonavir have possible benefits in patients who were treated before 12 days of symptom. The available doses are 400/100 mg or 200/100 mg. If lopinavir/ritonavir is used as an adjunctive agent for COVID-19, a dose of 400 mg/100 mg by mouth twice daily for 14 days is recommended. These agents still require the second line of COVID-19 treatment in cases where chloroquine is contraindicated[46]. The usage of lopinavir/ritonavir is associated with gastrointestinal toxicities, diarrhea and vomiting; however, administering it with food may ameliorate these effects. According to multiple collected data, lopinavir/ritonavir is not associated with teratogenicity effects in pregnant women with HIV, and can be used if there are no contraindications[46,48].

Ribavirin

Ribavirin is a prodrug of purine nucleoside analog, whose derivative in the liver closely mimics the purine analog guanosine that incorporates with RNA. The structural elements prohibit the subsequent addition of nucleoside analogs, effectively halting the synthesis of RNA. It is used for hepatitis C, B and respiratory viruses[49]. In 126 cases treated with ribavirin, hemolysis and anemia occurred in up to 76% and 49% of cases

Table 4: Italian Society of Infectious and Tropical Diseases Section Therapeutics Protocol [54, 55]

Clinical observation	Recommendation
Patient positive for COVID-19 asymptomatic or mild symptoms: (fever (> 37.5 ° C), cough, cold symptoms without dyspnea), age <70 years with no risk factors (COPD, diabetes and heart disease) and RX normal chest	Clinical observation, supportive care
Patient positive for COVID-19 with mild respiratory symptoms but age> 70 years and/or with risk factors (COPD, diabetes and heart disease) or symptomatic or mild symptoms (fever (> 37.5 ° C), cough, dyspnea on mild to moderate) and chest radiography with pneumonia framework	Lopinavir / ritonavir 200/50 mg cps, 2 x 2 / day (800 mg darunavir alternatively 1 cp / day + ritonavir 100 mg 1 cp / day or darunavir / cobicistat 1 cp 800/150 mg / day) 500 mg + chloroquine, 1 x 2 / day or hydroxychloroquinecps200 mg, 1 x 2 / day. Duration of therapy: 5 to 20 days, with timing to be determined according to clinical evolution.
Case of need for oxygen therapy or rapid clinical deterioration (see "supportive measures" and COVID respiratory severity scale)	Remdesivir requests for compassionate use. At the time of its availability suspend LPV / RTV (or DRV / b) and continue with: Remdesivir vials 150 mg period: 1 day 200 mg IV 30 minutes then 100 mg IV / day for another 9 days in combination with chloroquine 500 mg, 1 x 2. day or hydroxychloroquine 200 mg, 1 x 2 / day (duration of therapy: from 5 to 20 days, with timing to be determined according to clinical evolution). If the patient has a BCRSS score. Evaluate 2: dexamethasone 20 mg/day for 5 days and then 10 mg/day for 5 days (as indicated by intensivistica) and/or Tocilizumab
Positive Patient COVID for-19 with the x-ray of severe pneumonia, ARDS or global respiratory insufficiency, hemodynamic failure, need for mechanical ventilation (invasive or not)	Remdesivir 1 days 200 mg iv as a loading dose, then 100 mg/day (days 2-10) + chloroquine 500 mg, 1 x 2 / day or hydroxychloroquine 200 mg x 2 via SNG (duration of therapy: from 5 to 20 days, with timing to be determined according to clinical evolution).
Patients ARDS: after 24 hours from the diagnosis of ARDS.	Dexamethasone 20 mg / day for 5 days and then 10 mg / day for 5 days (as indicated by intensivistica) and / or tocilizumab.

CPS: Compendium of Pharmaceuticals and Specialties

respectively. Although the use of ribavirin as monotherapy is of no effect, it has potential activity when combined with other anti-viral agents such as lopinavir/ritonavir or chloroquine analogs. Oral ribavirin has been dosed as a 4-gram loading dose followed by 1.2 grams every eight hours in two small studies for SARS. In the management of COVID-19, data is limited to ongoing studies using a dosing strategy of 400 mg by mouth twice daily for 14 days as a part of a combination regimen[50]. Ribavirin needs special precaution when in use, because it is associated with hemolytic anemia, especially after taking a high dose (1-2 gm), which is needed for coronaviruses treatment. Ribavirin is a teratogen, with a significant potential for embryonic toxicity and is usually contraindicated in women who are pregnant and in male partners of those pregnant women. Ribavirin in combination with other immunosuppressive therapies, particularly azathioprine or interferon (IFN) can lead to severe pancytopenia[49].

Immune modulating agents

Interferon-alpha

Interferon is an endogenous protein released by the host cell in action of inflammation and infection. It stimulates the immune response against viral replication. It is up regulated in many viral infections, such as hepatitis. This nonspecific immune-modulatory response is an attractive reason for its use in COVID-19 treatment. When interferon is used for SARS, it has an action before exposure to infection via the inhibition of virus replication. However, there is still no approved action after virus exposure[51]. In vivo studies have yet to be able to replicate the same benefits, with some studies showing no influence on the disease course for MERS, while others suggest a small improvement in survival at 14 days, but not 28 days, when used in combination with ribavirin. Due to the lack of established human data with IFNs for COVID-19, this therapy should only be considered for COVID-19 as part of a clinical trial. There is no established dosing regimen for IFN in the treatment of COVID-19. The only available data used for MERS treatment was via using a dose of 180 μg per week for two weeks[51].

Tocilizumab

Tocilizumab is a humanized anti-interleukin 6 monoclonal antibody for the treatment of rheumatoid arthritis. It inhibits the interleukin 6 signaling pathway and competes with interleukin 6 binding sites on the cell membrane to inhibit the inflammation pathway. It's hypothesized that it works against cytokine storm with raised ferritin and interleukin-6 levels due to SARS-CoV-2. Recently published data from Wuhan indicates that tocilizumab added to lopinavir, methylprednisolone and oxygen therapy in 20 patients with severe COVID-19 resulted in rapid reductions in fever in all patients, improvement in oxygenation for 75%, and facilitated discharged from the hospital in 95% of patients[52]. Tocilizumab for most indications is

weight-based with a maximum dose of 800 mg. The dosing of tocilizumab for COVID-19 is still not well established. When used in a case series of patients with COVID-19, a one-time dose of intravenous tocilizumab 400 mg was administered. However, until now, there are no peer study approved uses of Tocilizumab[53].

International protocols for COVID-19 treatment guidelines

Italian protocol

The spread of the COVID-19 epidemic in Italy determined the need to standardize the therapeutic approach to offer the same indications for all hospitals in Italy. However, no specific drug has been previously approved for COVID-19 treatment. The Italian Society of Infectious and Tropical Diseases provided the following recommendation to explore the evidence about drugs likely to be efficacious in the treatment of COVID-19 as shown in Table 4[54,55]. The recommendations were based on clinical observations and symptoms. Table 5 shows Belgian protocols and recommendations in the treatment of COVID-19[56].

Management of critical illness and COVID-19: septic shock

Doctors have noticed septic shock in some adults when infected with COVID-19, where the treatment goal is to maintain mean arterial pressure (MAP) ≥65 mmHg, lactate ≥2 mmol/L. In the absence of hypovolemia, the child will suffer from septic shock with hypotension when systolic blood pressure <5th percentile or >2 SD (below normal for age) or suffers from two or more of the following: altered mental state; bradycardia or tachycardia (HR <90 bpm or >160 bpm in infants and HR <70 bpm or >150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia. When lactate measurement isn't available, blood pressure (*i.e.* MAP) and clinical signs of perfusion can be used to define shock. Strategies for the resuscitation of adult and pediatric patients with septic shock include conservative fluid regimens. The crystalloid fluid which include normal saline and Ringer's lactate that is given as bolus infusion, hypotonic crystalloids, starches or gelatins should not be used for resuscitation. Starches are associated with an increased risk of death and acute kidney injury. Gelatins are more expensive than crystalloids. Hypotonic solutions are less effective than isotonic at increasing intravascular volume. Treating sepsis also suggests the use of albumin when patients require substantial amounts of crystalloids, but this recommendation is based on low-quality evidence.

In adults with septic shock, 250-500 mL of the crystalloid fluid which includes normal saline and Ringer's lactate is given as rapid bolus in the first 15-30 minutes[28], in children 10-20 mL/kg crystalloid fluid is given as a bolus in the first 30-60 minutes, and checked for signs of fluid overload after each bolus[57]. Reduce or discontinue fluid administration if there is evidence of no response by the patient to fluid loading or if signs of volume overload appear on the patient (*e.g.* jugular venous distension, crackles on lung auscultation,

Table 5: Belgian recommendation for patients with COVID-19[56]

Clinical observation	Recommendation
Suspicion of COVID-19 (Mild-to-moderate symptoms (no dyspnea), No risk group	Symptomatic treatment. Use paracetamol as first-line
Suspicion of COVID-19. Mild-to-moderate symptoms (no dyspnea). Risk group or Suspicion of COVID-19 and alarming symptoms (dyspnea)	Case by case discussion, if possible with a communicable disease Specialist, to initiate an empirical antiviral therapy, supported the potential delay to get results (antiviral therapy is anticipated to be more efficient if started early within the course of the disease), orOn other considerations (high risk of secondary complications).
Confirmed COVID-19. Mild-to moderate disease (no O2 requirement/no evidence of pneumonia)	Consider start hydroxychloroquine (Plaquenil®) IF NO CONTRAINDICATION • 400 mg at suspicion/diagnosis; • 400 mg 12 h later • Followed by 200 mg BID up today 5. If no hydroxychloroquine available, consider chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5 or chloroquine phosphate 1000 mg at diagnosis and 500mg 12h later, followed by 300mg BID up today 5.
Confirmed COVID-19 Severe disease ≥ 1 of the following: Respiratory rate ≥30/min (adults), ≥40/min (children < 5), Blood oxygen saturation ≤93%, PaO2/FiO2 ratio 50% of the lung field within 24-48 hours	Start hydroxychloroquine (Plaquenil®) IF NO CONTRAINDICATION • 400 mg at diagnosis; • 400 mg 12 h later • Followed by 200 mg BID up today 5. Consider Lopinavir/ritonavir 400/100 mg (2 tablets of 200/50 mg) BID for 14 days) as second choice ONLY if hydroxychloroquine/chloroquine contra-indicated and provided it can be administered within 12 days after symptoms onset
Confirmed COVID-19 Critical disease ≥ 1 of the following: Acute Respiratory Distress Syndrome, Sepsis, Altered consciousness, and Multi-organ failure	Remdesivir (compassionate use) • 200 mg loading dose (IV, within 30 min) • 100 mg OD for 2 to 10 days. If Remdesivir unavailable: Consider hydroxychloroquine, crushed in the nasogastric tube, at the same dosage and monitoring as above; replace with Remdesivir if it becomes available.Tocilizumab and other interleukins (6 or 1) blockers: Some Chinese, Italian and (very limited) Belgian clinical experience (unpublished) suggest a favorable effect in the most critical patients

pulmonary edema on imaging or hepatomegaly in children), especially in patients with hypoxemic respiratory failure. Based on clinical response and improvement of perfusion targets, additional fluid boluses may be given (250-500 mL in adults or 10-20 mL/kg in children). The perfusion targets include MAP (>65 mmHg or age-appropriate targets in children), urine output (>0.5 mL/kg/hr in adults, 1 mL/kg/hr in children), and improvement of skin mottling and extremity perfusion, capillary refill, heart rate, level of consciousness and lactate. Notice indices for volume responsiveness to fluid administration. These indices include passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse pressure, inferior vena cava size, or stroke volume in response to changes in intrathoracic pressure during mechanical ventilation[28].

In pregnant women with sepsis and or septic shock, they may need to be placed in the lateral decubitus position to off-load the inferior vena cava to reduce hypotension[58]. Management of septic shock in adults includes administration of vasopressors, in case fluid administration does not restore adequate perfusion. In adults, norepinephrine is the first-line agent; epinephrine or vasopressin are preferred as the second line over dopamine. If patients do not respond to usual doses of norepinephrine, consider adding vasopressin rather than further titrating norepinephrine. In children, epinephrine is considered the first-line agent, and norepinephrine may be added if necessary. The initial blood pressure target is around 65 mmHg[59]. If signs of septic shock persist despite administration of fluids and vasopressors, the patient shall be given an inotrope agent such as dobutamine rather than further titrating norepinephrine. Corticosteroids are recommended for patients with sepsis in whom adequate fluids and vasopressor therapy didn't restore hemodynamic stability. In those cases, you should balance the potential small reduction in mortality with the prolonged shedding of coronavirus.

Adjunctive therapies for COVID-19: corticosteroids

Systemic corticosteroids are indicated as adjunctive therapies for COVID-19 in the case of asthma exacerbation or COPD and septic shock. Otherwise, it should be avoided due to the lack of effectiveness and possible harm including avascular necrosis, psychosis, diabetes and delayed viral clearance, in addition to higher risk of mortality and secondary infections[29]. When using corticosteroids, it is mandatory to monitor and treat hyperglycemia, hypernatremia and hypokalemia. When stopping corticosteroids, taper down the dose and monitor the recurrence of inflammation and signs of adrenal insufficiency[60].

Antenatal corticosteroid therapies are recommended for pregnant women at risk of preterm birth from 24 to 34 weeks of gestation when there is no clinical evidence of maternal infection. However, when a woman presents with mild COVID-19, the benefit of antenatal corticosteroid might outweigh the risks of potential harm to the mother.

Caring for pregnant women with COVID-19

Due to limited data, there is no evidence suggesting that pregnant women are at higher risk of severe illness or fetal compromise. Mother-to-child transmission is still not approved. Samples taken from amniotic fluid, cord blood, vaginal discharge, neonatal throat swabs and breast milk were negative. Pregnant women in the third trimester, especially those who develop pneumonia, may suffer from premature rupture of membranes, fetal distress, preterm birth, preeclampsia, and cesarean delivery for fetal distress. WHO recommends that cesarean section should be done only when medically justified[61,62]. Emergency delivery and pregnancy termination decisions are based on many factors such as gestational age, the severity of the maternal condition, and fetal viability and well-being. Neuraxial anesthetic advantages in laboring women providing good analgesia reduce cardiopulmonary stress from pain and anxiety in emergency cesarean, by which it limits the need for general anesthesia. The use of nitrous oxide for labor analgesia should be avoided, because of insufficient data about cleaning, filtering and potential aerosolization of nitrous oxide systems. The use of magnesium sulfate for maternal seizure prophylaxis or neonatal neuroprotection may further depress respiration. Consultation with maternal-fetal medicine and pulmonary/critical care specialists is advised. The use of interventions such as a birth ball or peanut ball should be limited because it can increase the risk of infection. Intrapartum oxygen has no proven fetal resuscitation benefit and should be abandoned. At delivery of patients with COVID-19, institutions have chosen to prohibit delayed cord clamping in term infants to minimize newborn exposure to the virus. Use acetaminophen to relieve postpartum pain if possible, as nonsteroidal anti-inflammatory drugs need to be used at the lowest effective dose.

Caring for infants and mothers with COVID-19: IPC and breastfeeding

No virus was found in the breast milk of six infected patients[62]. However, close contact during breastfeeding could transmit droplets to the baby. Breastfeeding protects against morbidity in the post-neonatal as it is a passive source of antibodies and other anti-infective factors. Therefore, standard infant feeding guidelines should be followed with appropriate

precautions for IPC. The earlier initiation of breastfeeding results in greater benefits, because of the dose-response effect. If mother and baby separation have been implemented because the mother is too unwell to breastfeed or express breast milk, the infant is fed expressed breast milk by another healthy caregiver who follows hygiene precautions. Follow strict hand washing before pumping, wear a mask during pumping, and the pumping equipment should be cleaned by a healthy person. If feeding by a healthy caregiver is not possible, mothers with confirmed COVID-19 should take precautions to prevent transmission of the virus to the infant during breastfeeding such as hand hygiene, use of a face mask, clean and disinfect surfaces which the symptomatic mother has been in contact. Due to the high prevalence of mental disorders among women in the postpartum period, more interventions should be implemented to these women[62].

Caring for older persons with COVID-19

COVID-19 affects the global population in drastic ways, older people face a greater risk of developing a severe illness because of underlying health conditions and many physiological changes that come with age which shall lead to decline in intrinsic capacity, manifesting as malnutrition, cognitive decline, depressive symptoms and potential underlying health conditions[9]. Early detection of inappropriate medication prescriptions is recommended to prevent adverse effects of drug or potential drug interactions with COVID-19 treatment.

Clinical research and specific anti-COVID-19 treatments

Many clinical trials are testing various potential antivirals, but until now there is no current evidence to recommend any specific anti-COVID-19 treatment. Collecting clinical data of all hospitalized patients is important to improve our understanding of the natural history of the disease. Investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials. Importantly, studies give proof that shows the transmission of this virus from human-to-human, along with many exported instances across the world. The geriatric population and people with comorbidities are at risk of infection of this virus and susceptible to serious outcomes, which can be associated with acute breathing distress syndrome (ARDS).

The are several limitations. The virus spreads very fast, thus the actual and accurate causes and effective treatment of COVID-19 are still unknown or unavailable and the number of active cases of the infection is rising every day. However, information about the disease, including the number of cases and death are changing every day. The global impact of this new pandemic is yet uncertain. The numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects. In Palestine, the treatment and management protocols of COVID-19 are similar to the strategies and protocols in other countries, especially those who follow the guidelines of WHO.

Management of neurological and mental manifestations associated with COVID-19

COVID-19 is associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, stroke, meningoencephalitis, impaired sense of smell or taste, anxiety, depression and sleep disorders. In many cases, neurological manifestations have been reported even without respiratory symptoms. Anxiety and depression appear to be common amongst people hospitalized for COVID-19; with one hospitalized cohort from Wuhan, China revealing over 34% of people experiencing symptoms of anxiety and 28% experiencing symptoms of depression. Series cases in France found that 65% of people with COVID-19 in intensive care units showed signs of confusion (or delirium), and 69% experienced agitation. Delirium, in particular, has been associated with increased mortality risk in the context of COVID-19. Moreover, there have been concerns related to acute cerebrovascular disease (including ischaemic and hemorrhagic stroke) in multiple case series from China, France, the Netherlands, and the United States of America. Case reports of Guillain-Barré syndrome and meningoencephalitis among people with COVID-19 have also been reported. It is recommended in patients with COVID-19 that measures to prevent delirium, an acute neuropsychiatric emergency, be implemented; and patients be evaluated using standardized protocols for the development of delirium. If detected, then immediate evaluation by a clinician is recommended to address any underlying cause of delirium and treat appropriately by providing basic mental health and psychosocial support for all persons with suspected or confirmed COVID-19. Prompt identification and assessment for anxiety and depressive symptoms in the context of COVID-19 should be considered; and to initiate psychosocial support strategies and first-line interventions, for the management of new anxiety and depressive symptoms. Psychosocial support strategies as the first-line intervention for the management of sleep problems in the context of acute stress are also needed[63,64].

In summary, patients with suspected or confirmed mild COVID-19 should be isolated to contain virus transmission according to the established COVID-19 care pathway. This can be done at a designated COVID-19 health facility, community facility, or at home (self-isolation). Patients with mild COVID-19 should be given symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration. Counsel patients with mild COVID-19 about signs and symptoms of complications that should prompt urgent care. Patients with suspected or confirmed moderate COVID-19 (pneumonia) should also be isolated to contain virus transmission. Patients with moderate illness may not require emergency interventions or hospitalization; however, isolation is necessary for all suspect or confirmed cases, and monitoring of signs or symptoms of disease progression for those patients is required. Severe patients should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, Venturi mask and mask with reservoir bag). Immediate administration of supplemental oxygen therapy to any patient with emergency signs and any patient without emergency signs and SpO_2 <90% are recommended. Similarly, patients must be closely monitored for signs of clinical deterioration, such as rapidly progressive respiratory failure and shock, and respond immediately with supportive care interventions. In patients with COVID-19 and mild ARDS, a trial of high flow nasal oxygen, non-invasive ventilation – continuous positive airway pressure, bilevel positive airway pressure, may be used. Prompt recognition of progressive acute hypoxaemic respiratory failure when a patient with respiratory distress fails to respond to standard oxygen therapy, adequate preparation to provide advanced oxygen/ventilatory support and endotracheal intubation is recommended. In patients with ARDS, especially young children or those who are obese or pregnant, who may desaturate quickly during intubation, implementation of mechanical ventilation using lower tidal volumes (4-8 mL/kg predicted body weight) and lower inspiratory pressures (plateau pressure <30 cm H_2O) are recommended. In adult patients with severe ARDS (PaO_2/FiO_2 <150), prone ventilation for 12-16 hours per day is recommended. It is better to use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion and fluid responsiveness. In patients with moderate or severe ARDS, a trial of higher positive end-expiratory pressure (PEEP) instead of lower PEEP is suggested and requires consideration of benefits versus risks. In COVID-19, we suggest the individualization of PEEP where the patient is monitored for effects (beneficial or harmful) and driving pressure during titration. In patients with moderate-severe ARDS (PaO_2/FiO_2 <150), neuromuscular blockade by continuous infusion should not be routinely used. Disconnecting the patient from the ventilator, which results in loss of PEEP, atelectasis and increased risk of infection of HCWs is avoided. In patients with excessive secretions or difficulty clearing secretions, consider the application of airway clearance techniques. These should be performed only if deemed medically appropriate. Patients with ARDS in whom a lung-protective ventilation strategy fails, extracorporeal membrane oxygenation is given to achieve adequate oxygenation and ventilation.

Recognize septic shock in adults when the infection is suspected or confirmed. Vasopressors are needed to maintain MAP ≥65 mmHg and lactate ≥2 mmol/L, in the absence of hypovolaemia. For the prevention of complications in hospitalized and critically ill patients with COVID-19, such as venous thromboembolism, low molecular weight heparin is used. For any other clinically suspected complications such as stroke, deep venous thrombosis, pulmonary embolism or acute coronary syndrome, appropriate diagnostic and management pathways should proceed immediately[63,64]. There are three broad approaches of drugs being investigated for the treatment of COVID-19 which include: antiviral drugs, that directly affect the coronavirus's ability to thrive inside the body; immunotherapies, drugs that can calm the immune system in patients who become seriously ill when their immune system overreacts and starts causing collateral damage to the body; and antibodies, either from survivors' blood or made in a lab, that can attack the virus.

WHO has recommended that several medicines shouldn't be administered or taken as prophylaxis for COVID-19. These drugs include chloroquine and hydroxychloroquine (+/- azithromycin), antivirals, (lopinavir/ritonavir, remdesivir, umifenovir, favipiravir), immunomodulators (tocilizumabm, Interferon-β-1a), and plasma therapy. WHO is also against the routine use of systemic corticosteroids for the treatment of viral pneumonia. For the treatment of other acute and chronic infections in patients with COVID-19, WHO is also against the use of antibiotic therapy or prophylaxis in suspected or confirmed mild COVID-19. Besides, antibiotics should not be prescribed in suspected or confirmed moderate COVID-19 unless there is clinical suspicion of bacterial infection. In suspected or confirmed severe COVID-19, the use of empiric antimicrobials to treat all likely pathogens are based on clinical judgment, patient host

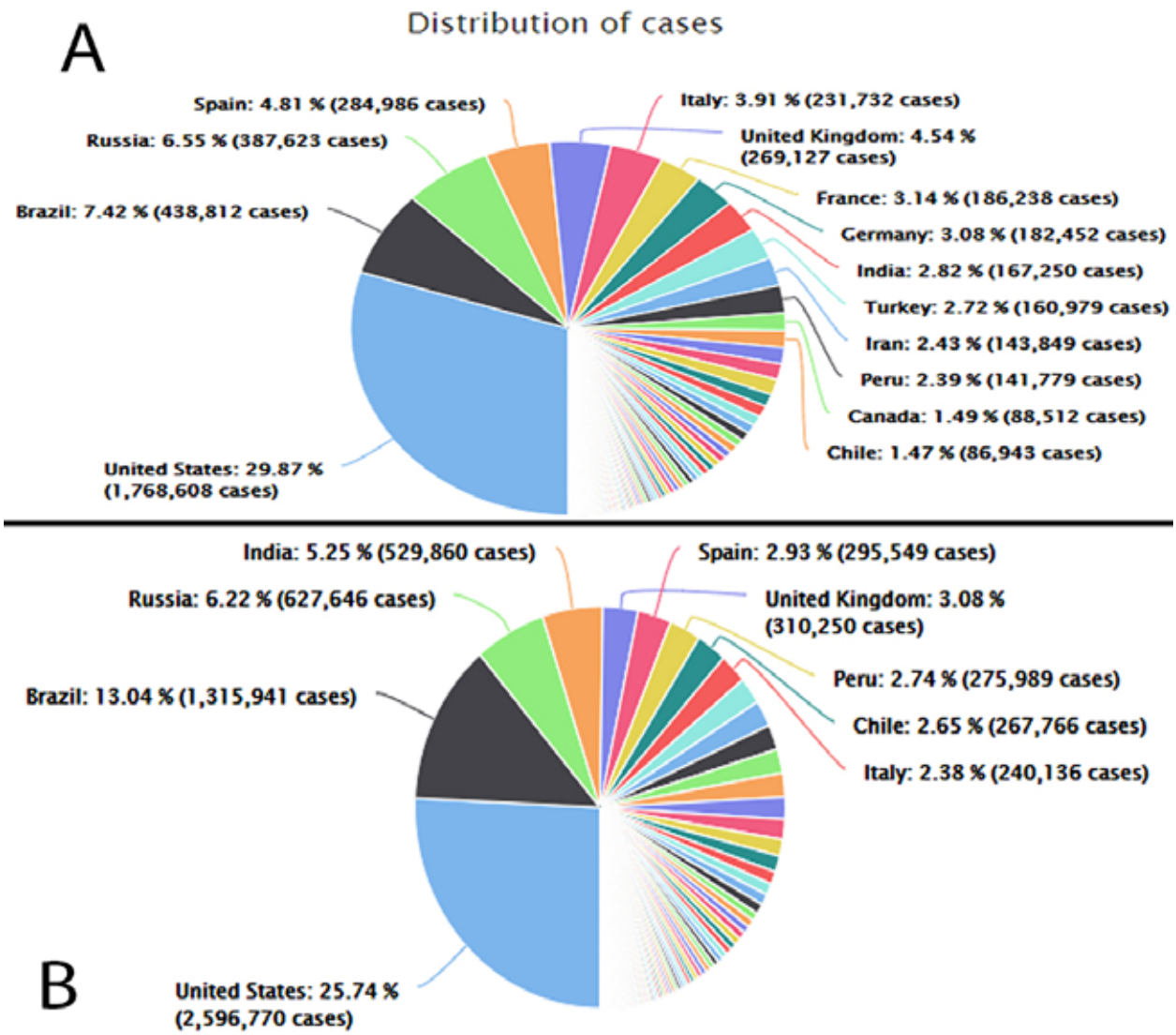


Fig 4: (A) Country-wise case distribution by end of May 2020; (B) Country-wise case distribution by June 28th, 2020[12].

factors and local epidemiology. This should be done as soon as possible (within 1 hour of initial assessment if possible), ideally, after blood cultures are obtained first. Antimicrobial therapy should be assessed daily for de-escalation[63,65,66].

When caring for patients with suspected and confirmed COVID19 that have underlying noncommunicable diseases, it is recommended to continue or modify their medicines according to the patient's clinical condition. For example, antihypertensive drugs should not routinely be stopped in patients with COVID-19, but therapy may need to be adjusted based on general considerations for patients with acute illness with maintaining normal blood pressure and renal function. Careful consideration should be given to the numerous clinically significant side-effects of medications that may be used in the context of COVID-19, as well as drug-drug interactions between medications, both of which may affect COVID-19 symptomatology (including effects on respiratory, cardiac, immune and mental and neurological function). Both pharmacokinetic and pharmacodynamic effects of the medications should be considered too[62,64]. The antiviral drug remdesivir gained an emergency use authorization from the Food and Drug Administration (FDA) on May 1, 2020, based on preliminary data showing a faster time to recovery of hospitalized patients with severe disease. However, remdesivir is considered the most promising antiviral drug. Also, other antiviral agents, immunotherapies and vaccines continue to be investigated and developed as potential

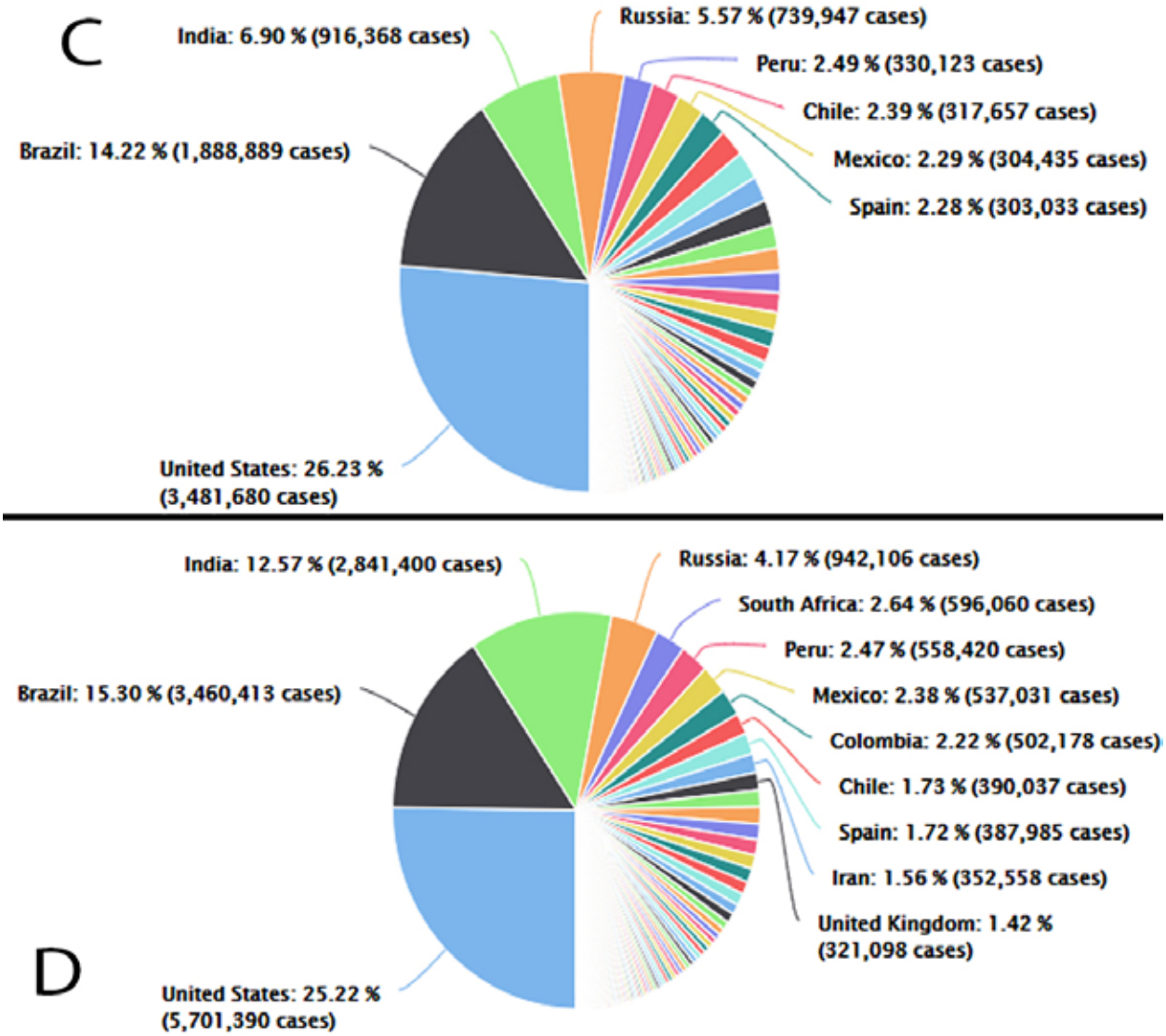


Fig 5: (C) Country-wise case distribution by July 14th, 2020; (D) Country-wise case distribution by August 20th, 2020[12].

therapies for COVID-19. Numerous collaborative efforts to discover and evaluate the effectiveness of antivirals, immunotherapies, monoclonal antibodies and vaccines have rapidly emerged. All infected patients should receive supportive care to help alleviate symptoms, and vital organ function should be supported in severe cases too as mentioned.

In Palestine, the treatment and management protocols of COVID-19 are similar to the strategies and protocols in other countries, especially those that follow the guidelines of WHO. The high outbreak of the disease in Hebron Governorate-Palestine has been caused by people meeting up with their families, attending wedding parties or funerals, and failing to follow health recommendations and maintain social distancing according to the Palestinian Ministry of Health officials. However, isolation and other precautions are the most important ways in reducing the outbreak of the disease, which prevents the transmission of the virus to others. From the data shown, it is clear that the outbreak of the disease and the number of deaths are still rising very sharply in most of the countries, with different increase rates. Figures 4 and 5 show the distribution of the cases (from June-August) in different countries and at different times. We can see from the gap differences between the cases that there were huge increases in the case even in a short period. However, this indicates that no country practically controlled the disease, or the management and treatment strategies were not optimum or even satisfying to achieve the controlling or preventing the outbreak and treatment of the disease. Figure 6 shows

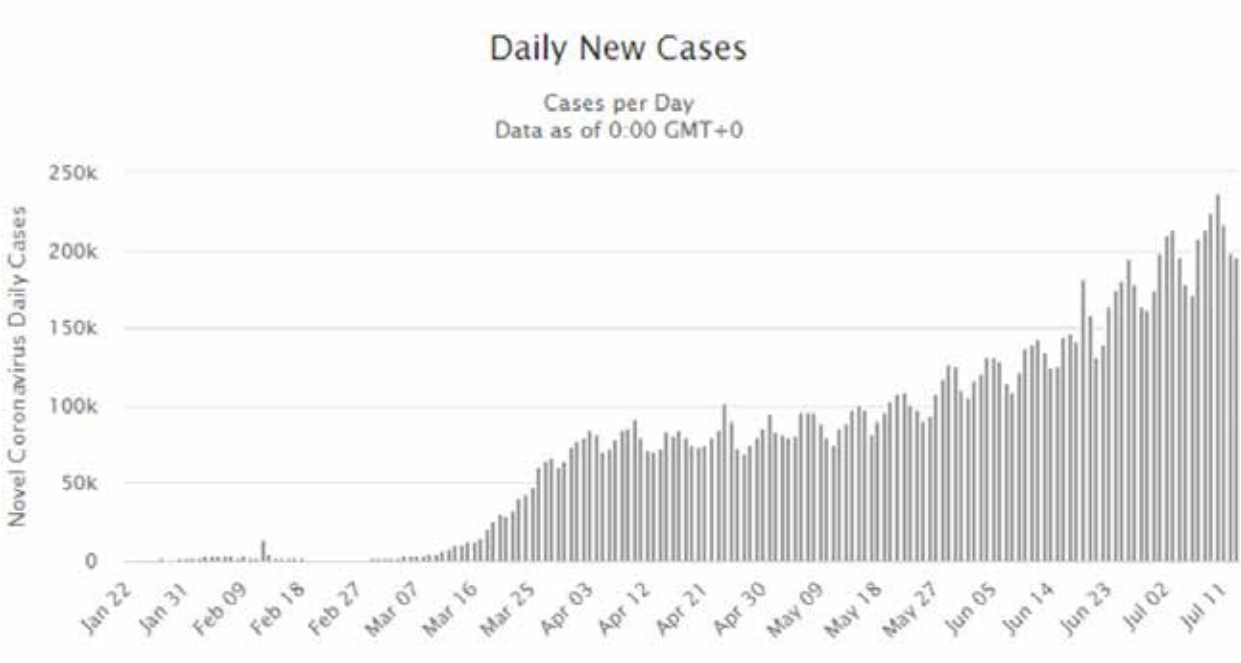


Fig 6: Daily cases (worldwide)[12].

the daily cases of the disease worldwide from January to July 2020. As of 19th August 2020, there are seven Arab countries that have significant cases of COVID-19, and they are among the 41 highest countries as shown in Table 1. The highest number of cases in Arab countries is in Saudi Arabia with 302,686 cases. The ranking and data including the total number of cases and deaths for these Arabic countries (Saudi Arabia, Iraq, Qatar, Egypt, Oman, Kuwait and UAE) were shown in Table 1.

As of 29th August 2020 at 17:57 GMT, the number of coronavirus cases in the world is 25,067,702 and the deaths are 844,180, with an increase of 2,456,840 cases (~10%) within only nine days. It is worth mentioning that the number of recovered patients is 17,411,642 (~70%), which is good. The ranking of the countries is changing every day, but the USA, Brazil, India and Russia remain at the top, as they have the highest cases of the disease. The number of coronavirus cases in these countries are 6,117,376 (USA), 3,819,077 (Brazil), 3,538,413 (India), and 985,346 (Russia) respectively. At the same time, the cases in Kuwait and Palestine are 84,224 and 35,397 (28,306 in the West Bank, 232 in Gaza, and 6,859 in East Jerusalem) respectively; they are ranking 37 and 65. The outbreak of the disease in the Gaza Strip was minimum and controlled (94 cases on 19th August), but has started rising in the last few days. Every day, 30-40 new cases are reported and today, Gaza Strip has 232 cases, with an increase of more than 138 cases (~60%), which is high. Thus, complete lockdown was announced in Gaza in order to control and stop the fast outbreak of COVID-19.

Recently, on 23rd August 2020, the FDA has issued guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency[67].

The guidance provides recommendations on the following:

- Pathways for use of investigational COVID-19 convalescent plasma
- Patient eligibility
- Collection of COVID-19 convalescent plasma, including donor eligibility and donor qualifications
- labeling and record keeping.

COVID-19 convalescent plasma has not yet been approved for use by FDA; it is regulated as an investigational product[67]. The Russian president Vladimir Putin announced on 11th August that the country's health regulator had become the first in the world to approve a coronavirus vaccine for widespread use — but scientists globally have condemned the decision as dangerously rushed. Russia hasn't completed large trials to test the vaccine's safety and efficacy, and rolling out an inadequately vetted vaccine could endanger people who receive it, researchers say. It could also impede global efforts to develop quality COVID-19 immunizations, they suggest[68].The vaccine has been tested in just 76 people[68]. The Russian

Ministry of Health announced that the vaccine cannot be used widely until 1st January 2021, presumably after larger clinical trials have been completed. Thus, COVID-19 is a serious public health crisis everywhere in the world, threatening humanity with extremely fast spread and mortality.

CONCLUSION

The COVID-19 pandemic is a very dangerous issue affecting people worldwide. Symptoms of this virus may vary from mild symptoms such as fever and cough to severe symptoms such as multi-organ failure and ARDS. The pandemic is still ongoing and no suitable treatments are available until now. Since the disease is a viral infection and viruses are known to undergo different antigenic shifting and antigenic drifting, there is still a problematic cause of importance toward better approaches in diagnosis and treatment, in addition to some comparative studies among different populations. As represented and shown, since many deaths resulted from COVID-19 in Iran and Italy, there may arise a further question whether the population's genetic or immune system traits and nutritional status might contribute to this pathogenesis. Hence, we provide here a review and some direct insights, and further directions on the situation and larger picture of SARS-CoV in terms of health pandemic status. Moreover, the review reveals the pathophysiology of the disease and the major symptoms in those infected patients among different age groups. Studies and investigations on the therapeutic and diagnostic approaches which are used to better overcome the viral disease is covered widely in this review. Despite controversial opinions about the origins of the virus and the main purposes, we shall be able to assess and shed light on the impact of this worldwide disaster only once the pandemic ends. Moreover, we shall improve our public, global, diagnostic and therapeutic tools to be helpful for any future pandemic that shall arise later on, perhaps due to natural origin or diplomatic and economic purposes. Without fundamental therapeutic interventions, current management is to reduce the spread of the virus and provide supportive care for diseased patients. Supportive treatment is still the main strategy in treating this disease; since no curative antiviral has been approved due to the lack of evidence and precise information. Isolating patients and other preventive and precautions are now the most important ways in reducing the outbreak of this virus; as these prevent the transmission of the virus to others or healthcare providers. However, there is an urgent need to develop targeted therapies. Understanding the disease and the different responses to this virus could help to find immune-based therapeutics or/ and conventional medicines. It is important to have the latest information, but we must ensure that the information is coming from trustworthy sources. Thus, a variety of helpful resources related to COVID-19 treatments and preventions have been collected.

ACKNOWLEDGMENT

The authors acknowledge the Palestinian Ministry of Health (MOH) for providing some information and data.

Authors contributions: Bara'a Shaladeh, Taima Alnatsheh and Ameera Zalloum collected the material and the data and wrote the first draft of the manuscript. Hatem Hejaz is the supervisor and did correction and editing and wrote the final draft of the manuscript.

Ethical considerations: The identities of patients remain confidential and was only used for research purposes. The procedures were accomplished upon obtaining permission from the Ethical Committee of Hebron University.

Conflict of interest and financial disclosure: The authors declare no competing financial interests and no conflicts of interest concerning the authorship and/ or publication of this article.

REFERENCES

1. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr 2020; 87(4):281-286.
2. European Centre for Disease Prevention and Control. COVID-19 pandemic. An agency of the European Union, Coronavirus disease, 2020, at https://www.ecdc.europa.eu/en. Accessed 1st May 2020.
3. Richman DD, Whitley RJ, Hayden FG. Clinical Virology. 4th Edition. Washington, DC: ASM Press; 2016. p. 18-25.
4. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV), Key facts, 2019 (11 March 2019), at https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)
5. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (NCPERE). Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel Coronavirus diseases (COVID-19) in China. China CDC Weekly 2020; 2(8): 113-122.
6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223):507-513.
7. Zeng LK, Tao XW, Yuan WH, Wang J, Liu X, Liu ZS. [First case of neonate infected with novel coronavirus pneumonia in China]. Zhonghua Er Ke Za Zhi 2020; 58(0):E009.

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective study. Lancet 2020; 395(10229):1054-1062.
9. Cheng ZJ, Shan J. 2019 Novel coronavirus: where we are and what we know. Infection 2020; 48(2):155-163.
10. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. J Hosp Infect 2020; 104(3):246-251.
11. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, *et al*. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med 2020; 382(12):1177-1179.
12. Worldometer Coronavirus. COVID-19 Coronavirus Pandemic, 2020, at https://www.worldometers.info/coronavirus/. Accessed 28th May -29th August 2020.
13. WHO. Occupied Palestinian territory. Updates on Coronavirus disease, 2020. (COVID-19) in oPt, at http://www.emro.who.int/pse/palestine-news/top-story.html. Accessed on 28th May-29th August 2020.
14. Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eighth update. RAPID RISK ASSESSMENT, 2020, at https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-coronavirus-disease-2019-eighth-update-8-april-2020.pdf. Accessed 8th April 2020.
15. WHO. Regional Office for the Eastern Mediterranean. Occupied Palestinian territory. Coronavirus disease 2019 (COVID-19) occupied Palestinian territory, 2020, at http://www.emro.who.int/pse/palestine-news/landing-page-for-covid19.html. Accessed 28th May -29th August 2020.
16. Sufang Tian, Hu W, Niu L, Liu H, Xu H, Xiao S-Y. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020; 15(5):700-704.
17. WHO. Influenza. WHO surveillance case definitions for ILI and SARI. Case definitions for influenza surveillance, 2014, at https://www.who.int/influenza/surveillance_monitoring/ili_sari_surveillance_case_definition/en/. Accessed 1st April 2020.
18. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8(5):475-481.
19. WHO. Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts. COVID-19: Clinical care, 2020, at https://www.who.int/publications/i/item/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts. Accessed 1st May, 2020.
20. Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, *et al*. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. JAMA 2009; 302(17):1872-1879.
21. WHO. Patient Safety: WHO Guidelines on Hand Hygiene in Health Care: a Summary. First Global Patient Safety Challenge Clean Care is Safer Care: 2009. 1-64, at https://apps.who.int/iris/bitstream/handle/10665/44102/9789241597906_eng.pdf?sequence=1, Accessed 10th April 2020.
22. Atkinson J, Chartier Y, Pessoa-Silva CL, Jensen P, Li Y, Seto W-H. Natural ventilation for infection control in health-care settings. G, World Health Organization, 2009. https://apps.who.int/iris/bitstream/handle/10665/44167/9789241547857_eng.pdf?sequence=1. Accessed 1st May 2020.
23. Drosten C, Seilmaier M, Corman VM, Hartmann W, Scheible G, Sack S, *et al*. Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection. Lancet Infect Dis 2013; 13(9):745-751.
24. Detsky ME, Jivraj N, Adhikari NK, Friedrich JO, Pinto R, Simel DL, *et al*. Will this patient be difficult to intubate? The Rational Clinical Examination Systematic Review. JAMA 2019; 321(5):493-503.
25. Adams J, Bartram J, Chartier Y, editors. Essential environmental health standards in health care. World Health Organization, 2008, at https://apps.who.int/iris/bitstream/handle/10665/43767/9789241547239_eng.pdf?sequence=1. Accessed 1st May 2020.
26. WHO. Maternal, newborn, child, and adolescent health: Oxygen therapy for children: a manual for health workers, 2008; 1-66, at https://apps.who.int/iris/bitstream/handle/10665/204584/9789241549554_eng.pdf?sequence=1. Accessed 8th May 2020.
27. Schultz MJ, Dunser MW, Dondorp AM, Adhikari NKJ, Iyer S, Kwizera A, *et al*. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. Intensive Care Med 2017; 43(5):612-624.
28. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al*. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017; 43(3):304-377.
29. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006; 3(9):e343.
30. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan Y-P, *et al*. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus [2019-nCoV] infected pneumonia [standard version]. Mil Med Res 2020; 7:4.
31. Huang P, Liu T, Huang L, Liu H, Lei M, Xu W, *et al*. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology 2020; 295(1):22-23.
32. WHO. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases Interim guidance 17 January 2020, at https://apps.who.int/iris/rest/bitstreams/1272454/retrieveAccessed 8th May 2020.
33. Kim SY, Park SJ, Cho SY, Cha R, Jee H-G, Kim G, *et al*. Viral RNA in blood as an indicator of severe outcome in Middle East Respiratory Syndrome coronavirus infection. Emerg Infect Dis 2016; 22(10):1813-1816.
34. Statista. COVID-19/Coronavirus. Facts and Figures 2020, at https://www.statista.com/page/covid-19-coronavirus. Accessed 28th May -29th August 2020.

35. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; 395(10223):473-475.
36. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systemic review. J Med Virol 2020; 92(5):479-490.
37. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, *et al*. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020; 382:929-936.
38. Xu X-W, Wu X-X, Jiang X-G, Xu K-J, Ying L-J, Ma C-L, *et al*. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020; 368:m606.
39. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis 2003; 3(11):722-727.
40. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 2004; 323(1):264-268.
41. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, *et al*. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005; 2:69.
42. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in the treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020; 14(1):72-73.
43. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, *et al*. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio 2018; 9(2):e00221-18.
44. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, *et al*. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon-beta against MERS-CoV. Nat Commun 2020; 11(1):222.
45. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, *et al*. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci USA 2020; 117(12):6771-6776.
46. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, *et al.* HKU / UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004; 59(3):252-256.
47. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, *et al*. Case of the index patient who caused tertiary COVID-19 transmission of infection in Korea: the application of lopinavir / ritonavir for the treatment of COVID -19 pneumonia infected monitored by quantitative RT-PCR. J Korean Med Sci 2020; 35(6):e79.
48. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al*. A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020; 382(19):1787-1799.
49. Crotty S, Cameron C, Andino R. Ribavirin's antiviral mechanism of action: lethal mutagenesis? J Mol Med (Berl) 2002; 80(2):86-95.
50. Barlow A, Landolf KM, Barlow B, Yeung SYA, Heavner JJ, Claassen CW, *et al*. Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019. Pharmacotherapy 2020; 40(5):416-437.
51. Haagmans BL, Kuiken T, Martina BE, Fouchier RAM, Rimmelzwaan GF, van Amerongen G, *et al*. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat Med 2004; 10(3):290-293.
52. Garbers C, Heink S, Korn T, Rose-John S. Interleukin-6: designing specific therapeutics for a complex cytokine. Nat Rev Drug Discov 2018; 17(6):395-412.
53. Lau SKP, Lau CCY, Chan K-H, Li CPY, Chen H, Jin D-Y, *et al*. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. J Gen Virol 2013; 94(Pt 12):2679-2690.
54. SIMIT– Italian Society of Infectious and Tropical Diseases, 2020, at https://www.omicsonline.org/societies/italian-society-of-infectious-and-tropical-diseases/. Accessed 8th May 2020.
55. Capalbo C, Aceti A, Simmaco M, Bonfini R, Rocco M, Ricci A, *et al*. The exponential phase of the COVID-19 pandemic in Central Italy: An integrated care pathway. Int J Environ Res Public Health 2020; 17(11):3792.
56. Belgian Society on Infectiology and Clinical Microbiology. IGGI. infectiologiegids guide d'infectiologie. covid-19/sars-cov-2. Belgian guidelines for the treatment of COVID-19. Treatment guidelines. Interim clinical guidance for patients with suspected or confirmed COVID-19 in Belgium, 2020, at https://www.bvikm.org/covid-19sars-cov-2. Accessed 8th May 2020.
57. WHO. Pocketbook of hospital care for children: guidelines for the management of common childhood illnesses. Geneva: World Health Organization; 2013, at https://apps.who.int/iris/bitstream/handle/10665/81170/9789241548373_eng.pdf?sequence=1.Accessed 11th May 2020.
58. Bridwell RE, Carius BM, Long B, Oliver JJ, Schmitz G. Sepsis in pregnancy: recognition and resuscitation. West J Emerg Med 2019; 20(5):822-832.
59. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, *et al*. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020; 46(Suppl 1):10-67.
60. Zhou CG, Packer CH, Hersh AR, Caughey AB. Antenatal corticosteroids for pregnant women with COVID-19 infection and preterm prelabor rupture of membranes: a decision analysis. J Matern Fetal Neonatal Med 2020; 1-9.
61. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, *et al*. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020; 9(1):51-60.
62. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, *et al.* Clinical characteristics and intrauterine vertical

transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020; 395(10226):809-815.
63. WHO. Clinical Management of COVID-19, 2020. Interim guidance 27 May 2020, at https://apps.who.int/iris/handle/10665/332196. Accessed 30th May 2020.
64. WHO. Clinical management of severe acute respiratory infection when novel coronavirus [nCoV] infection is suspected, 2020 (Accessed 9 Feb 2020, Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novelcoronavirus-[ncov]-infection-is-suspected)
65. Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, *et al*. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. Clin Infect Dis 2020; 70(9):1837-1844.
66. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect 2020; 9(1):687-690.
67. U.S. Food & Drug Administration. Recommendations for Investigational COVID-19 Convalescent Plasma. at https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. Accessed 29th August 2020.
68. Callaway E. Russia's fast-track coronavirus vaccine draws outrage over safety. Nature 2020; 584(7821):334-335.

Original Article

The diagnostic value of b-type natriuretic peptide, uric acid and cystatin-C in dyspneic Emergency Department patients with suspected heart failure

Gulcin Bacakoglu Senyurt[1], Oktay Eray[2], Ozlem Yigit[2], Atakan Yanikoglu[3]
[1]Department of Emergency Medicine, Alanya State Hospital, Antalya, Turkey
[2]Department of Emergency Medicine, Akdeniz University Medical Faculty, Antalya, Turkey
[3]Department of Cardiology, OFM Private Hospital, Antalya, Turkey

Kuwait Medical Journal 2022; 54 (1): 27 - 33

ABSTRACT

Objectives: This study evaluated the potential of Cystatin-C (Cys-C) and uric acid (UA) to predict the diagnosis of heart failure (HF) in patients with acute dyspnea compared with b-type natriuretic peptide (BNP) and echocardiographic (ECHO) findings.
Design: This was a methodological prospective study.
Setting: The study was conducted in the emergency department (ED) of a tertiary care university hospital.
Subjects: Patients presenting through the ED with dyspnea.
Interventions: ED physicians assessed the probability of HF in subjects, and if they thought that complaints were due to HF, they enrolled patients to the study prospectively. BNP, UA and Cys-C levels were measured, and all patients were evaluated with ECHO by the same cardiologist.
Main outcome measures: Diagnosing HF in undifferentiated dyspnea patients
Results: The mean age of the 94 enrolled patients was 70.7±10.4 years; 49 of them (52.1%) were male. ED physicians assessed HF in 67 (70%) patients and the cardiologist confirmed in 69 patients (73.4%). BNP levels (P=0.00) and UA levels (P=0.04) were significantly different; however, Cys-C levels were not (P=0.79). In multivariate analysis, only UA levels and clinical gestalt of the ED physician were strong independent predictors of HF.
Conclusions: Since BNP is an expensive laboratory test and there are some conflicting arguments about its diagnostic performance in ED, UA seems to be a cheap and easily accessible 'old' marker for diagnosing acute HF. The physician's gestalt for HF diagnosis is quite important and combining this gestalt with biomarkers in a model would be more useful.

KEY WORDS: diagnosis, dyspnea, emergency department, heart failure

INTRODUCTION

Heart failure (HF), often referred to as congestive heart failure (CHF), occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the body's demands[1]. 80% of acute HF patients present through the emergency department (ED), and dyspnea is their chief predominant complaint[2]. Delays in diagnosing HF result in increased mortality, hospital stays and treatment costs[3].

History and physical examination alone are often insufficient to rule in or rule out CHF. Patients often have comorbidities that contribute to their symptoms, thereby making the diagnosis difficult. Therefore, physicians in acute care settings require an accurate diagnostic test that will allow them to rapidly determine whether or not HF is the cause of the shortness of breath and dyspnea.

B-type natriuretic peptide (BNP) was proposed as a potentially valuable diagnostic test to augment the clinical diagnosis of HF. BNP levels are significantly higher in patients with dyspnea due to HF than from another cause. The American College of

Address correspondence to:
Ozlem Yigit, MD, Associate Professor of Emergency Medicine, Akdeniz University Medical Faculty, Department of Emergency Medicine, Antalya, Turkey. Tel: +90 505 6444286; E-mail: ozlemyigit@akdeniz.edu.tr

Emergency Physician clinical policy provides Level B recommendations that ''the addition of a single BNP or NT-proBNP measurement can improve the diagnostic accuracy compared to standard clinical judgment alone in ED patients to rule out HF"[4].

Previous studies have shown that elevated levels of serum uric acid (UA) are associated with adverse clinical outcomes in patients with chronic HF[5-7]. Some recent studies also showed that the serum UA level was an independent predictor in acute HF[8,9].

Cystatin-C (Cys-C), a low molecular weight protein, is a known biomarker reflecting renal function and is considered a cardiac prognostic factor, particularly in ischemic heart disease and chronic HF[10,11]. Since the relationship between Cys-C and cardiac prognosis appears to be either directly or indirectly due to hemodynamic effects, this marker is well suited for acute HF in the ED and has been widely investigated[12-15].

The current study evaluated the potential of Cys-C and UA to predict the diagnosis of HF in patients with acute dyspnea compared with BNP and echocardiographic findings.

SUBJECTS AND METHODS

Study design and setting

This methodological prospective study was conducted in the ED of a tertiary care university hospital. Our study was approved by the review board of the local Ethics Committee and financial support for the laboratory tests was provided by the Scientific Research Projects Coordination Unit. All patients enrolled in the study were given information and signed informed consent forms.

Selection of the participants

Eligible patients were enrolled in the study by the ED staff at presentation. To be eligible for the study, a patient had to have shortness of breath as the most prominent symptom. All patients underwent routine clinical examination by an ED physician (ED resident supervised by an ED attending physician). Physicians assessed the probability that the patient had HF as the cause of his/her symptoms and if they thought that complaints were due to HF, the patients were enrolled to the study. No specific criteria for the diagnosis of HF were determined and inclusion was left to the physician's judgment.

Exclusion criteria

Patients under 18 years of age and those whose dyspnea was clearly not secondary to CHF (for example, those with pulmonary disease) were excluded. Patients with acute myocardial infarction, unstable angina or cardiogenic shock, renal failure and dialysis therapy, trauma, malignancy, gout or digoxin overdose were also excluded.

Data collection

Once the patient was identified as having dyspnea due to HF, written informed consent was obtained, and 5cc blood sample was collected for measurement of BNP, UA and Cys-C. Blood samples were taken without tourniquet and centrifuged at 4000 rpm for five minutes, and then the separated plasma was transferred to Eppendorf tubes. Eppendorf tubes were first collected at -20 °C, then transferred to -80 °C and stored there until all samples were collected.

The ED physicians collected other data including information from the medical history, vital signs and physical examination findings. The treatment modalities for the patient did not change during the study period and was maintained by the ED physician according to usual protocols.

Laboratory test measurements

BNP measurements were determined using an electro-chemiluminescence immunoassay method on Elecys 2010 immunassay (Roche® Diagnostics, Mannheim, Germany) analyzer and results were given as pg/ml. Cys-C measurements were determined using the nephelometric technology on the BN™ II System (Siemens Healthcare Diagnostics Ltd, USA) and results were given as mg/l. UA measurements were determined using enzymatic and colorimetric technique on Roche Modular PPP chemistry analyzer (Roche Diagnostics, Mannheim, Germany) and results were given as mg/dl. All measurements were done at the same time after the completion of all study patients.

Echocardiograms

Echocardiography (ECHO) was used as a 'gold standard' for diagnosing heart failure and was performed to evaluate cardiac function after stabilization of the patient's hemodynamic status. All echocardiograms were done by the same cardiologist with Vivid 7 ultrasonography machine (General Electric, Milwaukee, Wisconsin, USA) by using a 1.5 - 4.0 MHz transducer. Echocardiograms were done during the ED evaluation in the daytime (8 am – 5 pm). Patients admitted at night and during weekends were taken to ECHO within 6-8 hours with the same cardiologist and the same machine.

Left atrium diameter, left ventricle end diastolic diameter, left ventricle end systolic diameter, interventricular septum diastolic diameter and posterior wall diastolic diameter were measured with two-dimensional imaging. Ejection fraction was calculated with bi-plane Simpson method. Mitral inflow patterns and velocities, tricuspid jet velocity and

systolic pulmonary artery pressure were measured. On tissue doppler, mitral annulus and lateral annulus velocities, peak early and late diastolic transmitral flow velocities and systolic velocity were measured.

ECHO parameters and clinical findings of the patient were evaluated by the cardiologist to determine if the patient's dyspnea was due to HF. This was accepted as final diagnosis for the patient.

Statistical analysis

The data analyses were performed using SPSS for Windows, version 15.0.0 (SPSS, Chicago, IL, USA) and Medcalc 11.0.4. All values are presented as the mean standard deviation for continuous variables and as frequencies and percentiles for discrete variables. Univariate comparisons were made with Student's t-test and Mann-Whitney U test as appropriate. The selected variables were derived from the univariate analysis and multivariate logistic regression analyses were performed. To evaluate and compare the prognostic incremental values of UA, BNP and Cys-C, individual parameters were added to the predictive model, which was constructed based on clinical and significant multivariate parameters. Receiver-operating characteristic (ROC) curves and the area under the curves were obtained. *P*-values were two-sided, and a *P*-value <0.05 was considered statistically significant.

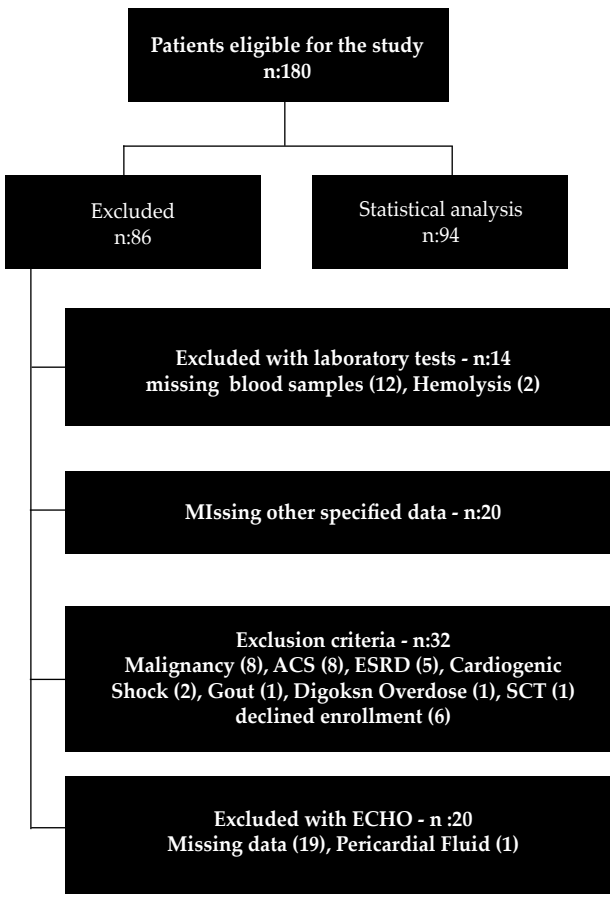


Fig 1: Patient flow chart of the study

RESULTS

During the study period, approximately 45,000 patients were admitted to the ED. 180 patients were enrolled to the study, out of which 86 of them were excluded from the study. The exclusion criteria for these patients are shown in Figure 1. Statistical analysis was done with the remaining 94 patients.

The mean age of the enrolled patients was 70.7±10.4 years (median: 71 years, min: 48, max: 95), and 49 of them (52.1%) were male. The mean breath per minute was 28.0±6.8 breath/min (median: 28, min-max: 14-50), and the mean artery pressure was 102±17.8 mmHg (median: 100.5, min-max: 61-150). The other vital signs and mean and median values are shown in Table 1.

Table 1: The demographics and median and mean values of the vital signs of patients

Vital signs	Mean ± SD N=94	Median (min-max) N=94
Age	70.7±10.5	71.0 (48-95)
Pulse	93.5±22.2	92.0 (41-150)
Breathing	28.0±6.8	28.0 (14-50)
Mean arterial pressure	102.0±17.8	100.5 (61-150)
Saturation	90.9±8.1	93.0 (60-100)
Fever	36.7±0.5	36.6 (36-38)

SD: standard deviation; Min: minimum; Max: maximum

ED physicians assessed CHF as the cause of dyspnea in 67 (70%) patients and the remaining 27 (30%) were assessed as combined heart and respiratory failure. The cardiologist confirmed HF in 69 patients (73.4%) after evaluating the ECHO parameters and clinical findings of the patient. Historical physical examination findings suggesting HF were evaluated in the study population. Distention of the jugular vein was found in 35 (37.2%) patients, hepatojugular reflux in 30 (31.9%) patients, pretibial edema in 56 (59.6%) patients and rales heard over the lung bases in 93 (98.9%) patients.

When we compared the patients without and with HF, BNP levels were different between groups (median: 1550 pg/ml vs 4737 pg/ml respectively, *P*=0.00) and the difference was statistically significant. Statistically significant difference was also found for UA levels (median: 6.20 mg/dl vs 7.30 mg/dl respectively, *P*=0.04). However, the difference between groups for Cys-C levels was not statistically significant (1.32 mg/L vs 1.25 mg/L respectively, *P*=0.79) (Table 2).

Table 2: The statistical differences and *P*-values for B-type natriuretic peptide, uric acid and Cystatin-C levels between the groups without and with heart failure

Laboratory tests	Patients with HF (n=69)		Patients without HF (n=25)		P
	Median (min-max)	Mean ± SD	Median (min-max)	Mean ± SD	
BNP	4737 (423 – 35000)	7975 ± 8160	1550 (65 – 35000)	5244 ± 9895	0.00
UA	7.3 (2.2 – 12.7)	7.36 ± 2.17	6.2 (1.9 – 12.8)	6.34 ± 2.72	0.04
Cys-C	1.25 (0.46 – 3.03)	1.41 ± 0.58	1.32 (0.62 – 2.85)	1.42 ± 0.57	0.79

BNP: B-type natriuretic peptide; UA: uric acid; Cys-C: Cystatin-C; HF: heart failure; SD: standard deviation; Min: minimum; Max: maximum

We also used a multiple logistic-regression model combining clinical findings and the laboratory test values to predict the final diagnosis. The predictors in the model included historical clinical examination findings (hepatojugular reflux, pretibial edema, rales heard over the lung bases), BNP, UA and Cys-C levels, and the clinical gestalt of the ED physician for predicting HF. In the multivariate analysis, the model showed that only UA levels and clinical gestalt of the ED physician were strong independent predictors of congestive heart failure (Table 3).

Table 3: Factors predicting heart failure

Laboratory tests	Odds ratio	95% Confidence Interval	*P*
BNP	1.00	1.00 – 1.00	0.10
UA	1.43	1.06 – 1.92	0.01
Cys-C	0.18	0.04 – 0.74	0.01
Physician's gestalt	1.74	1.16 – 2.60	0.01

BNP: B-type natriuretic peptide; UA: uric acid; Cys-C: Cystatin-C

The ROC analysis revealed that the sensitivity was 92.7% (95% CI, 83.9-97.6) for UA levels under 4.4 mg/dl, and the specificity was 92% (95% CI, 74-99) for UA levels over 10.4 mg/dl (Figure 2).

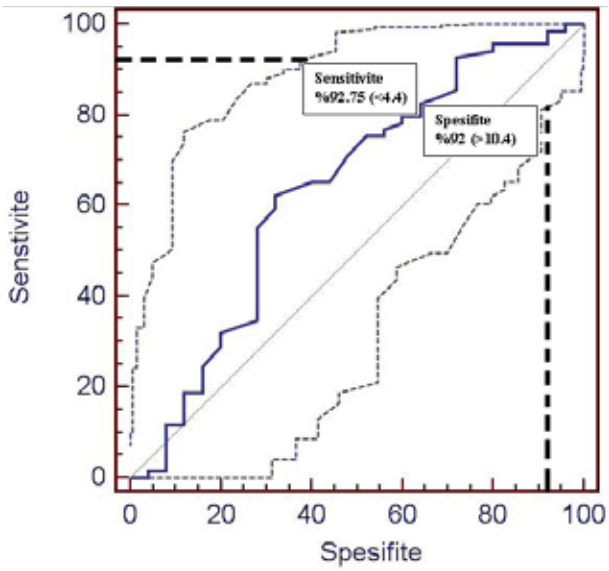


Fig 2: ROC analysis for serum uric acid levels

Limitations

Since our study was supported financially by the Scientific Research Projects Coordination Unit of our university, we had a limited budget for laboratory kits. As it could be seen in the patient flowchart, we had to exclude many patients unexpectedly because of missing data. This unexpected condition resulted in a relatively small patient population for the study and the confidence intervals were found less wide. Although we believe that there is no selection bias risk, this is also a weakness of our study.

DISCUSSION

Dyspnea is one of the most common presenting symptoms to the ED, which can be life threatening for patients. Since diagnostic modalities and treatment choices can significantly differ according to various causes of dyspnea, the differential diagnosis is important for emergency evaluation and for patient survival and disease prognosis. Acute HF is one of the most frequent diagnoses in emergency medicine, with 1-year mortality rates exceeding 25-30%[15]. We designated a good and reliable 'gold standard' for acute congestive heart failure diagnosis, by evaluating all patients with echocardiogram using new and old measuring techniques done by a single cardiologist. When we compared with this gold standard, BNP levels were found to be high in cardiac dyspnea patients; however, it was not an independent predictive factor in multivariate analysis model. Cys-C levels were not found to be significant for diagnosing acute heart failure in ED patients. UA levels were found to be significant both in univariate and multivariate analysis for predicting HF diagnosis in dyspnea patients, especially in selected level thresholds.

HF could be exacerbated or triggered by multifactorial potential factors such as the cardio-renal relationship. Renal insufficiency and worsening renal function are prevalent in acute HF, and they often coincide with diuretic unresponsiveness and inability to relieve congestion. Hence, preservation of

renal function is an important therapeutic goal in the treatment of acute heart failure[16]. Cys-C could play a key role as a useful renal marker, could be observed at increased levels in acute HF and it is related to cardiac prognosis even in elderly patients[17]. The prognostic effect seems to be independent of other renal function markers, and even in patients with normal creatinine values, elevated Cys- C levels have a powerful impact on prognosis[15]. Cys-C seems not to be affected by gender, age, body mass index or diet, leading to the suggestion that it be the preferred endogenous marker of renal function. Although the exact mechanism that causes Cys-C to be linked with the cardiovascular system was not identified clearly, cardiorenal hemodynamic interaction is primarily responsible for the relationship between Cys-C and the adverse outcomes. Recent studies showed that higher Cys-C levels were associated with increased risk of death both in short- and long term follow-up[12-17]. We studied Cys-C as a diagnostic test for HF in dyspneic patients in our study; however, we could not find any statistical significance both at univariate and multivariate analysis. The previous reports exploring Cys-C in acute HF looked for its prognostic properties and prediction of adverse events. In light of these reports and our results, it is possible to say that Cys-C in acute HF could be a useful marker for predicting increased risk; however, it is not useful as a diagnostic test.

Serum uric acid (SUA) is a byproduct of the terminal steps of purine catabolism. In HF, UA levels may rise due to increased purine catabolism resulting from tissue hypoxia, apoptosis, and/or enhanced or upregulated enzymatic activity. Therefore, UA could be used as a prognostic marker in HF progression[6]. Many studies have indicated that higher UA is a predictor of cardiovascular mortality in acute HF[18-20]. In two recent investigations, the authors assessed the role of UA in the prediction of early post-discharge event in patients with acute HF, and admission hyperuricemia was shown to be associated with higher risk of death or HF rehospitalization[8,9]. High UA levels increase all-cause mortality in patients with both acute and chronic HF, and this increase in risk seems to start at an SUA level of 7 mg/dL[6]. Also, a meta-analysis of published prospective studies suggests that elevated UA levels are associated with an increased risk of cardiovascular and all-cause mortality. However, high SUA appears to increase the risk of all-cause mortality for men but not for women[21]. Our study findings showed that high UA levels revealed favorable sensitivity and specificity rates for diagnosing HF in dyspneic patients, besides predicting mortality and risk groups. Additionally, UA was found as an independent factor in the multivariate analysis.

BNP is a cardiac neuro-hormone specifically secreted from the ventricles in response to volume expansion and pressure overload and has been studied widely as a potential tool to enhance the accuracy of HF diagnosis[22]. Although observational trials have shown promise to improve clinicians' diagnostic accuracy for HF in the ED, the role of these biomarkers in the acute management of dyspnea remains undefined. It can also paradoxically increase diagnostic uncertainty in low-risk populations[23]. Serum levels can be elevated by non-HF conditions like pulmonary hypertension, left ventricular hypertrophy, renal failure, acute coronary syndrome, atrial dysrhythmia, sepsis and lung cancer[23]. Mueller *et al* showed that patients who had BNP testing in the ED had earlier initiation of appropriate treatment, decreased hospital and intensive care unit admission rates, earlier discharge and decreased cost of treatment[24]. In contrast, the randomized controlled trial BNP in Shortness of Breath study conducted by Schneider *et al* showed that BNP testing in dyspneic patients presenting to the ED did not improve hospital admission rates, length of hospital stay or management in the ED[25]. A recent randomized controlled study conducted in Australia found that, although BNP values were significantly higher in patients with a final diagnosis of HF, in the real-life setting, adding the BNP test to clinical judgment did not significantly add to the accuracy of the disposition diagnosis of HF[26]. We found BNP levels higher in the HF patients in our study. The difference was statistically significant in the univariate analysis, however when we created a multivariate model, BNP was not an independent predictor for HF diagnosis. These findings are not contrary to previous reports, and also support the theory that using BNP testing not for differentiating all dyspneic patients but combining the test with the ED physicians' assessment of the probability of HF, will improve the diagnostic accuracy in real emergency setting. ED physicians' gestalt of probability of HF was also high in our study. ED physicians assessed HF as the cause of dyspnea in 70% of patients, and the cardiologist confirmed HF in 73.4% after evaluating the ECHO parameters and clinical findings of the patient.

For patients who present to EDs or urgent care settings with signs and symptoms suggestive of HF, BNP and NT-proBNP have good diagnostic performance to rule out, but lesser performance to rule in[27]. For good diagnostic performance to rule in, it is better to use BNP in a clinical model combining tests, as well as clinical findings and physician's gestalt. There are a few studies combining BNP and other biomarkers. Park *et al* found that the combination of UA and NT-ProBNP levels appears to be more useful than either marker alone as an independent predictor

for short-term outcomes in patients with acute HF[28]. FINN-AKVA study group concluded that combining Cys-C and NT-proBNP gives a new possibility to categorize patients into a wider spectrum of risk profiles with patients at very low risk of death at one end and cumulatively high risk at the other[15]. In the RELAX-AHF trial, seven circulating biomarkers [NT-proBNP, high sensitivity cardiac troponin T, soluble ST2, growth differentiation factor 15, cystatin-C, galectin-3, and high sensitivity C-reactive protein] were measured at baseline and on days 2, 5, 14 and 60. A multimarker approach based on a panel of serially evaluated biomarkers provides the greatest prognostic improvement unmatched by a single time point-based single marker strategy[29]. Kim TH *et al* evaluated whether Cys-C could be a useful prognostic indicator in acute HF and compared with UA and proBNP[17]. In their retrospective, observational analysis, the patients with cardiac events showed higher concentrations of Cys-C, UA and NT-proBNP and adding Cys-C, NT-proBNP and UA improved the prognostic ability of the model constructed based on the general risk factors. However, in the multivariate analysis, only Cys-C, but not NT-proBNP and UA, was related to the recurrence of cardiac events. This study evaluated the same biomarkers as our study; however, there are some major differences. First of all, they conducted a retrospective analysis and looked for the predictability of the biomarkers for cardiac events. We conducted a prospective trial, created a good and reliable 'gold standard' with ECHO done by single cardiologist, and evaluated the diagnostic performance of the studied biomarkers rather than their prognostic values. To our knowledge, our work is the unique prospective study conducted in an ED and evaluated diagnostic performance of these markers in a multivariate model.

CONCLUSION

In conclusion, UA reveals promising results for diagnosing HF in undifferentiated dyspnea patients in the ED. Since BNP is an expensive laboratory test and there are some conflicting arguments about its diagnostic performance in ED, UA seems as a cheap and easily accessible 'old' marker for diagnosing acute HF. The second outcome is that the physician's gestalt for HF diagnosis is quite important and combining this gestalt with biomarkers in a model would be more useful for differentiating patients.

ACKNOWLEDGMENT

The authors have no commercial associations or sources of support that might pose a conflict of interest. All authors have made substantive contributions to the study, and all authors endorse the data and conclusions.

REFERENCES

1. Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovasc Pathol 2012; 21(5):365-371.
2. Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med 2003; 4 Suppl 7:S21-30.
3. Wuerz RC, Meador SA. Effects of prehospital medications on mortality and length of stay in congestive heart failure. Ann Emerg Med 1992; 21(6):669-674.
4. Silvers SM, Howell JM, Kosowsky JM, Rokos IC, Jagoda AS, American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute heart failure syndromes. Ann Emerg Med 2007; 49(5):627-669.
5. Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, *et al*. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail 2014; 16(1):15-24.
6. Tamariz L, Harzand A, Palacio A, Verma S, Jones J, Hare J. Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis. Congest Heart Fail 2011; 17(1):25-30.
7. Niizeki T, Takeishi Y, Arimoto T, Okuyama H, Nozaki N, Hirono O, *et al*. Hyperuricemia associated with high cardiac event rates in the elderly with chronic heart failure. J Cardiol 2006; 47(5):219-228.
8. Okazaki H, Shirakabe A, Kobayashi N, Hata N, Shinada T, Matsushita M, *et al*. The prognostic impact of uric acid in patients with severely decompensated acute heart failure. J Cardiol 2016; 68(5):384-391.
9. Amin A, Chitsazan M, Abad FSA, Taghavi S, Naderi N. On admission serum sodium and uric acid levels predict 30 day rehospitalization or death in patients with acute decompensated heart failure. ESC Heart Fail 2017; 4(2):162-168.
10. Deo R, Shlipak MG, Ix JH, Ali S, Schiller NB, Whooley MA. Association of cystatin C with ischemia in patients with coronary heart disease. Clin Cardiol 2009; 32(11):E18-E22.
11. Dupont M, Wu Y, Hazen SL, Tang WHW. Cystatin C identifies patients with stable chronic heart failure at increased risk for adverse cardiovascular events. Circ Heart Fail 2012; 5(5):602-609.
12. Pérez-Calvo JI, Ruiz-Ruiz FJ, Carrasco-Sánchez FJ, Morales-Rull JL, Manzano-Fernandez S, Galisteo-Almeda L, *et al*. Prognostic value of serum cystatin C and N-terminal pro B-type natriuretic peptide in patients with acute heart failure. Eur J Intern Med 2012; 23(7):599-603.
13. Manzano-Fernández S, Januzzi JL Jr, Boronat-Garcia M, Bonaque-Gonzalez JC, Truong QA, Pastor-Perez FJ, *et al*. β –trace protein and cystatin C as predictors of long-term outcomes in patients with acute heart failure. J Am Coll Cardiol 2011; 57(7):849-858.
14. Campbell CY, Clarke W, Park H, Haq N, Barone BB, Brotman DJ. Usefulness of cystatin C and prognosis

following admission for acute heart failure. Am J Cardiol 2009; 104(3):389-392.
15. Lassus J, Harjola VP, Sund R, Siirila-Waris K, Melin J, Peuhkurinen K, *et al*. FINN-AKVA Study group: Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. Eur Heart J 2007; 28(15):1841-1847.
16. Tang WHW, Dupont M, Hernandez AF, Voors AA, Hsu AP, Felker GM, *et al*. Comparative assessment of short-term adverse events in acute heart failure with cystatin C and other estimates of renal function: results from the ASCEND-HF trial. JACC Heart Fail 2015; 3(1):40-49.
17. Kim TH, Kim H, Kim IC. The potential of cystatin-C to evaluate the prognosis of acute heart failure: A comparative study. Acute Card Care 2015; 17(4):72-76.
18. Pascual-Figal DA, Hurtado-Martinez JA, Redondo B, Antolinos MJ, Ruiperez JA, Valdes M. Hyperuricaemia and long-term outcome after hospital discharge in acute heart failure patients. Eur J Heart Fail 2007; 9(5):518-524.
19. Hamaguchi S, Furumoto T, Tsuchihashi-Makaya M, Goto K, Goto D, Yokota T, *et al*. JCARE-CARD Investigators. Hyperuricemia predicts adverse outcomes in patients with heart failure. Int J Cardiol 2011; 151(2):143-147.
20. Alimonda AL, Nunez J, Nunez E, Husser O, Sanchis J, Bodi V, *et al*. Hyperuricemia in acute heart failure. More than a simple spectator? Eur J Intern Med 2009; 20(1):74-79.
21. Zhao G, Huang L, Song M, Song Y. Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis 2013; 231(1):61-68.
22. Worster A, Balion CM, Hill SA, Santaguida P, Ismaila A, McKelvie R, *et al*. Diagnostic accuracy of BNP and NT-proBNP in patients presenting to acute care settings with dyspnea: A systematic review. Clin Biochem 2008; 41(4-5):250-259.
23. Carpenter CR, Keim SM, Worster A, Rosen P, BEEM (Best Evidence in Emergency Medicine). Brain natriuretic peptide in the evaluation of emergency department dyspnea: is there a role? J Emerg Med 2012; 42(2):197-205.
24. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, *et al*. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004; 350(7):647-654.
25. Schneider H-G, Lam L, Lokuge A, Krum H, Naughton MT, Smit PDV, *et al*. B-type natriuretic peptide testing, clinical outcomes, and health services use in emergency department patients with dyspnea: a randomized trial. Ann Intern Med 2009; 150(6):365-371.
26. Lokuge A, Lam L, Cameron P, Krum H, de Villiers S, Bystrzycki A, *et al*. B-type natriuretic peptide testing and the accuracy of heart failure diagnosis in the emergency department. Circ Heart Fail 2010; 3(1):104-110.
27. Balion C, Don-Wauchope A, Hill S, Santaguida PL, Booth R, Brown JA, *et al*. Use of Natriuretic Peptide Measurement in the Management of Heart Failure [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Nov. Report No.: 13(14)-EHC118-EF. AHRQ Comparative Effectiveness Reviews.
28. Park HS, Kim H, Sohn JH, Shin HW, Cho YK, Yoon HJ, *et al*. Combination of uric acid and NT-ProBNP: a more useful prognostic marker for short-term clinical outcomes in patients with acute heart failure. Korean J Intern Med 2010; 25(3):253-259.
29. Demissei BG, Cotter G, Prescott MF, Felker GM, Filippatos G, Greenberg BH, *et al*. A multimarker multi-time point-based risk stratification strategy in acute heart failure: results from the RELAX-AHF trial. Eur J Heart Fail 2017; 19(8):1001-1010.

Original Article

Potential parameters of functioning arteriovenous fistulas in the elderly

Radojica V Stolic[1], Vedrana Pavlovic[2], Suzana Matejic[3], Goran V Relic[3], Snezana Lazic[3], Dusica V Miljkovic[3]
[1]Department of Internal Medicine, Faculty of Medical Sciences, University of Kragujevac, Serbia
[2]Institute of Medical Statistics and Informatics, Faculty of Medicine, University of Belgrade, Serbia
[3]Faculty of Medicine, University of Pristina/Kosovska Mitrovica, Pristina/K.Mitrovica, Serbia

Kuwait Medical Journal 2022; 54 (1): 34 - 38

ABSTRACT

Objective: Creation of vascular access in the elderly represents a challenge for surgeons. We aimed to determine the potential parameters of arteriovenous fistula functioning in elderly patients.
Design: Retrospective cross-sectional study
Setting: Tertiary university hospital
Subjects: Three hundred and seventy-four old people who underwent operative interventions in order to create and resolve fistula complications
Intervention: In the period of 15 years, with information about the length of the fistula function, all parameters which could have an effect on functioning of the arteriovenous fistula were analyzed.
Main outcome measures: To determine the predictive parameters of functioning arteriovenous fistula for hemodialysis in the elderly
Results: Survival predictors of arteriovenous fistula, using univariant cox regression models, they are hemoglobin (B -0.00; SE 0.00; *P*=0.014), sodium (B -0.01; SE 0.00; *P*=0.003), creatinine (B 0.00; SE 0.00; *P*=0.053), triglyceride (B -0.25; SE 0.13; *P*=0.045), presence of catheter (B 0.324; SE 0.11; *P*=0.002), the use of Doppler ultrasound (B -0.26; SE 0.11; *P*=0.012), and diameter of the artery that was used for anastomosis (B -0.25; SE 0.11; *P*=0.024). Survival predictor of arteriovenous fistula, using Cox regression multivariate analysis, is preoperative mapping of blood vessels (B -1.18; SE 0.33; *P*=0.000).
Conclusion: Preoperative ultrasound mapping of blood vessels is an equally important predictive parameter of functioning of arteriovenous fistulas in older age for both males and females.

KEY WORDS: aged, renal dialysis, vascular fistula

INTRODUCTION

The 2012 Annual Report of the European Renal Association-European Dialysis and Transplant Association registry shows that patients aged 65-74 years and >75 years represent, respectively, 22 and 20% of the total prevalent renal replacement therapy population[1].

When Cimino and Brescia originally described the arteriovenous fistula in 1966, the dialysis population was a select group of young patients that excluded those with diabetes[2]. Today, studies show that older patients, women and patients with vascular disease or vascular disease risk factors are at greatest risk of having an arteriovenous fistula fail to mature[3]. Arteriovenous fistulas are recommended by many national clinical guidelines as the vascular access, but, there is concern about whether general guidelines also apply to the elderly population[4]. In fact, vascular access planning in the elderly is different from that in younger patients, and the Fistula First Initiative may not be the preferred approach for older patients because of their reduced life expectancy and conflicting results after surgery[5].

Epidemiological data show that one in nine Americans has chronic renal insufficiency and over half a million are dialysed, of which 55% are men and 45% are women. Although arteriovenous fistulae have been proven to be preferred for hemodialysis, it is less

Address correspondence to:
Professor Radojica Stolic, Faculty of Medical Sciences, Svetozar Markovic 69, 34000 Kragujevac, Serbia. Tel: +381 638372624; E-mail: radojica.stolic@med.pr.ac.rs

likely that women begin hemodialysis with an already formed arteriovenous fistula[6,7].

Guidelines for vascular approach agree that arteriovenous fistula is the best option for patients on hemodialysis, but there is no consensus on the optimal time for its creation. Only 18% of American patients begin hemodialysis by a newly established vascular approach, and this rate in Europe does not exceed 30-45%[8].

There is a significant discrepancy in literature about impact of gender differentiation on functioning of arteriovenous fistula[9]. Numerous studies report a lower prevalence of arteriovenous fistula use in women than men, but the reasons are inconsistent and not adequately clarified[10,11].

Vernaglione *et al*[12] found that arteriovenous fistulae have a lower rate of functioning in women, with a failure rate of 50%. Miller *et al*[10] showed that functional fistulas are lower by 30% in women than in men. They also recorded an inferior outcome in fistula in forearm region and in the upper arm area. Fewer studies, such as the research of Erkut *et al*[13] showed that there is no difference in the initiation of functional fistula, which at least gives hope that women could have the same level of functionality as men at the same time. By analyzing risk factors for arteriovenous fistula failure, Marcus *et al*[14] pointed to some clinical strategies that could improve the function of arteriovenous fistula, primarly pointing to the importance of perspective ultrasound mapping of blood vessels.

Astor *et al*[15] found that neither the race nor gender were important predictors of the function of permanent vascular access, but that early referral to nephrologists could be useful for initiating the hemodialysis process by creating the so-called "preventive fistulae".

The aim of our research was to determine the potential parameters of arteriovenous fistula functioning in the elderly.

SUBJECTS AND METHODS

The survey was conducted at the Center for Nephrology and Dialysis, Urology and Nephrology, Clinical Center Kragujevac, Serbia, as a retrospective, descriptive-analytic study that included all surgical interventions carried out for the purpose of creating and resolving complications of arteriovenous fistula over a period of fifteen years in patients for whom the information about the length of the fistula function was available. The total number of surgical interventions in this period was 1115 (718 (64.4%) in men and 397 (35.6%) in women). The basic requirement for patient selection was the length of the fistula function in patients who were older than 65 years. Length of the fistula function is defined by the time interval from its creation to thrombosis. On the basis of this criterion, 374 elderly people were registered.

In the study, we analyzed all relevant clinical and laboratory parameters which could have an effect on functioning of the arteriovenous fistula. We have evaluated the predictive effect of the positioning of the fistula (distal/proximal), length of the fistula function, type of arteriovenous anastomoses (termino-terminal/termino-lateral), the use of central-venous catheters for hemodialysis, pre-operative ultrasound mapping of the blood vessels, preventive creation of a fistula, the diameters of arteries and veins used for anastomosis and the values of systolic and diastolic arterial blood pressure. Likewise, the study also included biochemical parameters that were part of routine laboratory analyzes.

Table 1: Basic demographic and clinical characteristics of study patients

Variable	Values
Patients, n	374
Age (years, mean ± sd)	71.4±5.2
Gender, n(%)	
Male	255 (68.2%)
Female	119 (31.2%)
Positioning of arteriovenous fistula, n(%)	
Distal position	123 (32.9%)
Proximal position	251 (67.1%)
Length functioning arteriovenous fistula (months, median (range))	20(1-112)
Type of arteriovenous anastomosis, n (%)	
Termino-lateral	289 (77.3%)
Termino-terminal	85 (22.7%)
Insertion central venous catheter, n (%)	209 (55.9%)
Preoperative mapping blood vessels (Doppler), n (%)	192 (51.3%)
Type of fistula in relation to the time of creating, n (%)	134 (35.8%)
Vein diameter (mm, mean ± sd)	2.4±0.5
Artery diameter (mm, mean ± sd)	2.5±0.5
Systolic blood pressure (mmHg, mean ± sd)	147.2±27.3
Diastolic blood pressure (mmHg, mean ± sd)	78.5±13.8

The study was approved by the ethics committee of the Clinical Center Kragujevac in accordance with the Helsinki Declaration for Medical Research.

Statistical analysis

All statistical analyses were performed in SPSS 24.0 (SPSS Inc., Chicago, IL). Results were presented as frequency, percent, mean - standard deviation and median (where appropriate). In further analyses, both univariate and multivariate Cox regression models were applied with duration of arteriovenous fistula as a dependent variable. Kaplan Meier method was used to compare duration of arteriovenous fistulae related to binary variables like types of arteriovenous anastomosis, Doppler and dichotomised diameter of the vein variable.

Table 2: Basic biochemical characteristics of study patients

Variable	Values
Patients, n	374
Leukocytes (109/L), mean ± sd	8.6±5.3
Erythrocites(1012/L), mean ± sd	3.3±1.8
Hemoglobin (g/L), mean ± sd	94.4±15.6
Platelets (109), mean ± sd	211.9±77.2
Glycemia (mmol/L), mean ± sd	5.6±1.9
Sodium (mmol/L), mean ± sd	137.1±15.4
Potassium (mmol/L), mean ± sd	4.9±0.9
Total calcium (mmol/L), mean ± sd	1.8±0.5
Inorganic phosphorus (mmol/L), mean ± sd	2.0±0.4
Albumin (g/L), mean ± sd	34.4±6.1
Creatinine (μmol/L), mean ± sd	650.4±257.1
Urea (mmol/L), mean ± sd	25.7±9.6
Cholesterol (mmol/L), mean ± sd	4.3±1.2
Triglycerides (mmol/L), mean ± sd	1.5±0.8
Fibrinogen (g/L), mean ± sd	5.0±1.9

RESULTS

On average, our respondents were 71.4±5.2 years old. According to gender structure, there were 255 (68.2%) men and 119 (31.8%) women. Distally positioned fistulas in our study had 123 (32.9%) elderly people, while proximal positioned fistula had 251 (67.1%) respondents. According to the type of arteriovenous anastomosis, 289 (77.3%) elderly had a termino-lateral type, while 85 (22.7%) elderly had a termino-terminal type of anastomosis. Preventively created fistulas were recorded in 134 (35.8%) elderly people. Preoperative ultrasound mapping of the blood vessels used for anastomosis was performed in 192 (51.3%) elderly, and 209 (55.9%) elderly people had a central-venous catheter for hemodialysis. On average, lumen veins used for anastomosis are 2.4±0.5 mm while arteries are 2.5±0.5 mm. The mean systolic blood pressure registered during the operative intervention was 147.2±27.3 mmHg, while the mean diastolic blood pressure was 78.5±13.8 mmHg (Table 1).

Table 3: Univariate Cox regression models with arteriovenous fistula failure, as dependent variable

Variable	B	SE	P
Age (years)	0.01	0.01	0.284
Gender	-0.031	0.11	0.790
Positioning of arteriovenous fistula	0.17	0.10	0.119
Leukocytes	-0.01	0.01	0.273
Erythrocytes	-0.05	0.03	0.170
Hemoglobin	-0.00	0.00	0.014*
Platelets	0.00	0.00	0.800
Glycemia	-0.04	0.03	0.189
Sodium	-0.01	0.00	0.003*
Potassium	-0.07	0.06	0.204
Total calcium	-0.06	0.11	0.586
Inorganic phosphorus	-0.02	0.12	0.844
Albumin	0.00	0.00	0.378
Creatinine	-0.00	0.00	0.053*
Urea	0.00	0.00	0.124
Cholesterol	0.02	0.05	0.592
Triglyceride	-025	0.13	0.045*
Fibrinogen	0.02	0.04	0.623
Type of arteriovenous anastomosis	0.15	0.12	0.217
Insertion central venous catheter	0.324	0.11	0.002*
Preoperative mapping blood vessels (Doppler)	-0.26	0.11	0.012*
Type of fistula in relation to the time of creating	0.17	0.10	0.119
Vein diameter	-0.15	0.12	0.224
Artery diameter	-0.25	0.11	0.024*
Systolic blood pressure	-0.00	0.00	0.470
Diastolic blood pressure	0.00	0.00	0.914

*statistically significant parameters

We also analyzed biochemical parameters as part of the routine laboratory analyzes. The results are presented in Table 2 as mean value.

Univariant Cox regression model detected hemoglobin (B -0.00; SE 0.00; *P*=0.014); creatinine (B -0.00; SE 0.00; *P*=0.053); sodium (B -0.01; SE 0.00; *P*=0.003); triglyceride (B -0.25; SE 0.13; *P*=0.045); placement of central venous catheter (B 0.324; SE 0.11; *P*=0.002); preventive mapping of blood vessels (B -0,26; SE 0.11; *P*=0.012) and artery diameter which was used for anastomosis (B -0.25; SE 0.11; *P*=0.024) as statistically significant predictors of arteriovenous fistula survival (Table 3).

Table 4: Multivariate Cox regression models with arteriovenous fistula failure, as dependent variable

Variable	B	SE	P
Variable	B	SE	P
Hemoglobin	-0.00	0.00	0.348
Sodium	-0.03	0.03	0.463
Creatinine	0.00	0.00	0.832
Triglyceride	0.06	0.24	0.809
Preoperative mapping blood vessels (Doppler)	-1.18	0.33	0.000*
Diameter of the vein	-0.51	0.33	0.126

*statistically significant parameters

Logistic regression analysis test (multivariate Cox regression analysis) showed that predictive parameters of fistula function in the elderly are preoperative mapping of blood vessels used for arteriovenous anastomosis (B -1.18; SE 0.33; *P*=0.000) (Table 4).

DISCUSSION

There still exists limited data on the outcomes of arteriovenous fistulas placement in older patients with conflicting results in the literature[16]. A recent decision analysis on the vascular access choice in incident hemodialysis patients provided evidence that the arteriovenous fistula attempt strategy significantly diminish among older patients[17]. Despite significant success in the process of creating a functional arteriovenous fistula, there remains the challenge of precisely determining the predictive parameters of fistula maturation in the elderly, which in many studies, only for themselves, is described as a natural discriminator for the functioning of the fistula[18]. For this reason, our idea was to determine the factors that could predict the fistula functioning in people older than 65 years in relation to gender differentiation. One of the significant results of our study is negative correlation of creatinine and length of functioning of arteriovenous fistula in the elderly using univariant regression model, as well as the concentration of hemoglobin, sodium, triglycerides and use of central venous catheters. Almost no research exists on the predictive parameters of arteriovenous fistulae for hemodialysis in the elderly, in order to compare with our results, which leads us to think that adequate hemodialysis depuration is an important factor in the function of the fistula, but we did not confirm the predictive significance for these parameters.

There are authors who claim that elderly people are less suitable to dialysing via the arteriovenous fistula[10] because of the small caliber of blood vessels used for anastomosis. Inferior outcomes of fistula in the elderly are perceived by some authors as a consequence of decreased blood flow, primarily because of the smaller lumen of the artery[19,20]. Our findings confirmed that the lumen of the artery, in the univariate model, was a significant parameter of functioning of the old people fistula, but we did not confirm its predictive significance.

A study by Hod *et al* has shown that placing an arteriovenous fistula >6–9 months predialysis in the elderly is not associated with a better success rate[21]. Delaying arteriovenous fistula placement may in fact be better, in that some authors suggest that elderly patients with chronic kidney disease should be referred later to reduce the risk of creating an arteriovenous fistule that will never be used[22]. There is currently no general consensus as to the best dialysis vascular access for elderly patients with end stage renal disease, and debate continues[23], which means that vascular access may be optimized by considering individual patient characteristics, and a patient-based approach is recommended[24]. The results of our research have shown that 35.8% of elderly have a preventively created fistula, but this is not a predictive parameter of arteriovenous fistula function, which supports the need to investigate local and associated predictors of fistula function in order to make an appropriate decision about the time of creation of vascular access.

Marcus *et al*[14] found that the average rate of functioning arteriovenous fistula, after preoperative ultrasound mapping of blood vessels, was 487 days. There is no data on the functioning of arteriovenous fistula in old people. Caplin *et al*[25] do not find a significant difference in lumen vein size in preoperative mapping of blood vessels compared to gender[19]. The results of our study showed that more than half of the elderly had a preoperative mapping of blood vessels used for arteriovenous anastomosis and that this was one of the predictive parameters of arteriovenous fistula functionality. However, Doppler screening in our respondents is almost equally represented in both sexes, so it can be concluded that ultrasound mapping of blood vessels is an equally significant predictive parameter in both older men and older women.

In fact, good blood vessel identification for arteriovenous anastomosis significantly affects the length of the functioning of the fistula, wherefore this method is an important component of survival of the arteriovenous fistula.

Limitations of the study

The retrospective methodology of our study introduces inherent weaknesses to its design, because of the possibility of confounding and bias. We presented our own experiences that are based on the experience of a single operator (first author) so, perhaps, the results of our research cannot be generalizable to other centers.

CONCLUSION

Analyzing the results of our study, we found that preoperative ultrasound mapping of blood vessels is an equally important predictive parameter of functioning of arteriovenous fistulas, older age, both male and female.

ACKNOWLEDGMENT

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this research is partly supported by the Ministry of Education and Science of

Serbia, Grants III41010. The sponsor had no role in the study design or interpretation of results.

Author Contribution: Radojica V Stolic designed the topic, processed the database and wrote the manuscript; Vedrana Pavlovic did statistical data processing; Suzana Matejic, Goran V Relic, Snezana Lazic and Dusica V Miljkovic helped update the database, and read and approved the manuscript.

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Pippias M, Stel VS, Diez JMA, Afentakis N, Herrero-Calvo JA, Arias M, *et al*. Renal replacement therapy in Europe: a summary of the 2012 ERA-EDTA Registry Annual Report. Clin Kidney J 2015; 8(3):248-261.
2. Rayner HC, Pisoni RL, Gillespie BW, Goodkin DA, Akiba T, Akizawa T, *et al*. Creation, cannulation and survival of arteriovenous fistulae: data from the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2003; 63(1):323-330.
3. Monroy-Cuadros M, Yilmaz S, Salazar-Bañuelos A, Doig C. Risk factors associated with patency loss of hemodialysis vascular access within 6 months. Clin J Am Soc Nephrol 2010; 5(10):1787-1792.
4. Richardson Al, Leake A, Schmieder GC, Biuckians A, Stokes GK, Panneton JM, *et al*. Should fistula really be first in the elderly patients? J Vasc Access 2009; 10(3):199-202.
5. Weyde W, Letachowicz W, Kusztal M, Porazko T, Krajewska M, Klinger M. Outcome of autogenous fistula construction in hemodialyzed patients over 75 years of age. Blood Purif 2006; 24(2):190-195.
6. Pounds LL,Teodorescu VJ. Chronic kidney disease and dialysis access in women. J Vasc Surg 2013; 57:49S-53S.
7. Fila B, Ibeas J, Tey RR, Lovčić V, Zibar L. Arteriovenous fistula for haemodialysis: The role of surgical experience and vascular access education. Nefrologia (English Version) 2016; 36:89-94.
8. de Pinho NA, Coscas R, Metzger M, Labeeuw M, Ayav C, Jacquelinet C, *et al*. Vascular access conversion and patient outcome after hemodialysis initiation with a nonfunctional arteriovenous access: a prospective registry-based study. BMC Nephrol 2017; 18(1):74.
9. Wasse H, Hopson SD, McClellan W. Racial and gender differences in arteriovenous fistula use among incident hemodialysis patients. Am J Nephrol 2010; 32(3):234-241.
10. Miller CD, Robbin ML, Allon M. Gender differences in outcomes of arteriovenous fistulas in hemodialysis patients. Kidney Int 2003; 63(1):346-352.
11. Ethier J, Mendelssohn DC, Elder SJ, Hasegawa T, Akizawa T, Akiba T, *et al*. Vascular access use and outcomes: an international perspective from the dialysis outcomes and practice patterns study. Nephrol Dial Transplant 2008; 23(10):3219-3226.
12. Vernaglione L, Cristofano MG. Comorbid conditions and gender impact the primary survival of distal radio-cephalic arteriovenous fistula in patients on long-term hemodialysis. J Nephrol 2005; 18:276-281.
13. Erkut B, Unlu Y, Ceviz M, Becit N, Ates A, Colak A, *et al*. Primary arteriovenous fistulas in the forearm for hemodialysis: effect of miscellaneous factors in fistula patency. Ren Fail 2006; 28(4):275-281.
14. Marcus RJ, Marcus DA, Sureshkumar KK, Hussain SM, McGill RL. Gender differences in vascular access in hemodialysis patients in the United States: developing strategies for improving access outcome. Gender Med 2007; 4:193-204.
15. Astor BC, Eustace JA, Powe NR, Klag MJ, Sadler JH, Fink NE, *et al*. Timing of nephrologist referral and arteriovenous access use: the CHOICE Study. Am J Kidney Dis 2001; 38(3):494-501.
16. Konner K, Hulbert-Shearon TE, Roys EC, Port FK. Tailoring the initial vascular access for dialysis patients. Kidney Int 2002; 62(1):329-338.
17. Drew DA, Lok CE, Cohen JT, Wagner M, Tangri N, Weiner DE. Vascular access choice in incident hemodialysis patients: a decision analysis. J Am Soc Nephrol 2015; 26:183-191.
18. McGrogan DG, Field MA, Maxwell AP, Marie Y, Inston NG. Patient survival following arteriovenous fistula formation. J Vasc Access 2015; 16(3):195-199.
19. Masengu A, Maxwell AP, Hanko JB. Investigating clinical predictors of arteriovenous fistula functional patency in a European cohort. Clin Kidney J 2016; 9(1):142-147.
20. Silva MB Jr, Hobson RW 2nd, Pappas PJ, Haser PB, Araki CT, Goldberg MC, *et al.* Vein transposition in the forearm for autogenous hemodialysis access. J Vasc Surg 1997; 26(6):981-988.
21. Hod T, Patibandla BK, Vin Y, Brown RS, Goldfarb-Rumyantzev AS. Arteriovenous fistula placement in the elderly: when is the optimal time? J Am Soc Nephrol 2015; 26(2):448-456.
22. Schechter SM, Skandari MR, Zalunardo R. Timing of arteriovenous fistula creation in patients with CKD: a decision analysis. Am J Kidney Dis 2014; 63(1):95-103.
23. Bowling CB, Muntner P. Epidemiology of chronic kidney disease among older adults: a focus on the oldest old. J Gerontol A Biol Sci Med Sci 2012; 67(12):1379-1386.
24. Nadeau-Fredette AC, Goupil R, Montreuil B, Carignan A, Leblanc M. Arteriovenous fistula for the 80 years and older patients on hemodialysis: is it worth it? Hemodial Int 2013; 17(4):594-601.
25. Caplin N, Sedlacek M, Teodorescu V, Falk A, Uribarri J. Venous access: women are equal. Am J Kidney Dis 2003; 41(2):429-432.

Original Article

The results of patients undergoing partial nephrectomy for renal mass: robotic versus laparoscopic

Erem Asil[1], Bahri Gok[2], Erdem Koc[2], Kemal Ener[3], Abdullah Erdem Canda[4], Ali Fuat Atmaca[2]
[1]Department of Urology, Ankara City Hospital, Ankara, Turkey
[2]Department of Urology, Yildirim Beyazit University, School of Medicine affiliated with Ankara City Hospital, Ankara, Turkey
[3]Department of Urology, Umraniye Training and Research Hospital, Istanbul, Turkey
[4]Department of Urology, Koc University, School of Medicine, Istanbul, Turkey

Kuwait Medical Journal 2022; 54 (1): 39 - 44

ABSTRACT

Objective: Robotic surgery is an emerging trend nowadays, but when the costs are considered, there are question marks associated with preferring it to laparoscopic surgery. In this study, we examined the results of both approaches by comparing the intraoperative, postoperative and oncological outcomes of the patients who underwent robotic partial nephrectomy (RPN) and laparoscopic partial nephrectomy (LPN) for renal cell carcinoma in our clinic.
Design: Retrospective study
Setting: Ankara City Hospital, Turkey
Subject: A total of 96 patients who underwent LPN and RPN for renal mass between 2011 and 2018 and followed up for at least three months were included in the study.
Interventions: Preoperative patient data included age, gender, body mass index, smoking cessation, American Society of Anaesthesia physical status score, Padua score and renal nephrometry score.
Main Outcome Measure: Perioperative and postoperative data included duration of operation, warm ischemia time, blood loss, perioperative and post-operative complications (1-30 days) according to Clavien-Dindo classification.
Results: There was a significant difference between the groups in terms of hospital stay (3.6±1.1 days in the RPN group and 5.32±2.2 days in the LPN group). In the RPN group, renal artery clamp placement reduced the amount of bleeding compared to non-clamped patients, which was statistically significant.
Conclusion: Despite concerns about the higher cost of RPN in comparison to LPN, RPN is a safe and feasible approach in clinical T1 tumors with similar morbidity and oncologic outcomes and shorter hospital stay.

KEY WORDS: laparoscopic, partial nephrectomy, robotic

INTRODUCTION

At present, the number of incidentally identified renal tumors has increased due to developments in imaging modalities and more frequent usage in the clinic. According to recent guidelines, partial nephrectomy is the gold standard treatment method in T1 clinical stage renal tumors. There are studies showing that T2 clinical stage renal tumors can also be safely treated by partial nephrectomy[1].

Oncologic outcomes after open partial nephrectomy (OPN), laparoscopic partial nephrectomy (LPN) and robotic partial nephrectomy (RPN) have been reported to be similar to radical nephrectomy[2-4]. OPN is a more invasive procedure when compared to LPN. However, LPN has a long learning curve, and the duration of the operation varies depending on the experience of the surgeon. In recent years, with the introduction of robotic surgical technology, it is being used in partial nephrectomy operations with a shorter learning curve. Meta-analyses showed that RPN yielded better perioperative outcomes compared to LPN and OPN[5,6]. In this study, we compared the intraoperative, postoperative, and oncological outcomes of patients who underwent LPN and RPN for kidney masses.

SUBJECTS AND METHODS

A total of 96 patients who underwent LPN and RPN and had been followed up for at least three

Address correspondence to:
Bahri Gok, Department of Urology, Yildirim Beyazit University, School of Medicine, Ankara Ataturk Training and Research Hospital, Bilkent, Ankara 06800, Turkey. Tel: +90 5062856839; Fax: +90 3122912715; E-mail: drbahrigok@gmail.com

months in two centers between 2011 and 2018 were included. The condition of Institutional review board approval was waived as this was a retrospective study and all data were retrieved from electronic medical records. This study includes 74 patients who underwent RPN (daVinci Xi robotic surgical system, Intuitive Surgical Inc., Sunnyvale, CA, USA) and 22 patients who underwent LPN. Preoperative data of the patients were analyzed in terms of age, gender, body mass index (BMI), tobacco users, American Society of Anesthesia physical status score, PADUA score and RENAL nephrometry score. Renal nephrometry and PADUA scores of all patients were defined by radiological studies including abdominal computed tomography and magnetic resonance imaging. Perioperative and postoperative data including time of operation, warm ischemia time, estimated blood loss, perioperative and postoperative complications (1-30 days) were evaluated according to Modified Clavien-Dindo classification[7]. Postoperative pathological findings of the patients were evaluated according to Fuhrman nuclear grading system and histological subtypes were evaluated according to World Health Organization definition[8].

Surgical technique

The patients were placed in 60° flank position in all cases and procedures were performed transperitoneally. Operations for laparoscopic cases were carried out after placing ports according to traditional triangulation method for kidney surgery. In robotic surgery patients, port positions were placed differently to avoid collision of robotic arms. An 8 mm camera port was placed lateral to the rectus muscle at the level of umbilicus and 8 mm robotic ports were placed at least 8 cm away from each other, on the right and left sides of the camera port. If the fourth robotic arm was used, it was placed at least 8 cm away on the pelvic side to avoid collision with the other arms. A 10 mm assistant port was placed between the camera port and the robotic trocar on the right side of the camera port. In patients with a mass on the right side, an additional 5 mm port was placed under xiphoid for liver retraction, when needed. Pneumoperitoneum at 15 mmHg was maintained with CO_2 insufflation. Renal hilum was exposed after the colon was mobilized medially and the renal artery and vein were dissected (Figure 1). The mass was exposed after the surrounding adipose tissue was dissected. The contour of the mass was marked superficially with cautery by leaving 0.5 cm margin. A laparoscopic bulldog clamp was placed on the renal artery by the assistant. After excision of the tumor, it was placed into the endobag (Figure 2). Renal parenchymal repair was done using a 4-0 V-Loc (Covidien, New Haven, CT, USA) suture for internal renorrhaphy. In several cases, an absorbable fibrin sealant patch (TachoSil; Take da Pharmaceutical Company, Osaka, Japan) was applied to the tumor surface for adequate hemostasis and an external renorrhaphy was performed with a 3-0 V-Loc (Covidien) suture. Absorbable clips (Lapra-Ty (Ethicon Endosurgery, Inc., Cincinnati, OH, USA)) were placed reciprocally across the sutures outside the renal capsule (Figure 3). Intraabdominal pressure was decreased to 5 mmHg to check whether adequate hemostasis had been achieved. After insertion of a drain through the trocar site, the endobag was extracted.

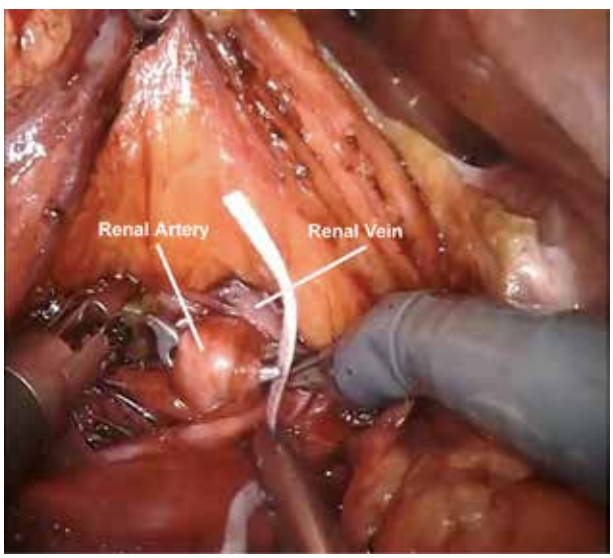


Fig 1: Release and suspension of renal vessels

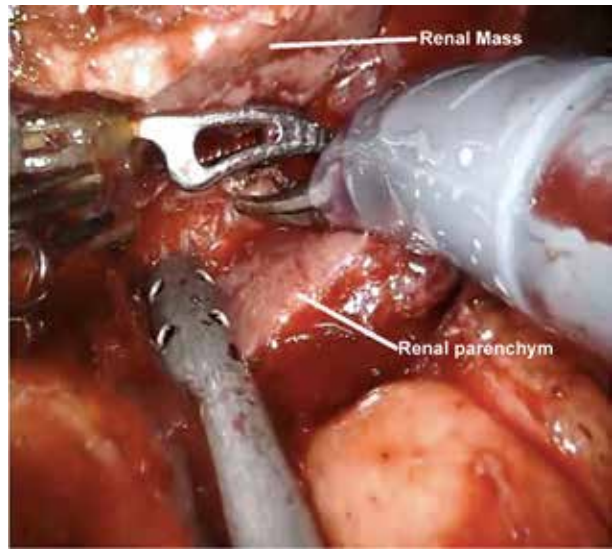


Fig 2: Excision of the mass from the renal parenchyma

Fig 3: Renal parenchymal repair after mass excision

Statistical analysis

Statistical analyses were performed by using Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) software. The suitability of continuous variables to normal distribution was evaluated with Kolmogorov-Smirnov test. Binary comparisons are performed by using student- test or Mann Whitney U test based on the distribution, and the discontinuous variables were analyzed by Chi square test. The effect of operation type and clamp on the amount of bleeding was assessed by 2x2 factorial ANOVA (by reducing the effects of BMI, age, operation time and tumor size). A value of P <0.05 was accepted as statistically significant in all analyzes.

RESULTS

The study included a total of 96 patients (74 RPN, 22 LPN) who were operated at two centers between 2011 and 2018. In the RPN group, 58 patients (78.4%) were males and 16 (21.6%) were females, while in the LPN group, 8 patients (36.4%) were males and 14 were (63.6%) female. The average follow-up period was 34±19.3 months in the RPN group and 30±19.3 months in the LPN group. There were no statistically significant differences between the groups in terms of age, BMI, American Society of Anaesthesia score, follow-up period, PADUA and RENAL nephrometry scores (P >0.05) (Table 1).

The mean duration of operation was 119.4±26.8 minutes in the RPN group and 145±30.6 minutes in the LPN group, which was not statistically significant (P=0.77). Twenty-seven patients in the RPN group and 5 patients in the LPN group were operated with zero ischemia technique. The mean warm ischemia time was 12.8±10.6 and 13.5±9.4 minutes in the patients who were operated with no clamp approach in the RPN and LPN groups respectively, which was not statistically significant (P=0.94). The mean estimated blood loss was 124±125.6 ml in the RPN group and 150±216.5 ml in the LPN group, which was also not statistically significant (P=0.13). The hospital stay was 3.6±1.1 days in the RPN group and 5.32±2.2 days in the LPN group. The difference was found to be statistically significant between the groups (P <0.05). The average size of the mass was 2.82 cm in the RPN group and 3.30 cm in the LPN group. There was no statistically significant difference between the groups (P=0.73) (Table 2).

The effects of the operation type and renal arterial clamping on estimated blood loss were analyzed after removing the effects of BMI, age, tumor size and operation time. In patients who underwent RPN, renal arterial clamping reduced the amount of hemorrhage significantly in comparison to non-clamped patients (P=0.034). However, in patients who underwent LPN, estimated blood loss was higher in patients with renal artery clamping (Table 3).

Table 1: Demographic data of patients

Demographic variables	Robotic partial nephrectomy (n = 74)	Laparoscopic partial nephrectomy (n = 22)	P
Age	53.3±10.9	56.9±11.8	0.09
Gender (M/F)	58/16	8/14	<0.05
BMI	28	27	0.22
ASA score (1/2/3)	33/31/10	1/19/2	
Follow-up time (months)	34±19.3	30±19.3	0.40
RENAL nephrometry score	6.07	6.41	0.21
PADUA score	7.55	7.36	0.49

BMI: body mass index; ASA: American Society of Anaesthesia

Table 2: Perioperative and postoperative results

Perioperative and postoperative variables	Robotic partial nephrectomy (n = 74)	Laparoscopic partial nephrectomy (n = 22)	P
Operation time (min)	119.4±26.8	145±30.6	0.77
Warm ischemia time (min)	12.8±10.6	13.5±9.4	0.94
Zero ischemia (n) (%)	27 (36.4%)	5 (22.7%)	0.22
Amount of bleeding (ml)	124±125.6	150±216.5	0.13
Duration of stay in hospital (days)	3.64±1.1	5:32±2.2	<0.05
Mass size (cm)	2.82	3.30	0.73
Fuhrman grade			
Benign	14	7	
1	8	4	
2	35	11	
3	16	0	
4	1	0	
Positive surgical margin (%)	3 (4.1%)	2 (9.1%)	0.87

Table 3: The effect of presence of operation type and clamp on bleeding

Operation type	Ischemic condition	Mean blood loss (ml)	Std. error	95% confidence interval		P*
				Lower bound	Upper bound	
RPN	No	201.103	29.080	143.313	258.892	
	Yes	90.541	21.412	47.989	133.093	0.713
LPN	No	82.034	66.332	-49.786	213.854	
	Yes	140.273	38.024	64.708	215.838	0.753

*2x2 Factorial ANOVA

Surgical margin positivity was positive in three patients (4%) for RPN and two (9%) patients in LPN group. None of the patients had intraoperative complications. Perioperative complications (0-30 days) were observed in two patients in the RPN group (Clavien Grade 1, no need for blood transfusion, treated by medical treatment) and in three patients in the LPN group (Clavien Grade 1, no need for blood transfusion, treated by medical treatment). No patients required re-hospitalization after discharge in either group. No postoperative complication was seen in any of the patients (30-90 days).

The histological subtypes in the postoperative pathologic evaluation of the patients are given in Table 4. Benign lesions were detected in 14 patients in the RPN group and in 7 patients in the LPN group.

Table 4: Postoperative patients' histopathological evaluation

Histopathological Subtypes	Robotic partial nephrectomy (n = 74)	Laparoscopic partial nephrectomy (n = 22)
Clear cell	42	11
Chromophobe	10	1
Papillary	8	3
Oncocytoma	4	3
Angiomyolipoma	1	1
Other benign lesions	9	3

DISCUSSION

Since RPN was first introduced in 2004[9], it has been used more frequently as an alternative to LPN due to three dimensional vision, magnified vision and more convinient suturing for the surgeons. Shorter duration of hospitalization, fewer analgesia requirements, patient satisfaction and similar oncological outcomes to OPN has made it comparable to OPN when performed by experienced surgeons[10]. Also, complex tumors such as those located in the hilar region and endophytic tumors are technically difficult for resection with the laparoscopic approach[9]. With the advantages provided by RPN, these tumors can be operated more easily when compared to the laparoscopic approach[11].

The disadvantages of robotic surgery are the high cost and the lack of tactile sensation[12]. Studies comparing RPN with OPN demonstrated an additional cost of US$ 1600 per patient[13]. In our series, the average cost per patient undergoing robotic surgery was US$ 2546 in 3 arms and US$ 2898 in 4 arms. The average cost per patient for laparoscopic partial nephrectomy was US$ 1078. As reported in the literature, robotic surgery seems to have a disadvantage in terms of cost compared to laparoscopy.

In our study, there was a significant difference between the groups in terms of the duration of hospitalization, although there was no difference between the groups in terms of estimated blood loss, perioperative and postoperative complications. Our clinic's experience in robotic surgery and the long learning curve in LPN can be considered as factors affecting the duration of hospitalization. The mean length of hospital stay in our study was 3.64±1.1 days in the RPN group and 5.32±2.2 days in the LPN group (P <0.05), while it was 2.5-5.2 days in RPN group and 2.9-5.3 days in LPN group in previous studies[11,14].

In studies on pathophysiology of acute ischemic renal failure, it was found that ischemia causes a decrease in glomerular filtration rate and an increase in acute kidney injury by three main mechanisms, including permanent vasoconstriction, obstruction of the tubules and reperfusion injury after blood flow[15,16]. In our series, the rate of zero ischemia was higher in patients who underwent RPN compared to those with LPN. This may be an advantage in the robotic group in terms of acute ischemic injury and it may be a cause for the lower duration of hospital stay in the robotic group. The lack of data showing patients' glomerular filtration rate changes is a drawback of our study.

Negative surgical margin should be a priority for patients undergoing partial nephrectomy according to American Urological Association guidelines[17]. Although there are conflicting results regarding the long-term clinical significance of positive surgical margin (PSM), it has been associated with disease recurrence in recent studies[18]. In the study performed by Xia *et al*, the centers were categorized according to the number of patients who were operated on, and in

the high-volume centers (24-43 patients), the PSM ratios were found to be lower than the low volume centers[19]. In their study, Shah *et al* revealed that poor pathological features (pT2-3a, Fuhrman grade 3-4) increases the recurrence risk in patients with PSM[20]. Previously published series on robotic PSM was found to be 7.7%[21-23]. In a study in which the results of high-volume centers were collected, PSM ratios were found between 1.7-3.2%[24]. In our study, PSM rate was found to be 4.1% in the RPN group and 9.1% in the LPN group. Recurrence was observed in one patient (Fuhrmann grade 4) who underwent LPN during 30 months of follow-up. This patient underwent open radical nephrectomy.

In the RPN group, renal artery clamping significantly reduced the amount of bleeding compared to patients who underwent zero ischemia technique. In the LPN group, the smaller number of patients with no clamp approach made statistical assessment difficult. Although there was no statistically significant difference between the amount of bleeding in the RPN and LPN group, estimated blood loss was more in the LPN group. Due to the small number of patients in the LPN group, we think that no statistically significant result could be obtained.

Unlike similar studies that made significant contributions to literature by reporting experiences of a single surgeon[25], the present study included the cases of more than one surgeon. This is one of the important advantages of this study and allowed us to compare results of the robotic and laparoscopic surgical approaches, after removing the influence of the surgeon's experience.

The retrospective nature of our study and the low number of patients in the LPN group were limiting factors.

CONCLUSION

Despite concerns about the higher cost of RPN in comparison to LPN, RPN is a safe and feasible approach in clinical T1 tumors with similar morbidity and oncologic outcomes and shorter hospital stay.

ACKNOWLEDGMENT

Disclosure: The authors have no potential conflicts of interest to disclose

Support: None

Author Contribution: Erem Asil wrote the original draft; Bahri Gok was involved with investigation and methodology; Erdem Koc curated data and investigated; Kemal Ener reviewed and edited the manuscript; Abdullah Erdem Canda reviewed and edited the manuscript and did language correction; Ali Fuat Atmaca did the conceptualization and prepared the methodology.

REFERENCES

1. Bertolo R, Autorino R, Simone G, Derweesh I, Garisto JD, Minervini A, *et al*. Outcomes of robot-assisted partial nephrectomy for clinical T2 renal tumors: A Multicenter Analysis (ROSULA Collaborative Group). Eur Urol 2018; 74(2):226-232.
2. Aboumarzouk OM, Stein RJ, Eyraud R, Haber GP, Chlosta PL, Somani BK, *et al*. Robotic versus laparoscopic partial nephrectomy: a systematic review and meta-analysis. Eur Urol 2012; 62(6):1023-1033.
3. Wu Z, Li M, Liu B, Cai C, Ye H, Lv C, *et al*. Robotic versus open partial nephrectomy: a systematic review and meta-analysis. PLoS One 2014; 9(4):e94878.
4. Zhang X, Shen Z, Zhong S, Zhu Z, Wang X, Xu T. Comparison of peri-operative outcomes of robot-assisted vs laparoscopic partial nephrectomy: a meta-analysis. BJU Int 2013; 112(8):1133-1142.
5. Choi JE, You JH, Kim DK, Rha KH, Lee SH. Comparison of perioperative outcomes between robotic and laparoscopic partial nephrectomy: a systematic review and meta-analysis. Eur Urol 2015; 67(5):891-901.
6. Xia L, Wang X, Xu T, Guzzo TJ. Systematic review and meta-analysis of comparative studies reporting perioperative outcomes of robot-assisted partial nephrectomy versus open partial nephrectomy. J Endourol 2017; 31(9):893-909.
7. Kaouk JH, Khalifeh A, Hillyer S, Haber GP, Stein RJ, Autorino R. Robot-assisted laparoscopic partial nephrectomy: step-by-step contemporary technique and surgical outcomes at a single high-volume institution. Eur Urol 2012; 62(3):553-561.
8. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982; 6(7):655-663.
9. Gettman MT, Blute ML, Chow GK, Neururer R, Bartsch G, Peschel R. Robotic-assisted laparoscopic partial nephrectomy: technique and initial clinical experience with DaVinci robotic system. Urology 2004; 64(5):914-918.
10. Jang HJ, Song W, Suh YS, Jeong US, Jeon HG, Jeong BC, *et al*. Comparison of perioperative outcomes of robotic versus laparoscopic partial nephrectomy for complex renal tumors (RENAL Nephrometry Score of 7 or Higher).Korean J Urol 2014; 55(12):808-813.
11. Wang AJ, Bhayani SB. Robotic partial nephrectomy versus laparoscopic partial nephrectomy for renal cell carcinoma: single-surgeon analysis of >100 consecutive procedures. Urology 2009; 73(2):306-310.
12. Phillips CK, Taneja SS, Stifelman MD. Robot-assisted laparoscopic partial nephrectomy: the NYU technique. J Endourol 2005; 19(4):441-445; discussion 445.
13. Mirheydar HS, Parsons JK. Diffusion of robotics into clinical practice in the United States: process, patient safety, learning curves, and the public health. World J Urol 2013; 31(3):455-461.
14. Pierorazio PM, Patel HD, Feng T, Yohannan J, Hyams ES, Allaf ME. Robotic-assisted versus traditional

laparoscopic partial nephrectomy: comparison of outcomes and evaluation of learning curve. Urology 2011; 78(4):813-819.
15. Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med 2007; 357(8):797-805.
16. Secin FP. Importance and limits of ischemia in renal partial surgery: experimental and clinical research. Adv Urol 2008; 2008:102461.
17. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, *et al*. Renal mass and localized renal cancer: AUA guideline. J Urol 2017; 198(3):520-529.
18. Khalifeh A, Kaouk JH, Bhayani S, Rogers C, Stifelman M, Tanagho YS, *et al*. Positive surgical margins in robot-assisted partial nephrectomy: a multi-institutional analysis of oncologic outcomes (leave no tumor behind). J Urol 2013; 190(5):1674-1679.
19. Xia L, Pulido JE, Chelluri RR, Strother MC, Taylor BL, Raman JD, *et al*. Hospital volume and outcomes of robot-assisted partial nephrectomy. BJU Int 2018; 121(6):900-907.
20. Shah PH, Moreira DM, Okhunov Z, Patel VR, Chopra S, Razmaria AA, *et al*. Positive Surgical margins increase risk of recurrence after partial nephrectomy for high risk renal tumors. J Urol 2016; 196(2):327-334.
21. Benway BM, Bhayani SB, Rogers CG, Dulabon LM, Patel MN, Lipkin M, *et al*. Robot assisted partial nephrectomy versus laparoscopic partial nephrectomy for renal tumors: a multi-institutional analysis of perioperative outcomes. J Urol 2009; 182(3):866-872.
22. Benway BM, Bhayani SB, Rogers CG, Porter JR, Buffi NM, Figenshau RS, *et al*. Robot-assisted partial nephrectomy: an international experience. Eur Urol 2010; 57(5):815-820.
23. Ploussard G, Haddad R, Kovac E, Richard P, Anidjar M, Bladou F, *et al*. Robot-assisted laparoscopic partial nephrectomy: Early single Canadian institution experience. Can Urol Assoc J 2013; 7(9-10):348-354.
24. Andrade HS, Zargar H, Caputo PA, Akca O, Kara O, Ramirez D, *et al*. Five-year oncologic outcomes after transperitoneal robotic partial nephrectomy for renal cell carcinoma. Eur Urol 2016; 69(6):1149-1154.
25. Simsek A, Yavuzsan AH, Colakoglu Y, Atar A, Sahin S, Tugcu V. Comparison of robotic and laparoscopic partial nephrectomy for small renal tumours. Arch Ital Urol Androl 2017; 89(2):93-96.

Original Article

S100 calcium binding protein expression in nasopharyngeal carcinoma, sinonasal papilloma and upper respiratory tract mucosa

Remzi Erten, Feyza Demir, Irfan Bayram
Department of Pathology, Faculty of Medicine, University of Van Yüzüncü Yıl, Van, Turkey

Kuwait Medical Journal 2022; 54 (1): 45 - 51

ABSTRACT

Objectives: The S100 calcium binding protein P (S100P) is a small member of the S100 protein family that is considered to play a role in carcinogenesis and has been shown to be overexpressed in some carcinomas. In this study, we aimed to evaluate an immunohistochemical (IHC) analysis of S100P expression in nasopharynx carcinoma (NPC), sinonasal papilloma (SNP) and upper respiratory mucosae.
Design: Prospective cross-sectional study
Setting: Department of Pathology, Faculty of Medicine, University of Van Yüzüncü Yıl, Van, Turkey
Subjects: Sixty-eight samples including NPC, SNP and non-neoplastic upper respiratory tract epithelia were included in the study.
Interventions: Samples stained with the S100P primary antibody using the IHC method.
Main outcome measures: The staining scores and intensities were calculated based on nuclear or nuclear/cytoplasmic staining.
Results: S100P staining was not detected in 17 out of 19 NPC cases but was detected in the epithelium of all cases of SNP and non-neoplastic upper respiratory tract. A significant difference was found among the groups regarding staining score and intensity.
Conclusion: Considering that S100P was not expressed in NPC but was expressed in the epithelium of normal nasopharynx, it can be asserted that our results indicated the loss of S100P expression in NPC. Our results also indicated that S100P, which is known to be expressed in urothelium, was also expressed in the upper respiratory tract epithelia.

KEY WORDS: nasopharyngeal carcinoma, S100 calcium binding protein P, upper respiratory tract

INTRODUCTION

S100 protein family is the largest calcium-binding protein family involving proteins such as S100 calcium binding protein (S100)A, S100B and S100P. These proteins also bind divalent ions such as copper, magnesium and zinc. Each member of the S100 family show tissue- and/or cell-specific expression patterns and also regulate intracellular processes such as protection against oxidative damage and calcium homeostasis[1]. S100P exerts its extracellular functions through its interaction with cell surface receptors such as the receptors for advanced glycation end products (RAGE)[2]. RAGE have been shown to trigger growth, survival and metastasis in some cancer types[3] and also to contribute to various diseases including Alzheimer's disease, diabetes and inflammation[4]. Activation of RAGE results in the activation of factor extracellular-regulated kinase and nuclear factor-κB[2]. On the other hand, the effects of S100P on cell proliferation, survival and signaling pathways can be inhibited by blocking the interaction between S100P and RAGE using anti-RAGE antibodies, administration of a peptide antagonist derived from amphoterin[5].

Sinonasal masses are divided into two main categories: neoplastic and non-neoplastic, whereby neoplastic masses are further divided as benign and malignant[6]. Nasal polyps are epithelial and stromal

Address correspondence to:
Remzi Erten, Department of Pathology, Van Yüzüncü Yıl University School of Medicine, Tuşba, Van, 65080, Turkey. Tel: +90 505 2425800; Fax: +90 432 2167519; E-mail: drerten@hotmail.com

proliferative non-neoplastic lesions that are not always accompanied by inflammation. However, inflammatory polyps accompanied by chronic inflammation are the most common types[7]. Inverted papillomas are rare tumors of the nasal cavity and paranasal sinuses, mostly seen in male gender aged around 50 years and characterized by nasal obstruction, nasal discharge and epistaxis[8]. Inverted papillomas are a locally aggressive subtype of benign sinonasal papillomas (SNPs) characterized by tendency for local recurrence and malignancy[9,10]. These tumors may involve dysplasia foci and even 2 to 27% of them may progress to invasive squamous cell carcinoma[11,12].

Nasopharyngeal carcinoma (NPC) is the most common tumor in the head and neck, often associated with numerous factors including Epstein-Barr virus (EBV)[13], with high incidences in North Africa, Southeast Asia and South China[14]. A previous study evaluating cancer survival based on a hospital-based cancer registry revealed that NPC was one of the 10 most common cancer types with a 5-year survival rate of 48.95%. The study also noted that of all the cancer types, corpus uteri carcinoma had the best prognosis with a 5-year survival rate of 81.08% and pancreatic cancer had the worst prognosis with a 5-year survival rate of 1.39%, and NPC had a moderate survival rate on this scale. Moreover, younger age was found to establish a significant correlation with higher survival rates among patients with NPC[15].

S100P was initially detected in the placenta[16], subsequently expressed in the esophageal squamous mucosa[17], and then found to be expressed in pancreatic cancers through immunohistochemical (IHC) analysis[18]. The S100P expression in breast cancer has been associated with poor prognosis[19]. Moreover, S100P has been shown to be regulated by androgens[20] and thus has been implicated to play a role in the etiology of prostate cancer[21]. S100P is highly expressed in the urothelial epithelium and urothelial carcinoma with high specificity and sensitivity, so this marker is closely associated with differentiation of the urothelial epithelium[22]. Considering that this marker shows high specificity and sensitivity in the urothelial epithelium and is highly expressed in the esophageal squamous epithelium[17], the present study aimed to evaluate S100P expression in upper respiratory tract epithelium and to investigate the role of S100P in nasal polyps, inverted papillomas, and particularly NPC which originate from this epithelium. Moreover, S100P can be the therapeutic target for some cancer types since it can be inhibited by RAGE. Accordingly, the present study aimed to contribute to the literature regarding the usability of S100P in the diagnosis and treatment protocols of NPC.

SUBJECTS AND METHODS

Tissue specimens

The study included the archival paraffin-embedded specimens from a total of previously diagnosed 68 patients including 19 patients with NPC, 15 patients with SNP (inverted type), 17 patients with inflammatory nasal polyp (INP) and 17 patients with noncancerous nasopharyngeal mucosa (NNPM) that were obtained from Van Yüzüncü Yıl University Medical School, Medical Pathology Laboratory. The 19 specimens of NPC comprised 15 undifferentiated carcinoma and 4 non-keratinizing squamous cell carcinoma. Clinical data including patient age and gender were obtained from pathological reports. The study was approved by Van Yüzüncü Yıl University Noninterventional Clinical Research Ethical Committee (Approval No. 09, Date: July 19, 2017).

Immunohistochemistry

Hematoxylin and eosin-stained slides were re-evaluated and the most suitable blocks for IHC analysis were selected. The blocks were cut into 4-µ thick sections and mounted on poly-L-lysine-coated slides for IHC stain for S100P. S100P (concentrated and prediluted polyclonal antibody, catalog No. API3010AA, BioCare Medical, USA) was used as the primary antibody at a dilution of 1:75. The slides were stained in a Ventana Benchmark XT IHC automated slide stainer with a Ventana Ultraview Dab Detection Kit using appropriate positive controls which consisted of noncancerous bladder tissues. All the slides were evaluated using an Olympus BX53F light microscope (Olympus, Tokyo, Japan) at different magnifications.

For S100P staining, the percentage, score and intensity of staining were evaluated based on nuclear or nuclear/cytoplasmic staining patterns. Samples

Table 1: Gender and age distribution of the groups

Gender and Age	NPC (n=19) (%)	SNP (n=15) (%)	INP (n=17) (%)	NNPM (n=17) (%)
Gender				
Female	6 (31.6)	5 (33.3)	5 (29.4)	8 (47.1)
Male	13 (68.4)	10 (66.7)	12 (70.6)	9 (52.9)
Age (years)				
Range	34-69	18-75	21-82	15-54
Mean	55.0	56.4	41.5	26.7

NPC: nasopharyngeal carcinoma; SNP: sinonasal papilloma; INP: inflammatory nasal polyp; NNPM: noncancerous nasopharyngeal mucosa

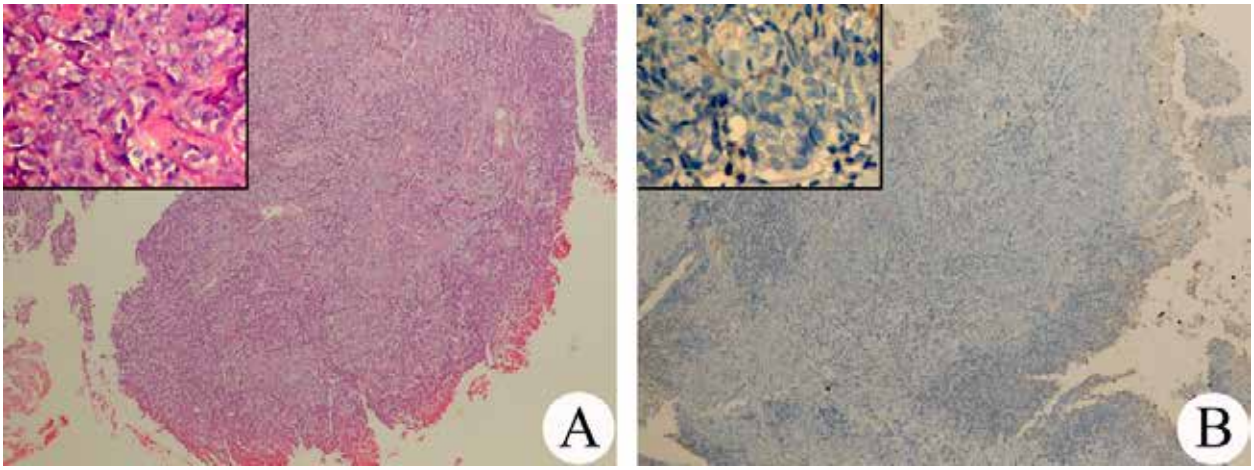


Fig 1: A, Hematoxylin and eosin staining in nasopharyngeal carcinoma (×100, inset ×400). **B,** Negative S100P staining in nasopharyngeal carcinoma (×100, inset ×400).

that were detected with cytoplasmic staining only were not accepted as stained. The staining score was evaluated based on the percentage of staining: negative, 0; <10%, 1 +; 10-70%, 2 +; > 70%, 3+[23]. Staining intensity was also divided into four grades: negative, 0; weak, 1 +; intermediate, 2 +; strong, 3+[24].

Statistical analysis

Data were analyzed using SPSS for Windows version 23.0 (Armonk, NY: IBM Corp., USA). Descriptive statistics were evaluated using Kruskal Wallis test and the significance of the differences between groups was evaluated by the Chi-square test. A *P*-value of <0.05 was considered significant.

Table 2: S100P expression in the specimens

Staining score and intensity	NPC (n=19) (%)	SNP (n=15) (%)	INP (n=17) (%)	NNPM (n=17) (%)
Staining score				
0	17 (89.5)	0	0	0
1 +	1 (5.3)	2 (13.3)	0	0
2 +	1 (5.3)	12 (80.0)	15 (88.2)	12 (70.6)
3 +	0	1 (6.7)	2 (11.8)	5 (29.4)
Staining intensity				
0	17 (89.5)	0	0	0
1 +	0	0	0	0
2 +	1 (5.3)	6 (40.0)	0	0
3 +	1 (5.3)	9 (60.0)	17 (100)	17 (100)

NPC: nasopharyngeal carcinoma; SNP: sinonasal papilloma; INP: inflammatory nasal polyp; NNPM: noncancerous nasopharyngeal mucosa

RESULTS

In our patients, male predominance was detected in each group. The patients were aged 18-82 years and had a mean age of 44.9 years (Table 1).

S100P expression was not detected in IHC staining in almost all the NPC cases (Table 2, Figure 1). In the remaining three groups (SNP, INP and NNPM), most of the cases had a staining score of 2 + and a staining intensity of 3 + (Table 2, Figures 2-4).

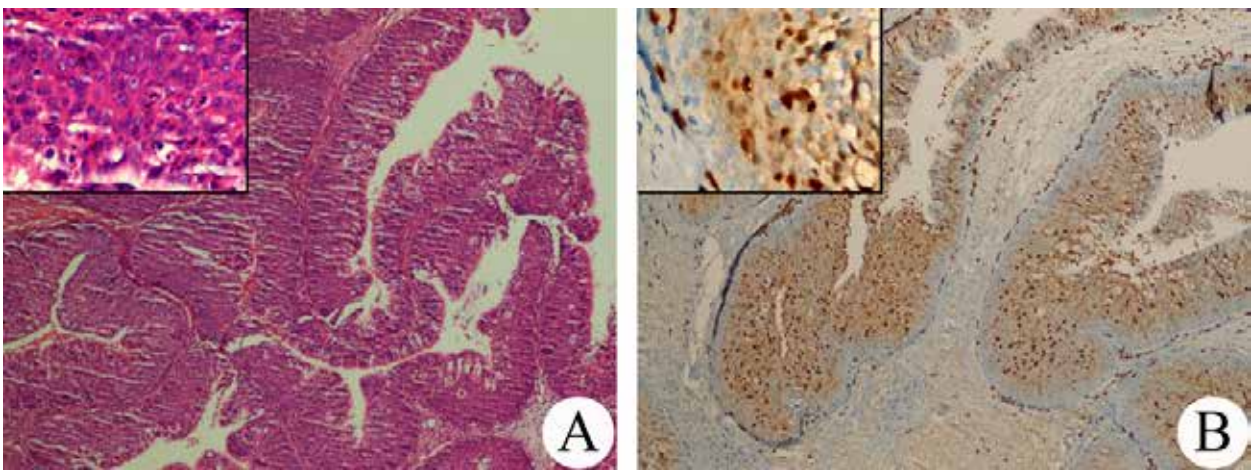


Fig 2: A, Hematoxylin and eosin staining in sinonasal papilloma (×100, inset ×400). **B,** Positive S100P staining in sinonasal papilloma (×100, inset ×400).

Table 3: Kruskal-Wallis test results

Staining percentage	Group	Median	Mean	SD	Min	Max	*P*
Percentage of staining	NPC	0.0 C	3.2	12.6	0.0	55.0	
	SNP	20.0 B	32.8	24.6	5.0	75.0	0.001
	INP	60.0 A	58.5	12.8	35.0	80.0	
	NNPM	70.0 A	62.9	15.3	30.0	85.0	

NPC: nasopharyngeal carcinoma; SNP: sinonasal papilloma; INP: inflammatory nasal polyp; NNPM: noncancerous nasopharyngeal mucosa

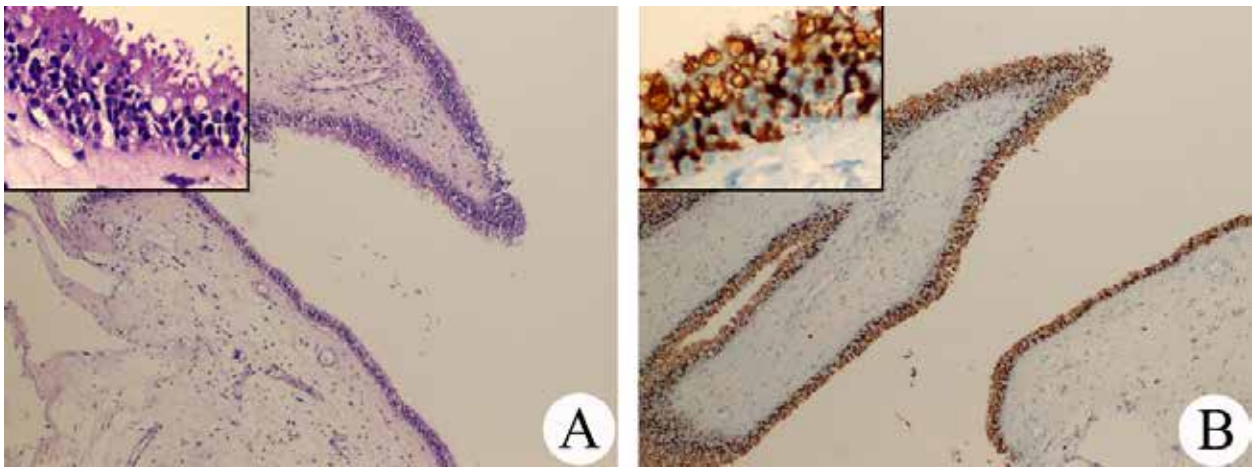


Fig 3: A, Hematoxylin and eosin staining in inflammatory nasal polyp (×100, inset ×400). **B,** Positive S100P staining in inflammatory nasal polyp (×100, inset ×400).

A chi-square test indicated a significant difference among the groups in terms of staining score and intensity (P <0.05). However, a Kruskal-Wallis test based on the percentages of staining showed no significant difference between the NNPM and INP cases that consisted of non-neoplastic upper respiratory tract mucosae. Based on the statistical differences detected among the groups, three different groups were established including NPC, SNP and non-neoplastic upper respiratory tract mucosae (NNPM and INP). However, the statistical difference was more significant for NPC when the two groups with no statistical difference (*i.e.* NNPM vs. INP) were separately compared with NPC and SNP (Table 3).

In all four groups, S100P staining was stronger in the upper half of the epithelium. Moreover, lots of the cases detected with S100P staining showed weak staining or no staining in the basal part of the epithelium.

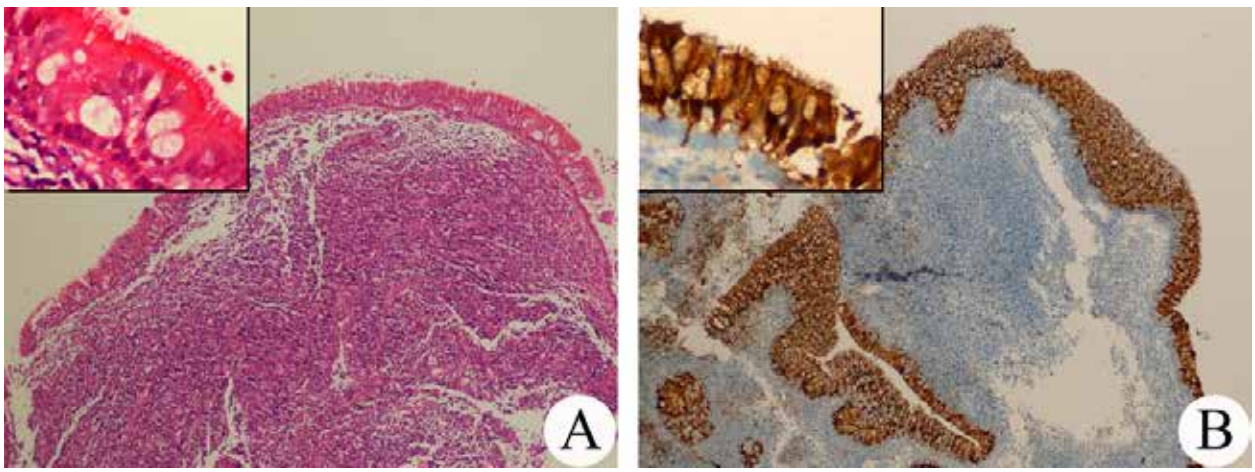


Fig 4: A, Hematoxylin and eosin staining in noncancerous nasopharyngeal mucosa (×100, inset ×400). **B,** Positive S100P staining in noncancerous nasopharyngeal mucosa (×100, inset ×400).

DISCUSSION

S100P, which is expressed in a number of solid cancers[22], has been implicated as a marker of aggressive features in these cancers such as cell proliferation[2]. Similarly, Vera-Sempere *et al* showed that the S100 protein is a marker of NPC with no prognostic significance between clinical survival and prognosis[25].

Higgins *et al* detected positive IHC staining for S100P in 78% of the cases with bladder urothelial carcinoma, 62% of the cases with gastric carcinoma, 60% of the cases with esophageal adenocarcinoma, 30% of the cases with pancreatic carcinoma, 20% of the cases with colorectal carcinoma, 14% of the cases with hepatocellular carcinoma, 10% of the cases with lung carcinoma, 7% of the cases with ovarian carcinoma and only 2% of the cases with prostatic adenocarcinoma. Additionally, no S100P staining was observed in the cases with invasive ductal carcinoma, adrenal carcinoma, uterine cervical adeno and squamous cell carcinoma, endometrial carcinoma, esophageal squamous cell carcinoma, gallbladder carcinoma, seminoma, squamous cell carcinoma, melanoma, renal cell carcinoma and thyroid carcinoma[22]. In our study, the rate of S100P expression in the NPC cases was 10.5%, which could be a novel rate for S100P expression in solid cancers.

Tsuji *et al* reported that RAGE and EBV-encoded latent membrane protein 1 (LMP1) are expressed equally in NPC, suggesting these expressions are accompanied by increased angiogenesis and lymph node metastasis, which could implicate the involvement of RAGE in EBV-induced carcinogenesis[26]. This study is similar to our study since it showed that the rate of S100 expression did not reach the reported rates of RAGE and LMP1 expression in NPC and no statistical relationship was found between increased angiogenesis and lymph node metastasis and in our study S100P did not show a high rate of expression in NPC.

Liu *et al* reported that S100P expression was detected in 57.7% of the cases with NPC as compared to 16.7% of patients with benign inflammation[27]. In our study, we obtained different outcomes; S100P staining was detected in only two out of 19 cases with NPC and strong S100P expression was detected in all the cases with NNPM that occurred secondary to inflammatory processes. In addition, unlike the staining detected in the basal layer of the epithelium in the study by Liu *et al*[27], the staining in our cases was detected in the upper half of the epithelium. On the other hand, there are very few studies in the literature in which S100P expression is detected in nasopharyngeal localization.

Liu *et al* also noted that the decreased S100P expression induced by the silencing of genes triggered the decrease in the expression of some factors such as epidermal growth factor receptor, cluster of differentiation 44, matrix metalloproteinase 2 and matrix metalloproteinase 9 that play a role in contact inhibition and in cell proliferation and migration. In addition, the authors also reported that RAGE expression was decreased in the cases with silenced S100P expression, as detected by western blot analysis[27]. On the other hand, Arumugam *et al* showed that S100P leads to mitogen activation in adenocarcinomas by using the protein kinase signaling pathway through the RAGE-dependent pathway[2]. Similarly, Liu *et al* also suggested that tumor development can be prevented by the silencing of S100P, S100P plays a key role in the development and progression of NPC, and S100P can be the therapeutic target in NPC[27].

Sato *et al* detected S100P expression in normal esophageal epithelial cells in the process of differentiation and suggested that S100P may have a role in the development of normal epithelial cells. The authors also reported that the staining pattern was strong suprabasal staining which was detected in the upper half of the epithelium, similar to the staining pattern detected in our cases[17].

Literature indicates that S100P can be expressed in both cancerous and noncancerous urothelial epithelium and thus can be a urothelial marker[22]. In our study, S100P was expressed in noncancerous nasopharyngeal and nasal mucosa epithelia, which were different epithelia than those reported in the literature.

CONCLUSION

In conclusion, the results indicated that the strong suprabasal S100P expression detected in non-neoplastic upper respiratory tract mucosae implicated that S100P may have a role in the normal development of some epithelia in the upper respiratory tract, as shown by the literature. Accordingly, although no molecular examination was performed and the number of patients was limited in our study, the absence of S100P expression in 17 out of 19 cases with NPC can be considered as loss of expression. Moreover, considering the slight loss of expression in the cases with SNP, which has a potential for malignancy, and the marked loss of expression in the cases with NPC, S100P is highly likely to disappear during cancer formation. With regards to the findings presented by Tsuji *et al* who evaluated the markers of NPC including RAGE, LMP1, and S100, we consider that the effect of EBV is induced by RAGE and that S100 as well as S100P, which have no apparent role in

the development of NPC, could be proteins that only use the same receptors with LMP1. On the other hand, our results also implicated that S100P, since it was expressed in noncancerous nasopharyngeal epithelium, may show loss of expression as part of carcinogenesis in a similar way to markers such as P53 or via some other mechanisms. With regards to the study that presented different findings than our findings, we consider that S100P may be confirmed as a therapeutic target once it is proven to be a tumor suppressor or trigger or by which mechanisms it functions as a tumor suppressor or trigger. Since there is little documentation of S100P expression in upper respiratory tract and a wide range of immune expression findings in the literature, further studies are needed to further investigate S100P expression in this novel anatomical localization.

ACKNOWLEDGMENTS

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding/Support Statement: None

Presented orally at the 27th National Pathology Congress, Antalya, Turkey, November 15-18, 2017.

Authors' contribution: All authors contributed to the conception, data collection, literature search, writing the manuscript and final approval of the paper submitted.

REFERENCES

1. Donato R. S100: a multigenic family of calcium-modulated proteins of the EF-hand type with intracellular and extracellular functional roles. Int J Biochem Cell Biol 2001; 33(7):637-668.
2. Arumugam T, Simeone DM, Schmidt AM, Logsdon CD. S100P stimulates cell proliferation and survival via receptor for activated glycation end products (RAGE). J Biol Chem 2004; 279(7):5059-5065.
3. Taguchi A, Blood DC, del Toro G, Canet A, Lee DC, Qu W, *et al*. Blockade of RAGE-amphoterin signalling suppresses tumour growth and metastases. Nature 2000; 405(6784):354-360.
4. Stern D, Yan SD, Yan SF, Schmidt AM. Receptor for advanced glycation endproducts: a multiligand receptor magnifying cell stress in diverse pathologic settings. Adv Drug Deliv Rev 2002; 54(12):1615-1625.
5. Huttunen HJ, Fages C, Kuja-Panula J, Ridley AJ, Rauvala H. Receptor for advanced glycation end products-binding COOH-terminal motif of amphoterin inhibits invasive migration and metastasis. Cancer Res 2002; 62(16):4805-4811.
6. Bist SS, Varshney S, Baunthiyal V, Bhagat S, Kusum A. Clinico-pathological profile of sinonasal masses: An experience in tertiary care hospital of Uttarakhand. Natl J Maxillofac Surg 2012; 3(2):180-186.
7. Bhattacharyya D, Das TK, Mukherjee S, Mahata M. Study of heterogeneity of sino-nasal lesions in urban population of north Kolkata and its fringes- a 5-year retrospective analysis: experience of a tertiary care centre. Int J Res Med Sci 2018; 6(1):82-87.
8. Batsakis JG, Suarez P. Schneiderian papillomas and carcinomas: a review. Adv Anat Pathol 2001; 8(2):53-64.
9. Mirza S, Bradley PJ, Acharya A, Stacey M, Jones NS. Sinonasal inverted papillomas: recurrence, and synchronous and metachronous malignancy. J Laryngol Otol 2007; 121(9):857-864.
10. Raveh E, Feinmesser R, Shpitzer T, Yaniv E, Segal K. Inverted papilloma of the nose and paranasal sinuses: a study of 56 cases and review of the literature. Isr J Med Sci 1996; 32(12):1163-1167.
11. Lawson W, Kaufman MR, Biller HF. Treatment outcomes in the management of inverted papilloma: an analysis of 160 cases. Laryngoscope 2003; 113(9):1548-1556.
12. Sauter A, Matharu R, Hörmann K, Naim R. Current advances in the basic research and clinical management of sinonasal inverted papilloma (review). Oncol Rep 2007; 17(3):495-504.
13. Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. Lancet 2016; 387(10022):1012-1024.
14. Tang LL, Chen WQ, Xue WQ, He YQ, Zheng RS, Zeng YX, *et al*. Global trends in incidence and mortality of nasopharyngeal carcinoma. Cancer Lett 2016; 374(1):22-30.
15. Chen JG, Chen HZ, Zhu J, Yang YL, Zhang YH, Huang PX, *et al*. Cancer survival in patients from a hospital-based cancer registry, China. J Cancer 2018; 9(5):851-860.
16. Becker T, Gerke V, Kube E, Weber K. S100P, a novel Ca(2+)-binding protein from human placenta. cDNA cloning, recombinant protein expression and Ca2+ binding properties. Eur J Biochem 1992; 207(2):541-547.
17. Sato N, Hitomi J. S100P expression in human esophageal epithelial cells: Human esophageal epithelial cells sequentially produce different S100 proteins in the process of differentiation. Anat Rec 2002; 267(1):60-69.
18. Crnogorac-Jurcevic T, Missiaglia E, Blaveri E, Gangeswaran R, Jones M, Terris B, *et al*. Molecular alterations in pancreatic carcinoma: expression profiling shows that dysregulated expression of S100 genes is highly prevalent. J Pathol 2003; 201(1):63-74.
19. Wang G, Platt-Higgins A, Carroll J, de Silva Rudland S, Winstanley J, Barraclough R, *et al*. Induction of metastasis by S100P in a rat mammary model and its association with poor survival of breast cancer patients. Cancer Res 2006; 66(2):1199-1207.
20. Amler LC, Agus DB, LeDuc C, Sapinoso ML, Fox WD, Kern S, *et al*. Dysregulated expression of androgen-responsive and nonresponsive genes in the androgen-independent prostate cancer xenograft model CWR22-R1. Cancer Res 2000; 60(21):6134-6141.

21. Averboukh L, Liang P, Kantoff PW, Pardee AB. Regulation of S100P expression by androgen. Prostate 1996; 29(6):350-355.
22. Higgins JPT, Kaygusuz G, Wang L, Montgomery K, Mason V, Zhu SX, *et al*. Placental S100 (S100P) and GATA3: markers for transitional epithelium and urothelial carcinoma discovered by complementary DNA microarray. Am J Surg Pathol 2007; 31(5):673-680.
23. Nakata K, Nagai E, Ohuchida K, Hayashi A, Miyasaka Y, Aishima S, *et al*. S100P is a novel marker to identify intraductal papillary mucinous neoplasms. Hum Pathol 2010; 41(6):824-831.
24. Levy M, Lin F, Xu H, Dhall D, Spaulding BO, Wang HL. S100P, von Hippel-Lindau gene product, and IMP3 serve as a useful immunohistochemical panel in the diagnosis of adenocarcinoma on endoscopic bile duct biopsy. Hum Pathol 2010; 41(9):1210-1219.
25. Vera-Sempere FJ, Micheau C, Llombart-Bosch A. S-100 protein positive cells in nasopharyngeal carcinoma (NPC): absence of prognostic significance. A clinicopathological and immunohistochemical study of 40 cases. Virchows Arch A Pathol Anat Histopathol 1987; 411(3):233-237.
26. Tsuji A, Wakisaka N, Kondo S, Murono S, Furukawa M, Yoshizaki T. Induction of receptor for advanced glycation end products by EBV latent membrane protein 1 and its correlation with angiogenesis and cervical lymph node metastasis in nasopharyngeal carcinoma. Clin Cancer Res 2008; 14(17):5368-5375.
27. Liu Y, Wang C, Shan X, Wu J, Liu H, Liu H, *et al*. S100P is associated with proliferation and migration in nasopharyngeal carcinoma. Oncol Lett 2017; 14(1):525-532.

Original Article

The relationships between fasting plasma glucose and insulin resistance, glucose effectiveness, first- and second-phase insulin secretion in overweight and middle-aged Chinese

Chin-Yu Chen[1], Chung-Ze Wu[2,3], Chang-Hsun Hsieh[4], Yao-Jen Liang[5], Dee Pei[6]
[1]Faculty of Medicine, School of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, ROC
[2]Division of Endocrinology, Department of Internal Medicine, Shuang Ho Hospital, New Taipei, Taiwan, ROC
[3]Division of Endocrinology and Metabolism, School of Medicine, College of Medicine, Taipei Medical University, Taipei city, Taiwan, ROC
[4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical School, Taiwan, ROC
[5]Department and Institute of Life-Science, Fu-Jen Catholic University, New Taipei, Taiwan, ROC
[6]Division of Endocrinology and Metabolism, Department of Internal Medicine, Fu-Jen Catholic Hospital, Cardinal Tien Hospital, Fu Jen Catholic University, School of Medicine, New Taipei City, Taiwan, ROC

Kuwait Medical Journal 2022; 54 (1): 52 - 59

ABSTRACT

Objectives: To evaluate the effect of diabetes factors (DFs) such as insulin resistance (IR), glucose effectiveness (GE), first- and second-phase insulin secretion (FPIS and SPIS, respectively) on glucose metabolism and investigate which factor has the most profound impact in subjects within the same age group and with the same age and body mass index (BMI). Our aim is to show that the 'net' effects of the DFs could be determined independent of age and BMI.
Design: A cross-sectional study
Setting: MJ Health Screening Centers and other hospitals
Subjects: We enrolled 28 men and 21 women of the same age (50 years old) and BMI (26 kg/m^2)
Interventions: No special intervention
Main outcome measures: IR, FPIS, SPIS and GE were measured using the equations developed by our group.
Results: In men, whereas SPIS is negatively correlated to fasting plasma glucose (FPG), IR shows a positive correlation. In women, both SPIS and GE are negatively associated with FPG. Besides, in women, FPG and GE had the highest r values followed by SPIS. However, for men, the order is SPIS and IR, respectively.
Conclusion: In the middle-aged, overweight Chinese population, FPG was positively correlated to IR in men and negatively correlated to GE in women. At the same time, FPG was negatively correlated to SPIS in both genders. The FPG was most highly correlated to SPIS in men and GE in women.

KEY WORDS: glucose intolerance, glucose metabolism, type 2 diabetes

INTRODUCTION

Recently, the World Health Organization reported that the global prevalence of type 2 diabetes (T2D) has doubled since 1980 in the adult population[1]. Moreover, an estimated 1.5 million deaths were caused by diabetes in 2012. Taiwan is no exception; a recent report found a 70% increase in the total diabetic population in Taiwan from 2000 to 2009[2]. Obesity is one of the important risk factors for explaining this higher prevalence[3].

Address correspondence to:
Dee Pei, M.D., Division of Endocrinology and Metabolism, Department of Internal Medicine, Fu-Jen Catholic University Hospital, No.69, Gueizih Rd., Taishan Dist., New Taipei City 24352, Taiwan (R.O.C.). Tel: +886 2 85128888; Fax: +886 2 22193506; E-mail: peidee@gmail.com

It is generally accepted that T2D is a metabolic disorder caused by both impaired insulin sensitivity (insulin resistance, IR) and insulin secretion. Insulin secretion is actually biphasic with first and second phase insulin secretion (FPIS and SPIS, respectively)[4,5]. In the past, many studies explored the roles of IR and FPIS in glucose metabolism. However, due to the limitations in available measuring methods, investigators have been unable to focus on SPIS[5,6]. Other than these aforementioned three factors, glucose effectiveness (GE) also plays an important role in the development of diabetes. For instance, GE was found to be an independent predictor of diabetes across different races[7]. However, it is interesting to note that GE has long been overlooked. In the present study, we denote these four factors as diabetes factors (DFs).

One of the criteria for the diagnosis of T2D is increased fasting plasma glucose (FPG) levels[8]. FPG is an indicator of glucose metabolism status. Thus, understanding which of the four DFs most directly affect glucose metabolism and FPG is of great interest. In the past, nearly all related studies investigating the relative effects of DFs on FPG faced two major confounding factors: age and body mass index (BMI). If these two factors were not accounted for, the relationships between the DFs and FPG could not be evaluated precisely[9-12]. Therefore, statistical methods are most commonly used to solve this problem. To our knowledge, there has been no study done in a meticulously selected cohort with the same age and BMI to investigate the relationships between FPG and DFs. In this study, we enrolled subjects from the same age group (50-year-old) and BMI (26 kg/m^2), in order to try answering these two questions: 1) what are the relationships between FPG and DFs in non-diabetic, overweight subjects; and 2) what is the relative tightness of association amongst FPG and DFs.

SUBJECTS AND METHODS

Twenty-eight men and 21 women with exactly the same age (50 years old) and BMI (26.3 kg/m^2) were chosen randomly from MJ Health Screening Center, Cardinal Tien hospital and Tri-Service general hospital in Taiwan between 2012-2013. The participants received health examinations before the study was conducted. MJ Health Screening Center is a local chain clinic which provides regular health assessments for its patients. Cardinal Tien hospital is a local district hospital, and Tri-Service General Hospital is a medical center. To minimize the selection bias, we obtained data from these three different levels of health facilities. The data collected were used for research purposes only. All study participants gave informed consent and were de-identified for the analysis. Subjects taking any medications for treating hypertension, diabetes and hyperlipidemia were excluded. All methods and procedures were approved by the institutional review board of MJ Health Screening Center.

On the day of the study, blood was drawn for biochemical analysis. A standard physical examination was performed, which included measuring systolic blood pressure (SBP), diastolic blood pressure (DBP) and BMI (kg/m^2). At the same time, a questionnaire was given to collect their medical history.

FPG was analyzed through a glucose oxidase method (YSI 203 glucose analyzer, Yellow Springs Instruments, Yellow Springs, USA). Each participant was asked to fast for 10 hours before blood samples were taken from the antecubital vein for various biochemical analyses. Plasma was separated from blood within one hour by centrifugation, and FPG and lipid profiles were measured. Serum levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) concentrations were determined using an enzymatic cholesterol assay after dextran sulfate precipitation. Using the dry, multilayer analytical slide method with the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Tokyo, Japan), total cholesterol and triglycerides (TG) were measured.

The equations used for calculating IR, FPIS, SPIS and GE are listed below. Every unit is described in international units. To test the reliability and validity of our equations, 30% of the participants were used for external validation. When conducting these studies, since nearly 70% of the participants took part in the process of the construction of the equations, the latter's reliability was secured.

1. IR: The IR was estimated by the insulin suppression test for 327 participants. The r value between the obtained and calculated GE was 0.581 (P <0.001). IR was calculated as previously described:
   IR = log (1.439 + 0.018 X sex - 0.003 X age + 0.029 X BMI - 0.001 X SBP + 0.006 X DBP + 0.049 X TG - 0.046 X HDLC - 0.0116 X FPG) X 10 $^{3.333}$ [13]
2. FPIS: The FPIS was measured from the intravenous glucose tolerance test by frequent sampling for 186 participants. The r value between the measured and calculated GE was 0.671 (P <0.000). FPIS was calculated using the following equation:
   FPIS = $10^{(1.477 - 0.119 \text{ X FPG} + 0.079 \text{ X BMI} - 0.523 \text{ X HDLC})}$ [14]
3. SPIS: The SPIS was measured by a modified glucose infusion test with a low dose for 82 participants. The r value between the measured and calculated GE was 0.65 (P = 0.002). SPIS was

Table 1: Demographic and diabetes factor data of men and women

Biochemistry and diabetes factors	Men	Women	*P*-value
Number of patients	28	21	
Body mass index (kg/m^2)	26.436±0.320	26.375±0.341	0.523
Systolic blood pressure (mmHg)	124.036±18.502	123.810±22.297	0.969
Diastolic blood pressure (mmHg)	80.000±11.261	76.048±11.944	0.242
Fasting plasma glucose (mg/dl)	101.643±13.436	105.048±24.365	0.568
HDL-C (mg/dl)	40.429±15.938	44.143±11.943	0.375
LDL-C (mg/dl)	119.786±47.409	144.476±42.792	0.066
Triglyceride (mmol/dl)	2.034±1.628	1.556±0.825	0.224
GE (10-2 ·dL ·min-1 ·kg-1)	0.016±0.002	0.017±0.002	0.486
IR (10-4 ·min-1 ·pmol-1 ·L-1)	3.716±0.019	3.706±0.012	0.062
Log_FPIS (μU/min)	2.360±0.185	2.310±0.171	0.353
Log_SPIS (pmol/mmol)	-0.983±0.051	-0.973±0.029	0.486

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Log FPIS: log transformation of first phase insulin secretion; Log SPIS: log transformation of second phase insulin secretion; IR: insulin resistance; GE: glucose effectiveness.
Data shown are mean ± SD

calculated using the following equation:
SPIS = $10^{(-2.4 - 0.088 \text{ X FPG} + 0.072 \text{ X BMI})}$ [15]

4. GE: The GE was measured by constant sampled intravenous glucose tolerance test for 227 participants. The r value between the measured and calculated GE was 0.43 (P = 0.001). GE was calculated using the following equation:
GE = (29.196 - 0.103 X age - 2.722 X TG - 0.592 X FPG) X 10^{-3} [16]

Statistical analysis

All statistical analyses were performed using SPSS 19.0 (IBM Inc., Armonk, New York). Data are presented as mean ± standard deviation. All data were tested for normal distribution with the Kolmogorov–Smirnov test and for homogeneity of variances with Levene's test. The data of FPIS and SPIS were log transformed before analysis due to the fact that they were not normally distributed. The t-test was performed to evaluate the differences between normal and diabetic groups.

Simple correlation was applied to evaluate the relationships of two independent variables such as FPG and DFs. The r values indicate how highly correlated two parameters are. The higher the r value, the higher the correlation. We did not adjust potential confounding factors such as age, BMI or gender. This is because these factors were already accounted for in the equations.

RESULTS

Table 1 presents the results of the demographic characteristics and biochemical data. Overall, there were no differences between men and women.

The results of the correlation analyses between FPG and the four DFs are shown in Table 2. In men, SPIS was negatively correlated to FPG, whereas IR had a positive association to FPG. Results in women are different from those in men. Both SPIS and GE are negatively associated with FPG. In addition, the originally significant association between FPG and IR in men is non-significant in women.

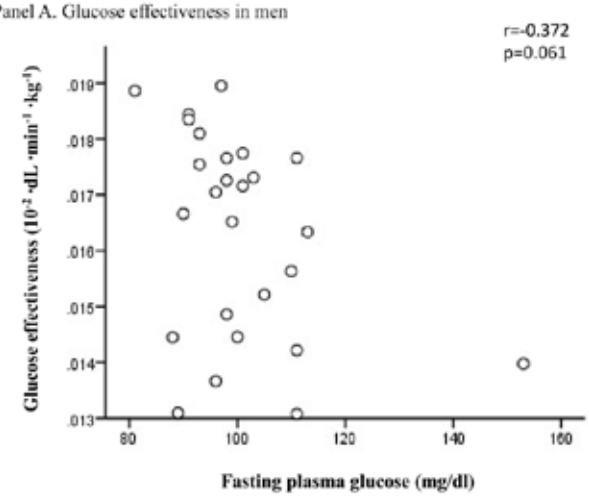
Figure 1 (Fig 1A: GE in men, Fig 1B: GE in women, Fig 1C: IR in men, Fig 1D: IR in women, Fig 1E: FPIS in men, Fig 1G: FPIG in women, Fig 1G: SPIS in men, Fig 1H: SPIS in women) is the graphic representation of the results from Table 2. The r and p values of each relationship are shown on the right upper corner of the figures.

Table 2: Results of simple correlation between fasting plasma glucose and the four diabetes factors

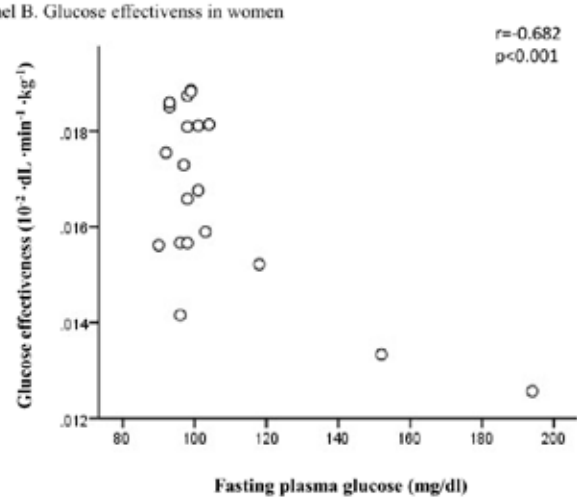
The diabetes factors	r	*P*
Men		
Log transformation of first phase insulin secretion	0.337	0.085
Log transformation of second phase insulin secretion	-0.895	< 0.001
Insulin resistance	0.479	0.012
Glucose effectiveness	-0.372	0.061
Women		
Log transformation of first phase insulin secretion	-0.262	0.279
Log transformation of second phase insulin secretion	-0.538	0.021
Insulin resistance	0.239	0.340
Glucose effectiveness	-0.682	< 0.001

Finally, the relative tightness of the significant slopes between FPG and DFs are shown in Figure 2. (Fig 2A: Comparison of the significant relationships (IR and SPIS) in men, Fig 2B: Comparison of the significant relationships (GE and SPIS) in women). This information shows how these factors contribute to glucose dysregulation. The higher r value implies a greater influence of that particular DF. In women, FPG and GE have the highest r values followed by SPIS. However, in men, the order is SPIS then IR.

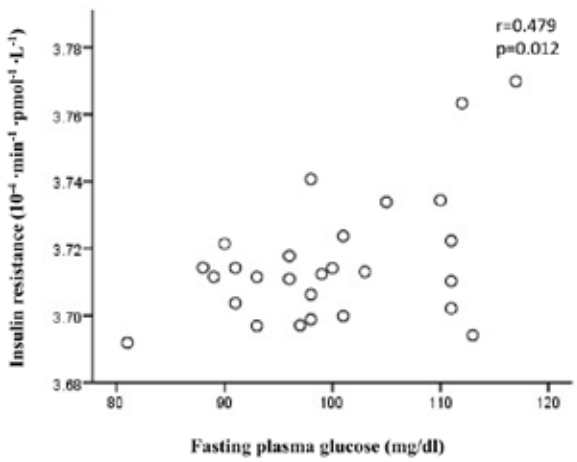
Panel A. Glucose effectiveness in men



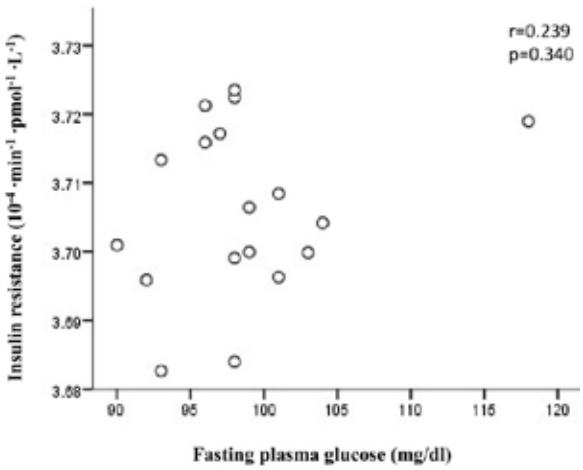
Panel B. Glucose effectivenss in women



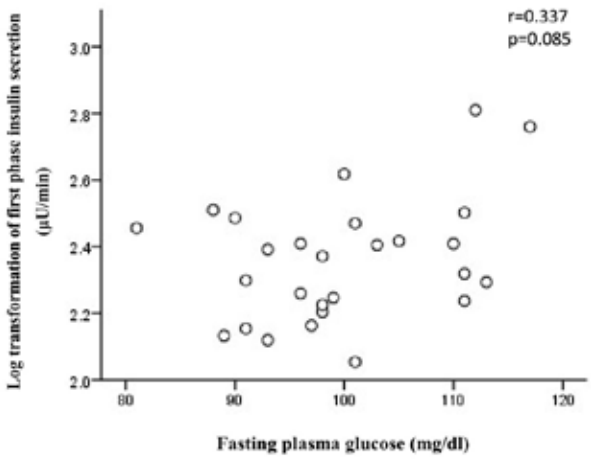
Panel C. Insulin resistance in men



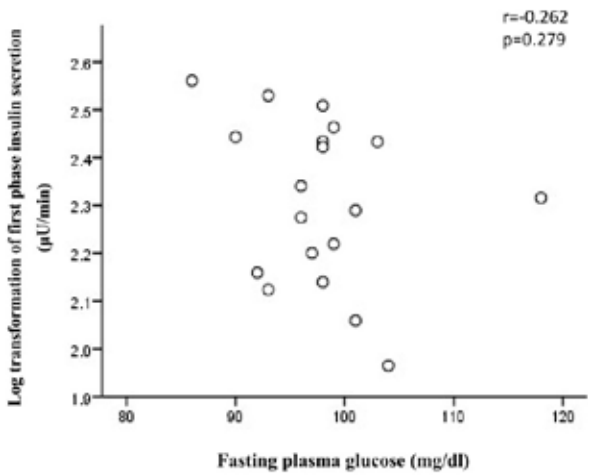
Panel D. Insulin resistance in women



Panel E. First phase insulin secretion in men



Panel F. First phase insulin secretion in women



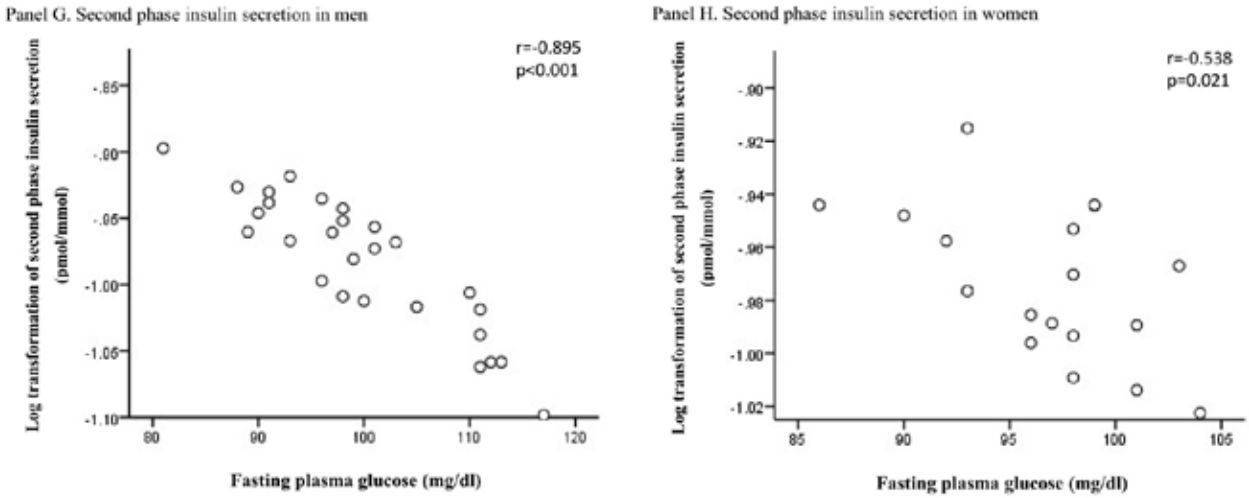


Fig 1: The scatter plots of fasting plasma glucose and the four diabetes factors; *i.e.*, glucose effectiveness (panel A for men, B for women), insulin resistance (panel C for men, D for women), first phase insulin secretion (panel E for men, F for women) and second phase insulin secretion (panel G for men and H for women). The r and p values are shown on the upper corner.

DISCUSSION

In the present study, we controlled for age (50 years old) and BMI (26 kg/m^2) to observe the 'net' relationships between FPG and the four DFs. Generally speaking, our findings are not surprising, *i.e.*, FPG is negatively related to both GE and SPIS, but positively related to IR. However, these relationships are mildly different in their significance between men and women. The only non-significant relationship comes from the correlation between FPG and FPIS. Finally, in men, the highest r value is noted between FPG and SPIS, followed by IR. As for women, GE and FPG have the highest r values followed by SPIS.

The effect of adiposity on DFs

It should be noted that, in the present study, we enrolled overweight subjects (BMI = 26 kg/m^2). Thus, to interpret our results, the effects of adiposity on the DFs were considered. It is well-known that obesity could increase IR. Moreover, subjects with higher BMI would have more insulin secretion compared to leaner subjects[10,16-18]. These effects could be further validated if after obesity reduction, the IR is also improved[9]**.** As for the GE, there have been no studies focusing on this area. However, Ferguson *et al* showed that GE is related to inflammation[19]. At the same time, inflammation is strongly related to increased adipose tissue. Increased free fatty acids and triglycerides could induce oxidative stress and trigger the activation of inflammatory pathways[20]. Thus, it could be concluded that adiposity is indirectly related to decreased GE through the effects of inflammation.

The relationship between FPG and IR

In the present study, we found that FPG was positively correlated to IR but only more significantly in men. The relationship between FPG and IR has long been recognized. As early as 1979, Holman *et al* showed that the basal plasma glucose level is determined by a simple feed-back loop between IR and insulin secretion in patients with maturity onset of diabetes[21]. Later on, based on this original observation, their group developed the important equation known as the homeostasis model assessment (HOMA) for IR and β–cell function. This equation has been widely used in many important clinical and epidemiological studies. Interestingly, to our knowledge, there is only one study directly focusing on the relationship between FPG and IR which was done by our group. By using the insulin suppression test, a relatively more accurate method to quantify IR, our results showed that the r value is 0.106 between FPG and IR[22]. It is interesting to note that the r values are different in these studies. This discrepancy can be easily explained by the equation of HOMA-insulin resistance (HOMA-insulin resistance = FPG/(FPI X 22.5)). In this equation, it can be clearly seen that although IR does relate to FPG, their relationship is also affected by a third factor, the fasting plasma insulin (FPI). Thus, under different insulin levels, the r values are also different.

Relationship between FPG, FPIS and SPIS

To the best of our knowledge, very few studies focused on the relationships between FPG and insulin secretion, both FPIS and SPIS. Godsland *et al* used an

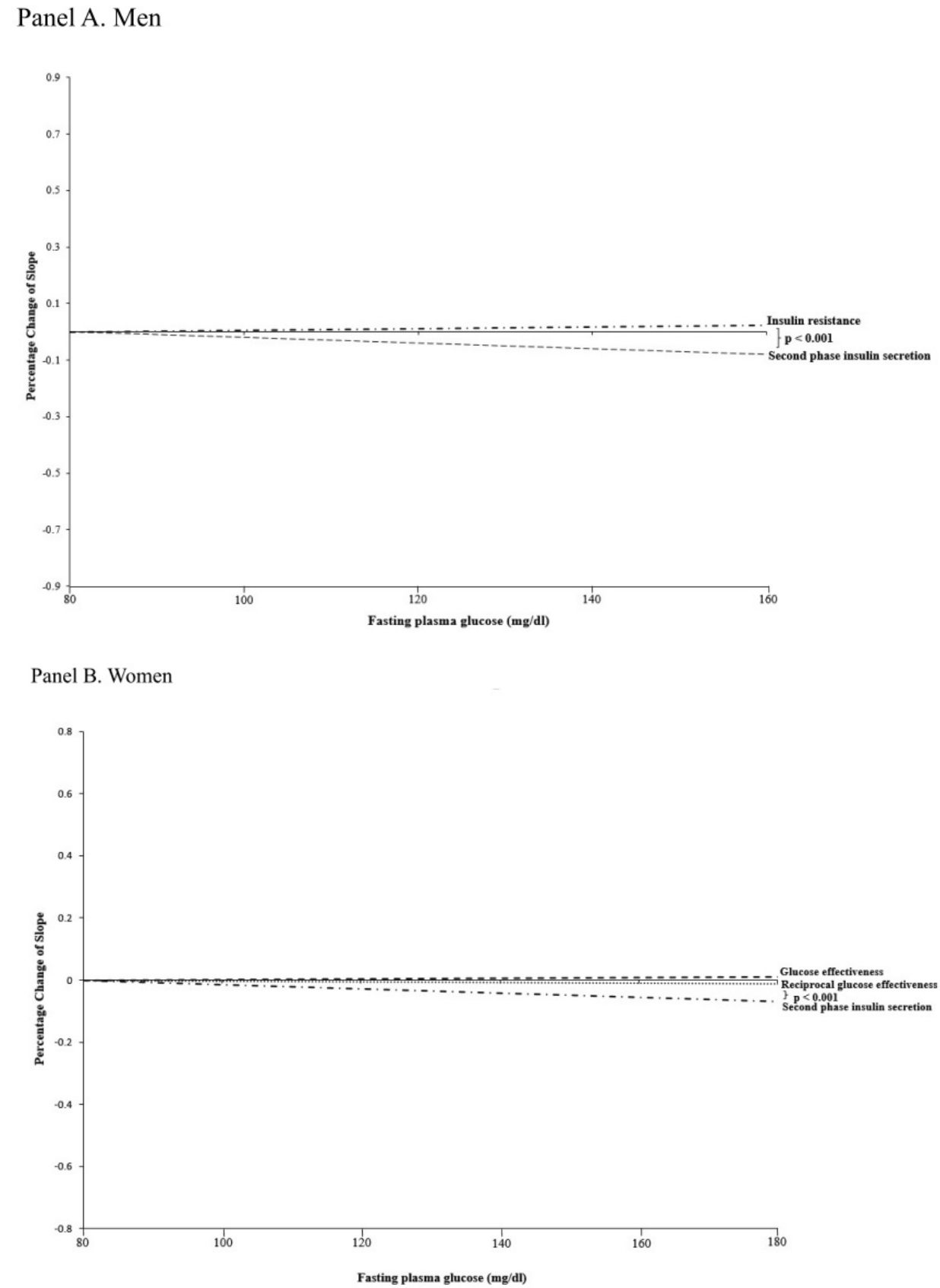


Fig 2: The graphic comparison of the significant relationships between fasting plasma glucose and diabetes factors. The results of men are shown in panel A and women shown in panel B.

intravenous glucose tolerance test to quantify both phases of insulin secretion in 553 men without diabetes[23]. Their results showed that the FPG is negatively related to FPIS. The r values ranged from -0.0048 to -0.457, according to the different methods they used. As for the SPIS, there were no significant correlations. To explain the different associations between FPIS and SPIS, the authors specifically pointed out that this was due to the method used to measure SPIS. The glucose injected during the intravenous glucose tolerance test is mainly eliminated by the FPIS rather than the SPIS. Thus, underestimation of the SPIS was expected. Comparing their work to the present study, it is interesting to note that both age and BMI were similar to the present study. However, we did not find a significant correlation in FPIS. On the contrary, significant negative associations are noted for both men and women (r = -0.895 and -0.538, respectively). There are several possibilities to explain this discrepancy. First, ethnic difference might be the cause, since deterioration of beta-cell function is known to be more important than IR in Asians[24]. Second, both studies used different methods. Third, it should be stressed again that we only enrolled subjects of the same age group and BMI. Thus, we did not use any statistical methods to adjust the potential confounding effects derived from these two factors.

The relationship between FPG and GE

GE is the ability of glucose to increase its own uptake and suppress its own production. Less attention has been put on its role in the development of diabetes. This is partly due to the fact that the test to measure GE is time and labor intensive[25]. Interestingly, in the aforementioned study by Godsland *et al*, they also evaluated the relationship between FPG and GE. Their results showed that GE was significantly and negatively correlated to GE (r = -0.226), and their findings are in line with the present study[23]. Based on the evidence provided, the role of GE should be more important than previously considered for the development of diabetes.

Gender difference in the relationships between FPG, IR and GE

In our study, there are gender differences in IR and GE. For IR, this phenomenon is well-known since men and women have different body compositions such as fat distribution. This characteristic further determines the IR due to the fact that adipose tissue is now considered an endocrine organ which secretes many cytokines. These 'toxic cytokines' will induce IR. However, there is no related study to explore whether GE is different in men and women. Still, it could be hypothesized that obesity relates to inflammation, and inflammation could further affect GE[19]. Thus, it is reasonable to postulate that a difference of GE does exist between men and women.

Limitations

First, one may challenge the accuracy of our equations. However, as stated in the methods, they were derived from a large cohort and were externally validated. Thus, to measure these four DFs together in one person would be difficult without these equations. Second, the n number of this study is relatively small. The necessary collateral drawback was caused by the fact that we wanted to prioritize enrolling subjects with exactly the same age and BMI. Finally, the present study was done in a single Han race, thus, extrapolation to other ethnic groups should be exercised with caution.

CONCLUSION

In conclusion, in the most high risk group for diabetic development (age = 50 years old, BMI = 26 kg/m^2), FPG was positively correlated to IR in men and negatively correlated to GE in women. At the same time, FPG was negatively correlated to SPIS in both genders. However, there was no significant association between FPG and FPIS. The highest correlation with FPG was SPIS in men and GE in women.

ACKNOWLEDGMENT

There is no conflict of interest in the present study to any other organizations.

Author contributions:

Dee Pei: study conception and design; Chung-Ze Wu: acquisition of data; Chang-Hsun Hsieh: analysis and interpretation of data; Chin-Yu Chen: drafting of manuscript; Yao-Jen Liang: critical revision

Funding resources: This study was funded by the Cardinal Tien Hospital grant No. CTH105A-210 and CTH-104-1-2A13.

REFERENCES

1. Global report on diabetes https://www.who.int/diabetes/global-report/en/ (Accessed date: 06-Apr-2016)
2. Li HY, Jiang YD, Chang CH, Chung CH, Lin BJ, Chuang LM. Mortality trends in patients with diabetes in Taiwan: a nationwide survey in 2000-2009. J Formos Med Assoc 2012; 111(11):645-650.
3. Wilmot EG, Davies MJ, Yates T, Benhalima K, Lawrence IG, Khunti K. Type 2 diabetes in younger adults: the emerging UK epidemic. Postgrad Med J 2010; 86(1022):711-718.

4. Polonsky KS, Sturis J, Bell GI. Seminars in Medicine of the Beth Israel Hospital, Boston. Non-insulin-dependent diabetes mellitus - a genetically programmed failure of the beta cell to compensate for insulin resistance. N Engl J Med 1996; 334(12):777-783.
5. Caumo A, Luzi L. First-phase insulin secretion: does it exist in real life? Considerations on shape and function. Am J Physiol Endocrinol Metab 2004; 287(3):E371-E385.
6. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979; 237(3):E214-E223.
7. Lorenzo C, Wagenknecht LE, Rewers MJ, Karter AJ, Bergman RN, Hanley AJG, *et al*. Disposition index, glucose effectiveness, and conversion to type 2 diabetes: the Insulin Resistance Atherosclerosis Study (IRAS). Diabetes Care 2010; 33(9):2098-2103.
8. American Diabetes association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33(Suppl 1):S62-S69.
9. Bloomgarden ZT. Insulin resistance: current concepts. Clin Ther 1998; 20(2):216-231; discussion 215.
10. Chiu KC, Cohan P, Lee NP, Chuang LM. Insulin sensitivity differs among ethnic groups with a compensatory response in beta-cell function. Diabetes Care 2000; 23(9):1353-1358.
11. Lopez X, Bouche C, Tatro E, Goldfine AB. Family history of diabetes impacts on interactions between minimal model estimates of insulin sensitivity and glucose effectiveness. Diabetes Obes Metab 2009; 11(2):123-130.
12. Akehi Y, Oketa A, Mitsuyoshi Y, Yoshida R, Ohkubo K, Yamashita T, *et al*. [The effects of age on insulin sensitivity and insulin secretion in Japanese subjects with normal glucose tolerance]. Rinsho Byori 2007; 55(10):901-905. Article in Japanese
13. Wu CZ, Lin JD, Hsia TL, Hsu CH, Hsieh CH, Chang JB, *et al*. Accurate method to estimate insulin resistance from multiple regression models using data of metabolic syndrome and oral glucose tolerance test. J Diabetes Investig 2014; 5(3):290-296.
14. Lin JD, Hsu CH, Liang YJ, Lian WC, Hsieh CH, Wu CZ, *et al*. The estimation of first-phase insulin secretion by using components of the metabolic syndrome in a chinese population. Int J Endocrinol 2015; 2015:675245.
15. Lin Y-T, Wu CZ, Lian WC, *et al*. Measuring second phase of insulin secretion by components of metabolic syndrome. Int J Diabetes Clin Diagn 2015; 2(1):113-118.
16. Chen YL, Lee SF, Pei C, Pei D, Lee CH, He CT, *et al*. Predicting glucose effectiveness in Chinese participants using routine measurements. Metab Syndr Relat Disord 2016; 14(8):386-390.
17. Chiu KC, Chuang LM, Yoon C. Comparison of measured and estimated indices of insulin sensitivity and beta cell function: impact of ethnicity on insulin sensitivity and beta cell function in glucose-tolerant and normotensive subjects. J Clin Endocrinol Metab 2001; 86(4):1620-1625.
18. Lin JD, Chang JB, Wu CZ, Pei D, Hsieh CH, Hsieh AT, *et al*. Identification of insulin resistance in subjects with normal glucose tolerance. Ann Acad Med Singapore 2014; 43(2):113-119.
19. Ferguson JF, Shah RY, Shah R, Mehta NN, Rickels MR, Reilly MP. Activation of innate immunity modulates insulin sensitivity, glucose effectiveness and pancreatic beta-cell function in both African ancestry and European ancestry healthy humans. Metabolism 2015; 64(4):513-520.
20. Lohse R, Schubert J. [Treatment of advanced metastasizing prostatic carcinoma]. Dtsch Gesundheitsw 1972; 27(26):1238-1241.
21. Holman RR, Turner RC. Maintenance of basal plasma glucose and insulin concentrations in maturity-onset diabetes. Diabetes 1979; 28(3):227-230.
22. Hsieh CH, Hung YJ, Wu CZ, Lee SS, Lee CH, Chen CY, *et al*. Insulin resistance & secretion in subjects with normal fasting plasma glucose. Indian J Med Res 2006; 124(5):527-534.
23. Godsland IF, Jeffs JAR, Johnston DG. Loss of beta cell function as fasting glucose increases in the non-diabetic range. Diabetologia 2004; 47(7):1157-1166.
24. Fukushima M, Usami M, Ikeda M, Nakai Y, Taniguchi A, Matsuura T, *et al*. Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. Metabolism 2004; 53(7):831-835.
25. Basu A, Rizza RA. Glucose effectiveness: measurement in diabetic and nondiabetic humans. Exp Clin Endocrinol Diabetes 2001; 109 Suppl 2:S157-165.

Original Article

An evaluation of factors that are predictive of the success of antibiotic treatment in tubo-ovarian abscess cases

Sunullah Soysal, Didem Soysal, Dilan Cetin, Tanju Pekin
Department of Obstetrics and Gynecology, Marmara University, Istanbul, Turkey

Kuwait Medical Journal 2022; 54 (1): 60 - 65

ABSTRACT

Objective: To assess which factors were predictive of the success of antibiotics in treating tubo-ovarian abscess (TOA) cases
Design: Retrospective clinical research
Setting: Tertiary university hospital in Istanbul, Turkey
Subjects: One hundred and eight patients aged between 27-70 diagnosed with TOA between January 2014 and August 2018
Interventions: The first group comprised patients who had successfully been treated with antibiotics (Group A) and the second group comprised patients who had received antibiotics but who underwent surgery for TOA due to antibiotic treatment failure (Group B).
Main outcome measures: A comparison was conducted of the pre- and post-treatment patient parameters.
Results: The hemoglobin levels were higher in the group in whom antibiotic treatment was successful (Group A; 11.1±1.4 g/dL) compared to the group who had to undergo surgery due to unsuccessful antibiotic treatment (Group B; 10.5±1.7 g/dL). The median TOA size was 5.5 cm in Group A (successful antibiotic treatment) and 6.4 cm in Group B (surgery in response to unsuccessful antibiotic treatment) when assessed using ultrasound. The median TOA size was 5.0 cm for Group A and 6.2 cm for Group B using computed tomography (CT). The median duration of hospitalization was 8 and 10 days for groups A and B, respectively. The cut-off levels that were predictive of the successful antibiotic treatment of TOAs were 6.7 cm using ultrasound and 6.6 cm using CT.
Conclusion: TOA size was a good indicator of the likelihood of successful antibiotic treatment.

KEY WORDS: adnexitis, antibiotics, treatment failure

INTRODUCTION

Pelvic inflammatory disease (PID) is a genital infection that covers a large spectrum of conditions, ranging from endometritis to tubo-ovarian abscess (TOA) formation[1].

PID is seen in 10% of reproductive women[2]. Although *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are usually implicated in PID, bacterial vaginosis-associated pathogens, including anaerobes, *Gardnerella vaginalis, Haemophilus influenzae,* enteric Gram-negative rods and *Streptococcus agalactiae* are also associated with it[3]. Younger age of coitarche, multiple sexual partners, nonuse of barrier contraception, and infection with chlamydia or gonorrhea are the risk factors that have been identified for development of PID[4]. Although there is a concern about whether intrauterine device insertion or use increases the risk of PID, evidence shows that the risk of PID is low among intrauterine device users[5,6].

Infertility, ectopic pregnancy, chronic pelvic pain and recurrent PID are long term complications of PID, which can be decreased with prompt diagnosis and treatment. Delay in diagnosis and treatment of PID can lead to the postinflammatory sequelae of the upper genital tract. Therefore, women at risk for sexually transmitted diseases who are experiencing pelvic or lower abdominal pain with cervical motion tenderness, uterine tenderness or adnexal tenderness should be empirically treated for PID after exclusion of other illnesses[7].

Address correspondence to:
Sunullah Soysal, Zümrütevler mahallesi handegül sok kiptaş adatepe sitesi A4 blok daire 73 maltepe, İstanbul, Turkey. Tel: +90 505 7959557; E-mail: drsunullah@yahoo.com

TOA formation is a complication of PID and is seen in 10-15% of cases[8]. TOAs are generally managed using antibiotics and drainage. Successful treatment with antibiotics, without the need for drainage, is achieved in 70% of cases[9-12]. The current study objective was to assess which factors were predictive of the success of antibiotics in treating TOAs.

SUBJECTS AND METHODS

A retrospective study was performed to determine the risk factors for TOA and identify which were predictive of antibiotic efficacy in treating patients with TOA who presented at a single tertiary university hospital in Istanbul, Turkey. Approval to conduct the study was granted by the local ethics committee of the hospital. The medical records of 108 patients (aged 27-70) diagnosed with TOA between January 2014 and August 2018 were reviewed. TOA diagnosis was made according to the classic PID findings of abdominopelvic pain, cervical and adnexal sensitivity to a bimanual examination, along with one or more minor criteria, such as fever, leukocytosis, a high erythrocyte sedimentation rate and the presence of an adnexal lesion (*i.e.*, a complex adnexal mass without peristalsis and with thick, well-formed walls) using ultrasound. Routine computed tomography (CT) imaging was performed to exclude other adnexal mass etiologies. Patients who underwent both the initial ultrasonography and CT were included in the study.

Exclusion criteria were uncertainty of diagnosis, the absence of CT, a co-existing malignancy or pregnancy, patients who underwent surgery on admission, and those who refused antibiotic treatment. Data of interest obtained from the records included the patient demographics (age, gravidity and parity), medical history (*e.g.*, hypertension, diabetes mellitus and surgery), current symptoms (vaginal discharge, abdominal pain and fever), site of the abscess (left, right or bilateral), and maximum abscess diameter using ultrasound and CT.

White blood cell (WBC) count, platelet count, hemoglobin levels, neutrophil to lymphocyte ratio (NLR), red blood cell distribution (RDW), serum C-reactive protein (CRP) and the procalcitonin levels of patients were recorded on admission to hospital and at discharge. Duration of hospital stay, change in the size of abscess after antibiotic use, urine test results, blood tests results, and the results of the cervicovaginal and abscess cultures (only for the surgically treated patients) were also obtained.

All of the patients received 900 mg of intravenous clindamycin every eight hours with an intravenous loading dose (2 mg/kg) of gentamicin, followed by a maintenance dose (1.5 mg/kg) of gentamicin every eight hours as the antibiotic treatment, according to the Centers for Disease Control and Prevention guidelines[1].

One hundred and eight patient records were reviewed. Twelve, two and four patients were excluded because they had not undergone CT, had a co-existing malignancy, and because of uncertainty of diagnosis, respectively. One patient refused surgical treatment and was also excluded from the study. The patients were grouped according to treatment modality. The first group comprised patients who had successfully been treated with antibiotics (Group A). The second group comprised patients who had received antibiotics but who underwent surgery for TOA due to antibiotic treatment failure (Group B). Antibiotic failure was defined as the lack of a decrease in abscess size within 48-72 hours of the treatment. The surgery was performed using laparoscopy or laparotomy. Hysterectomy and bilateral salpingo-oophorectomy were carried out in postmenopausal patients. The type of surgery was adjusted from abscess drainage to bilateral salpingectomy depending on whether or not patients of reproductive age wished to bear children.

Statistical analysis

The descriptive statistics were expressed as the mean ± standard deviation or median and interquartile range. The distribution of the variables was analyzed using histogram graphics and the Kolmogorov-Smirnov test. The comparisons of the quantitative values were carried out using the Independent samples T test for normally distributed data and Mann-Whitney U test for non-normally distributed data. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off levels for successful antibiotic treatment. A *P*-value of <0.05 was considered to be statistically significant. All the statistical analyses were carried out on a personal computer with SPSS, version 15.0 analysis software (IBM Corporation, New York, USA).

RESULTS

Eighty-nine patients were diagnosed with TOA during the study period. Of these, 37 (42%) were successfully treated with antibiotics, while the remainder (n=52, 58%) required surgery after the failure of antibiotic treatment. The difference in median age, gravidity status, and parity status of the patients was similar between the two groups (Table 1). Twenty-nine patients in Group A and 39 patients in Group B were premenopausal. Pelvic pain was the most common symptom in both groups (Group A: 87% vs. Group B: 81%). Only 5% of the patients in Group A and 12% of the patients in Group B were febrile. The

Table 1: Age, gravidity and parity status of the groups

Age and parity	Group A Median (IQR)	Group B Median (IQR)	P-value
Age	38.4±9.5	40.6±8.8	0.265[a]
Gravida	2.0 (1.0-3.0)	3.0 (1.0-4.0)	0.369[b]
Parity	2,0 (1.0-3.0)	2.0 (1.0-3.0)	0.676[b]
Abortion	0.0 (0.0-0.0)	0.0 (0.0-0.5)	0.333[b]
Cesarean section	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.586[b]

[a] t test in independent groups, [b] Mann Whitney u test

differences in symptoms, menopausal state and the medical history of the patients (data not shown) were without statistical significance.

The difference in the localization of abscess formation and bilateral involvement between the treatment groups was not statistically significant. Blood culture positivity was not detected in either group following analysis. Genital cultures were obtained (Group A: n=21, 57%; Group B: n=27, 52%) (P = >0.05). Two of the cultures were positive (*G. vaginalis* [n=1], *Staphylococcus aureus* [n=1]) in Group A, and five of them were positive in Group B (*S. agalactiae* [n=2], *Enterococcus* spp. [n=2], *G. vaginalis* [n=1]). The difference in the positive genital cultures was not significant between the two groups. Abscess aspiration cultures were obtained from 25 patients (48%) in Group B. *Bacteroides fragilis* (32%) was the most isolated microorganism.

The blood test results of the patients were evaluated on the first day of hospitalization. Hemoglobin levels were higher in the group in whom antibiotic treatment was successful (Group A; 11.1±1.4 g/dL) compared to the group who had to undergo surgery due to unsuccessful antibiotic treatment (Group B; 10.5±1.7 g/dL) (P < 0.05). The differences in WBC, platelet count, CRP and procalcitonin levels, RDW and NLR between the groups were without statistical significance (Table 2). The blood test results prior to discharge from the hospital were also evaluated. There was no significant difference in CRP, procalcitonin levels, RDW and WBC count between the groups. The hemoglobin levels were lower at discharge from hospital in Group

Table 2: Blood test results of two groups in the first day of hospitalization

Blood markers	Group A Median (IQR)	Group B Median (IQR)	P-value
CRP (mg/dL)	139.0 (101.0-179.0)	172.0 (96.0-257.0)	0.143[a]
N/L ratio	6.9 (4.6-10.4)	8.0 (5.0-14.6)	0.287[a]
Procalcitonin (ng/mL)	0.0 (0.0-0.0)	0.0 (0.0-0.3)	0.090[a]
RDW (g/dL)	14.6 (13.5-16.0)	14.8 (13.4-16.1)	0.977[a]
WBCx100 (µl/ml)	138.1±55.8	154.1±55.3	0.185[b]
HB (g/dL)	11.1±1.4	10.5±1.7	0.047[b]
Platelet x10^2	3322.4±995.8	3624.0±1314.2	0.243[b]

CRP: c-reactive protein; N/L: neutrophil/lymphocyte; RDW: red cell distribution width; WBC: white blood cell; HB: hemoglobin
[a] Mann whitney u test, b t test in independent groups

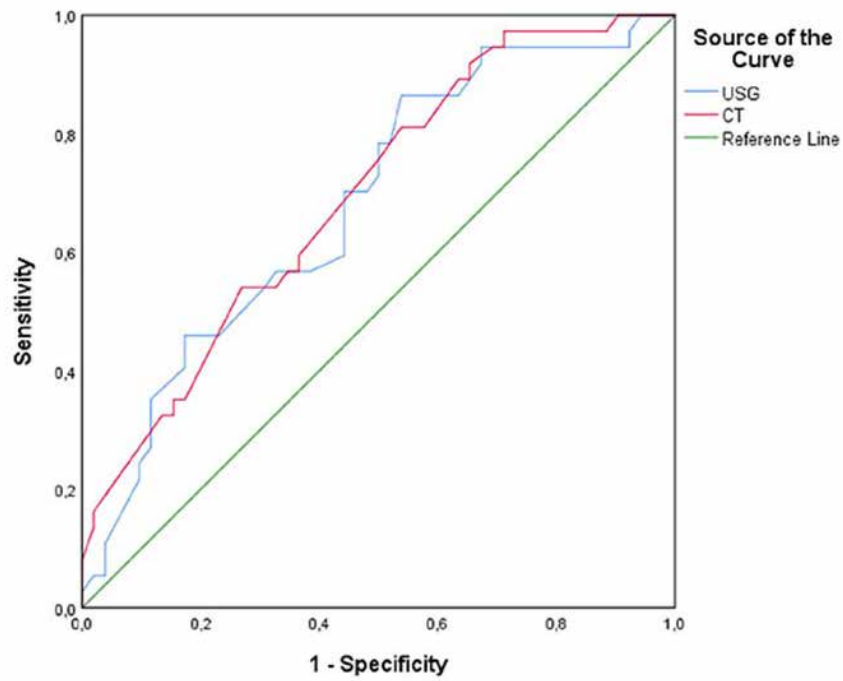


Fig. 1: ROC curve for cut off levels of the lesion in ultrasound and CT for prediction of treatment of tubaovarian abscess without surgery

B subjects (10.6±1.1 vs. 10.0±1.2 g/dL) compared to the Group A subjects (P <0.05). This finding is consistent with blood loss during surgery. Similarly, the NLR (2.0) and platelet count (3717.6±1048.8) was higher in Group B compared to Group A (respective figures of 3.2 and 4285.8±1275.0), which can be attributed to inflammatory changes due to surgical stress (P <0.05).

The groups were evaluated with respect to lesion size and duration of hospitalization. The median TOA size in the first day of hospitalization was 5.5 cm and 6.4 cm using ultrasound (P = 0.003), and 5.0 cm and 6.2 cm using CT for Groups A and B, respectively (P = 0.002). A more substantial decrease in the size of the lesion was observed within 48-72 hours of treatment in Group A compared to Group B (P <0.001). The median length of stay in hospital was 8 and 10 days for Groups A and B, respectively (P <0.001) (Table 3).

Table 3: Lesion size in ultrasound and CT and hospitalization periods

Lesion Size and Hospitalization Period	Group A Median (IQR)	Group B Median (IQR)	P-value*
Size in ultrasound (cm)	5.5 (4.3-6.4)	6.4 (5.5-8.1)	0.003
Size in CT	5.0 (4.0-6.0)	6.2 (5.0-9.0)	0.002
Decrease in size (cm)	2.0 (2.0-3.0)	0.0 (0.0-0.0)	<0.001
Hospitalization time (day)	8.0 (6.0-9.0)	10.0 (8.0-15.0)	<0.001

CT: computed tomography
*Mann whitney u test

ROC curve analysis was used to define the size of the lesions in relation to their ability to predict antibiotic failure based on the ultrasound and CT findings (Figure 1). The ROC curve indicated cut-off points of 6.7 cm (ultrasound) and 6.6 cm (CT) in predicting the successful antibiotic treatment of cases of TOA (Table 4).

DISCUSSION

TOA is a late complication of PID and contributes significantly to the admission to hospital of patients with genital infections[7]. TOA treatment usually comprises the administration of antibiotics and surgery. The current study's aim was to define factors that were predictive of the success of antibiotic treatment (*i.e.*, without the need for surgery).

The treatment modalities for TOA differ. Twenty-nine (25%) of the 119 patients evaluated in the study by Reed *et al* underwent surgery after antibiotic treatment[13]. A poor prognosis was attributed to 87 (80%) of the patients (who were managed surgically or discharged after 7 days of antibiotic therapy) in the study by Topçu *et al*, and 85 of them were treated with surgery[14]. Twenty-five percent of antibiotic-treated patients (n=61) required an additional intervention in the study by Farid *et al*[15]. The current study finding in this regard was that 59% of the TOA cases required surgical treatment.

TOA cases are usually associated with polymicrobial infection by anaerobic, aerobic and facultative organisms. *Escherichia coli, B. fragilis, Peptostreptococcus* spp., *Peptococcus* spp. and anaerobic *Streptococcus* are the most commonly isolated organisms in TOA patients[9,10]. In another Turkish study, the most commonly isolated microorganism was *E. coli*[14]. In our study, *B. fragilis* was the most frequently identified microorganism in abscess cultures.

There are conflicting results about the effect of age on the success of antibiotic treatment. It has been reported that older age is poorly prognostic of successful antibiotic treatment in TOA cases[16-18]. Elsewhere, an age-related difference was not found in relation to TOA prognosis[14,15,19]. In the current study, age was not predictive of antibiotic success.

Bilateral TOA lesions were found to be a predictor of antibiotic failure in TOA in previous studies[14,16,20]. In contrast, unilaterality of TOA was not shown to be a predictor of antibiotic success by Farid *et al*[15]. The location site and bilateral TOA involvement were not predictive of the success of antibiotic treatment in TOA in our study.

There are conflicting results on the use of inflammatory markers in TOA to predict antibiotic success. Increased WBC count has been demonstrated in patients who underwent surgery compared to those in whom antibiotic treatment was successful[14-16,20]. Conversely, a difference in WBC count was not observed between the groups treated with antibiotics and those treated with surgery in other studies[17,19]; supported by the current study finding.

Table 4: ROC curve analysis results for cut off levels for prediction of success in treating tubo-ovarian abscess with antibiotics

Imaging modality	Cut Off (cm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	%95 CI	
							Lower limit	Upper limit
Ultrasound	6.7	86.5	46.2	53.3	82.8	0.682	0.571	0.794
CT	6.6	81.1	46.2	51.7	77.4	0.695	0.586	0.803

ROC: receiver operating characteristic; CT: computed tomography; PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve; CI: confidence interval

CRP levels have also been evaluated in TOA. Although elevated CRP levels have been shown to be a poor prognostic factor for antibiotic treatment success elsewhere[14,16,19,20], a significant difference in CRP levels between Groups A and B was not seen in the present research.

TOA diameter has been demonstrated to be an important predictor of antibiotic treatment failure; specifically, a large TOA diameter was associated with the need for a surgical intervention[7,14,15,17,19,21]. A similar finding was observed in the current study.

Different cut-off levels have been proposed in various studies to predict antibiotic success. A diameter of 5.2 cm was identified as the cut-off point for antibiotic treatment success in a study that used multiple imaging (ultrasound, CT and magnetic resonance imaging)[15]. Elsewhere, this value was reported to be 6.5 cm[16,19]. In a different study, a diameter of 4.8 cm was shown to be a poor prognostic factor for TOA[14]. Cut-off values of 6.6 cm and 6.7 cm were ascertained in the current study using CT and ultrasound, respectively, to predict antibiotic success in TOA.

Other parameters, such as serum procalcitonin levels, NLR, RDW and platelet count were not predictive of the successful antibiotic treatment of TOA in the present research, a finding that is in conflict with that of a previous study[16].

The retrospective study design and absence of data related with the long term complications, like recurrence of the disease, tubal infertility and chronic pelvic pain were the major limitations in this study. Study strengths included the large sample size and the use of two imaging modalities to diagnose TOA.

CONCLUSION

A TOA diameter of ≤ 6.6 cm (using CT) and 6.7 cm (using ultrasound) were predictive of the successful use of antibiotic treatment in the current study. Other parameters, such as age, CRP, WBC, procalcitonin levels, platelet count RDW, and NLR did not effectively predict the successful treatment of TOA with antibiotics.

ACKNOWLEDGMENT

We thank Abdullah Sarioz for his support in performing data and statistical analysis of the patients.

Author contributions: All authors contributed to the design of the study, data collection, statistical analysis and final version of the paper submitted.

Disclosure statement: The authors declare no conflicts of interest.

Funding sources: The authors have no funding to declare.

REFERENCES

1. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recommendations and reports: Morbidity and mortality weekly report. Recommendations and Reports 2015; 64(RR3):1-137.
2. Newkirk GR. Pelvic inflammatory disease: a contemporary approach. Am Fam Physician 1996; 53(4):1127-1135.
3. Ness RB, Kip KE, Hillier SL, Soper DE, Stamm CA, Sweet RL, *et al*. A cluster analysis of bacterial vaginosis–associated microflora and pelvic inflammatory disease. Am J Epidemiol 2005; 162(6):585-590.
4. Jossens MR, Eskenazi B, Schachter J, Sweet RL. Risk factors for pelvic inflammatory disease: a case control study. Sex Transm Dis 1996; 23(3):239-247.
5. Mohllajee AP, Curtis KM, Peterson HB. Does insertion and use of an intrauterine device increase the risk of pelvic inflammatory disease among women with sexually transmitted infection? A systematic review. Contraception 2006; 73(2):145-153.
6. Grimes DA. Intrauterine device and upper-genital-tract infection. Lancet 2000; 356(9234):1013-1019.
7. Chappell CA, Wiesenfeld HC. Pathogenesis, diagnosis, and management of severe pelvic inflammatory disease and tuboovarian abscess. Clin Obstet Gynecol 2012; 55(4):893-903.
8. McNeeley SG, Hendrix SL, Mazzoni MM, Kmak DC, Ransom SB. Medically sound, cost-effective treatment for pelvic inflammatory disease and tuboovarian abscess. Am J Obstet Gynecol 1998; 178(6):1272-1278.
9. Wiesenfeld HC, Sweet RL. Progress in the management of tuboovarian abscesses. Clin Obstet Gynecol 1993; 36(2):433-444.
10. Landers DV, Sweet RL. Tubo-ovarian abscess: contemporary approach to management. Rev Infect Dis 1983; 5(5):876-884.
11. Ginsburg DS, Stern JL, Hamod KA, Genadry R, Spence MR. Tubo-ovarian abscess: a retrospective review. Am J Obstet Gynecol 1980; 138(7 Pt2):1055-1058.
12. Sweet RL, Schachter J, Landers DV, Ohm-Smith M, Robbie MO. Treatment of hospitalized patients with acute pelvic inflammatory disease: comparison of cefotetan plus doxycycline and cefoxitin plus doxycycline. Am J Obstet Gynecol 1988; 158(3 Pt 2):736-741.
13. Reed SD, Landers DV, Sweet RL. Antibiotic treatment of tuboovarian abscess: comparison of broad-spectrum β-lactam agents versus clindamycin-containing regimens. Am J Obstet Gynecol 1991; 164(6 Pt 1):1556-1562.
14. Topçu H, Kokanalı K, Güzel A, Tokmak A, Erkılınç S, Ümit C, *et al*. Risk factors for adverse clinical outcomes in patients with tubo-ovarian abscess. J Obstet Gynaecol 2015; 35(7):699-702.
15. Farid H, Lau TC, Karmon AE, Styer AK. Clinical characteristics associated with antibiotic treatment failure for tuboovarian abscesses. Infect Dis Obstet Gynecol 2016; 2016:5120293.

16. Inal ZO, Inal HA, Gorkem U. Experience of tubo-ovarian abscess: a retrospective clinical analysis of 318 patients in a single tertiary center in middle Turkey. Surg Infect (Larchmt) 2018; 19(1):54-60.
17. Uyar I, Gulhan I, Sipahi M, Cetin F, Hanhan HM, Ozeren M. Risk factors for surgery in patients with tuba-ovarian abscess. Archives of gynecology and obstetrics 2012; 286:973-975.
18. Hager WD, Eschenbach DA, Spence MR, Sweet RL. Criteria for diagnosis and grading of salpingitis. Obstet Gynecol 1983; 61(1):113-114.
19. Güngördük K, Guzel E, Asicioğlu O, Yildirim G, Ataser G, Ark C, *et al*. Experience of tubo-ovarian abscess in western Turkey. Int J Gynecol Obstet 2014; 124(1):45-50.
20. Fouks Y, Cohen A, Shapira U, Solomon N, Almog B, Levin I. Surgical intervention in patients with tubo-ovarian abscess: Clinical predictors and a simple risk score. J Minim Invasive Gynecol 2019; 26(3):535-543.
21. Sordia-Hernández LH, Serrano Castro LG, Sordia-Piñeyro MO, Morales Martinez A, Sepulveda Orozco MC, Guerrero-Gonzalez G. Comparative study of the clinical features of patients with a tubo-ovarian abscess and patients with severe pelvic inflammatory disease. Int J Gynecol Obstet 2016; 132:17-19.

Original Article

Comparison of single-port versus two-port thoracic sympathectomies

Hakan Keskin[1], Sirin Akdeniz[1], Cemal Kemaloglu[2], Emel Gunduz[3], Makbule Ergin[1], Abdullah Erdogan[1]
[1]Department of Thoracic Surgery, Akdeniz University Faculty of Medicine, Antalya, Turkey
[2]Department of Cardiovascular Surgery, Akdeniz University Faculty of Medicine, Antalya, Turkey
[3]Department of Anesthesiology, Akdeniz University Faculty of Medicine, Antalya, Turkey

Kuwait Medical Journal 2022; 54 (1): 66 - 71

ABSTRACT

Objective: To compare single-port and two-port video-assisted thoracoscopic sympathectomies for treatment of hyperhidrosis in terms of postoperative complications and patient satisfaction.
Design: Cross-sectional survey design with telephone interviews
Setting: Multispecialty tertiary care teaching hospital.
Subjects: Ninety-four patients with complaints of hyperhidrosis who underwent 166 thoracic sympathectomies with video-assisted thoracoscopic surgery between January 2009 and July 2017 were interviewed with a predetermined questionnaire. Other relevant data were extracted from patient files.
Interventions: Not applicable
Main Outcome Measures: Length of hospital stay, duration of operation, occurrence of pneumothorax, compensatory sweating, postoperative pain, postoperative tube thoracostomy and dissatisfaction related to surgical scars
Results: Fifty-three patients who underwent a total of 97 single port endoscopic thoracic sympathectomies (ETS) had a mean age of 23.1 years, whereas 41 patients who underwent a total of 69 two ETS had a mean age of 23.6 years. Mean duration of operation and mean hospital stay were 15.64 minutes and 1.84 days for single-port ETS, and 19.44 minutes and 1.76 days for two-port ETS. For single-port ETS, there was postoperative pneumothorax in 23 of 97 cases, 18 of which were treated with tube thoracostomy, and for two-port ETS, in 10 of 69 cases, nine of which were treated with tube thoracostomy. The majority of the pneumothoraces were in patients who were operated on towards the beginning of the study duration.
Conclusions: Provided that surgeons have adequate experience, single-port ETS is associated with similar rates of complications and better patient satisfaction, and thus, is preferable to two-port ETS.

KEY WORDS: hyperhidrosis, sympathectomy, video-assisted thoracic surgery

INTRODUCTION

Hyperhidrosis is a disease characterized by eccrine sweat glands secreting more sweat than is necessary for thermoregulation[1]. Its incidence is not well-established. One study reported that hyperhidrosis is seen in about 1-2.8% of the general population[2]. Although hyperhidrosis has no gender or age predilection, referrals for a complaint of excessive sweating are more common in young women. One of the major reasons for this is that hyperhidrosis alone can trigger self-consciousness and social anxiety.

Hyperhidrosis can be categorized as either primary or secondary. Secondary hyperhidrosis may be a disease process, like in hyperthyroidism, pheochromocytoma, tuberculosis, *etc*., or a side effect of drugs like acetaminophen, bethanechol, pilocarpine, *etc*. Primary hyperhidrosis has no identifiable etiology[3]. The presence of at least two of the following criteria is diagnostic for primary hyperhidrosis, assuming localized excessive sweating continues for at least six months and thorough investigation cannot reveal an underlying cause[4].

Address correspondence to:
Sirin Akdeniz, Department of Thoracic Surgery, Akdeniz University Faculty of Medicine, Dumlupınar Bulvari Akdeniz Universitesi Hastanesi, 07059, Antalya, Turkey. Tel: +90 5052708024; E-mail: sirinakdeniz@hotmail.com

1. Sweating is bilateral and symmetrical.
2. The frequency of episodes of excessive sweating is at least once a week.
3. Symptoms have a negative impact on daily life and social interactions.
4. The onset of symptoms is before 25 years of age.
5. Family history is positive.
6. There is no sweating during sleep.

Hyperhidrosis should be promptly treated to alleviate its effects on the social life of patients and also to prevent contact dermatitis and fungal and bacterial skin infections that it may cause. Medical treatment may be topical (aluminum chloride, aluminum chlorohydrate) or systemic (atropine, propantheline, glycopyrrolate). For secondary hyperhidrosis, the underlying cause should be treated first. Surgical treatment includes endoscopic thoracic sympathectomy and axillary subcutaneous curettage for axillary hyperhidrosis. For primary and secondary hyperhidrosis with inadequate clinical response to medical treatment, the most effective treatment is endoscopic thoracic sympathectomy (ETS). This procedure is also used in the treatment of reflex sympathetic dystrophy, upper extremity ischemia and Raynaud phenomenon.

SUBJECTS AND METHODS

In this study, data from files of 94 patients who underwent 166 ETS between January 2009 and July 2017 was retrospectively analyzed. All patients gave informed written consent to anonymous use of data from their medical files for publication purposes. Ethical approval for this study was obtained from Akdeniz University Medical Faculty Clinical Research Ethics Committee (approval ID: 20.12.2017/746). Patients' gender, age, presenting complaints, number of ports, levels of thoracic sympathetic ganglions cauterized, treatment results and any complications were noted. Long-term outcomes, *i.e.*, current level of satisfaction related to the surgery, dissatisfaction pertaining to surgical scars, postoperative pain and postoperative pattern of sweating were obtained by follow-up questionnaires that were carried out through telephone calls. The questionnaire is given in Table 1. All patients went through preoperative evaluation with blood chemistry, complete blood count, basic hemostatic screening, electrocardiography, chest x-ray and spirometry by a consulting anesthesiologist. All operations were done under general anesthesia with a double-lumen endotracheal tube in the posterolateral thoracotomy position. The first side to be operated was chosen ipsilateral to the non-dominant extremity of the patient and operation for the other side was planned at least one month after discharge. We avoided operating patients on both sides in the same session to reduce the rate of complications and for the patient to be clearly able to compare the effect of the surgery with the non-operated side on their body. All patients were operated by the same surgery and anesthesiology team comprising of consultants and residents. Duration of the operation was obtained from the patients' files, where the anesthesiologist records time of commencement of anesthesia, the beginning of the surgery as in the first incision, the end of the surgery as in the last suture and the patients' exit from the operating room. Duration of operation was the interval between the first incision to the last suture, and preoperative anesthesia care was not included. In single-port operations, the port was opened in the third intercostal space along the mid-axillary line, whereas in two-port operations, the ports were in the fifth and third intercostal spaces along mid-axillary and anterior axillary lines, respectively. Sympathetic ganglions were sequentially dissected and cut by cauterization starting from T2 and ending in T3 or T4 or T5. Sharp surgical instruments were not used in the thoracic cavity for ablation of sympathetic ganglia. Afterwards, residual intrathoracic air was drained with a 12F or 14F suction catheter through a port incision with the other end under a water seal, while the collapsed lung was expanded with positive pressure ventilation. Intrathoracic negative pressure was assumed to be achieved when there were no more bubbles under the water seal, after which the operation was ended. If the bubbles did not stop for a considerable amount of time, a 24F thoracic catheter was inserted through the port incision and sutured in place. All patients were transferred to the post-anesthesia care unit, where an anterior-posterior chest x-ray was taken in the postoperative first hour. If there was pneumothorax in the chest x-ray, a tube thoracostomy through a separate incision was performed before weaning and extubation.

Statistical analysis on acquired data was performed with IBM SPSS Statistics software version 23. Kolmogorov-Smirnov test was used to test for normality of the continuous variables. To define the sample, variables showing normal distribution were summarized as means and standard deviations; variables not showing normal distribution as median, minimum and maximum values; categorical variables as totals and percentages. When parametric test assumptions were met, the difference of the means of two independent groups was compared with Student's t-test; when they were not, the non-parametric alternative Mann-Whitney U test was used. For identifying statistical difference between categorical variables, the chi-square test was used. All statistical analyses were conducted with a confidence level of 95% (or significance level α=0.05)

Table 1: Telephone survey questionnaire for evaluation of long-term outcomes

Questions	Answers
After the surgery, did you have any excess sweating anywhere? If yes, how long did it last? Do you currently have such complaints?	Yes/No and open-ended
On a scale of 1 to 10, 1 being very bad and 10 being perfect, how would you rate the appearance of your surgical scars?	Scale of 1 to 10
Would you recommend this operation to an acquaintance with similar symptoms?	Yes/No
*Our records show that you have had the operation on only one side. Why is that?	Open-ended

*For patients who underwent the operation on only one side

RESULTS

Thirty-five of the patients were male and 59 were female. Mean age of the patients was 24.2 (range: 18-30) years for males and 22.9 (range: 18-31) years for females. Of the 53 patients who had sympathectomy with a single port (19 males and 34 females), 44 of them went through bilateral sympathectomy in two separate sessions, eight patients were operated only on the left side and one patient only on the right side, which makes a total of 97 operations with a single port. Of the 41 patients (M=16, F=25) who had sympathectomy with two ports, 28 of them were operated on both sides, whereas 12 patients only had left sympathectomy and one patient only had right sympathectomy, totaling 69 operations with two ports. Mean duration of operation, as measured from the first surgical incision until the last primary skin suture, was 17.1 (range: 11-38) minutes. There was no operative mortality. One patient was converted to axillary mini-thoracotomy (a 4-5 cm incision) for management of intercostal hemorrhage, after which a 28F drain was placed in the pleural space. Mean length of hospital stay was 1.81 (range: 1-6) days. There were three groups regarding the levels of the sympathetic ganglions cauterized, 115 of the operations were thoracic sympathectomies between and including levels T2 and T4, 17 operations between and including levels T2 and T5, and 12 operations on levels T2 and T3. Statistical analysis of these groups did not reach significant difference in the rates of pneumothorax, compensatory sweating and postoperative pain.

There was pneumothorax in the postoperative anterior-posterior chest x-ray after 15 (9%) operations, nine of which were treated with tube thoracostomy and the other six were treated with oxygen therapy alone. In 18 (10.8%) of the operations, failure to achieve intrathoracic negative pressure as evidenced by continuous bubbling led to placement of a 24F pleural drain intraoperatively. For a total of 27 operations that required a chest tube, it was removed after 1.9 days on average (range: 1-5). Though the rate of pneumothorax is higher for patients operated with a single port, the difference in the rates of pneumothorax is not significant between single-port or two-port operations (P=0.142). Furthermore, the percentage of pneumothorax complications treated with oxygen therapy alone among all cases of postoperative pneumothorax was higher for single-port operations, which probably reflects the tendency of the surgical team towards a more minimally-invasive approach to peri- and postoperative patient care. The majority of the operations with a complication of pneumothorax were patients operated during the earlier part of the study duration, in other words, when the surgical team had not yet fully developed their skills for thoracic sympathectomy with single-port videothoracoscopy, which could potentially lead to higher rate of pneumothorax complications.

Postoperatively, all patients were observed to have ceased perspiration in the hands ipsilateral to the operated side immediately after the operation. Compensatory sweating was seen in thirteen patients. These patients were followed up conservatively and were recommended an over-the-counter (non-prescription) antiperspirant cream containing aluminum hydroxychloride to use as necessary. For eleven of those, compensatory sweating was reduced to acceptable levels in three months even without the recommended cream. Two patients that had no reduction in their compensatory sweating were prescribed topical 19% aluminum hydroxychloride cream (licensed for topical treatment of hyperhidrosis by The Turkish Health Ministry) and recommended to apply it on clean and dry skin before bedtime. Patient compliance with recommendations largely improved symptom control and any side effects were minor skin irritation due to excessive dryness, which was controlled with adjustments of dosage.

The most common complaint in the early postoperative period was pain. Patients expressed having acute pain after 41.5% of 69 operations. Non-steroid anti-inflammatory drugs (in combination with opioids if necessary) were adequate in controlling postoperative pain, except for nine patients who experienced postoperative pain for one month.

The results of the questionnaire about long-term outcomes showed that, of 22 patients, when asked why they only had ETS on one side, 12 patients claimed

Table 2: Demographic characteristics of the patients and rates of complications of single-port or two-port sympathectomies

Categories	Single port	Two-port	P-value
Males/Females	19/34	16/25	N/A*
Mean age	23.1	23.6	N/A
Number of operations	n=97	n=69	N/A
Unilateral sympathectomy on the right side	1	1	N/A
Unilateral sympathectomy on the left side	8	12	N/A
Bilateral sympathectomy	44	28	N/A
Mean duration of operations	15.64±3.08 min.	19.44±3.24 min.	<0.001
Mean length of hospital stays	1.84±1.05 days	1.76±0.95 days	0.199
Pneumothorax	23 (23.71%)	10 (14.49%)	0.142
Early postoperative pain	31 (31.95%)	38 (55.07%)	<0.001
Tube thoracostomy	18 (18.55%)	9 (13.04%)	0.386
Compensatory sweating	7 (7.21%)	6 (8.69%)	0.751
Mean points given for cosmetic appearance of surgical scars	8.04	7.33	<0.001

* Not applicable

they had ETS on the other side in another medical facility and six patients stated they did not wish to have ETS in the other side because of the postoperative pain they would experience. Four patients said they had postponed the surgery due to private reasons.

There was postoperative Horner's syndrome in two patients and the conditions of both patients were seen to have resolved during follow-up. This complication may have arisen due to unnoticed minor anatomical varieties in these individuals or heat effect of cauterization dissipating in nearby tissues or directly through the nerve itself. The fact that the patients' conditions have resolved during follow-up confirms only minor damage to the first thoracic sympathetic ganglion.

Demographic characteristics of the patients and rates of complications of single-port and two-port operations are given in Table 2.

DISCUSSION

ETS for the treatment of hyperhidrosis was first described by Hughes in 1942[5]. This operation gained popularity in the 1990s, when the double-lumen endotracheal tube became widely available. Today, it is a safe and effective treatment modality in patients who do not respond to medical treatment. Recent years have spawned controversies and advancements in thoracic sympathectomy. All approaches aim at reducing complications, minimizing or, if possible, avoiding hospitalization, minimizing operation time while still providing effective and satisfactory treatment of hyperhidrosis.

Erdik *et al*[6] reported that ETS with two ports is a safe and effective treatment for hyperhidrosis and vasospastic arterial disease. Chen *et al*[7] reported that single port ETS is associated with less postoperative pain and more aesthetically pleasing surgical scars. Currently, no consensus has been reached on the optimal number of ports in ETS.

Mean duration of operation depends on the surgeon's experience, appropriate placement of the double-lumen endotracheal tube, physical characteristics of the patient and user-friendliness of the equipment. Mean duration of operation has been reported to be as low as 13 minutes and up to 47.4 minutes[8,9]. In this study, the mean duration of operation was 15.64 minutes for single port ETS and 19.44 minutes for two-port ETS, the difference of which was statistically significant (P=0.001). The longer operating times may be attributed to incision and closure of the surgical wound for the second thoracoport in two-port ETS.

Mean days of postoperative hospitalization after ETS varies among different institutions and ranges between 1.2 and 6.7 days[10,11]. In this study, there was no statistically significant difference in postoperative length of stay in hospital between single-port or two-port ETS. Complications or interventions that prolong hospitalization are the presence of a pneumothorax, treatment of pneumothorax with tube thoracostomy, and postoperative pain. In a comparison of patients with any or all of these conditions to patients without, it was seen that the presence of any of these conditions was associated with a statistically significant increase in the length of stay in hospital (P=0.001).

For two-port ETS, incisions for the thoracoports were placed in 5th intercostal space along the mid-axillary line and in the 3rd intercostal space along the anterior axillary line. With two ports, thoracoscope and endoscopic tools have different angles upon entry into the thoracic cavity, thus are easier to handle, which translates to a lower probability of lung injury and pneumothorax. An injury of the lung parenchyma could cause a pneumothorax, which, if large enough,

would be treated with tube thoracostomy, all of which would lead to longer hospitalization, more postoperative pain, and more dissatisfaction with surgical scars. It is, therefore, of utmost importance to avoid parenchymal lung injury during ETS. In our study, two-port ETS was associated with fewer cases of pneumothorax (14.49% versus 23.71%), though it was not statistically significant (*P*=0.142). On closer look, most of the cases of pneumothorax with single-port ETS were among the first 30 cases. If the first 30 cases of single-port ETS are excluded from the cohort, the rate of pneumothorax in single-port ETS matches that of two-port ETS. Since the rate of pneumothorax decreases after a number of cases, it may be reasonable to assume that the difference is attributable to the surgeon's lack of experience with single-port ETS.

Pain in the early postoperative period is the most prominent issue delaying the patient's discharge. In a multi-center study carried out by the "Thoracic Sympathectomy Cooperative Group" in Spain, the rate of cases with postoperative pain persisting beyond 15 days was reported to be 1.4%[12]. In our study, 9 (5.4%) patients expressed having persistent postoperative pain, though none beyond 1 month postoperatively. Acute postoperative pain can be managed by either medical treatment alone or in combination with an epidural or paravertebral blockade or intercostal nerve block[13], while chronic postoperative pain might benefit from other interventions like transcutaneous electrical nerve stimulation, low-level laser therapy or radiofrequency ablation. We managed postoperative pain with a combination of opioid and non-opioid analgesics. Young *et al*[14] reported their views on 12 retrospective and prospective studies and concluded that more studies are needed to ascertain that single-port ETS is associated with considerably less postoperative pain than two-port ETS. In this study, a higher rate of patients who had two-port ETS expressed having postoperative pain, which was statistically significant. The higher rate of postoperative pain could be mainly attributed to the higher probability of intercostal neuralgia as a result of two-port incisions instead of one.

The main cause of dissatisfaction regarding surgical scars is tube thoracostomy. In the questionnaires for the long-term outcomes in this study, patients who had a chest tube inserted either intraoperatively or postoperatively gave significantly lower scores regarding their satisfaction about their surgical scars. Furthermore, the presence of a chest tube was the single most important determinant of a longer hospital stay.

Compensatory sweating, with an incidence of 3% to 98%[8], is one of the complications that surgeons and patients alike would rather avoid, though it cannot be predicted whether it will occur in any one patient. Part of this variability may be attributed to the climate in which the patient lives, with warmer climates causing more compensatory sweating, though data in this area is inconclusive[15]. Riet *et al*[16] emphasized that sympathectomy limited to T3 level would decrease rates of compensatory sweating. It should be kept in mind that, for vasomotor and sudomotor (secretomotor to sweat glands) effects of the sympathetic innervation of the hand, T2 level ganglion is considered to be the main branch[17]. Sympathectomy limited to T3 level may not provide adequate reduction in complaints in hyperhidrosis. In addition, in a study conducted by Leseche *et al*[18], though sympathetic ganglia were removed in varying segments (T1-T2, T1-T3, T2-T3, T2-T4), it had no effect on compensatory sweating. Therefore, for a satisfactory reduction in hyperhidrosis, we opted for sympathectomies starting from the T2 level. Using surgical clips to achieve sympathetic block without transecting or cauterizing the sympathetic ganglia is a plausible method to allow easy reversal of the procedure, should the level of compensatory sweating be overwhelming enough for the patient to endure reoperation. Yet, using surgical clips to achieve sympathetic block and removing them later cannot really guarantee avoidance of nerve damage; coupled with nerve regeneration being as slow as it is, it's not surprising that alleviation of compensatory sweating with the removal of surgical clips is successful in only 60% of patients[19]. Compensatory sweating in cases of sympathectomy by means of cauterization of the sympathetic ganglia proves to be much harder to treat. Teleranta *et al*[20] and Haam *et al*[21] reported that treatment with reconstruction using sural or intercostal nerve, respectively, may provide an improvement of the symptoms for some cases with compensatory sweating. For our patients, the rate of compensatory sweating was 7.2% for single-port ETS and 8.6% for two-port ETS, though there was no statistically significant difference.

On analysis of the data from patients' telephone surveys, dissatisfaction related to surgical scars was significantly higher in two-port ETS than single-port ETS (*P*=0.001). Specifically, patients who underwent tube thoracostomy gave much lower scores for the cosmetic appearance of their surgical scars, with a statistically significant difference (*P*=0.001).

96.3% of the patients expressed that they would recommend the procedure to an acquaintance with similar symptoms. The patients who expressed they would advise against the procedure were also almost universally the patients experiencing persistent postoperative pain.

CONCLUSION

ETS is a safe and effective treatment for hyperhidrosis, albeit some complications. Single-port ETS, compared to two-port ETS, is associated with less postoperative pain, less dissatisfaction with surgical scars and shorter operation times with similar rates of complications, provided the surgeon has adequate experience. We believe single-port ETS is a more effective procedure with better overall patient satisfaction.

ACKNOWLEDGMENT

Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the materials discussed in the manuscript.

Authors' contributions. Abdullah Erdogan, Makbule Ergin and Hakan Keskin designed the study. Makbule Ergin, Hakan Keskin and Emel Gunduz collected the data. Cemal Kemaloglu, Sirin Akdeniz and Hakan Keskin performed the analysis and wrote the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Gee S, Yamauchi PS. Nonsurgical management of hyperhidrosis. Thorac Surg Clin 2008; 18(2):141-155.
2. Jeong JY, Park HJ. Sympathicotomy under local anesthesia: a simple way to treat primary hyperhidrosis. Ann Thorac Surg 2010; 90(5):1730-1731.
3. Haider A, Solish N. Focal Hyperhidrosis: diagnosis and management. CMAJ 2005; 172(1):69-75.
4. Hornberger J, Grimes K, Naumann M, Glaser DA, Lowe NJ, Naver H, *et al*. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol 2004; 51(2):274-286.
5. Hughes J. Endothoracic sympathectomy. Proc R Soc Med 1942; 35(9):585-586.
6. Erdik O, Karasu S, Haberal İ, Yıldızhan A, Ayata A, Yıldırım A. Surgical results of 349 thoracoscopic sympathectomies. Turk Gogus Kalp Dama 2006; 14(4):290-294
7. Chen YB, Ye W, Yang WT, Shi L, Guo XF, Xu ZH, *et al*. Uniportal versus biportal video-assisted thoracoscopic sympathectomy for palmar hyperhidrosis. Chin Med J (Engl) 2009; 122(13):1525-1528.
8. Döngel İ, Özkan B, Tanju S, Toker A. Palmar ve aksiller hiperhidroz tedavisinde iki taraflı torakoskopik sempatektominin uzun dönem sonuçları: Sekiz yıllık deneyim. Turk Gogus Kalp Dama 2013; 21(4):990-994
9. Bilgin M, Oğuzkaya F, Haberal A. Palmar Hiperhidroziste İki Taraflı Torakoskopik Sempatektomi. Solunum Hastalıkları 2005; 16(4):184-187.
10. Us MH, Baltarlı A, Çakır O, İnan K, Tarhan A, Erdik O, *et al*. Thuracoscopıc thoracal sympathectomy. Turk Gogus Kalp Dama 1999; 7(6):457-458.
11. Dumont P, Hamm A, Skrobala D, Robin P, Toumieux B. Bilateral thoracoscopy for sympathectomy in the treatment of hyperhidrosis. Eur J Cardiothorac Surg 1997; 11(4):774-775.
12. García-Franco CE, España A. [Usefulness of bilateral sympathectomy using video-assisted thorascopic surgery in the treatment of essential hyperhidrosis]. Actas Dermosifiliogr 2008; 99(7):523-527. Article in Spanish.
13. Yeung JHY, Gates S, Naidu BV, Wilson MJA, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev 2016; 2(2):CD009121.
14. Young R, McElnay P, Leslie R, West D. Is uniport thoracoscopic surgery less painful than multiple port approaches? Interact Cardiovasc Thorac Surg 2015; 20(3):409-414.
15. Lai YT, Yang LH, Chio CC, Chen HH. Complications in patients with palmar hyperhidrosis treated with transthoracic endoscopic sympathectomy. Neurosurgery 1997; 41(1):110-115.
16. Riet M, Smet AA, Kuiken H, Kazemier G, Bonjer HJ. Prevention of compensatory hyperhidrosis after thoracoscopic sympathectomy for hyperhidrosis. Surg Endosc 2001; 15(10):1159-1162.
17. Oğuzkaya F, Hasdıraz L. Torakoskopik Sempatektomi. Türk Nöroşir Derg 2009; 19(3):153-157
18. Lesèche G, Castier Y, Thabut G, Petit MD, Combes M, Cerceau O, *et al*. Endoscopic transthoracic sympathectomy for upper limb hyperhidrosis: limited sympathectomy does not reduce postoperative compensatory sweating. J Vasc Surg 2003; 37(1):124-128.
19. Miller DL, Force SD. Temporary thoracoscopic sympathetic block for hyperhidrosis. Ann Thorac Surg 2008; 85(4):1211-1216.
20. Telaranta T. Secondary sympathetic chain reconstruction after endoscopic thoracic sympathicotomy. Eur J Surg Suppl 1998; (580):17-18.
21. Haam SJ, Park SY, Paik HC, Lee DY. Sympathetic nerve reconstruction for compensatory hyperhidrosis after sympathetic surgery for primary hyperhidrosis. J Korean Med Sci 2010; 25(4):597-601.

Original Article

Perioperative hemodynamics in hypertensive patients undergoing shoulder surgery with interscalene block in the sitting position: An observational study

[1]Mahmut Sami Tutar, [2]Betul Kozanhan
[1]Department of Anesthesiology and Reanimation, Konya Numune Hospital, Konya, Turkey
[2]Department of Anesthesiology and Reanimation, Konya Education and Research Hospital, Konya, Turkey

Kuwait Medical Journal 2022; 54 (1): 72 - 79

ABSTRACT

Objective: To investigate the effects of the interscalene block technique on blood pressure changes in medically controlled hypertensive patients undergoing shoulder arthroscopy in the sitting position.
Design: A prospective and observational study
Setting: Operating room and postoperative recovery area
Subjects: Sixty-four American Society of Anesthesiologists I-II adult (medically controlled hypertensive (n=32) and normotensive (n=32)) patients scheduled to have elective arthroscopic shoulder surgery with the interscalene block technique.
Intervention(s): Ultrasound-guided interscalene block administered using 15/cc 0.5% bupivacaine and 5/cc 2% lidocaine. Blood pressures and heart rate were recorded at five-minute intervals for 60 minutes.
Main outcome measures: The relationship between the interscalene block and 20% or more increase in the systolic blood pressure at any time interval compared to the baseline
Results: None of the normotensive patients had 20% or more increase in the systolic blood pressure. However, 62.5% of the hypertensive patients had 20% or higher systolic blood pressure values after the interscalene block during the follow-up (P<0.0001). Four hypertensive patients developed a hypertensive crisis after interscalene block.
Conclusions: Consequently, interscalene block caused an increase in the blood pressures of medically controlled hypertensive patients. In daily practice, caution is warranted when selecting the anesthesia type, especially in patients with uncontrolled hypertension and with comorbidities, who cannot tolerate acute upsurges in blood pressure.

KEY WORDS: carotid sinus baroreceptors, complication, hypertension, interscalene block, ultrasound

INTRODUCTION

Interscalene block (ISB) is a regional anesthesia technique applied by blocking the roots or trunks of the brachial plexus between the anterior and middle scalene muscles. The ISB technique in shoulder surgery has several advantages, including less post-operative pain, reduced opioid requirements and opioid-related side effects and higher patient satisfaction[1,2]. However, significant complications associated with ISB may develop. Most of the problems are related to the spread of the local anesthetic agent to the surrounding anatomical structures via the fascial sheath[3]. These anatomical structures can be the stellate ganglion, phrenic nerve and contralateral brachial plexus[4-6].

It was shown that local anesthetic spread after ISB might extend to the carotid sinus receptors[7]. In fact, carotid sinus baroreceptors play an essential role in the dynamic control of blood pressure[8]. There are limited case reports about the disturbances in the autonomic nervous system and the presence of hypertension as a result of an undesired blockade of carotid baroreceptors with local anesthetics after ISB[3,9]. However, perioperative hypertension increases the frequency of blood loss, renal damage, as well as cardiovascular and cerebrovascular events[10]. Therefore, especially in hypertensive patients, it is

Address correspondence to:
Mahmut Sami Tutar, Department of Anesthesiology and Reanimation, Konya Numune Hospital, Konya, Turkey. Tel: +90 5552723704; Fax: +90 33232367232; E-mail: masatu42@gmail.com

vital to preserving the hemodynamic stability during the perioperative period.

The effects of ISB in hypertensive patients on blood pressure changes during shoulder arthroscopic surgery while sitting are still not well elucidated. We aimed to investigate the effects of the ISB technique on blood pressure changes in hypertensive patients undergoing shoulder arthroscopy in the sitting position.

SUBJECTS AND METHODS

Approvals for this prospective and observational research were obtained from the Necmettin Erbakan University Ethical Committee (Approval number: 2017/938). This study was carried out between July 2017 and February 2018 at the Anesthesiology and Reanimation Clinics of Konya Education and Research Hospital. Written informed was consent obtained from all participants.

Inclusion criteria

We enrolled American Society of Anesthesiologists (ASA) I-II patients who were scheduled to have elective shoulder surgery with the ISB technique, who were normotensive or had controlled hypertension.

Exclusion criteria

Participants were excluded if vital signs might be affected by regional anesthesia (history of chronic opioid or benzodiazepine use, severe renal and hepatic insufficiency, advanced respiratory and cardiovascular disease), ASA-III class and above, body mass index (BMI) >35 kg/m^2, have uncontrolled hypertension or without regular medical treatment, are not eligible for ISB application (allergy to local anesthetic drugs and diaphragm paralysis), and in case of failed ISB attempt.

Design of the study

The patients were divided into two groups as normotensives (Group N) and hypertensives (Group H). The demographic data (age, height, weight, gender and intervention side), antihypertensive drug use, history of hypertension and the presence of additional diseases were recorded.

The same experienced anesthesiologist performed all ISB applications. Patients were placed in the 45 degrees sitting or "beach chair" position, which could be achieved by elevating the back of the operating table, and this position was maintained during the study period. Noninvasive blood pressure, peripheral oxygen saturation and electrocardiography monitoring was performed in all patients. An intravenous 16G or 18G cannula was placed in the antecubital region followed by the infusion of 0.9% sodium chloride solution. All patients were lightly sedated with 1-2 mg midazolam, and the sedation was assessed using the Ramsay sedation score[11].

After the appropriate aseptic conditions were achieved, ISB was applied using both a nerve stimulator (Pajunk, Multistim Sensor, Germany) and USG guidance (Esaote brand MyLabFive-Esaote Europe BV Philipsweg 1 6227 AJ Maastricht The Netherlands). The block was administered with 15/cc 0.5% Bupivacaine (Bustesin 0.5%, Verm Drugs), and 5/cc 2% Lidocaine (Jetmonal Lidocaine Hydrocloride 20 mgml^{-1},Adeka Drugs) without adrenaline. The effectiveness of the sensorial block was evaluated by the pinprick test at the fifth and sixth cervical dermatomes, and the loss of shoulder abduction was considered as a successful motor block.

Blood pressure and heart rate of the patients were recorded at five-minute intervals for 60 minutes. The time intervals were named as: T0: the baseline; T1: after premedication and before ISB; T2: after ISB; and "T5-T60 (each five-minute intervals in sequence). During the study, 20% or more increase in the systolic blood presssure (SBP) at any time interval compared to the T1 time was defined as hypertension[12]. Nitroglycerin was administered in case of hypertension. On the other hand, a "hypertensive crisis" was defined as the mean SBP ≥180 mmHg or diastolic blood pressure (DBP) ≥110 mmHg at any time interval.

Sample size calculation

In the light of pilot data, 29 patients in each group should be included in the study to calculate 20% or more SBP compared with T1 time by a 2x2 mixed ANOVA model using 80% power for 0.128 eta-square effect size and 5% type-1 error. The sample size calculation revealed a total of 64 patients after considering a 10% drop-out rate.

Statistical analysis

The SAS University Edition 9.4 (SAS Institute Inc., Cary, NC, USA) program was used for data analysis. The continuous variables were expressed as the mean

Table 1: Demographical and clinical characteristics of the participants

Characteristics	All patient, n=64	Group H n=32	Group N n=32	*P*-value
Male/female (n)	18/46	4/28	14/18	0.005
Age (years)	58.5±5.1	59.4±4.4	57.6±5.6	0.17
BMI (kg/m^2)	29.5±3.4	29.5±3.4	28.8±3.0	0.10
Block side (right/left) (n)	42/22	19/13	23/9	0.29
ASA1/ASA2 (n)	17/47	0 /32	17/15	<.0001

Values are presented as mean ± SD or number of patients
BMI: body mass index; ASA: American Society of Anesthesiologists

and standard deviation, and categorical variables were expressed as numbers and percentages. The standard deviation values for continuous variables were provided in parentheses next to their mean values, and the proportions of categorical variables were specified in brackets along with their numerical values. The independent samples t-test and mixed effect models ANOVA were used in the analysis of continuous variables. The Chi-square test was used to compare categorical variables and P <0.05 was considered as statistically significant.

RESULTS

A total of 79 cases were included in the study. After the exclusion criteria, data for the remaining 64 cases were evaluated (Figure 1). Demographic data of the patients are shown in Table 1. The mean duration of diagnosis was 8.1±4.9 years in the hypertensive patients. The Ramsay sedation score was similar between the groups (P>0.05). There was no statistically significant difference between the two groups concerning the heart rate changes over time. However, for the HR values, the time and group effects were significant in both groups (P<0.0001 and P=0.013, respectively), but there was no statistically significant difference regarding time-group interaction (P=0.44) (Figure 2). There was a statistically significant difference between the two groups concerning the SBP changes over time. Also, the time effect, group effect, and time-group interaction were statistically significant between

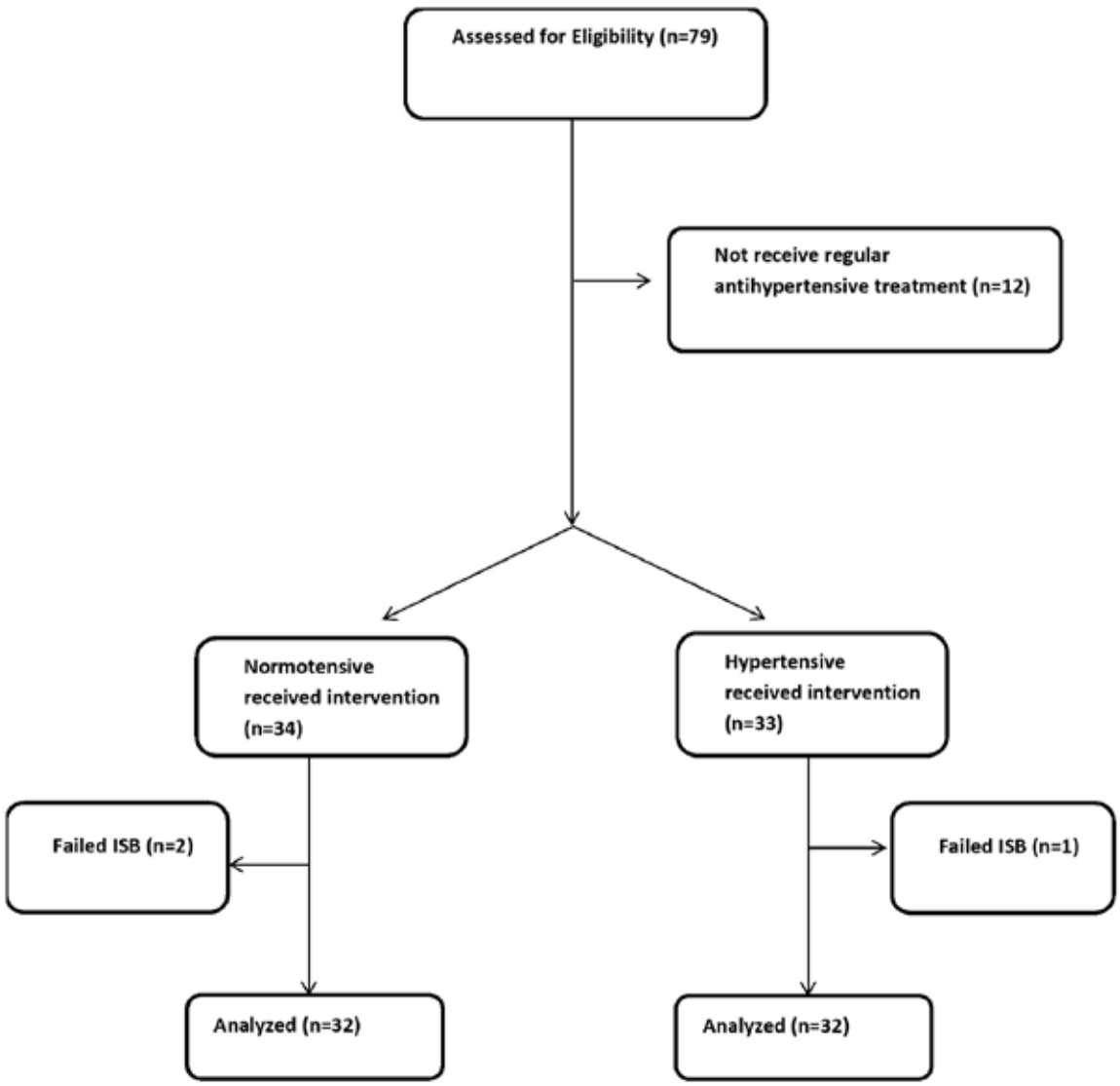


Fig 1: Consort diagram of the patients included in study.

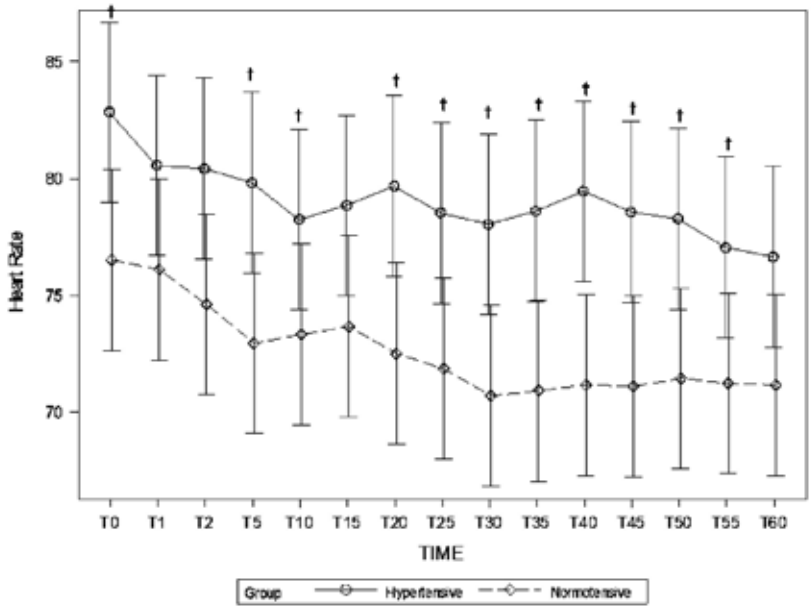


Fig 2: Heart rate values in groups according to time, †: *P*<0.05

the two groups (*P*<0.0001, *P*<0.0001 and *P*<.0001, respectively). None of the patients in Group N had 20% or more increase in the SBP. However, 62.5% of the hypertensive patients had 20% or higher SBP values after ISB during the follow-up (*P*<0.0001) (Figure 3). In group H, patients with high BMI, advanced age, female sex and left-sided surgery had 20% or more increase in SBP. However, these increases were not statistically significant (*P*>0.05).

DBP changes over time were similar between the groups over time. While the time effect was significant between the two groups (*P*<0.0001), there was no statistically significant difference in the group effect and time-group interaction (*P*=0.06 and *P*=0.0505, respectively)(Figure 4). A total of 16 patients (50%) in group N and 27 patients (84.3%) in group H had 20% or more increase in the DBP after ISB when each time interval was compared with T1 (*P*=0.003). In all

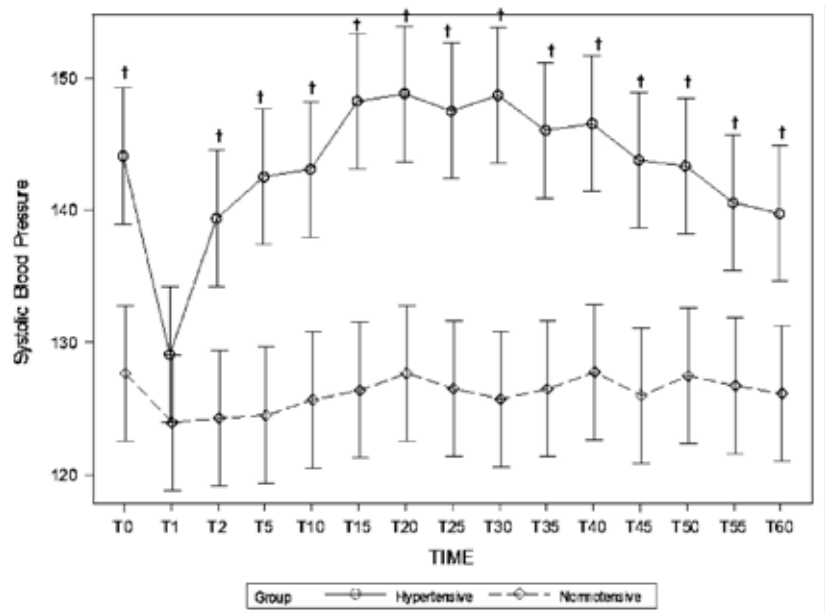


Fig 3: Systolic arterial blood pressure values in groups according to time, †: *P*<0.05

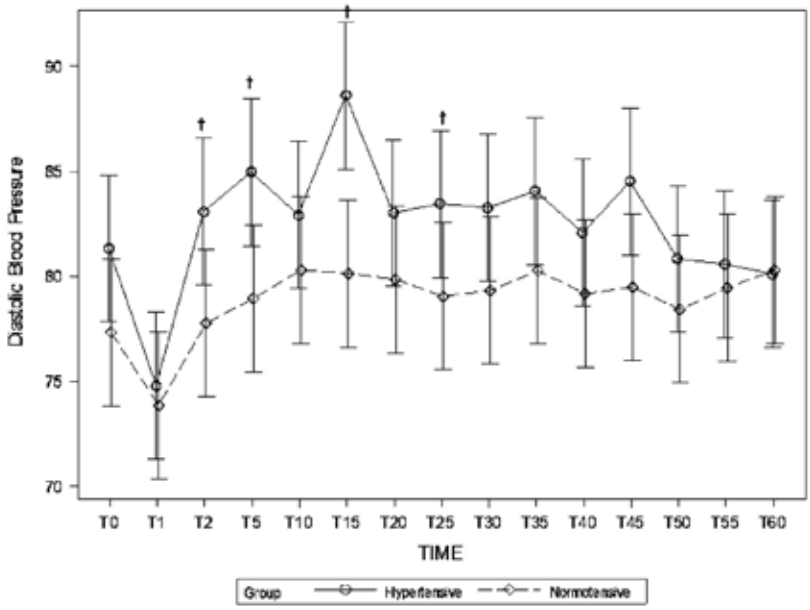


Fig 4: Diastolic arterial blood pressure values in groups according to time, †:*P*<0.05

participants, patients with high BMI, advanced age, female sex, and left-sided surgery had 20% or more increased in the DBP. However, these increases were not statistically significant (*P*>0.05).

The mean blood pressure (MBP) changes were similar between the two groups over time. While the time effect and group effect were significant between the two groups (*P*<0.0001 and *P*=0.0004, respectively), there was no statistically significant difference regarding time-group interaction (*P*=0.09) (Figure 5). There was a 20% or more increase in the mean blood pressure in seven patients in Group N, 18 patients in Group H, and this difference was statistically significant (*P*=0.005). In all participants, patients with high BMI, advanced age, female gender and left-sided surgery had 20% or more increase in the MBP. However, these increases were not statistically significant (*P*>0.05). Horner syndrome was observed

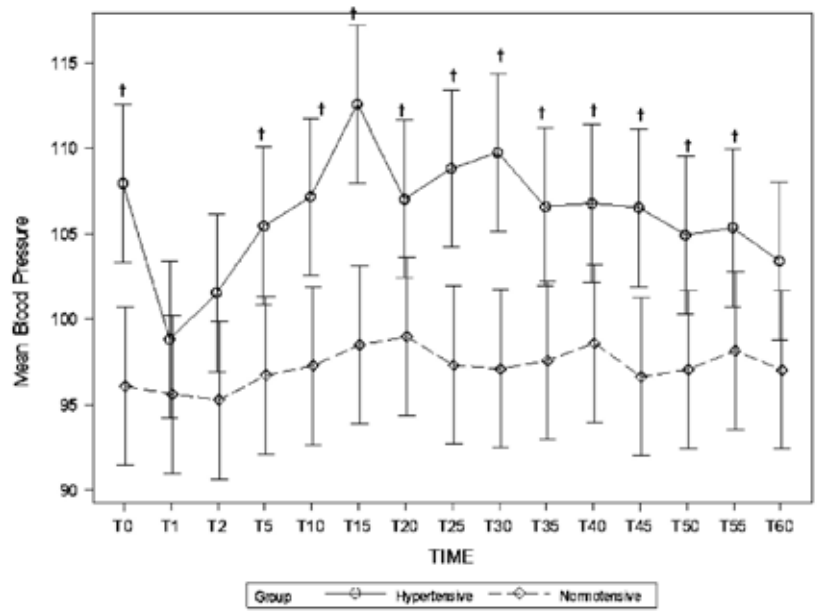


Fig 5: Mean arterial blood pressure values in groups according to time, †: *P*<0.05

in 18 of the patients (8 in Group H, 10 in Group N). In group H, 4 patients (12.5%) had hypertensive crisis after the ISB application.

DISCUSSION

Hypertension is a progressive cardiovascular disease affecting approximately 30-45% of the adult population in Europe, and its prevalence is rapidly increasing with age[13]. Therefore, ISB is frequently applied in hypertensive patients as well as normotensive patients in the daily anesthesia practice. In this prospective observational study, we detected that 62.5% of the hypertensive patients who were under medical treatment had 20% or higher SBP values after ISB compared to the T1 time.

There are few cases in the literature about high blood pressure levels occuring in the early period after ISB administration[3,9,14]. Gianesello *et al* compared the blood pressure changes with ISB and reported higher SBP and DBP values in patients who underwent blockage with neurostimulation than patients who underwent blockage with ultrasound at the 15th minute[15]. The authors suggested that ISB, administered in normotensive patients using ultrasound-guided and low-dose local anesthetics, could reduce the incidence of increases in the blood pressure.

The spread of local anesthetic agents to the surrounding tissues can explain high blood pressure values associated with ISB. Winnie has shown that the brachial plexus sheath is a tubular extension of the prevertebral fascia and that local anesthetic agents have both a downward and upward spread in the cervical area in interscalene brachial plexus injections[16]. Yang *et al* demonstrated the diffusion of the contrast agent given by the interscalene and supraclavicular approach into the brachial plexus sheath through computed tomography and reported greater perimuscular and intramuscular accumulation in the interscalene approach[7]. They also reported that the contrast agent reached the anterior scalene muscle in 90% of the patients and reached the carotid sheath in 50% of the patients. The vagus in the carotid sheath and the phrenic nerve behind it can involuntarily be blocked during the brachial plexus anesthesia with the interscalene approach[8]. In the present study, autonomic nerves from the carotid baroreceptors are probably suppressed or blocked by the spreading of the local anesthetic agent to the barosensitive region, possibly due to the anatomical neighborhood, and for this reason, we believe that an unresponsive sympathetic activity and increase in blood pressure may occur.

Gianesello *et al* argued that the incidence of this unintended hemodynamic event could be reduced by ultrasound-guided and low-dose local anesthetic usage in normotensive patients[15]. Although ISB was performed with ultrasound guidance and low dose local anesthetic in our study, there was an increase in blood pressure compared to the baseline values in both hypertensive and normotensive patients. However, patients who had 20% or more increase in blood pressure values compared to the T1 time were statistically more in the hypertensive group than the normotensive group.

Changes in cardiovascular functions during the aging process are accompanied by compensated baroreflex integrity deterioration[17]. High blood pressure in the elderly patients may be due to an age-related decrease in the baroreflex sensitivity, changes in basal sympathetic nerve activity and a decrease in systemic vascular response. In the present study, the mean age of the patients was higher than 50 years. Therefore, despite the low-dose local anesthetics, the age factor may be responsible for elevated blood pressure in the participants.

Besides age, many studies have pointed out that gender is an effective factor in the autonomic control of the heart rate and blood pressure regulation[18-20]. It is known that sympathetic vascular regulation in men and parasympathetic effect in women are more dominant. Also, resting sympathetic vasomotor tonus tends to decrease in women, whereas baroreflex blood pressure buffering is less effective in women than men[21,22]. Since women have a better parasympathetic activity, it's known that even partially reduced vagal afferents may cause stronger high-pressure baroreflexes[20]. In our study, the relationship between the elevation of blood pressure and gender could not be elucidated clearly due to the high number of female patients. However, all of the patients who developed hypertensive crisis were women.

In the perioperative period, various factors such as anxiety, pain and discomfort may also be involved in increased blood pressure. Most patients are concerned about anesthesia and surgical procedures. For this reason, light sedation may be useful to reduce potential anxiety and prevent undesirable discomfort before performing a peripheral nerve block. Therefore, all patients were treated with midazolam before the ISB.

The purpose of controlling perioperative blood pressure is to maintain the peripheral organ function. In general, since the safe blood pressure limit is not known in hypertensive patients, it is recommended to keep the blood pressure 20% compared to the initial values[22]. Patients with hypertension are more likely to have intraoperative blood pressure lability, which may lead to myocardial ischemia. There are no randomized clinical trial data about the optimal blood pressure during the intraoperative period. However, it is recommended to provide a blood pressure lower

than 130/80 mmHg in the intraoperative period, especially in people who are older and have additional comorbidities[23]. In a case report, angina was reported due to high blood pressure after brachial plexus block. Accordingly, the authors suggested that contralateral baroreceptor mechanisms could not prevent hypertensive responses in patients with uncontrolled hypertension[9]. In the present study, SBP over 180 mmHg was detected in four patients. However, there was only one patient who had a 160 mmHg or higher SBP at one hour after ISB administration, and none of the patients had additional cardiovascular complications such as arrhythmia and angina. Probably, the effective contralateral baroreceptor mechanism in medically controlled hypertensive patients prevented the prolonged duration of this complication.

A relationship was detected between increased diastolic pressure (notably >90 mmHg) and postoperative mortality in a recent analysis of more than one million patients[24]. These findings are quite striking when considering that diastolic hypertension is a more potent cardiovascular risk factor than systolic hypertension up to the age of 50 in non-surgical environments. We observed an increase in the SBP after ISB only in the hypertensive group. 20% or more increase in the DBP and MBP values after ISB were detected in both the normotensive and hypertensive groups. However, these increases were significantly higher in the hypertensive group. On the other hand, age 50 is the threshold; SBP is a stronger cardiovascular risk factor than DBP after this age[25]. Therefore, we think that the increase in SBP is more critical in the elderly.

There are several limitations to this study. First, because of the high number of females, the relationship between elevated blood pressure and sex could not be evaluated. However, all patients with the hypertensive crisis were females. Second, the hemodynamic parameters of the patients were followed up for 60 minutes after the ISB. Another limitation was that the hemodynamic follow-up was performed in a 45-degree sitting position to exclude the effect of possible hemodynamic changes during the transition from supine to sitting position. Further studies are also needed to check the additional contribution of position changes on hemodynamics.

CONCLUSION

In conclusion, ISB with low dose local anesthetic under the guidance of USG resulted in an increase in blood pressure levels in hypertensive patients, whose blood pressure was medically controlled. In four patients, the blood pressure reached the level of hypertensive crisis. However, no cardiovascular complications were observed in any of the patients. In daily practice, caution is warranted when selecting the anesthesia type, especially in patients with uncontrolled hypertension and with comorbidities, who cannot tolerate acute upsurges in blood pressures.

ACKNOWLEDGMENTS

Financial support and sponsorship: none

Conflicts of interest: none

Contribution: Mahmut Sami Tutar contributed to designing the study and preparation of the manuscript. He also contributed to data collection and conduction of the study. Betul Kozanhan contributed to data analysis, writing, and design of this study.

REFERENCES

1. Long TR, Wass CT, Burkle CM. A perioperative interscalene blockade: an overview of its history and its current clinical use. J Clin Anesth 2002; 14(7):546–556.
2. Fredrickson MJ, Stewart AW. Continuous interscalene analgesia for rotator cuff repair: a retrospective comparison of the effectiveness and the cost in 205 patients from a multi-provider private practice setting. Anaesth Intensive Care 2008; 36(6):786-791.
3. Jahagirdar SM, Prabhu CR, Parthasarathy S. Transient hypertension after an ınterscalene block-The Presentation of a rare complication with an anatomical explanation. J Clin Diagn Res 2012; 6(10):1768-1769.
4. Seltzer JL. Hoarseness and the Horner's Syndrome after an interscalene brachial pleksus block. Anesth Analg 1977; 56(4):585-586.
5. Urmey WF, McDonald M. A hemidiaphragmatic paresis during an interscalene brachial pleksus block: its effects on the pulmonary function and the chest wall mechanics. Anesth Analg 1992; 74(3):352-557.
6. Urmey WF, Talts KH, Sharrock NE. One hundred percent incidence of hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia as diagnosed by ultrasonography. Anesth Analg 1991; 72(4):498-503.
7. Yang WT, Chui PT, Metreweli C. Anatomy of the normal brachial plexus revealed by sonography and the role of sonographic guidance in anesthesia of the brachial plexus. Am J Roentgenol 1998; 171(6):1631-1636.
8. Timmers HJLM, Wieling W, Karemaker JM, Lenders JW. Denervation of carotid baro-and chemoreceptors in humans. J Physiol 2003; 553(Pt 1):3-11.
9. Chakithandy S, Kelly P, Barron J. Unexpected outcome (positive or negative) including adverse drug reactions: Hypertensive emergency as a complication of brachial plexus block. BMJ case reports 2011; bcr0120113754.
10. Lonjaret L, Lairez O, Minville V, Geeraerts T. Optimal perioperative management of arterial blood pressure. Integr Blood Press Control 2014; 7:49-59.
11. Ramsay MAE, Savage TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone-alphadolone. BMJ 1974; 2(5920):656-659.
12. Goldberg ME, Larijani GE. Perioperative hypertension. Pharmacotherapy 1998; 18(5):911-914.

13. Lapage KG, Wouters PF. The patient with hypertension undergoing surgery. Curr Opin Anesthesiol 2016; 29(3):397-402.
14. Hernandez A, Salgado I, Agreda G, Botana C, Casas M, Nogueron M. Hypertensive crisis after interscalene block for shoulder surgery: A-485. Eur J Anaesth 2006; 23:126.
15. Gianesello L, Magherini M, Pavoni V, Horton A, Nella A, Campolo MC. The influence of interscalene block technique on adverse hemodynamic events. J Anesth 2014; 28(3):407-412.
16. Winnie AP. Interscalene brachial plexus block. Anesth Analg 1970; 49(3):455-466.
17. Laitinen T, Hartikainen J, Vanninen E, Niskanen L, Geelen G, Länsimies E. Age and gender dependency of baroreflex sensitivity in healthy subjects. J Appl Physiol 1998; 84(2):576-583.
18. Ryan SM, Goldberger AL, Pincus SM, Mietus J, Lipsitz LA. Gender and age-related differences in heart rate dynamics: are women more complex than men? J Am Coll Cardiol 1994; 24(7):1700-1707.
19. Liao D, Barnes RW, Chambless LE, Simpson Jr RJ, Sorlie P, Heiss G. Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability: The ARIC study. J Am Coll Cardiol 1995; 76(12):906-912.
20. Huikuri HV, Pikkuja SM, Airaksinen KJ, Ikaheim MJ, Rantala AO, Kauma H, *et al*. Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. Circulation 1996; 94(2):122-125.
21. Evans JM, Ziegler MG, Patwardhan AR, Ott JB, Kim CS, Leonelli FM, *et al*. Gender differences in autonomic cardiovascular regulation: spectral, hormonal, and hemodynamic indexes. J Appl Physio 2001; 91(6):2611-2618.
22. Lines D. Hypertension and Anaesthesia. S Afr Fam Pract 2014; 56(5):9-15.
23. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, *et al*. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged≥75 years: a randomized clinical trial. JAMA 2016; 315(24):2673-2682.
24. Venkatesan S, Myles PR, Manning HJ, Mozid AM, Andersson C, Jørgensen ME, *et al*. Cohort study of preoperative blood pressure and risk of 30-day mortality after elective non-cardiac surgery. Br J Anaesth 2017 ;119(1):65-77.
25. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, *et al*. Does the relation of blood pressure to coronary heart disease risk change with aging?: The Framingham Heart Study. Circulation 2001; 103(9):1245-1249.

Original Article

Psychological workplace violence against physicians in a large teaching hospital, Eastern Province, Saudi Arabia

Nouf A AlShamlan[1], Nithya Jayaseeli[2], Abdullah S Aljoudi[1]
[1]Department of Family and Community Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam 31433, Saudi Arabia
[2]Research Support Unit, King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Kuwait Medical Journal 2022; 54 (1): 80 - 87

ABSTRACT

Objectives: To assess the prevalence, characteristics and consequences of verbal abuse among physicians, and to determine its association with physicians' demographic and occupational characteristics
Design: Cross-sectional study
Settings: King Fahd Hospital of the University, Saudi Arabia
Subjects: By total sample, the study included 359 physicians.
Intervention: We used a self-administered questionnaire that was developed by the World Health Organization to collect the data.
Main Outcome Measures: Prevalence of verbal abuse against physicians
Results: During the 12-month period prior to the study, more than one-third of physicians experienced verbal abuse (36.5%). Patients and their relatives carried out most incidents. The majority of physicians didn't report the cases; most of them believed that reporting is useless. After logistic regression analysis, physicians with a higher degree of worrying about violence in the workplace were more likely to face verbal abuse. Residents were more likely to be exposed to verbal abuse than consultants.
Conclusion: Workplace verbal abuse is a significant problem. The presence of a high number of cases in addition to the low reporting rates is an alarming issue. An effective reporting system should be established, and all physicians should be supported, reassured and encouraged to report.

KEY WORDS: abuse, healthcare

INTRODUCTION

Violence is an alarming global issue that affects the wellbeing of communities[1], with violence in the workplace becoming an increasing problem. The health care sector in particular is at higher risk of violent incidents[2]. Approximately one-quarter of all violent acts in the workplace happen in the health sector[2]. There is no consensus on a unified definition of workplace violence. The Joint Program on Workplace Violence in the Health Sector defined workplace violence as: "incidents where staff are abused, threatened or assaulted in circumstances related to their work, including commuting to and from work, involving an explicit or implicit challenge to their safety, well-being or health"[3]. There are two main types of workplace violence: psychological (the most reported form of violence) and physical[2]. Psychological violence is defined as: "intentional use of power, including threat of physical force, against another person or group, that can result in harm to physical, mental, spiritual, moral or social development"[2]. Psychological violence can take many forms: verbal abuse (the most common), bullying/mobbing, harassment and threats[2].

The prevalence of workplace violence among health care providers varies in the literature between

Address correspondence to:
Nouf A AlShamlan, Department of Family and Community Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam 31433, Saudi Arabia. Tel: +966 504901406; E-mail: nashamlan@iau.edu.sa

studies. Differences in the methodologies and definitions used can explain this variation. The actual size of the problem is unknown, and the available information indicates that current knowledge reflects only the tip of the iceberg[2]. One study, conducted among 240 physicians and nurses in five public hospitals in Palestine, showed that the majority of the participating staff (80.4%) experienced violence over a one-year period, mostly non-physical (60%)[4]. Schablon *et al*[5] conducted a study in 39 health care facilities among 1973 participants in Germany to investigate the frequency of aggressive assaults against employees, and approximately 78% faced verbal aggression**.** All health care workers are at risk of verbal abuse. One study reported that physicians working in emergency departments experienced verbal abuse more frequently than nurses[6].

The relationships between health care providers' characteristics and exposure to violence are conflicting. Data reveal that younger and less experienced staff are more vulnerable to violence[4,5]. Both females and males are at risk of violence, but females have a greater risk of violence, especially of the psychological type, than males[2]. Working in some settings could increase the risk of violence either due to contact with aggressive and volatile patients such as in emergency settings, or due to contact with psychiatric patients or those under the influence of alcohol[7,8]. Altinbas *et al*[9] conducted a cross-sectional study of 186 psychiatrists working in mental health services within five hospitals in Turkey. They reported that 71% of psychiatrists were exposed to assaults during their professional life. There are two main sources of workplace violence: patients or their relatives[6], and staff members[2]. Reporting incidents of violence is an important process, and it is the first step toward prevention[2]. However, the majority of health care providers do not report the cases to the relevant authorities. In one study of 270 staff working in the emergency departments of six hospitals in Turkey, it was revealed that incidents of verbal threat were not reported to managers in 65.3% of cases[6]. Several reasons contribute to underreporting of workplace violence such as: a belief that violence is normal part of the job[9], lack of action after a previous report, and fear of the negative impacts of reporting[10].

In recent years, the mass media has reported many instances of workplace violence against health care workers in Saudi Arabia, whilst limited studies on this problem have been carried out. In the hospital setting, one study was carried out in two public hospitals in Riyadh city among physicians and nurses[10], and approximately 67% of 383 health care workers were exposed to violence with verbal abuse[10]. Moreover, Al-Shamlan *et al*[11] conducted a study of 391 nurses working in a teaching hospital in Khobar city, and 30.7% of nurses were exposed to verbal abuse during a one-year period[11]. In primary health care settings, one study was conducted in Al-Hassa[12] and another in Riyadh city[13]. The study conducted in Al-Hassa showed that among 1091 primary health care staff, 28% of them were abused, with psychological violence occurring in 89% of cases[12]. On the other hand, the study conducted in Riyadh revealed that among 270 health care workers, approximately 45.6% of them were exposed to violence during a one year period, mostly non-physical violence (99.2%) in the form of verbal attacks (94.3%) and intimidation (22.0%)[13].

The present study was planned to assess the state workplace among physicians, and to potentially recommend the development of rules and regulations to protect them from workplace violence. Thus, this study was conducted with two main objectives: (1) To assess the prevalence, characteristics and consequences of verbal abuse; and (2) to determine the demographic and occupational characteristics associated with verbal abuse among physicians.

SUBJECTS AND METHODS

This cross-sectional study was conducted at King Fahd Hospital of the University (KFHU), Eastern Province, Saudi Arabia, between November and December 2016. KFHU is a referral hospital for the whole Eastern Province, providing many services such as emergency services, outpatient, inpatient, operations and other services. It is a teaching hospital, providing training to undergraduate students and postgraduate residents. The study population included all available physicians working in direct contact with patients during the study period. Medical interns were excluded. The questionnaires were delivered to 400 physicians who were employed in medical or surgical departments of the hospital. Medical departments included internal medicine, radiology, pediatrics, neurology, family medicine, dermatology, emergency medicine and psychiatry. Surgical departments included obstetrics and gynecology, anesthesiology, surgery, urology, neurosurgery, ophthalmology, orthopedics and ENT.

The data were collected using a self-administered questionnaire that had been developed by the Joint Programme on Workplace Violence in the Health Sector from the World Health Organization, the International Council of Nurses, the International Labor Office, and Public Services International[3], and been previously used[14-19]. The standard language in the hospital is English; therefore, the English version of the questionnaire was used. The questionnaire has two sections. The first section included questions to collect demographic and occupational data from the participants (see Table 1). The second section concerned

Table 1: Demographic and occupational characteristics of physicians in King Fahd Hospital of the University, Khobar (2016, n= 359).

Characteristics	Number	Percent
Age (n=359)		
<30 years	148	41.2
30-39 years	113	31.5
≥40 years	98	27.3
Sex (n=356)		
Female	143	40.2
Male	213	59.8
Marital status (n=353)		
Single	89	25.2
Married	261	73.9
Divorced/widow/widower	3	0.9
Work experience in the health sector (n=358)		
≤5 years	176	49.2
6-15 years	102	28.5
>15 years	80	22.3
Work in shifts (n=357)		
No	198	55.5
Yes	159	44.5
Work between 6 pm and 7 am (n=359)		
No	90	25.1
Yes	269	74.9
Worried about violence in the workplace (n=354)		
Not worried at all	115	32.5
A little worried	102	28.8
Moderately worried	82	23.2
Worried	23	6.5
Very worried	32	9.0
Presence of procedures for reporting of violence in the workplace (n=351)		
Yes	137	39.0
No	64	18.2
Don't know	150	42.8
Specialty (n=359)		
Medical	200	55.7
Surgical	159	44.3
Job title/ professional status (n=358)		
Resident*	186	52
Specialist	57	15.9
Consultant	115	32.1

*includes all physicians under postgraduate training programs

exposure to workplace verbal abuse in the previous 12 months. Verbal abuse is defined as "promised use of physical or psychological force resulting in fear of harm or other negative consequences to the targeted individuals or groups, including behaviors that humiliates, degrades or otherwise indicates a lack of respect for the dignity and worth of an individual." This section consisted of questions about the last incident of verbal abuse experienced, its characteristics, consequences and the reactions of victims.

We modified the questionnaire to meet the objectives of the study and to be appropriate for the Saudi culture. Two experts in the field reviewed the questionnaire to enhance the content validity; they agreed on the modifications. The Cronbach's alpha reliability coefficient of the questionnaire was 0.9. Approval of the study was obtained from the Institutional Review Board Committee at the University of Dammam.

The data were collected during interactions in physicians' offices, morning reports and academic activities, after obtaining approval from the departmental heads. The investigator explained the aim of the study and the questionnaire to all participants and obtained informed verbal consent. Written consent was also obtained through the questionnaire. The researcher reassured participants that there would be no adverse impact as a result of participation, and anonymity was maintained. Information from the questionnaire was kept confidential and used only for the study purposes.

The collected data were coded, entered into, and analyzed using Statistical Package for Social Sciences version 16.0. All variables were categorical and therefore frequency and percentages were used for the descriptive statistics. Associations between verbal abuse and participant characteristics were assessed using chi-squared tests or fisher's exact tests. Univariate logistic regression followed by multivariate logistic regression analysis was performed on all significant risk factors, adjusted for the effects of each other to assess the association between independent variables and exposure to verbal abuse. Variables with *P*-values <0.05 were considered significant factors for verbal abuse and were included in the final multivariate logistic regression model.

RESULTS

Of 400 physicians enrolled in the study, 359 (89.8%) returned the completed questionnaires. Table 1 describes the demographic and occupational characteristics of the surveyed physicians. Most participants were not aware of the procedure for reporting workplace violence (42.8%). Approximately 55.7% of respondents were employed in medical departments and 44.3% worked in surgical departments. Most participants were residents (52%), followed by consultants (32.1%) and specialists (15.9%).

During the preceding 12 months, more than one-third of the physicians experienced verbal abuse (36.5%), with most reporting having been abused sometimes (60%), and 28.5% reporting that they were abused once. The most common attackers were patients (34.5%) and relatives of patients (32.8%). Staff members were also a source of abuse in 22.6% of cases. Most violent actions were carried out by males (61.1%), followed by both males and females in 20.6% of cases. Approximately two-thirds of participants believed that the incidents could have been prevented (66.9%, Table 2).

Table 2: Frequency and characteristics of verbal abuse events against physicians during the last 12 months in King Fahd Hospital of the University, Khobar (2016, n= 359)

Characteristics	Number	Percent
Exposure to verbal abuse in the last 12 months (n=359)		
Yes	131	36.5
No	228	63.5
Frequency of verbal abuse in the last 12 months (n=130)		
All the time	15	11.5
Sometimes	78	60.0
Once	37	28.5
Identity of attacker (n=177)*		
Patient	61	34.5
Relatives of patient	58	32.8
Staff member	40	22.6
Management/supervisor	9	5.1
External colleague	5	2.8
General public	2	1.1
Other	2	1.1
Sex of attacker (n=131)		
Male	80	61.1
Female	24	18.3
Both	27	20.6
The incident could have been prevented (n=127)		
Yes	85	66.9
No	42	33.1

*Multiple responses allowed

The majority of verbally abused physicians reported that no investigation had been conducted concerning the causes of the abuse (71.9%). Physicians exposed to verbal abuse did not report the incidents in 84% of cases, citing the following reasons: the uselessness of the reporting system (43.6%), the incidents were not important (22.1%), or they were afraid of negative consequences as a result of reporting the abuse (12.1%). The majority of physicians said that their supervisors did not provide them with counseling (83.3%), opportunities to speak about the incidents (73.8%), or any other support (75%). Almost half of physicians were very dissatisfied (45.9%) with the manner in which the incidents were handled (Table 3).

Table 4 shows the association between physician characteristics and exposure to verbal abuse during the preceding 12 months. Exposure to verbal abuse was significantly more common among younger physicians, females, those with less experience of the job, those who work in shifts, and those who worked on evening or night shifts (between 6 p.m. and 7 a.m.). An increased level of worry about workplace violence was significantly associated with increased incidents of verbal abuse during the preceding year (*P*=0.000). Physicians employed in medical departments were verbally abused more often than physicians employed in surgical departments (*P*=0.015). Most victims were residents (45.2%), followed by specialists (35.1%) and consultants (23.5%, *P*=0.001).

Univariate logistic regression followed by multivariate logistic regression analysis was performed on all significant risk factors, adjusted for the effects of each other to assess the association between independent variables and exposure to verbal abuse. (Tables 5 and 6). Results indicated an increased odds of verbal abuse for physicians with an increased degree of worry about violence in the workplace. Compared to residents, consultants had a reduced odds of verbal abuse (OR: 0.30, 95% CI 0.11-0.85, *P*=0.023) (Table 6).

DISCUSSION

Limited studies on workplace violence have been conducted in Saudi Arabia. The current study aimed to assess the exposure of physicians to workplace verbal abuse. Approximately 36.5% of physicians who took part in the study reported experiencing verbal abuse during the preceding year. The prevalence of verbal abuse in our study was lower than that reported

Table 3: Reaction to and consequences of verbal abuse experienced during the last 12 months by physicians in King Fahd Hospital of the University, Khobar (2016, n=131)

Reaction to and consequences of the abuse incident	Number	Percent
Action taken to investigate the causes of the incident (n=128)		
Yes	17	13.3
No	92	71.9
Don't know	19	14.8
Barriers to report the incident (n=140)*		
Useless	61	43.6
It was not important	31	22.1
Afraid of negative consequences	17	12.1
Didn't know who to report to	17	12.1
Felt ashamed	5	3.6
Felt guilty	1	0.8
Other	8	5.7
Intervention taken by employer/ supervisor Counselling (n=120)		
Yes	20	16.7
No	100	83.3
Opportunity to speak about/ report it (n=122)		
Yes	32	26.2
No	90	73.8
Other support (n=120)		
Yes	30	25.0
No	90	75.0
Level of satisfaction in which the incident was handled (n=122)		
Very dissatisfied	56	45.9
Dissatisfied	32	26.3
Moderately satisfied	26	21.3
Satisfied	6	4.9
Very satisfied	2	1.6

*Multiple responses allowed

Table 4: Exposure to verbal abuse according to demographic and occupational characteristics of the participated physicians, King Fahd Hospital of the University, Khobar (2016, n=359)

Characteristics	Experienced verbal abuse in the last 12 months		$\chi 2$	*P*-value
	Yes (%)	No (%)		
Age			8.495	0.014
<30 years (n=148)	62 (41.9)	86 (58.1)		
30-39 years (n=113)	45 (39.8)	68 (60.2)		
≥40 years (n=98)	24 (24.5)	74 (75.5)		
Sex			6.997	0.008
Female (n=143)	64 (44.8)	79 (55.2)		
Male (n=213)	66 (31.0)	147 (69.0)		
Marital status			5.040*	0.062
Single (n=89)	41 (46.1)	48 (53.9)		
Married (n=261)	86 (33.0)	175 (67.0)		
Divorced/Widow/Widower (n=3)	1 (33.3)	2 (66.7)		
Work experience in the health sector			10.674	0.005
≤5 years (n=176)	74 (42.0)	102 (58.0)		
6-15 years (n=102)	40 (39.2)	62 (60.8)		
>15 years (n=80)	17 (21.2)	63 (78.8)		
Work in shifts			10.397	0.001
No (n=198)	57 (28.8)	141 (71.2)		
Yes (n=159)	72 (45.3)	87 (54.7)		
Work between 6 p.m. and 7 a.m.			6.197	0.013
No (n=90)	23 (25.6)	67 (74.4)		
Yes (n=269)	108 (40.1)	161 (59.9)		
Worried about violence in the workplace			38.285	0.000
Not worried at all (n=115)	19 (16.5)	96 (83.5)		
A little worried (n=102)	37 (36.3)	65 (63.7)		
Moderately worried (n=82)	40 (48.8)	42 (51.2)		
Worried (n=23)	14 (60.9)	9 (39.1)		
Very worried (n=32)	19 (59.4)	13 (40.6)		
Presence of procedures for reporting of violence in the workplace			1.113	0.573
Yes (n=137)	53 (38.7)	84 (61.3)		
No (n=64)	25 (39.1)	39 (60.9)		
Don't know (n=150)	50 (33.3)	100 (66.7)		
Specialty			5.915	0.015
Medical (n=200)	84 (42.0)	116 (58.0)		
Surgical (n=159)	47 (29.6)	112 (70.4)		
Job title/ professional status			14.46	0.001
Resident (n=186)	84 (45.2)	102 (54.8)		
Specialist (n=57)	20 (35.1)	37 (64.9)		
Consultant (n=115)	27 (23.5)	88 (76.5)		

* Fisher's exact test

by Fnais *et al*[20], who found that 84% of residents under training programs in three National Guard Hospitals in Saudi Arabia experienced at least one type of discrimination and harassment. Their study included different types of harassment: verbal, academic, physical, sexual, and discrimination by gender, physical appearance, or area of origin, broader than that of our study which measured only the verbal type of violence. It is possible that the current study may have underestimated the real levels of violence, due to the reluctance of the participants to report incidents of violence in their workplaces. This may also have occurred due to recall bias, as this study measured the incidents of violence that were experienced during the previous 12-month period.

We used a standardized survey that has been used by many authors from different countries and with procedures which allow us to compare our results with such previous findings. The prevalence of verbal abuse against health care providers found during the preceding year in different countries is as follows: Australia (67%), South Africa (52-60.1%), Portugal (27.4-51%), Thailand (47.7%), Lebanon (40.9%), Brazil (39.5%) and Bulgaria (32.2%)[2]. Most attackers in our study were patients and their relatives. This result is congruent with many previous studies[13,21]. Additionally, staff members were responsible for many cases of verbal abuse, a finding that is also in line with many previous studies[21,22]. This finding is crucial, as supervisors should encourage a positive work

Table 5: Univariate logistic regression showing the association of demographic and occupational characteristics of physicians with exposure to verbal abuse in the last 12 months, King Fahd Hospital of the University, Khobar (2016)

Characteristics	OR (95% CI)	*P*-value
Age		
<30 years	1 (reference)	
30-39 years	0.92 (0.56-1.51)	0.736
≥40 years	0.45 (0.26-0.79)	0.006
Sex		
Female	1 (reference)	
Male	0.55 (0.36-0.86)	0.008
Work experience in the health sector		
≤5 years	2.69 (1.46-4.97)	0.002
6-15 years	2.39 (1.23-4.66)	0.010
>15 years	1 (reference)	
Work in shifts		
No	1 (reference)	
Yes	2.05 (1.32-3.17)	0.001
Work between 6 p.m. and 7 a.m.		
No	1 (reference)	
Yes	1.95 (1.15-3.33)	0.014
Worried about violence in the workplace		
Not worried at all	1 (reference)	
A little worried	2.88 (1.52-5.43)	0.001
Moderately worried	4.81 (2.50-9.27)	0.000
Worried	7.86 (2.98-20.76)	0.000
Very worried	7.38 (3.12-17.45)	0.000
Specialty		
Medical	1 (reference)	
Surgical	0.58 (0.37-0.90)	0.015
Job title/ professional status		
Resident	1 (reference)	
Specialist	0.66 (0.35-1.21)	0.180
Consultant	0.37 (0.22-0.63)	0.000

OR: Odds ratios; CI: Confidence interval

environment for staff members based on mutual respect.

Although a workplace violence reporting procedure was established at KFHU at the end of 2014, almost half of physicians weren't aware of this procedure (42.8%). Moreover, the majority of physicians in the current study did not report the incidents. The most reported cause for under reporting of such cases was the "uselessness" of the reporting procedure. Underreporting of violence is a common finding and documented by many previous studies[21]. Additionally, 66.9% of verbally abused physicians said that the incidents were preventable, also in line with previous studies where most victims report that the violent acts were preventable[11,13,22]. Many physicians in our study mentioned that they did not report the incident because the attack was not important. In addition, other studies have found that many victims thought that violence is a part of their job[9,10,23]. Additionally, the majority of physicians in the current study reported that no investigations were undertaken as a result of the abuse. This can also explain why most physicians in our study did not report the cases. In agreement with this explanation, Blando *et al*[24] reported that a lack of action after reporting and variation in perceptions of violence, are the major barriers to effective implementation of workplace violence prevention programs. Other causes of underreporting in our study included subjects not knowing who to report the incidents to, or being afraid of negative consequences after reporting, findings that are in agreement with other studies[10]. Moreover, the majority of physicians in our study didn't receive counseling, an opportunity to speak about the attack or report it to their supervisors, or any other support. Consequently, most physicians in our study were very dissatisfied with the manner in which the incident was handled.

An important finding in this study is that verbal abuse is significantly more prevalent among physicians who have a higher degree of worry about workplace violence. This is consistent with previous studies[25]. The cyclical model of violence which was studied by Whittington and Wykes[26] suggested that stress induced by exposure to violence could affect staff performance and leads to an adoption of behaviors which can increase the possibility of a recurrence of violence. This study revealed that residents are at greater risk of verbal abuse than specialists and consultants. Consultants are usually respected by both patients, relatives of patients, and by other staff members because they are at the top of hierarchy in

Table 6: Multivariate logistic regression model* showing the association of demographic and occupational characteristics of physicians with exposure to verbal abuse in the last 12 months, King Fahd Hospital of the University, Khobar (2016)

Characteristics	OR (95% CI)	*P*-value
Worried about violence in the workplace		
Not worried at all	1 (reference)	
A little worried	2.93(1.47-5.84)	0.002
Moderately worried	3.97 (1.95-8.10)	0.000
Worried	5.95 (2.11-16.74)	0.001
Very worried	6.98(2.74-17.79)	0.000
Job title/ professional status		
Resident	1(reference)	
Specialist	0.44 (0.17-1.11)	0.080
Consultant	0.30 (0.11-0.85)	0.023

OR: Odds ratios; CI: Confidence interval

*The model was adjusted for age, sex, work experience in health sector and work in shifts

Working hours between 6 pm to 7 am and specialty (medical vs. surgical)

the medical profession. Additionally, residents who are undergoing training could be vulnerable to violence because of this professional hierarchy in the medical field as shown by Miedema *et al*[27].

Regarding the strengths of this study, most authors in the literature focus on specific work settings, such as the emergency or psychiatric settings, whereas our study included physicians from different specialties. We used a standardized instrument to allow for better comparisons between our findings and those of other studies. This study did have some limitations: (1) it was a cross-sectional study, so causality of the observed associations cannot be determined; (2) physicians were chosen only from one hospital in the Eastern Province of Saudi Arabia, therefore, the results cannot necessarily be generalized to all health care providers in the Kingdom; (3) recall bias could have been an issue regarding history of past events. We tried to decrease recall bias by limiting the questions to the last attack which occurred in the previous year.

CONCLUSION

This study revealed that verbal abuse is prevalent among physicians, and that most perpetrators were patients and their relatives. We suggest the following recommendations:

- Increasing public awareness of health care workers' rights.
- Establishing counseling programs for health care supervisors to help the employee in need.
- Establishing an effective reporting system and encouraging health care providers to report all cases using this system.
- A national study of workplace violence among health care providers in Saudi Arabia is required to estimate the total burden of the phenomenon.
- Longitudinal studies are needed to provide more understanding of the problem, its determinants, and the impacts on victims and the health care system.

ACKNOWLEDGMENT

The researcher acknowledges the help of Miss. Shrooq Al Ghamdi in the creation of the database, and the help of Dr. Danah AlShamlan, Dr. Fatima Fakhroo, Dr. Iba AlFawaz, Dr. Reema AlOtaibi and Dr. Sarah AlArifi in the data collection process. I also thank Dr. Reem AlShamlan and Dr. Abeer AlShamlan for their help in the editing process. The cooperation from physicians who participated in this study is highly appreciated. The content is under the responsibility of the researcher and does not represent the views of the King Fahd Hospital of the University or the Imam Abdulrahman Bin Faisal University.

Source of funding: Self-funded

Conflict of interests: The authors declare no conflicts of interest.

REFERENCES

1. Krug EG, Dahlberg LL, Mercy JA, Zwi AB, Lozano R, editors. World Report on Violence and Health. Geneva: World Health Organization, 2002. Available from: http://whqlibdoc.who.int/publications/2002/9241545615_eng.pdf?ua=1. Accessed October 15, 2016.
2. Martino V. Workplace violence in the health sector: Country Case Studies. Brazil, Bulgaria, Lebanon, Portugal, South Africa, Thailand and an additional Australian study. Geneva: World Health Organization, 2002.
3. Joint Programme on Workplace Violence in the Health Sector of the International Labor Office, the International Council of Nurses, the World Health Organization, and the Public Services International.[Accessed October 15, 2016] Available at: www.who.int/violence_injury_prevention/violence/interpersonal/en/WVquestionnaire.pdf.
4. Kitaneh M, Hamdan M. Workplace violence against physicians and nurses in Palestinian public hospitals: a cross-sectional study. BMC Health Services Research 2012; 12:469.
5. Schablon A, Zeh A, Wendeler D, Peters C, Wohlert C, Harling M, *et al.* Frequency and consequences of violence and aggression towards employees in the German healthcare and welfare system: a cross-sectional study. BMJ Open 2012; 2(5):e001420.
6. Talas MS, Kocaoz S, Akguc S. A survey of violence against staff working in the emergency department in ankara, Turkey. Asian Nurs Res 2011; 5(4):197-203.
7. Magnavita N, Heponiemi T. Violence towards health care workers in a Public Health Care Facility in Italy: a repeated cross-sectional study. BMC Health Serv Res 2012; 12:108.
8. Fujita S, Ito S, Seto K, Kitazawa T, Matsumoto K, Hasegawa T. Risk factors of workplace violence at hospitals in Japan. J Hosp Med 2012; 7(2):79-84.
9. Altinbas K, Altinbas G, Turkcan A, Oral ET, Walters J. A survey of verbal and physical assaults towards psychiatrists in Turkey. Int J Soc Psychiatry 2011; 57(6):631-6.
10. Algwaiz WM, Alghanim SA. Violence exposure among health care professionals in Saudi public hospitals. A preliminary investigation. Saudi Med J 2012; 33(1):76-82.
11. Al-Shamlan NA, Jayaseeli N, Al-Shawi MM, Al-Joudi AS. Are nurses verbally abused? A cross-sectional study of nurses at a university hospital, Eastern Province, Saudi Arabia. J Family Community Med 2017; 24(3):173-180.
12. El-Gilany AH, El-Wehady A, Amr M. Violence against primary health care workers in Al-Hassa, Saudi Arabia. J Interpers Violence 2010; 25(4):716-734.
13. Al-Turki N, Afify AA, AlAteeq M. Violence against health workers in Family Medicine Centers. Journal of

Multidisciplinary Healthcare 2016; 9:257-266.
14. Deeb M. Working paper. Geneva: ILO/ICN/WHO/PSI Joint Programme on Workplace Violence in the Health Sector; Workplace violence in the health sector – Lebanon country case study. https://www.who.int/violence_injury_prevention/injury/en/WVsynthesisreport.pdf
15. Ferrinho P, Antunes A, Biscaia A, *et al.* Working paper. Geneva: ILO/ICN/WHO/PSI Joint Programme on Workplace Violence in the Health Sector; Workplace violence in the health sector – Portuguese case studies. https://www.who.int/violence_injury_prevention/violence/en/wpv_lebanon.pdf?ua=1
16. Palácios M, Loureiro dos Santos M, Barros do Val M, *et al.* Working paper. Brazil. Geneva: ILO/ICN/WHO/PSI Joint Programme on Workplace Violence in the Health Sector; Workplace violence in the health sector – country case study. https://www.who.int/violence_injury_prevention/violence/interpersonal/en/WVcountrystudyportugal.pdf
17. Sripichyakan K, Thungpunkum P, Supavititpatana B. Working paper. Thailand. Geneva: ILO/ICN/WHO/PSI Joint Programme on Workplace Violence in the Health Sector; Workplace violence in the health sector – a case study. https://www.who.int/violence_injury_prevention/violence/interpersonal/en/WVBrazil.pdf
18. Steinman S. Working paper. South Africa. Geneva: ILO/ICN/WHO/PSI Joint Programme on Workplace Violence in the Health Sector; Workplace violence in the health sector – country case study. https://www.who.int/violence_injury_prevention/violence/interpersonal/en/WVcountrystudythailand.pdf
19. Tomev L, Daskalova N, Ivanova V. Working paper. Bulgaria. Geneva: ILO/ICN/WHO/PSI Joint Programme on Workplace Violence in the Health Sector; Workplace violence in the health sector – country case study. https://www.researchgate.net/profile/Susan_Steinman1/publication/237076002_Workplace_Violence_in_the_Health_Sector_Country_Case_Study_South_Africa/links/0deec51b49f6d4a816000000/Workplace-Violence-in-the-Health-Sector-Country-Case-Study-South-Africa.pdf
20. Fnais N, al-Nasser M, Zamakhshary M, Abuznadah W, Al Dhukair S, Saadeh M, *et al.* Prevalence of harassment and discrimination among residents in three training hospitals in Saudi Arabia. Ann Saudi Med 2013; 33(2):134-139.
21. ALBashtawy M, Al-Azzam M, Rawashda A, Batiha AM, Bashaireh I, Sulaiman M. Workplace violence toward emergency department staff in Jordanian hospitals: a cross-sectional study. J Nurs Res 2015; 23(1):75-81.
22. Zafar W, Siddiqui E, Ejaz K, Shehzad MU, Khan UR, Jamali S, *et al.* Health care personnel and workplace violence in the emergency departments of a volatile metropolis: results from Karachi, Pakistan. J Emerg Med 2013; 45(5):761-772.
23. Vezyridis P, Samoutis A, Mavrikiou PM. Workplace violence against clinicians in Cypriot emergency departments: a national questionnaire survey. J Clin Nurs 2015; 24(9-10):1210-1222.
24. Blando J, Ridenour M, Hartley D, Casteel C. Barriers to effective implementation of programs for the prevention of workplace violence in hospitals. Online J Issues Nurs 2015; 20(1):5.
25. Liu H, Zhao S, Jiao M, Wang J, Peters DH, Qiao H, *et al.* Extent, nature, and risk factors of workplace violence in public tertiary hospitals in china: a cross-sectional survey. Int J Environ Res Public Health 2015; 12(6):6801-6817.
26. Whittington R, Wykes T. An observational study of associations between nurse behaviour and violence in psychiatric hospitals. J Psychiatr Mental Health Nurs 1994; 1(2):85-92.
27. Miedema B, MacIntyre L, Tatemichi S, Lambert-Lanning A, Lemire F, Manca D, *et al.* How the medical culture contributes to coworker-perpetrated harassment and abuse of family physicians. Ann Fam Med 2012; 10(2):111-117.

Original Article

Clinicopathologic assessment of patients with ovarian granulosa cell tumor in a tertiary medical center

Tufan Oge, Duygu K Comert, Yusuf Cakmak, Isik Sozen
Department of Obstetrics and Gynecology, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey

Kuwait Medical Journal 2022; 54 (1): 88 - 92

ABSTRACT

Objectives: To evaluate the clinic-pathological characteristics and management of adult granulosa cell tumor in a university clinic
Design: Retrospective study
Setting: Department of Obstetrics and Gynecology, Eskisehir Osmangazi University School of Medicine
Subjects: Forty-eight patients with diagnosis of adult granulosa cell tumors between 2005-2014
Intervention: Clinicopathologic assessment of patients with adult granulosa cell tumors who underwent surgical treatment and had follow up visits at our institution
Main outcome measure: Patients' age, body mass index, menopausal status, presenting manifestation, tumor size, CA 125 level, stage of the disease, surgical treatment, recurrence, adjuvant therapy, endometrial sampling, pathology and operation records
Results: Abdominal pain and vaginal bleeding were common symptoms. The median tumor size was 8 cm (2-20cm). The majority of patients were FIGO stage I (87.5%). Four patients had well-differentiated endometrioid adenocarcinoma of the endometrium. Chemotherapy was administered as an adjuvant treatment to patients with stage IC, II, and IV disease. The recurrence of the disease was noted in five patients (10.4%). While three of them were FIGO stage IC, two of them were stage IVA. The median recurrence time was 50 months. The most common recurrence site was intraabdominal peritoneum. Surgery and chemotherapy were used in the treatment of recurrent disease.
Conclusion: Most of the patients with adult granulosa cell tumors are diagnosed in stage I. Although recurrence is rare, recurrence can be seen even in the early stage. Lifelong follow up should be recommended. The endometrium should be evaluated before or after the diagnose. Attention should be given to endometrial sampling.

KEY WORDS: adult type, granulosa cell tumor, ovarian cancer, ovary, sex cord stromal tumor

INTRODUCTION

Granulosa cell tumors (GCT) derive from the gonadal stroma and it is the most common malignant sex cod stromal tumors[1]. They account for 2-5% of all ovarian cancers[2]. GCT can occur in all ages. However, perimenopausal women are mostly affected[3]. It is divided into two subtypes according to histological findings: adult type (AGCT) and juvenile type. AGCTs are more common than the juvenile type[4]. As GCT produce estrogen, patients will refer to hospital with hyperestrogenic symptoms like menstrual irregularities and endometrial hyperplasia[5,6]. Most of the patients present with stage I disease and it is usually unilateral[7]. Primary treatment of this tumor is surgery. The extensiveness of surgery will be decided based on the patient's fertility desire[3]. Complete surgical staging and adjuvant treatment are controversial because of the low recurrence rate and low incidence of lymph node metastasis[8]. As five-year overall survival is above 90%, AGCT has a good prognosis. Even with its good prognosis, late recurrences will cause morbidity and mortality, and it will be difficult to manage[9]. Most of the recurrences occur more than five years after primary treatment. Therefore, long term follow-ups are required[10]. The rarity of AGCTs makes it challenging to decide primary and recurrence disease treatment.

The objective of this study is to evaluate the clinic-pathological characteristics and management of these rare tumors in a university clinic.

Address correspondence to:
Duygu Kavak Comert, M.D., Department of Obstetrics and Gynecology, Eskisehir Osmangazi University School of Medicine, 26100. Eskisehir, Turkey. Tel: +90 506 5015353; Fax : +90 222 2398412; E-mail: duygukavak@yahoo.com

SUBJECTS AND METHODS

Retrospectively, we reviewed a total of 48 patients with the diagnosis of AGCT at Eskisehir Osmangazi University between 2005-2014. The study was approved by the ethics committee (2019-296).

Patients who were diagnosed with AGCT, underwent surgical treatment and had follow-up visits at our institution were included the study. Ultrasound scan of pelvis was performed by a gynecologist oncologist before the surgery. Frozen section was used for intraoperative assessment of pelvic mass in all of the 48 patients. The extension of the surgery was decided according to the results of the frozen section and patient's fertility desire. Our exclusion criteria were sex cord-stromal tumors other than granulosa type, having surgery out of our institution, no follow-up visits, and incomplete records and pathologic information. It was found that 82 patients had sex-cord stromal tumors, 32 of them had sex cord stromal tumor other than granulosa type, and 2 of them quit their follow-up. Thirty-four patients were excluded from the study and the records from 48 patients with diagnosis of granulosa cell tumors were included.

The data included age, body mass index (BMI), menopausal status, presenting manifestation, tumor size, CA 125 level, stage of disease according to International Federation of Gynecology and Obstetrics (FIGO), surgical treatment, recurrence, adjuvant therapy, endometrial sampling were obtained from hospital database system, pathology and operation records, and patients health records. BMI, a measure of body fat, was calculated by weight in kilograms divided by height in meters squared. Surgical treatment was defined as primary fertility-sparing staging, primary non-conservative staging, and not staged surgery, either total abdominal hysterectomy and bilateral salpingo-oophorectomy or unilateral salpingo-oophorectomy (USO). For fertility sparing surgery, the uterus and at least one adnexa were conserved. USO or USO with staging surgery was performed to preserve the fertility. After treatment, patients were examined every three months in the first two years, every six months the consecutive three years and then annually.

Statistical analysis was performed by using SPSS 20.0 software.

RESULTS

Forty-eight women were identified with a diagnosis of AGCT between 2005-2014 in our institution. The median age and BMI of the patients at the time of diagnosis were 50 years (range: 22-70 years) and 28.5 kg/m² (range: 23-44 kg/m²) respectively. Of the patients, 18 (37.5%) of them were premenopausal. Abdominal pain and vaginal bleeding were common symptoms causing the patient to come to the hospital. Most of our patients had a unilateral disease (95.8%). The median tumor size was 8 cm (2-20cm). When the preoperative CA125 values were evaluated, it was seen that only 14 patients (29.16%) had elevated CA125 level. The majority of patients were FIGO stage I (87.5%). The endometrial assessment was performed to 15 patients preoperatively. Four patients had well-differentiated endometrioid adenocarcinoma of the endometrium, three of them were known preoperatively. Other endometrial alterations were endometrial hyperplasia and polyp (Table 1). The majority of patients were treated by staging surgery (70.7%). Preserving of uterus was decided according to patient's age and fertility desire. Complete pelvic and paraaortic lymphadenectomy were performed to surgically staged patients. Except for four patients

Table 1: Characteristics of patients with adult granulosa cell tumor

Patient characteristics	Number of patients (n=48)	Percentage/ range
Age (years, median)	50	22-70
BMI (kg/m², median)	28.5	23-44
Menopausal status		
Premenopausal	18	37.5%
Postmenopausal	30	62.5%
Presenting manifestation, n (%)		
Vaginal bleeding	20	41.6%
Abdominal mass	6	12.5%
Abdominal pain	22	45.8%
Ovarian tumor		
Unilateral	46	95.8%
Bilateral	2	4.1%
Tumor size (cm, median)	8	2-20
CA 125 level		
Elevated (>35 IU/ml)	14	29.1%
Normal	34	70.8%
FIGO stage		
IA	20	41.6%
IB	0	0
IC	22	45.8%
II	2	4.1%
III	0	0
IV	4	8.3%
Endometrial pathology		
Normal	29	60.4%
Endometrial polyp	5	10.4%
Hyperplasia	10	20.8%
Carcinoma	4	8.3%
Follow up time (months, median)	83	22-155
Recurrence	5	10.4%
Recurrence time (months, median)	50	37-133
Died of disease	4	8.3%

BMI: body mass index; FIGO: International Federation of Gynecology and Obstetrics.

with stage IV disease, optimal cytoreduction was achieved. Two patients who had FIGO stage IB endometrial cancer and FIGO stage other than I AGCT received chemotherapy and radiotherapy as adjuvant treatment. One patient had concomitant stage IB1 cervical cancer that was determined in pathology specimen and was referred to adjuvant radiotherapy. Chemotherapy was administered as adjuvant treatment to patients with stage IC, II, and IV disease (Table 2). One patient could not receive adjuvant chemotherapy because of her medical condition. While twenty-two patients received bleomycin, etoposide and cisplatin chemotherapy, five patients received paclitaxel and carboplatin chemotherapy.

Table 2: Surgical procedure type and adjuvant treatment

Treatment	Number of patients (n=48)	Percentage
Surgical treatment		
Primary fertility sparing staging	2	4.1
Primary non-conservative staging	32	66.6
Not staged (TAH+BSO)	10	20.8
Not staged (USO/cystectomy)	4	8.3
Adjuvant chemotherapy	24	50
Adjuvant radiotherapy	1	2
Adjuvant radiotherapy+ chemotherapy	2	4.1

TAH+BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy; USO: unilateral salpingo-oophorectomy.

Recurrence of disease was noted in five patients (10.4%). While three of them were FIGO stage IC, two of them were stage IVA. The median recurrence time was 50 months. We diagnosed the recurrence histologically by surgery in two patients and by radiologic guided biopsy in three patients. The most common recurrence site was intraabdominal peritoneum. Surgery and chemotherapy were used in the treatment of recurrent disease (Table 3).

Four patients died because of the disease. Three of them had recurrence of the disease. One of them had recurrence in the liver and chemotherapy was used for treatment. The other two had recurrence in the intraabdominal peritoneum. Chemotherapy was used for one of them for treatment of recurrent disease. Both surgery and chemotherapy were used for treatment of the other intraabdominal recurrence. Despite ongoing treatment, three had progressive disease and died because of recurrence. The last patient who died because of the disease had FIGO stage IVB disease. After surgery, the patient was referred to chemotherapy as adjuvant treatment; however ,she could not receive chemotherapy because of her medical condition and died because of the progression of liver parenchymal metastasis.

DISCUSSION

Our study showed that most of the patients with AGCT are diagnosed in stage I of the disease. Although recurrences are rare, recurrence can be seen even in the early stage, and patients should stay in follow up. Due to secreting estrogen, endometrium should be evaluated before or after the diagnosis. CA125 value may not always rise like ovarian epithelial tumors.

Compatible with the literature, the median age of our study population at the time of diagnosis was 50 years (22-70 years), most of them were postmenopausal and median BMI was 28.5 kg/m² (23-44 kg/m²). As in our study, the most reported presenting symptoms are vaginal bleeding and abdominal mass in the literature[11,12]. In a systemic review, Levin *et al* reported that stage I disease ranges 74-95%, stage II disease ranges 5.1-11%, stage III disease ranges 0.8-10% and stage IV disease ranges 0.5-8.6%[1]. Our results showed that FIGO stage I disease was 87.5% among patients with AGCT.

Lee *et al* analyzed 68 patients with AGCT and reported endometrial pathology was found in 26.4% of them, of which 2.9% were endometrial cancer[11]. Some studies informed higher rates of endometrial cancer (6.2%, 17%)[12,13]. In our study population, endometrial alterations were endometrial hyperplasia, polyp and endometrial cancer. We found that endometrial cancer

Table 3: Characteristics of patients with recurrence

Case	Age (years)	FIGO stage	Tumor size (cm)	Initial treatment	Recurrence Time (months)	Site of recurrence	Treatment of recurrence Surgery+	Outcome
1	30	IC	6	USO	37	Intraabdominal Peritoneum	Chemotherapy	DOD
2	45	IVA	8	Staging surgery	40	Liver	Chemotherapy	DOD
3	34	IC	10	Staging surgery	133	Vagen vault	Surgery+ Chemotherapy	NED
4	38	IC	10	TAH+BSO	50	Paraaortic Lymph node	Chemotherapy	NED
5	54	IVA	11	Staging surgery	97	Intraabdominal Peritoneum	Chemotherapy	DOD

FIGO: International Federation of Gynecology and Obstetrics; TAH+BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy; USO: unilateral salpingo-oophorectomy; DOD: die of disease; NED: no evidence of disease

was seen 8.3% of patients. All these findings highlight the importance of endometrial sampling in management of AGCT. Preoperative endometrial sampling can be used to guide patient management and to inform them.

We evaluated CA125 value as a tumor marker in AGCT and 29.1% of our patients showed elevated CA125 level (55±78 IU/ml). In a case-control study, Yesilyurt *et al* stated that GCT patients had elevated CA125 level (64.5±130 IU/ml)[14]. Another study evaluated patients with AGCT by Lee *et al* reported 13.1% of patients had elevated levels[11]. CA125 level is not expected to rise as in epithelial ovarian cancer; determining preoperative CA125 level will be important in following the patient postoperatively, if she had high level of CA125.

The standard treatment of AGCT is surgery. Hysterectomy and bilateral salpingo-oophorectomy should be performed according to the patient's fertility desire[1]. Surgical resection with negative margins is considered as best treatment[15]. Performing lymphadenectomy is controversial. While some researchers mention lymph node status as a prognostic factor for survival and recommend complete surgical staging[16,17], some researchers are against lymph node dissection because of the low rate of lymph node metastasis[18,19]. We performed pelvic and paraaortic lymphadenectomy to most of our patients (70.7%). None of them had lymph node metastasis. We have still been performing surgical staging to patients with AGCT at our clinic; however, we cannot claim the necessity of lymph node dissection.

The role of adjuvant chemotherapy and radiotherapy is controversial. In our study, half of our patients and all of the patients with recurrence received bleomycin, etoposide and cisplatin or paclitaxel and carboplatin as adjuvant chemotherapy. For patients with high-risk stage I tumors and higher stages, it can be acceptable to recommend adjuvant chemotherapy. Platinum-based chemotherapy is one of the recommended options[20]. Adjuvant radiotherapy is usually to palliate late-stage isolated recurrences[1]. None of our patients received adjuvant radiotherapy because of AGCT. Two patients with endometrial carcinoma and one patient with cervical cancer were referred to adjuvant radiotherapy.

Studies in the literature identified that stage of disease at diagnosis and size of the tumor were correlated with recurrence[11,13,21]. In our study, three of five patients with recurrence were stage IC and the median tumor size was 10 cm in recurrence disease. It can be said that small study population may contribute to this recurrence in patients with the early-stage. Even if this is the case, based on our findings, we argue that recurrence can be seen in stage I disease. As follow-up visits are important to detect the recurrence early, patients should stay in follow up.

There were some limitations to our study. First, the methodological design of the current study is retrospective; therefore, it has got some inherent biases such as selection bias and information bias. First, the study group both included patients with fertility desire and patients underwent complete cytoreduction surgery. Therefore, there is not a single surgical procedure for this rare neoplasm. It may be better to perform a multicenter study to reach an adequate number of patients who underwent same surgical procedure to conclude a better result. Nevertheless, the extent of our study group may be accepted as adequate from a single center who underwent surgery with the same surgery and oncology team. Second, the other limitation is lack of long-term survival analysis of the patients. It is very difficult to make a study about a very rare ovarian neoplasm and its long-term survival comparing with different stages and types of ovarian cancer. Most of our patients were diagnosed mostly in stage IA and IC. Moreover, it is also difficult to comment on chemotherapy regimen in patients with stage IC. Lastly, during the time, paclitaxel carboplatin regimens were more preferable regimen than bleomycin, etoposide and cisplatin, and our study group included patients who received both chemotherapy regimens. Therefore, it is difficult to conclude a uniform result, but the main aim of our study is not to compare chemotherapy regimens directly. Moreover, single-center experience gives similar treatment protocols with similar surgery and oncology team.

CONCLUSION

In conclusion, most of the patients with AGCT are diagnosed in stage I. Although recurrences are rare, even in the early stage, recurrence can be seen. Lifelong follow up should be recommended. Due to estrogen secretion, endometrium should be evaluated before or after the diagnosis. Attention should be given to endometrial sampling especially in patients with conservative surgery.

ACKNOWLEDGMENT

Authors have no conflict of interest.

Author contribution:

Tufan Oge performed the operations, designed the study, wrote the article; Duygu K Comert helped to perform operations, comment on and edited the article, statistical analyses; Yusuf Cakmak helped to perform operations, collected the data, comment on the article; Isik Sozen collected the data, comment on the article, statistical analyses.

REFERENCES

1. Levin G, Zigron R, Haj-Yahya R, Matan LS, Rottenstreich A. Granulosa cell tumor of ovary: A systematic review of recent evidence. Eur J Obstet Gynecol Reprod Biol 2018; 225:57-61.
2. Li J, Bao R, Peng S, Zhang C. The molecular mechanism of ovarian granulosa cell tumors. J Ovarian Res 2018; 11(1):13.
3. Suri A, Carter EB, Horowitz N, Denslow S, Gehrig PA. Factors associated with an increased risk of recurrence in women with ovarian granulosa cell tumors. Gynecol Oncol 2013; 131(2):321-324.
4. Dridi M, Chraiet N, Batti R, Ayadi M, Mokrani A, Meddeb K, *et al*. Granulosa cell tumor of the ovary: A retrospective study of 31 cases and a review of the literature. Int J Surg Oncol 2018; 2018:4547892.
5. DiSaia P, Creasman W, Mannel R, McMeekin DS, Mutch D. Clinical Gynecologic Oncology, 9th ed. Elsevier, Oxford, 2018, 348-50.
6. Oge T, Ozalp SS, Yalcin OT, Kabukcuoglu S, Arslan E. Ruptured granulosa cell tumor of the ovary as a cause of acute abdomen in postmenopausal woman. Case Rep Oncol Med 2012; 2012:451631.
7. Young RH. Ovarian sex cord-stromal tumours and their mimics. Pathology 2018; 50(1):5-15.
8. Gurumurthy M, Bryant A, Shanbhag S. Effectiveness of different treatment modalities for the management of adult-onset granulosa cell tumours of the ovary (primary and recurrent). Cochrane Database Syst Rev 2014; 2014(4):CD006912.
9. Wang D, Xiang Y, Wu M, Shen K, Yang J, Huang H, *et al*. Is adjuvant chemotherapy beneficial for patients with FIGO stage IC adult granulosa cell tumor of the ovary? J Ovarian Res 2018; 11(1):25.
10. Oseledchyk A, Gennarelli RL, Leitao MM, Jr., Aghajanian CA, Iasonos A, Zivanovic O, *et al*. Adjuvant chemotherapy in patients with operable granulosa cell tumors of the ovary: a surveillance, epidemiology, and end results cohort study. Cancer Med 2018; 7(6):2280-2287.
11. Lee IH, Choi CH, Hong DG, Song JY, Kim YJ, Kim KT, *et al*. Clinicopathologic characteristics of granulosa cell tumors of the ovary: a multicenter retrospective study. J Gynecol Oncol 2011; 22(3):188-195.
12. Hauspy J, Beiner ME, Harley I, Rosen B, Murphy J, Chapman W, *et al*. Role of adjuvant radiotherapy in granulosa cell tumors of the ovary. Int J Radiat Oncol Biol Phys 2011; 79(3):770-774.
13. Mangili G, Ottolina J, Gadducci A, Giorda G, Breda E, Savarese A, *et al*. Long-term follow-up is crucial after treatment for granulosa cell tumours of the ovary. Br J Cancer 2013; 109(1):29-34.
14. Yesilyurt H, Tokmak A, Guzel AI, Simsek HS, Terzioglu SG, Erkaya S, *et al*. Parameters for predicting granulosa cell tumor of the ovary: a single center retrospective comparative study. Asian Pac J Cancer Prev 2014; 15(19):8447-8450.
15. Seagle BLL, Ann P, Butler S, Shahabi S. Ovarian granulosa cell tumor: A National Cancer Database study. Gynecol Oncol 2017; 146(2):285-291.
16. Ertas IE, Gungorduk K, Taskin S, Akman L, Ozdemir A, Goklu R, *et al*. Prognostic predictors and spread patterns in adult ovarian granulosa cell tumors: a multicenter long-term follow-up study of 108 patients. Int J Clin Oncol 2014; 19(5):912-920.
17. Chan JK, Zhang M, Kaleb V, Loizzi V, Benjamin J, Vasilev S, *et al*. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary--a multivariate analysis. Gynecol Oncol 2005; 96(1):204-209.
18. Park JY, Jin KL, Kim DY, Kim JH, Kim YM, Kim KR, *et al*. Surgical staging and adjuvant chemotherapy in the management of patients with adult granulosa cell tumors of the ovary. Gynecol Oncol 2012; 125(1):80-86.
19. Brown J, Sood AK, Deavers MT, Milojevic L, Gershenson DM. Patterns of metastasis in sex cord-stromal tumors of the ovary: can routine staging lymphadenectomy be omitted? Gynecol Oncol 2009; 113(1):86-90.
20. National Comprehensive Cancer Network. Ovarian cancer (version 1.2017). Accessed http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf; Sep 20,2018.
21. Sakr S, Abdulfatah E, Thomas S, Al-Wahab Z, Beydoun R, Morris R, *et al*. Granulosa cell tumors: Novel predictors of recurrence in early-stage patients. Int J Gynecol Pathol 2017; 36(3):240-252.

Original Article

The potential role of neutrophil to lymphocyte ratio in predicting prostate cancer in patients who underwent transrectal ultrasonography guided biopsy

Ismail Basmaci, Ibrahim H Bozkurt, Ozgu Aydogdu, Ertugrul Sefik, Serdar Celik, Tansu Degirmenci
Department of Urology, Health Sciences University, Bozyaka Training and Research Hospital, Izmir, Turkey

Kuwait Medical Journal 2022; 54 (1): 93 - 97

ABSTRACT

Objective: To investigate the relation of neutrophil lymphocyte ratio (NLR) with the diagnosis of prostate cancer (PCa) in patients who underwent transrectal ultrasonography guided biopsy (TRUS-bx)
Design: Retrospective study
Setting: Department of Urology, Health Sciences University, Bozyaka Training and Research Hospital, Izmir, Turkey
Subjects: This retrospective analysis included data from 172 consecutive patients who underwent TRUS-bx.
Interventions: Transrectal ultrasonography guided biopsy
Main outcome measures: The correlation of pre-biopsy NLR and finding PCa in TRUS-bx
Results: Group 1 was composed of 115 patients in whom pathology was reported benign, and group 2 included 57 patients in whom pathology was reported as PCa. There was no statistically significant difference in NLR between the benign disease subgroups. Group 2 was divided into three subgroups according to Gleason score and total prostate specific antigen (PSA). Mean NLR was not significantly different between these subgroups. A receiver operating characteristic curve analysis was used to calculate a cut-off value for NLR and the threshold provided by the analysis was 2.23. We identified 89 patients (51.7%) with a high NLR (≥2.23) and 83 patients (48.3%) with a low NLR (<2.23). A high NLR was significantly associated with finding PCa in TRUS-bx (*P*=0.006), older age (*P*=0.038), total PSA >10 (*P*=0.002), but not with prostate volume, benign disease subgroups or Gleason score (Gleason score=6 vs. Gleason score>6).
Conclusions: NLR may be used to predict potential PCa in patients who underwent TRUS bx.

KEY WORDS: Neutrophil lymphocyte ratio, prostate cancer, TRUS bx

INTRODUCTION

The incorporation of prostatic specific antigen (PSA) in clinical practice revolutionized diagnosis and modified the epidemiology of prostate cancer (PCa). Although it lacks many of the characteristics of an ideal tumor marker and is not tumor specific, PSA is still the most commonly used marker for diagnosis and follow-up of PCa. To increase the diagnostic accuracy of PSA, some parameters including % free PSA, PSA density, PSA velocity and PSA doubling time has been used. Also, some molecular derivatives and isoforms of PSA came into the market for the same reason[1]. There is increasing evidence to support the role of immune response as an important factor in human cancer development and progression. It has been hypothesized that the synthesis of inflammatory cytokines triggered by the tumor microenvironment alters acute phase reactants and hematologic components, including serum neutrophil and lymphocyte counts[2,3]. The neutrophil to lymphocyte ratio (NLR) has been reported to be an easily measured, highly reproducible and cheap marker of systemic immune response associated with outcomes of several malignancies including renal cell carcinoma, ovarian, lung and gastrointestinal cancer[4-7]. The aim of the present study is to investigate the relation

Address correspondence to:
Ismail Basmaci, MD, Department of Urology, Health Sciences University, Bozyaka Training and Research Hospital, Izmir, Turkey. Tel: +90 5053482790; E-mail: ibasmaci@yahoo.com

between NLR and the diagnosis of PCa in transrectal ultrasonography guided biopsy (TRUS-bx).

SUBJECTS AND METHODS

This retrospective analysis included data from 172 consecutive patients with available pre-biopsy complete blood count who underwent TRUS-bx between 2013 and 2015 in our clinic. The clinicopathological data and pre-biopsy NLR were retrieved from medical charts and electronic records of the patients retrospectively. NLR was defined as the ratio of absolute neutrophil count to absolute lymphocyte count. The indications of TRUS-bx were elevated PSA and/or abnormal digital rectal examination findings. A negative urine culture was obtained from all patients prior to TRUS-bx and periprostatic local anesthesia was performed with 2% lidocaine. Of all the patients, 140 had TRUS-bx for the first time, 27 had second biopsy, and five had third or more. All cases were evaluated by a single pathologist. The patients were divided into two groups. Group 1 was composed of 115 patients in whom pathology was reported as non-cancerous and Group 2 included 57 patients in whom pathology was reported as prostate adenocarcinoma. The general characteristics of the two groups are summarized in Table 1. The correlation of pre-biopsy NLR and finding PCa in TRUS-bx was assessed. The histopathology of the non-cancer group reports were subclassified as chronic prostatitis, benign prostate hyperplasia (BPH), high grade prostate intraepithelial neoplasia and atypical small acinar proliferation. The correlation of pre-biopsy NLR and these subgroups were also assessed. The correlation of NLR with the Gleason score and total PSA were assessed in Group 2.

All procedures were performed in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Statistical analyses were performed with the Statistical Package of Social Sciences (SPSS, Chicago, IL) version 21. Categorical variables were presented as numbers. Continuous variables were presented as means and standard errors of mean, and compared using the independent sample t test and one-way anova test. In patients with PCa, a receiver operating characteristics (ROC) curve was performed to detect the optimal threshold for NLR. The threshold value was developed with an equal emphasis on sensitivity and specificity with the use of Youden's index. The area under curve was used to quantify the effectiveness of NLR in diagnosing PCa. The patients were divided into two groups according to the cut-off value of NLR. These two groups were compared with Chi-square test, Fisher's exact test and independent sample two test. Statistical significance was set at a *P*-value of 0.05.

RESULTS

The mean age of patients was 63.4±0.7 and 64.1±1.1 in Group 1 and Group 2, respectively (Table 1). In Group 1, 90 patients (78.3%) underwent biopsy for the first time, while 22 (19.1%) and 3 (2.6%) patients had second and third biopsies respectively. In Group 2, 50 patients (87.7%) underwent prostate biopsy for the first time, while 5 (8.8%), 1 (1.8%) and 1 (1.8%) patients had second, third and fourth biopsy procedures respectively.

Table 1: Comparison of patients' characteristics between group 1 (non-cancer) and group 2 (prostate cancer)

Variables	Group 1 (n=115)	Group 2 (n=57)	*P**
Age (years)	63.4±0.7	64.1±1.1	0.58
Total PSA (ng/ml)	10.1±1.3	20.8±3.6	0.001
Prostate volume (ml)	57.2±2.4	41.9±2.1	<0.001
Neutrophil- lymphocyte ratio	2.9±0.2	3.3±0.4	0.425

*independent sample t test; PSA: prostate specific antigen; results are summarized as mean±standard error

The histopathology revealed chronic prostatitis in 47, BPH in 36, high grade prostate intraepithelial neoplasia in 28 and atypical small acinar proliferation in four patients in Group 1. There was no statistically significant difference in NLR between these non-cancer disease subgroups (*P*=0.690). Group 2 was divided into three subgroups according to Gleason

Table 2: Comparison of neutrophil-lymphocyte ratio in subgroups of patients

NLR according to subgroups	n	Neutrophil-lymphocyte ratio	*P**
Group 1	115		0.690
Chronic prostatitis	47	3.3±0.4	
BPH	36	2.8±0.3	
HGPIN	28	2.9±0.5	
ASAP	4	2.0±0.4	
Group 2	57		0.277
Gleason score ≤6	24	3.4±0.6	
Gleason score =7	20	3.8±0.7	
Gleason score ≥8	13	2.3±0.8	
tPSA < 10	28	2.9±0.3	0.140
10≤ tPSA <20	15	4.5±1.2	
tPSA ≥20	14	2.9±0.4	

*one-way anova test; neutrophil-lymphocyte ratio results are given as mean±standard error.
BPH: benign prostate hyperplasia; HGPIN: high grade prostatic intraepithelial neoplasia; ASAP: atypical small acinar proliferation; tPSA: total prostate specific antigen

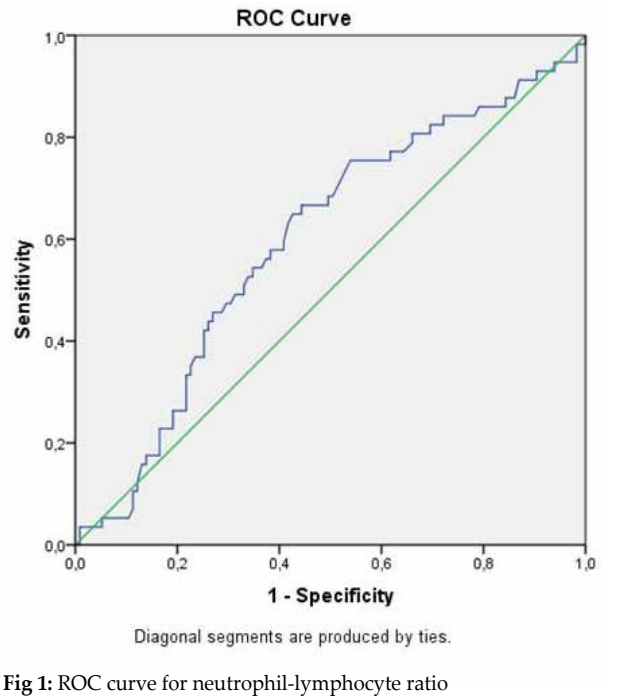


Fig 1: ROC curve for neutrophil-lymphocyte ratio

score and total PSA. Mean NLR was not significantly different between these subgroups (*P*=0.277, *P*=0.140) (Table 2).

ROC curve analysis was used to calculate a cut-off value for NLR. ROC analysis resulted in an area under curve of 0.597 for NLR (*P*=0.39). The threshold provided by the analysis was 2.23 (sensitivity: 0.667, specificity: 0.557, 95% CI: 0.507-0.687) (Figure 1). We identified 89 patients (51.7%) with a high NLR (≥2.23) and 83 patients (48.3%) with a low NLR (<2.23). A high NLR was significantly associated with finding PCa in TRUS-bx (*P*=0.006), older age (*P*=0.038) and total PSA >10 (*P*=0.002), but not with prostate volume, non-cancer disease subgroups or Gleason score (Gleason score=6 vs. Gleason score>6) (Table 3).

Table 3: Comparison of patients' characteristics according to the threshold value of N/L

Patients' characteristics	N/L ≥2.23 (n=89)	N/L<2.23 (n=83)	*P*
Age, year (mean±SE)	64.8±0.9	62.4±0.8	0.038*
Prostate volume, ml (mean±SE)	52.7±2.4	51.4±2.8	0.167*
Total PSA, ng/ml (mean±SE)	15.8±2.3	11.5±2.0	0.730*
Chronic prostatitis	23	24	0.651**
BPH	16	20	0.324**
HGPIN	11	17	0.149**
ASAP	1	3	0.279**
Prostate cancer	38	19	0.006**
Gleason score=6	13	10	0.275**
Gleason score>6	25	9	
Gleason score≤7	29	15	
Gleason score>7	9	4	1.000†
tPSA≤10	49	64	
tPSA>10	40	19	0.002**

N/L: neutrophil-lymphocyte ratio; SE: standard error; BPH: benign prostate hyperplasia; HGPIN: high grade prostatic intraepithelial neoplasia; ASAP: atypical small acinar proliferation; tPSA: total prostate specific antigen

*independent sample two test; **Chi-square test; †Fisher's exact test

DISCUSSION

There is a link between inflammation and development of cancer[8]. Cancer related inflammation reduces antitumor immunity by recruiting regulatory T cells and activating chemokines, which results in tumor growth and metastasis. The mechanism between cancer, neutrophilia and leukocytosis remains unclear; however, cancer has been shown to produce granulocyte colony-stimulating factors. An enhanced neutrophil response and/or suppression of lymphocytes leading to a high NLR might promote carcinogenesis and inhibit antitumor immune response[8,9].

Chronic inflammation is responsible for malignant tumors of epithelial origin. Increased white blood cell (WBC) count due to chronic inflammation is responsible for the development and progression of malignant tumors of epithelial origin including lung, breast, colon, hepatic, thyroid, prostate, gastric, bladder, intestine, and esophageal cancer[2,5,10-15]. There is a limited number of studies investigating the possible relationship between inflammation and WBCs and its subtypes in patients with prostate cancer. So far, a few inflammation biomarkers have been investigated for the potential role in carcinogenesis in prostate cancer. Mengus *et al*[16] evaluated interleukin IL-7 levels in patients with localized prostate cancer and BPH. The authors reported that the level of IL-7 was higher in patients with prostate cancer. Similarly, Beer *et al*[17] reported that elevated C-reactive protein was associated with poor prognosis in patients with metastatic prostate cancer.

Studies have shown that neutrophil count were not only associated with presence of cancer, but also with stage and prognosis of the disease. There were relationships between increased mortality rates and increased neutrophil counts in patients with bronchoalveolar cancer, renal cell carcinoma and malignant melanoma[11-18]. In addition, increased neutrophil counts were reported to be a strong and independent prognostic factor for overall survival, recurrence and cancer-specific survival in patients with renal cancer and head and neck tumors[19,20]. In the presence of neutrophil infiltration, grade of glial tumor was increased[21]. However, hypothetical relationship between increased neutrophil and poor

prognosis in cancer has not been widely accepted. In gastric cancers, good prognosis was associated with high neutrophil count[22]. Fujita *et al*[23] showed that there was a good relationship with increased neutrophil count and benign prostate biopsy. The authors also reported that if there was a higher risk for poorly differentiated prostate cancer (low neutrophil counts with high PSA count and neutropenia), biopsy samples were required.

A high baseline NLR was found to be a predictor of poor prognosis in many cancers[12-15]. Minardi *et al*[24] reported that in patients with PCa, those with NLR higher than three showed a higher incidence of recurrence; these observations, together with age and total PSA, were able to predict recurrence. Walsh *et al*[12] showed that if preoperative NLR was >5 in patients, cancer-related mortality was statistically significantly higher in colorectal cancer. In addition, Nakahara *et al*[25] reported that in advanced non-small cell lung carcinoma, NLR was an independent prognostic factor in fine needle aspiration biopsy specimen. Vartolomei *et al*[26] demonstrated in patients with renal cancers, that abnormal NLR (>2.7) was not only associated with adverse pathological features and worse oncologic outcomes, but also predicted the presence of lymph node metastases, muscle-invasive and non-organ-confined disease. They also reported that the potential of NLR could be in the preoperative clinical decision-making regarding lymphadenectomy indication and extent, and patient counseling regarding conservative therapy. In another study, Yuksel *et al*[27] found that NLR were statistically significantly higher in patients with testicular cancer compared with the control group. They reported that NLR can be used as a simple test in the diagnosis of testicular cancer besides the well-known accurate serum tumor markers. With regards to the prostate, there is scarce data about the role of NLR in differentiating malignancy from benign disorders. There are only two articles that focused on the ability of NLR to discriminate the prostate adenocarcinoma from benign disease[23,28]. In these studies, many parameters were evaluated for predicting the biopsy outcome; including WBC, differential white cell count (neutrophil, lymphocyte, basophile, eosinophil and monocyte), NLR, platelet to lymphocyte (PLR) ratio and C-reactive protein. Fujita *et al*[23] found that the WBC and neutrophil count were significantly higher in the negative biopsy group compared to the positive biopsy group, while the other leukocyte subsets were not significantly different between two groups. Logistic regression analysis revealed that only neutrophil score was an independent predictor of the outcome of biopsy (P<0.05). They also evaluated the patients with PSA levels <10 ng/ml to exclude the possibility that severe inflammation or advanced prostate cancer that increase PSA might have skewed the results, and they found that the results of this subgroup analysis were consistent with the entire group results (P<0.05). In another study, Kaynar *et al*[28] evaluated the role of NLR and PLR inflammation markers in prostate cancer and BPH specimens. Authors also assessed the correlation of each marker with benign disease subgroups (BPH and chronic prostatitis), Gleason score and PSA levels (0-4 ng/ml, 4-10 ng/ml and >10 ng/ml). In this study, NLR was not significantly different between the benign and malign groups. Authors reported that mean PLR values were significantly different in the BPH and PCa groups only if the PSA level was 10 ng/ml or above (P=0.044). The NLR and PLR parameters did not significantly correlate with Gleason score and PSA in the malign group (P >0.05).

In our study, we found no statistically significant correlation between NLR and benign disease subgroups and Gleason score. However, a high NLR (≥2.23) was significantly associated with finding prostate cancer in TRUS-bx (P=0.006), older age (P=0.038) and total PSA >10 (P=0.002). A recent published study reported a similar finding to our results, that NLR (4.22) level of PCa group has been found to be significantly higher compared to BPH (3.57) group[29].

Limitations of our study includes its retrospective design, lack of patients evaluated with multi-parametric magnetic resonance imaging (due to its unavailability at the time) and relatively limited number of patients enrolled in the study.

CONCLUSION

We found that patients with pre-biopsy NLR score ≥2.23 have a higher chance of having prostate cancer in their TRUS-bx specimens. Therefore, we suggest that NLR may be an useful marker and may be used to predict PCa in patients undergoing TRUS-bx. However, further large-scale studies are required to confirm these findings.

ACKNOWLEDGMENTS

None

Conflict of interest: None

Author's contribution: Ismail Basmaci, Ibrahim H Bozkurt and Ozgu Aydogdu designed the study; Ertugrul Sefik and Serdar Celik collected the data collection; Serdar Celik and Tansu Degirmenci analyzed the data; Ismail Basmaci and Ibrahim H Bozkurt wrote the manuscript; Tansu Degirmenci and Ismail Basmaci did final editing.

REFERENCES

1. Placer J, Morote J. [Usefulness of prostatic specific antigen (PSA) for diagnosis and staging of patients with prostate cancer]. Arch Esp Urol 2011; 64(8):659-680. Article in Spanish.
2. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008; 454(7203):436-444.
3. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation and cancer. Cell 2010; 140(6):883-899.
4. Pichler M, Hutterer GC, Stoeckigt C, Chromecki TF, Stojakovic T, Golbeck S, *et al*. Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients. Br J Cancer 2013; 108(4):901-907.
5. Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, *et al*. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother 2009; 58(1):15-23.
6. Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. J Thorac Cardiovasc Surg 2009; 137(2):425-428.
7. Perez DR, Baser RE, Cavnar MJ, Balachandran VP, Antonescu CR, Tap WD, *et al*. Blood neutrophil-to-lymphocyte ratio is prognostic in gastrointestinal stromal tumor. Ann Surg Oncol 2013; 20(2):593-599.
8. Feng JF, Huang Y, Liu JS. Combination of neutrophil lymphocyte ratio and platelet lymphocyte ration is a useful predictor of postoperative survival in patients with esophageal squamous cell carcinoma. Onco Targets Ther 2013; 6:1605-1612.
9. Gueron G, De Servi A, Vazquez E. Advanced prostate cancer: reinforcing the strings between inflammation and the metastatic behavior. Prostate Cancer Prostatic Dis 2012; 15(3):213-221.
10. Ardies CM. Inflammation as cause for scar cancers of the lung. Integr Cancer Ther 2003; 2(3):238-246.
11. Wislez M, Rabbe N, Marchal J, Milleron B, Crestani B, Mayaud C, *et al*. Hepatocyte growth factor production by neutrophils infiltrating bronchioloalveolar subtype pulmonary adenocarcinoma: role in tumor progression and death. Cancer Res 2003; 63(6):1405-1412.
12. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol 2005; 91(3):181-184.
13. Margolis KL, Rodabough RJ, Thomson CA, Lopez AM, McTiernan A, Women's Health Initiative Research Group. Prospective study of leukocyte count as a predictor of incident breast, colorectal, endometrial, and lung cancer and mortality in postmenopausal women. Arch Intern Med 2007; 167(17):1837-1844.
14. Goswami B, Rajappa M, Sharma M, Sharma A. Inflammation: its role and interplay in the development of cancer, with special focus on gynecological malignancies. Int J Gynecol Cancer 2008; 18(4):591-599.
15. Cho H, Kim JH. Multiplication of neutrophil and monocyte counts (MNM) as an easily obtainable tumour marker for cervical cancer. Biomarkers 2009; 14(3):161-170.
16. Mengus C, Le Magnen C, Trella E, Yousef K, Bubendorf L, Provenzano M, *et al*. Elevated levels of circulating IL-7 and IL-15 in patients with early stage prostate cancer. J Transl Med 2011; 9:162.
17. Beer TM, Lalani AS, Lee S, Mori M, Eilers KM, Curd JG, *et al*. C-reactive protein as a prognostic marker for men with androgen-independent prostate cancer: results from the ASCENT trial. Cancer 2008; 112(11):2377-2383.
18. Fridlender ZG, Albelda SM. Tumor-associated neutrophils: friend or foe? Carcinogenesis 2012; 335):949-955.
19. Jensen HK, Donskov F, Marcussen N, Nordsmark M, Lundbeck F, von der Maase H. Presence of intratumoral neutrophils is an independent prognostic factor in localized renal cell carcinoma. J Clin Oncol 2009; 27(28):4709-4717.
20. Trellakis S, Farjah H, Bruderek K, Dumitru CA, Hoffmann TK, Lang S, *et al*. Peripheral blood neutrophil granulocytes from patients with head and neck squamous cell carcinoma functionally differ from their counterparts in healthy donors. Int J Immunopathol Pharmacol 2011; 24(3):683-693.
21. Fossati G, Ricevuti G, Edwards SW, Walker C, Dalton A, Rossi ML. Neutrophil infiltration into human gliomas. Acta Neuropathol 1999; 98(4):349-354.
22. Caruso RA, Bellocco R, Pagano M, Bertoli G, Tigoli L, Inferrera C. Prognostic value of intratumoral neutrophils in advanced gastric carcinoma in a high-risk area in northern Italy. Mod Patho 2002; 15(8):831-837.
23. Fujita K, Imamura R, Tanigawa G, Nakagawa M, Hayashi T, Kishimoto N, *et al*. Low serum neutrophil count predicts a positive prostate biopsy. Prostate Cancer Prostatic Dis 2012; 15(4):386-390.
24. Minardi D, Scartozzi M, Montesi L, Santoni M, Burattini L, Bianconi M, *et al*. Neutrophil-to-lymphocyte ratio may be associated with the outcome in patients with prostate cancer. Springerplus 2015; 4:255.
25. Nakahara Y, Mochiduki Y, Miyamoto Y, Nakahara Y, Katsura Y. Prognostic significance of the lymphocyte-to-neutrophil ratio in percutaneous fine needle aspiration biopsy specimen of advanced nonsmall cell lung carcinoma. Cancer 2005; 104(6):1271-1280.
26. Vartolomei MD, Mathieu R, Margulis V, Karam JA, Roupret M, Lucca I, *et al*. Promising role of preoperative neutrophil-to-lymphocyte ratio in patients treated with radical nephroureterectomy. World J Urol 2016 2017; 35(1):121-130.
27. Yuksel OH, Verit A, Sahin A, Urkmez A, Uruc F. White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: a simple secondary serum tumor marker. Int Braz J Urol 2016; 42(1):53-59.
28. Kaynar M, Yildirim ME, Gul M, Kilic O, Ceylan K, Goktas S. Benign prostatic hyperplasia and prostate cancer differentiation via platelet to lymphocyte ratio. Cancer Biomark 2015; 15(3):317-323.
29. Adhyatma KP, Prapiska FF, Siregar GP, Warli SM. Systemic inflammatory response in predicting prostate cancer: The diagnostic value of neutrophil-to-lymphocyte ratio. Open Access Maced J Med Sci 2019; 7(10):1628-1630.

Original Article

The relationships between hemoglobin and diabetogenic factors in young Chinese adults

Yen-Shan Yang[1], Jiunn-Diann Lin[2], Chung-Ze Wu[2], Dee Pei[3], Yao-Jen Liang[4], Yen-Lin Chen[5]
[1]Department of Medicine, School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan
[2]Division of Endocrinology, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University; Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[3]Department of Internal Medicine, Cardinal Tien Hospital, School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan
[4]Department of Life Science, Graduate Institute of Applied Science and Engineering, College of Science and Engineering, Fu Jen Catholic University, Taipei, Taiwan
[5]Department of Pathology, Cardinal Tien Hospital, School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan

Kuwait Medical Journal 2022; 54 (1): 98 - 105

ABSTRACT

Objective: Four diabetogenesis factors (DF) are recognized as the pathophysiology for diabetes; increased insulin resistance (IR); decreased glucose effectiveness (GE); first- and second-phase insulin secretion (FPIS and SPIS). The relationships between hemoglobin (Hb), IR and FPIS are well investigated. However, little is known about the associations between Hb and the other two DFs. Nowadays, the incidence of type 2 diabetes has increased dramatically in young adults in Taiwan. A group of young adults are enrolled for investigating relationships between Hb and the DFs.
Design: Cross-sectional study
Setting: Health check-up centers and hospitals
Subjects: 21,112 and 20,687 healthy males and females (18-27 years old) were recruited.
Main outcome measures: The four DFs were measured by the equations published in our previous studies. Participants were divided into quartiles by Hb levels, and ANOVA was used to compare the differences of DFs in these four groups. Then simple correlation was applied to evaluate the correlation between Hb and the DFs.
Results: In both genders, IR, FPIS and SPIS had negative trends from the lower to the higher Hb quartiles, but GE had a positive one. Simple correlation showed negative relationships between Hb and FPIS, SPIS and IR, similarly, it was positive for GE. Besides, GE is most closely related to Hb, followed by IR, SPIS and FPIS.
Conclusions: Our study showed that in young Chinese adults, all the DFs except GE were negatively correlated with Hb. Among these correlations, GE had the highest r value, followed by IR, SPIS and FPIS.

KEY WORDS: first phase insulin secretion, glucose effectiveness, insulin resistance, second phase insulin secretion

INTRODUCTION

Due to the increasing prevalence of obesity in recent years, type 2 diabetes (T2D) has become an endemic disease in many countries[1,2]. Owing to the various symptoms and accompanying complications, it influences not only individuals' health but also has serious impacts on society in many different aspects. As a result, searching for modalities for early detection and treatments are important issues for health providers. However, many parts of the underlying pathophysiology of T2D still remain unclear.

Until now, it is generally agreed that there are four diabetogenesis factors (DF): increased insulin resistance (IR), diminished first- and second-phase insulin secretion (FPIS, SPIS, respectively) and glucose effectiveness (GE). IR refers to the diminished ability

Address correspondence to:
Yen-Lin Chen, Department of Pathology, Cardinal Tien Hospital, No.362, Zhongzheng Rd., Xindian Dist., New Taipei City 23137, Taiwan (R.O.C.). Tel: +886-2-22193391; Fax: +886-2-22193506; E-mail: anthonypatho@gmail.com

of cells to respond to the action of insulin in transporting glucose from plasma to glucose-utilizing tissues[3]. FPIS is the insulin secreted from the storage granules and after acute glucose loading within the first 10 minutes. The following newly produced insulin is the SPIS[4,5]. GE is the ability of glucose per se to promote its own disappearance from the plasma, which includes suppression of its production and stimulation of its uptake[6]. However, other than IR, the other three factors were much less investigated[4,7-9]. This may be because the methods for measuring FPIS, SPIS and GE are both time-consuming and expensive.

In the past, researchers have found the level of hemoglobin (Hb) was positively correlated with the chance of having T2D[10]. The underlying mechanisms might be due to the evidence showing that IR was positively and FPIS was negatively related to the level of Hb[11-13]. Both associations could be explained by oxidative stress[14,15]. However, little is known about the correlations between Hb, SPIS and GE. In the present study, we enrolled 41,799 non-diabetic subjects. By using the equations developed by our group, four DFs were measured simultaneously in one subject. Our purposes were: 1. Is Hb related to DFs individually? 2. If there is a significant relationship, which one is the closest? Thus, we can understand the roles of Hb in the pathogenesis of T2D more thoroughly.

SUBJECTS AND METHODS

The data of the study participants were collected from MJ Health Screening Centers, which are private chain clinics around Taiwan. It provides its members regular health examination. The study protocol was approved by the institutional review board and the data obtained were used for research purposes only. 21,112 males and 20,687 females aged between 18 and 27 years old were randomly recruited and underwent health checks at the time of the study. All the participants gave informed consent and they were anonymous in the analysis. Participants with obesity (body mass index (BMI) ≥25 kg/m^2), and/or taking any medications that are known to affect blood pressure, glucose and lipid levels were excluded. Subjects were divided into two groups: those with metabolic syndrome (MetS+), and those without (MetS-), according to the World Health Organization criteria[16].

On the day of the study, individual current medical history was obtained; thorough questionnaire and standard physical examinations were performed, including measurement of body weight, height, waist circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP). BMI was calculated as the weight (kg) divided by the square of the subject's height (m^2). Each participant was instructed to have fasted for 10 hours before samples of blood were drawn from the antecubital vein for biochemical analysis. Plasma was separated from blood within one hour and stored at 30°C until the analysis for fasting plasma glucose (FPG) and lipid profiles. FPG was measured using a glucose oxidase method (YSI 203 glucose analyzer, Yellow Springs Instruments, Yellow Springs, USA). Total cholesterol and triglycerides (TG) were measured by the dry, multilayer analytical slide method with the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol concentration were analyzed through an enzymatic cholesterol assay after dextran sulfate precipitation.

The equation used to calculate IR, FPIS, SPIS and GE are listed below, which were taken from our study groups. All units are in international units. To demonstrate the reliability of our equations, here is a short statement. When we performed these data, approximately 70% of the participants were used to build the equation while the data from the remaining 30% were used as external validation. Thus, the accuracy of the equations could be tested.

1. IR: In total, there were 327 subjects enrolled. The IR was measured by insulin suppression test. The r value between the measured and calculated GE was 0.581 (P <0.001). It was published in 'Journal of Diabetes Investigation' in 2013.
   IR = log (1.439 + 0.018 X sex - 0.003 X age + 0.029 X BMI - 0.001 X SBP + 0.006 X DBP + 0.049 X TG - 0.046 X HDLC - 0.0116 X FPG) X 10 $^{3.333}$ [17]
2. FPIS: In total, there were 186 subjects enrolled. The FPIS was measured by frequently sampled intravenous glucose tolerance tests. The r value between the measured and calculated GE was 0.671 (P <0.000). It was published in 'International Journal of Endocrinology' in 2015.
   FPIS = $10^{(1.477 - 0.119 \text{ X FPG} + 0.079 \text{ X BMI} - 0.523 \text{ X HDLC})}$ [18]
3. SPIS: In total, there were 82 participants. The SPIS was measured by a modified low dose glucose infusion test. The r value between the measured and calculated GE was 0.65 (P=0.002). It was published in 'Metabolic Syndrome and Related Disorders' in 2016.
   SPIS = $10^{(-2.4 - 0.088 \text{ X FPG} + 0.072 \text{ X BMI})}$ [19]
4. GE: In total, there were 227 participants. The GE was measured by frequent sampled intravenous glucose tolerance tests. The r value between the measured and calculated GE was 0.43 (P=0.001). It was published in 'Metabolic Syndrome and Related Disorders' in 2016.
   GE = (29.196 - 0.103 X age - 2.722 X TG - 0.592 X FPG) X10 $^{-3}$ [20]

Table 1: Basic information and DFs between MetS(-) and MetS(+) in young adults

Demographic data and diabetes factors	MetS (-)	MetS (+)	*P*
Male			
n	19367	1745	
Age (year)	24.3 ± 2.5	24.6 ± 2.5	<0.001
Body mass index (kg/m2)	22.9 ± 3.0	28.8 ± 4.5	<0.001
Waist circumference	77.3 ± 7.7	92.1 ± 10.5	<0.001
Systolic blood pressure (mmHg)	118.9 ± 12.3	132.8 ± 12.1	<0.001
Diastolic blood pressure (mmHg)	68.4 ± 8.7	76.9 ± 9.9	<0.001
Fasting plasma glucose (mg/dl)	93.6 ± 6.7	100.5 ± 10.8	<0.001
Triglyceride (mg/dl)	88.0 ± 43.3	173.7 ± 74.0	<0.001
HDL-C (mg/dl)	51.4 ± 11.4	39.5 ± 8.2	<0.001
Cholesterol (mg/dl)	175.2 ± 31.2	192.1 ± 35.9	<0.001
LDL-C (mg/dl)	106.2 ± 28.5	117.9 ± 32.3	<0.001
FPIS (μU/min)	125.3 ± 145.5	513.3 ± 589.558	<0.001
SPIS (pmol/mmol)	0.072 ± 0.060	0.203 ± 0.207	<0.001
IR (10-4 · min-1 · pmol-1 · L-1)	3.688 ± 0.021	3.735 ± 0.026	<0.001
GE (10-2 · dL · min-1 · kg-1)	0.021 ± 0.001	0.018 ± 0.002	<0.001
Hemoglobin (103/μ L)	15.3 ± 1.2	14.3 ± 1.4	<0.001
Female			
n	20177	510	0.415
Age (year)	24.3 ± 2.4	24.2 ± 2.6	<0.001
Body mass index (kg/m2)	21.2 ± 2.6	29.1 ± 5.4	<0.001
Waist circumference	67.7 ± 6.0	84.9 ± 11.0	<0.001
Systolic blood pressure (mmHg)	107.2 ± 11.2	125.5 ± 13.9	<0.001
Diastolic blood pressure (mmHg)	63.0 ± 8.1	73.3 ± 10.5	<0.001
Fasting plasma glucose (mg/dl)	90.1 ± 7.0	100.3 ± 14.3	<0.001
Triglyceride (mg/dl)	69.8 ± 31.1	146.6 ± 67.4	<0.001
HDL-C (mg/dl)	61.4 ± 13.9	43.2 ± 7.8	<0.001
Cholesterol (mg/dl)	174.6 ± 30.1`	184.7 ± 34.4	<0.001
LDL-C (mg/dl)	99.3 ± 26.6	111.9 ± 30.3	<0.001
FPIS (μU/min)	73.5 ± 123.6	574.7 ± 800.4	<0.001
SPIS (pmol/mmol)	0.055 ± 0.046	0.231 ± 0.254	<0.001
IR (10-4 · min-1 · pmol-1 · L-1)	3.674 ± 0.019	3.735 ± 0.031	<0.001
GE (10-2 · dL · min-1 · kg-1)	0.022 ± 0.001	0.019 ± 0.002	<0.001
Hemoglobin (103/μ L)	14.2 ± 1.5	13.3 ± 1.2	

MetS(-): without metabolic syndrome; MetS(+): with metabolic syndrome; FPIS: first phase insulin secretion; SPIS: second phase insulin secretion; IR: insulin resistance; GE: glucose effectiveness; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Logγ-GT: log γ-Glutamyl transpeptidase.
Data are shown as mean ± SD.

Statistical analysis

All statistical analyses were performed using the SPSS software version 19.0 (IBM Inc., Armonk, New York). The data are expressed as mean ± standard deviation. All data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variances with the Levene's test. Data of FPIS, SPIS and TG were log transformed before analysis because they were not normally distributed. The *t*–test was used to compare the differences between the MetS+ and MetS- groups of two genders separately. To evaluate the differences of the mean values of the four groups, from the highest to the lowest levels of Hb, one-way ANOVA was used, followed by Bonferroni test for post-hoc examination.

Simple correlation was applied to determine the association between concentrations of IR, FPIS, SPIS and GE with Hb. The slopes of those DFs with Hb of two genders were also obtained separately in linear regression analysis. Since the units and scales of the four lines were different, it was impossible to compare their relationships. As a result, for each DF, we took the highest value of the variable as 100% and the lowest as 0%. The other continuous value between the two extremes were then converted into percentage correspondingly. Thus, though using the method, those variables originally belonging to different units and scales can be compared with each other in the two genders.

Among these four factors, in both genders, only GE showed a positive correlation when Hb is higher, while the other three DFs are negatively related to Hb. As a consequence, a mirror-line (or reciprocal line) was plotted for GE in order to compare their relationships.

RESULTS

In total, 41,799 subjects were enrolled in the study, including 21,112 males and 20,687 females. In Table 1,

Table 2: The relationships between Hb and basic information/DFs in young adults (18-27 years)

Demographic data and diabetes factors	Hemoglobin 1	Hemoglobin 2	Hemoglobin 3	Hemoglobin 4	Total	*P*
Male						
n	5336	5386	5183	5207	21112	
Age (year)	24.7±2.4[234]	24.2±2.5[1]	24.2±2.61	24.3±2.5[1]	24.3±2.5[1]	<0.001
Body mass index (kg/m2)	24.5±4.0[234]	23.1±3.3[1]	23.0±3.3[1]	23.0±3.2[1]	23.4±3.5	<0.001
Waist circumference	81.3±9.9[234]	77.7±8.5[1]	77.4±8.6[1]	77.7±8.1[1]	78.5±9.0	<0.001
Systolic blood pressure (mmHg)	121.7±13.1[234]	119.5±12.8[1]	119.6±12.5[1]	119.2±12.7[1]	120.0±12.8	<0.001
Diastolic blood pressure (mmHg)	70.5±9.5[234]	68.7±9.0[1]	68.7±9.0[1]	68.5±8.9[1]	69.1±9.1	<0.001
Fasting plasma glucose (mg/dl)	95.3±8.4[234]	93.7±7.4[1]	93.7±6.9[1]	94.0±6.7[1]	94.2±7.4	<0.001
Triglyceride (mg/dl)	135.6±73.3[234]	83.8±39.4[13]	79.3±30.3[12]	80.9±27.5[1]	95.1±52.2	<0.001
HDL-C (mg/dl)	47.4±11.5[234]	51.2±11.7[1]	51.6±11.5[1]	51.5±11.4[1]	50.4±11.6	<0.001
Cholesterol (mg/dl)	186.1±34.4[234]	173.4±30.9[1]	173.0±30.5[1]	173.9±29.8[1]	176.6±31.9	<0.001
LDL-C (mg/dl)	111.5±30.8[234]	105.4±28.2[1]	105.5±28.4[1]	106.2±28.1[1]	107.2±29.0	<0.001
FPIS (μU/min)	216.8±313.6[234]	141.8±214.4[1]	136.7±224.2[1]	132.5±193.7[1]	157.266±243.7	<0.001
SPIS (pmol/mmol)	0.103±0.112[234]	0.077±0.078[1]	0.076±0.081[1]	0.076±0.082[1]	0.083±0.090	<0.001
IR (10-4 · min-1 · pmol-1 · L-1)	3.703±0.029[234]	3.689±0.023[1]	3.688±0.023[1]	3.688±0.022[1]	3.692±0.025	<0.001
GE (10-2 · dL · min-1 · kg-1)	0.019±0.002[234]	0.021±0.001[13]	0.021±0.001[12]	0.021±0.001[1]	0.021±0.002	<0.001
Hemoglobin (103/μ L)	13.5±0.9[234]	15.0±0.3[134]	15.8±0.2[124]	16.7±0.5[123]	15.3±1.3	<0.001
White blood cell count (103/μ L)	6.5±1.8[4]	6.4±1.5[34]	6.6±1.6[24]	6.8±1.7[123]	6.6±1.6	<0.001
Platelet count (103/μL)	265.5±58.4[234]	245.9±49.8[14]	242.8±49.4[1]	241.1±49.3[12]	248.9±52.8	<0.001
r-GT	15.1±14.1[234]	21.1±18.1[134]	23.0±20.4[124]	26.9±27.4[123]	21.5±20.9	<0.001
Logγ-GT	1.099±0.234[234]	1.245±0.240[134]	1.283±0.239[124]	1.331±0.262[123]	1.238±0.259	<0.001
Uric acid (mg/dl)	6.0±1.5[234]	6.9±1.5[134]	7.1±1.4[124]	7.2±1.4123[123]	6.8±1.5	<0.001
Female						
n	4847	5256	5114	5470	20687	
Age (year)	24.6±2.3[34]	24.4±2.4[34]	24.0±2.5[12]	24.0±2.5[12]	24.3±2.4	<0.001
Body mass index (kg/m2)	21.9±3.4[34]	21.8±3.3[34]	21.2±2.6[124]	20.9±2.2[123]	21.4±2.9	<0.001
Waist circumference	69.4±7.6[34]	69.0±7.4[34]	67.5±6.0[12]	67.0±5.5[12]	68.2±6.7	<0.001
Systolic blood pressure (mmHg)	108.7±11.9[34]	108.4±12.0[34]	106.8±11.5[12]	106.7±11.1[12]	107.6±11.6	<0.001
Diastolic blood pressure (mmHg)	64.0±8.6[34]	63.7±8.5[34]	62.8±8.1[12]	62.5±8.0[12]	63.2±8.3	<0.001
Fasting plasma glucose (mg/dl)	91.7±8.3[123]	91.1±7.91[34]	89.5±6.6[12]	89.0±6.4[12]	90.3±7.4	<0.001
Triglyceride (mg/dl)	88.6±38.9[123]	82.0±40.41[34]	62.3±27.3[124]	55.8±15.1[123]	71.7±34.6	<0.001
HDL-C (mg/dl)	58.7±14.3[34]	59.3±14.2[34]	62.3±13.9[12]	63.0±13.4[12]	60.9±14.1	<0.001
Cholesterol (mg/dl)	178.9±30.9[34]	177.0±31.0[34]	172.7±30.0[12]	171.3±28.5[12]	174.9±30.2	<0.001
LDL-C (mg/dl)	102.4±27.4[34]	101.2±27.8[34]	97.9±26.5[12]	97.1±25.2[12]	99.6±26.8	<0.001
FPIS (μU/min)	108.1±253.9[34]	101.8±242.0[34]	73.1±136.1[12]	62.3±79.0[12]	85.8±191.3	<0.001
SPIS (pmol/mmol)	0.067±0.083[34]	0.065±0.081[34]	0.056±0.055[12]	0.051±0.035[12]	0.060±0.066	<0.001
IR (10-4 · min-1 · pmol-1 · L-1)	3.681±0.0241[23]	3.679±0.0241[34]	3.673±0.019[124]	3.670±0.017[123]	3.676±0.022	<0.001
GE (10-2 · dL · min-1 · kg-1)	0.021±0.0011[23]	0.021±0.0011[34]	0.022±0.001[124]	0.022±0.001[123]	0.022±0.001	<0.001
Hemoglobin (103/μ L)	12.2±0.91[23]	13.7±0.31[34]	14.6±0.3[124]	16.0±0.6[123]	14.2±1.5	<0.001
White blood cell count (103/μ L)	5.9±1.71[23]	6.1±1.61[34]	6.3±1.7[124]	6.7±1.7[123]	6.3±1.7	<0.001
Platelet count (103/μL)	246.5±65.01[23]	231.9±53.81[34]	220.5±53.1[124]	215.6±50.1[123]	228.2±56.8	<0.001
γ-GT	16.7±34.2[34]	19.0±31.7[34]	25.8±38.3[124]	33.8±45.4[123]	24.1±38.5	<0.001
Log γ-GT	1.083±0.270[234]	1.152±0.275[124]	1.293±0.278[134]	1.416±0.276[123]	1.242±0.304	<0.001
Uric acid (mg/dl)	5.2±1.4[234]	5.6±1.5[124]	6.3±1.6[134]	6.7±1.5[123]	6.0±1.6	<0.001

MetS(-): without metabolic syndrome; MetS(+): with metabolic syndrome; FPIS: first phase insulin secretion; SPIS: second phase insulin secretion; IR: insulin resistance; GE: glucose effectiveness; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Logγ-GT: log γ-Glutamyl transpeptidase.
Data are shown as mean ± SD.

they were divided into MetS (-) and MetS (+) as aforementioned. In both genders, other than HDL-C, GE and Hb, all the other components were higher in MetS (+) group.

Table 2 depicts the demographic, biochemistries and DFs after the data of participants were stratified into quartiles according to their Hb levels. It can be noted that all the parameters had a negative trend from the lower to the higher Hb quartiles, while GE and HDL-C were positively related to Hb. Table 3 showed the results of simple correlation between Hb and four DFs. In both men and women, negative correlations can be noted between Hb and FPIS, SPIS and IR. And between Hb and GE, the relationship becomes positive.

The comparisons of the closeness between these parameters are shown in Fig 1 (panel A for female and B for male, respectively). GE had the highest r value, following by IR, SPIS and FPIS in both genders.

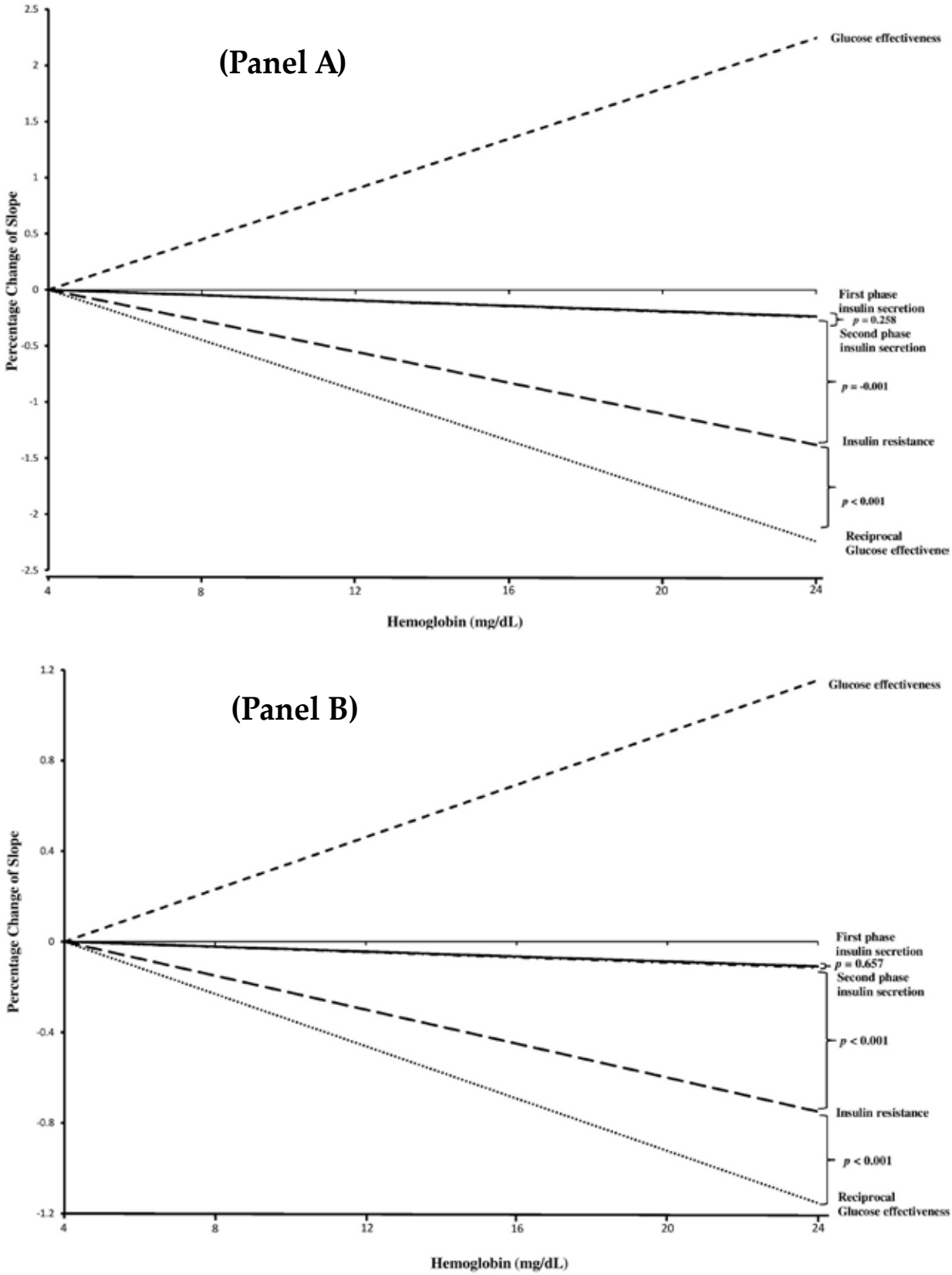


Fig 1: The comparisons of the relationships between hemoglobin and four diabetes factors in men (panel A) and women (panel B). It could be noted that glucose effectiveness had the tightest relationship with hemoglobin followed by insulin resistance, second phase insulin secretion and first phase insulin secretion. All of these slopes are significantly different from each other.

Table 3: The results of simple correlation between hemoglobin and four diabetes factors

Diabetes factors	Men	Women
First phase insulin secretion	-0.133*	-0.089*
Second phase insulin secretion	-0.115*	-0.088*
Insulin resistance	-0.245*	-0.185*
Glucose effectiveness	0.410*	0.367*

**P*-value <0.001

DISCUSSION

In the present study, our results showed that the orders of the relationship closeness in both genders from the highest to the lowest were GE, IR, SPIS and FPIS. In both genders, all the DFs except for GE were negatively related to Hb. To our knowledge, there have been very few studies focusing on the relationships between Hb and the four DFs, particularly in this age group. Our study is the first to analyze these relationships simultaneously in the same individual. We believe that the results could provide deeper understanding about the pathophysiology for T2D. To further understand our findings, we will discuss these relationships separately in the following paragraphs.

The relationship between Hb and IR

In the present study, we have shown that there was a negative correlation between Hb and IR. Moreover, the r^2 was the second highest among the four DFs. This is unusual. Our findings are contradictory to three other studies. However, in the first study done by Moan *et al*, there were only 20 men[21]. The second study done by Reaven *et al* enrolled 150 subjects. By using insulin suppression study, they quantified IR. The r^2 was only around 0.176; in addition, the mean age of their cohort was 49 and 43 years old for men and women respectively. Since we enrolled much younger subjects in our study (24.7 years old in average), sex hormones may play important roles in the relationships. For example, for females, a study conducted by Sivaporn Sivasinprasasn *et al* using ovariectomized rats as model also demonstrated a negative relationship between estrogen and obese-insulin resistance[22]. As for males, Li *et al* found testosterone was significantly and negatively associated with the level of insulin resistance in men[23]. At the same time, testosterone has been suggested to stimulate the production of Hb[24]. Though the mechanisms are not clearly understood, the above studies might provide evidence to support our results.

The relationship between Hb and insulin secretion

There have been very few studies focused on the relationships between Hb and insulin secretion. In the present study, our data suggests that subjects with higher Hb levels had lower insulin secretion, both first and second-phase. This finding is in line with the reports done by others. For example, Shimodaira *et al* showed a similar finding; however, only in men (r=-0.197 for men and -0.082 for women) [11]. At the same time, Hanley *et al* also demonstrated decreased β-cell function across the Hb quartiles[25], although the underlying molecular mechanisms still remain unclear. The fact that anemia could induce iron overload might cause oxidative impairment of mitochondria, which are abundant in β-cells. Thus, the pancreatic function might be damaged, leading to decrease of insulin secretion.

The relationship between GE and Hb

GE has long been proved to be an important factor of diabetes[26]; however, there has been no study to examine its relationship with Hb. Our study is the first to demonstrate that there was a positive association between these two factors. To explain our finding, we hypothesized that obesity might play a key role to connect Hb and GE. By using oral glucose tolerance test, also, it is well-known that obesity is often associated with multiple metabolic syndromes including hypertriglyceridemia[27,28]. What's more, free fatty acid could also promote glucogenesis in liver and reduce glucose oxidation[18-22]. On the other hand, erythropoietin, an important hormone for Hb production, is suggested to be involved in the regulation of obesity through a signaling pathway. The level of erythropoietin is elevated during hypoxia, which may be induced by obesity[29,30]. From the above discussion, we can conclude that obesity is related to higher GE and to higher Hb.

Although abundance of clinical studies have proved a relatively higher prevalence of anemia in diabetic patients[31], the relationships among those four DF and Hb should still be further discussed considering the complex physical and chemical interactions involved. In the present research, we believe the analysis provides important information related to the pathophysiology of diabetes. However, there were still several limitations. First, the study was cross-sectional, so the evidence is not as solid as a longitude one. Second, the method we used for measurement of the four factors might be less accurate or precise compared to traditional ones; however, the large number of the study cohort might be able to compensate this defect. Third, the study was conducted on a homogenous ethnic group. Exercising our results to other ethnic groups should be done with caution.

CONCLUSION

In conclusion, our data showed that the order of the closeness in both genders from the highest to the lowest was GE, IR, SPIS and FPIS in young Chinese. In both genders aged between 18 and 27 years old, IR, FPIS and SPIS were negatively, while GE was positively correlated with Hb.

ACKNOWLEDGMENTS

The authors wish to thank the study assistants for their help in data preparation and collection.

Authors contribution: Yen-Shan Yang primarily wrote the manuscript; Jiunn-Diann Lin revised the manuscript; Chung-Ze Wu gave suggestions on how to write the manuscript; Dee Pei analyzed the data; Yao-Jen Liang gave statistical suggestion; and Yen-Lin Chen created the hypothesis of this manuscript.

Conflict of interest: None

Funding resources: This study was funded by the grant from Cardinal Tien Hospital No. CTH105A-214

REFERENCES

1. Tseng CH, Chong CK, Heng LT, Tseng CP, Tai TY. The incidence of type 2 diabetes mellitus in Taiwan. Diabetes Res Clin Pract 2000; 50 Suppl 2:S61-S4.
2. Lin C-C, Li C-I, Hsiao C-Y, Liu C-S, Yang S-Y, Lee C-C, *et al*. Time trend analysis of the prevalence and incidence of diagnosed type 2 diabetes among adults in Taiwan from 2000 to 2007: a population-based study. BMC Public Health 2013; 13:318.
3. Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. Annu Rev Nutr 2005; 25:391-406.
4. Polonsky KS, Sturis J, Bell GI. Seminars in Medicine of the Beth Israel Hospital, Boston. Non-insulin-dependent diabetes mellitus—a genetically programmed failure of the beta cell to compensate for insulin resistance. N Engl J Med 1996; 334(12):777-783.
5. Caumo A, Luzi L. First-phase insulin secretion: does it exist in real life? Considerations on shape and function. Am J Physiol Endocrinol Metab 2004; 287(3):E371-E385.
6. Tonelli J, Kishore P, Lee DE, Hawkins M. The regulation of glucose effectiveness: how glucose modulates its own production. Curr Opin Clin Nutr Metab Care 2005; 8(4):450-456.
7. Nakamura Y, Nishida T. Effect of hemoglobin concentration on the oxidation of linoleic acid. J Lipid Res 1971; 12(2):149-154.
8. Neuman JC, Fenske RJ, Kimple ME. Dietary polyunsaturated fatty acids and their metabolites: Implications for diabetes pathophysiology, prevention, and treatment. Nutr Healthy Aging 2017; 4(2):127-140.
9. Zeyda M, Stulnig TM. Obesity, inflammation, and insulin resistance–a mini-review. Gerontology 2009; 55(4):379-386.
10. Facchini FS, Carantoni M, Jeppesen J, Reaven GM. Hematocrit and hemoglobin are independently related to insulin resistance and compensatory hyperinsulinemia in healthy, non-obese men and women. Metabolism 1998; 47(7):831-835.
11. Shimodaira M, Okaniwa S, Nakayama T. Investigation of the relationship between hemoglobin and serum iron levels and early-phase insulin secretion in non-diabetic subjects. Acta Diabetologica 2016; 53(5):783-789.
12. Gyawali P, Richards RS, Nwose EU, Bwititi PT. Whole-blood viscosity and metabolic syndrome. Clin Lipidol 2012; 7(6):709-719.
13. Baron AD, Clark MG. Role of blood flow in the regulation of muscle glucose uptake. Annu Rev Nutr 1997; 17(1):487-499.
14. Yuan T, Fan W-B, Cong Y, Xu H-D, Li C-J, Meng J, *et al*. Linoleic acid induces red blood cells and hemoglobin damage via oxidative mechanism. Int J Clin Exp Pathol 2015; 8(5):5044-5052.
15. Ditzel J, editor. Changes in red cell oxygen release capacity in diabetes mellitus. Federation Proceedings 1979; 38:2484-2488.
16. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15(7):539-553.
17. Wu CZ, Lin JD, Hsia TL, Hsu CH, Hsieh CH, Chang JB, *et al*. Accurate method to estimate insulin resistance from multiple regression models using data of metabolic syndrome and oral glucose tolerance test. J Diabetes Investig 2014; 5(3):290-296.
18. Lin JD, Hsu CH, Liang YJ, Lian W-C, Hsieh C-H, Wu C-Z, *et al*. The estimation of first-phase insulin secretion by using components of the metabolic syndrome in a chinese population. Int J Endocrinol 2015; 2015:675245.
19. Lin YT, Wu CZ, Lian WCH, Hsieh CH, Pei D, *et al*. Measuring second phase of insulin secretion by components of metabolic syndrome. Int J Diabetes Clin Diagn 2015; 2:113-118.
20. Chen Y-L, Lee S-F, Pei C, Pei D, Lee C-H, He C-T, *et al*. Predicting glucose effectiveness in Chinese participants using routine measurements. Metab Syndr Relat Disord 2016; 14(8):386-390.
21. Moan A, Nordby G, Os I, Birkeland KI, Kjeldsen SE. Relationship between hemorrheologic factors and insulin sensitivity in healthy young men. Metabolism 1994; 43(4):423-427.
22. Sivasinprasasn S, Sa-Nguanmoo P, Pratchayasakul W, Kumfu S, Chattipakorn SC, Chattipakorn N. Obese-insulin resistance accelerates and aggravates cardiometabolic disorders and cardiac mitochondrial dysfunction in estrogen-deprived female rats. Age (Dordr) 2015; 37(2):28.
23. Li C, Ford ES, Li B, Giles WH, Liu S. Association of testosterone and sex hormone-binding globulin with metabolic syndrome and insulin resistance in men. Diabetes Care 2010; 33(7):1618-1624.
24. Bachman E, Travison TG, Basaria S, Davda MN, Guo W, Li M, *et al*. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. J Gerontol A Biol Sci Med Sci 2014; 69(6):725-735.

25. Hanley AJG, Retnakaran R, Qi Y, Gerstein HC, Perkins B, Raboud J, *et al*. Association of hematological parameters with insulin resistance and β-cell dysfunction in nondiabetic subjects. J Clin Endocrinol Metab 2009; 94(10):3824-3832.
26. Weiss R, Magge SN, Santoro N, Giannini C, Boston R, Holder T, *et al*. Glucose effectiveness in obese children: relation to degree of obesity and dysglycemia. Diabetes Care 2015; 38(4):689-695.
27. Feingold KR, Grunfeld C. Obesity and dyslipidemia. 2015.
28. Bays HE, Toth PP, Kris-Etherton PM, Abate N, Aronne LJ, Brown WV, *et al*. Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. J Clin Lipidol 2013; 7(4):304-383.
29. Ban J-J, Ruthenborg RJ, Cho KW, Kim J-W. Regulation of obesity and insulin resistance by hypoxia-inducible factors. Hypoxia (Auckl) 2014; 2:171-183.
30. Alnaeeli M, Raaka BM, Gavrilova O, Teng R, Chanturiya T, Noguchi CT. Erythropoietin signaling: a novel regulator of white adipose tissue inflammation during diet-induced obesity. Diabetes 2014; 63(7):2415-2431.
31. Sahay M, Kalra S, Badani R, Bantwal G, Bhoraskar A, Das AK, *et al*. Diabetes and Anemia: International Diabetes Federation (IDF)–Southeast Asian Region (SEAR) position statement. Diabetes Metab Syndr 2017; 11 Suppl 2:S685-S695.

Case Report

Surgical management of ectopic mediastinal thyroids: Clinical experience of 5 cases and review of the literature

Kenan Can Ceylan, Guntug Batihan, Seyda Ors Kaya
Department of Thoracic Surgery, University of Health Sciences, Dr Suat Seren Chest Diseases and Surgery Medical Practice and Research Center, Turkey

Kuwait Medical Journal 2022; 54 (1): 106 - 110

ABSTRACT

Ectopic thyroid tissue (ETT) is a rare cause of mediastinal masses and there are only few case reports of mediastinal ETT reported. Several surgical procedures such as median sternotomy, posterolateral thoracotomy and more recently, video-assisted thoracoscopic surgery have been described in the literature for approach to mediastinal masses.

This study retrospectively analyses 164 patients who underwent surgical resections for mediastinal masses in our department between 2002 and 2017. In 5 out of 164 patients, mediastinal masses were diagnosed as mediastinal ETT. Surgical procedures, ETT localization, histopathological results, perioperative and postoperative complications were noted.

Complete surgical excision were performed in all cases. There were no complications in the perioperative and postoperative period.

ETTs are extremely rare causes of mediastinal masses, but they must be considered in the differential diagnosis of all mediastinal masses. Surgical excision must be applied in proper cases, due to the risk of compression of neighboring structures and malignant transformation.

KEY WORDS: ectopic thyroid, mediastinal mass, surgery

INTRODUCTION

Ectopic thyroid tissue (ETT) is a rare cause of mediastinal masses and it accounts for only 1% of mediastinal tumors[1].

ETT could be found anywhere along the path of initial embryologic descent of the thyroid gland from the floor of the primitive foregut to its normal pre-tracheal position. Most ETTs are found along this path of decent, while about 10% have been found in other anatomical locations. Mediastinal localization of the ETT constitutes less than 1% of all ectopic thyroid cases[2-4]. Few case reports of mediastinal ETT have been reported. In most of the cases, mediastinal ETT were located in the anterior or middle mediastinum. In only three cases, the ETTs were located in the posterior mediastinum and the preferred surgical approach were sternotomy and thoracotomy[5,6]. Several surgical procedures such as median sternotomy, posterolateral thoracotomy and more recently, video-assisted thoracoscopic surgery (VATS) have been described in the literature for approach to mediastinal masses[4]. We reported a retrospective case series of five patients with mediastinal ETT. We have successfully applied VATS procedure in these three cases.

The aim of this study is to evaluate clinical and radiological presentation of mediastinal ETT and demonstrate our surgical approach in these patients.

CASE REPORT

The study was approved by the ethical committee of Dr Suat Seren Chest Diseases and Surgery Medical Practice and Research Center.

This study retrospectively analyses 164 patients who underwent surgical resections for mediastinal masses in our department between 2002 and 2017.

Address correspondence to:
Guntug Batihan, MD, Department of Thoracic Surgery, 35110, University of Health Sciences, Dr Suat Seren Chest Diseases and Surgery Medical Practice and Research Center, Yenisehir, Gaziler Street 331, Izmir, Turkey. Tel: 090 0 2324333333; Fax: 090 0 2324587262; E-mail: gbatihan@hotmail.com

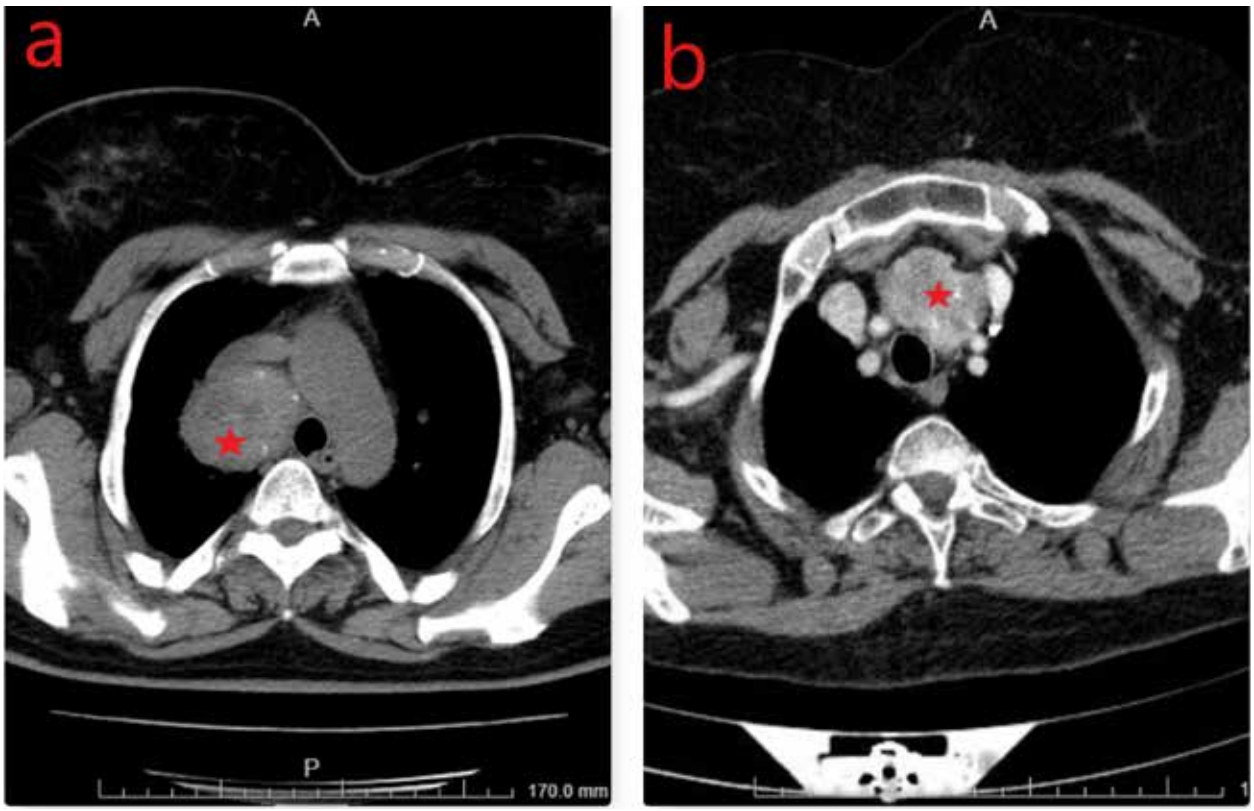


Fig 1: Thorax CT images of three cases. Mediastinal ectopic thyroid tissues (arrow) were located in anterior mediastinum (figure 1a), middle mediastinum (figure 1b) and posterior mediastinum (figure 1c). In these three cases, we preferred VATS procedure and no complication was seen.

In 5 out of 164 patients, mediastinal masses were diagnosed as mediastinal ETT. Demographic data and clinicopathological features were extracted from the medical records. All patients had undergone thyroid function tests, ultrasonography, chest X-ray, pulmonary function tests and computerized tomography scan of the neck and chest. Percutaneous transthoracic fine needle aspiration was performed in two cases whose masses were located in anterior mediastinum, and transbronchial needle aspiration was performed in the other three cases with paratracheal masses. However, in two of these cases, the diagnosis could not be obtained because of the lack of sufficient material in the biopsy procedure.

Complete surgical excision performed in all cases. Surgical procedures, ETT localization, histopathological results, perioperative and postoperative complications were noted.

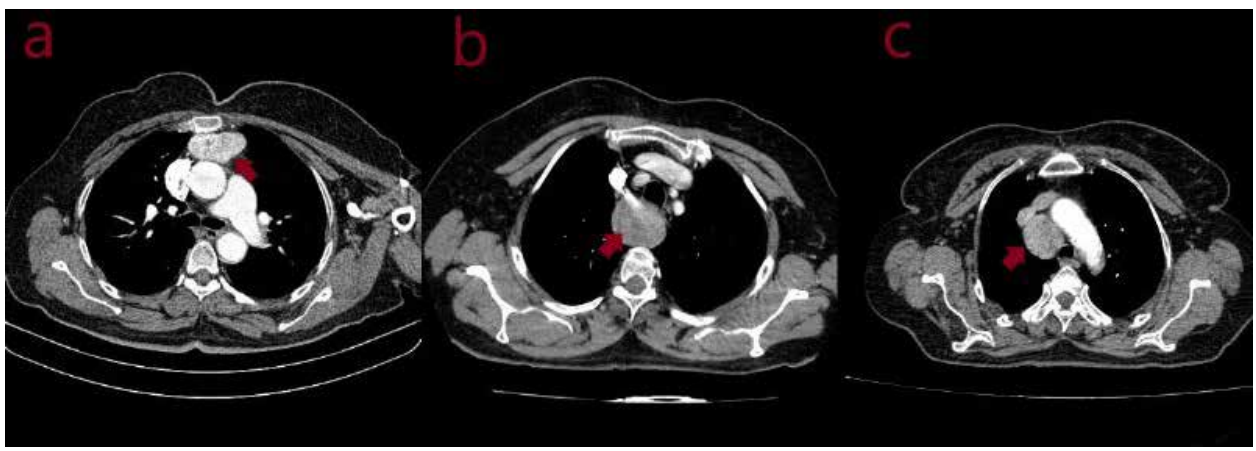


Fig 2: A. Chest CT image of the patient with large paratracheal ETT. Because of the size of the mass, we preferred right thoracotomy. B. Anterior mediastinal ETT was seen in this chest CT. ETT was excised with the incision of partial sternotomy.

Characteristic features of the patients

The median age was 64 years (range: 56-70 years) and all patients were female. All patients were euthyroid, except one patient who had a hyperthyroidism, which was controlled preoperatively. Mediastinal ETT was in the anterior (2 cases), middle (2 cases) and posterior mediastinum (1 case). VATS was applied successfully in three cases (Figure 1). Due to the localization and the size of the ETT, partial sternotomy and lateral thoracotomy were applied in the other two cases (Figure 2). Frozen section was studied in all cases and the diagnosis of ETT was confirmed (Figure 3). Median operation time was 165 minutes (range: 120-220 minutes) and median size of the ETT was 5 cm (range: 4-7.5 cm). Median chest tube duration was 2 days (range: 1-3 days) and median hospital stay was 3 days (range: 2-4 days). No complications were seen in the perioperative and postoperative period (Table 1).

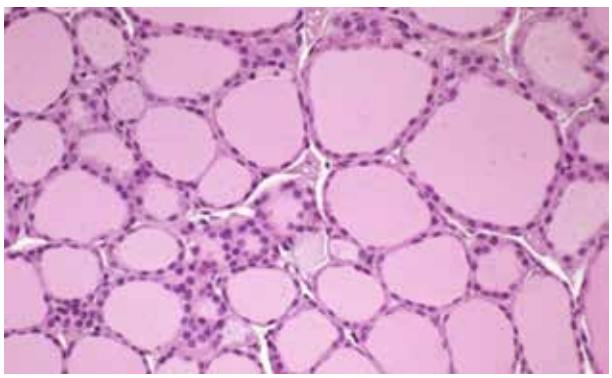


Fig 3. Pathological examination of one of the specimens that was excised from mediastinum demonstrating normal thyroid tissue (H & E, original magnification 200×)

Surgical technique

Right sided bi-portal VATS was applied in three cases. 1 cm incision, as a camera port, was made in the right seventh intercostal space at the mid-axillary line and a 3 cm utility incision was made in the right fourth intercostal space at the anterior axillary line. The mediastinal pleura was incised over the ETT. Blunt and sharp dissection were performed to mobilize the mass from the surrounding structures. The vascular pedicle was identified and divided with the harmonic scalpel, and ETT was removed from the thoracic cavity with endoscopic bag. Partial sternotomy and thoracotomy were also applied in other cases due to the size and the localization of the ETT.

ETTs can be in all compartments of the mediastinum as in our cases, therefore it is very important to identify relations of the mass to surrounding structures. VATS provide a great exposure to identify adjacent tissues and allows safe dissection; therefore, it is a good alternative to conventional procedures in proper cases.

DISCUSSION

As a result of abnormal gland migration, ETT could be found anywhere along the path of embryologic descent of the thyroid gland. Lingual thyroid tissue accounts for 90% of these abnormalities[7-12]. ETT in the mediastinum with no connection to the cervical thyroid gland is very rare, and we could find only a small number of cases in the literature (Table 2)[1-12].

Mediastinal ETT is usually asymptomatic and detected incidentally, but in some cases dyspnea, dysphagia, chest pain and chronic cough would be seen due to the compression of neighboring structures[10-12].

ETT usually demonstrates high computerized tomography density on plain scan due to the iodine content as well as intense and sustained intravenous contrast enhancement. Some authors advocate the follow-up of the ETT rather than resection in asymptomatic patients, but we prefer surgical excision due to the risks of malignant transformation, progressive enlargement, hemorrhage within the mass causing respiratory failure and compression of neighboring vital mediastinal organs[5,6]. ETTs would be located in any compartment of the mediastinum, therefore different approaches such as sternotomy, thoracotomy and VATS can be used (Table 2). VATS is a safe and feasible procedure for mediastinal ETTs and we applied it in our three cases without any complication. VATS have potential benefits like decreased postoperative pain, reduced length of hospital stay and fewer postoperative complications. Although traditional surgical approaches may be required in large tumors, VATS is a good alternative in appropriate patients.

Table 1: Characteristic features of patients

Case	Age/ Gender	Localization	ETT size	Symptom	Type of surgery	Operation duration	Complication
1	60/F	Middle mediastinum	7.5x5.5 cm	Chest pain	Right thoracotomy	135 min	None
2	56/F	Anterior mediastinum	5x4 cm	None	Partial sternotomy	120 min	None
3	68/F	Anterior mediastinum	5x4 cm	Chest pain	Right VATS	220 min	None
4	64/F	Posterior mediastinum	6x5 cm	Cough	Right VATS	165 min	None
5	70/F	Middle mediastinum	4x3 cm	None	Right VATS	200 min	None

Table 2: Literature review of mediastinal ETTs which were surgically excised.

Year	Author	Title	ETTa size	Localization	Type of surgery	Age/ Gender	Symptom
2003	Gamblin TC, *et al*[1]	Ectopic thyroid.	*	Anterior mediastinum	Cervical incision +Median sternotomy	61/F	Dyspnea
2004	Kawakami M, *et al*[2]	A case of mediastinal goiter	2.5x3.5 cm	Anterior mediastinum	Cervical incision +Median sternotomy	51/F	Asymptomatic
2004	Bodner J, *et al*[3]	Ectopic mediastinal thyroid adenoma	*	Middle mediastinum	RATS	72/F	*
2007	Perrot M, *et al*[4]	Surgical management of mediastinal goiters: when is a sternotomy required? (4 cases)	*	**	Median sternotomy	*	*
2008	Karapolat S, *et al*[5]	Ectopic posterior mediastinal thyroid: a case report	5x5 cm	Posterior mediastinum	Thoracotomy	74/M	Chest pain
2009	Demirhan R, *et al*[6]	Posterior Mediastinal Ectopic Thyroid: An Unusual Cause for Dysphagia	7x5.5 cm	Posterior mediastinum	Median sternotomy	62/M	Dysphagia
2009	Guimaraes MJ, *et al*[7]	Ectopic thyroid in the anterior mediastinum(2 cases)	12X9 cm	Anterior mediastinum	*	40/F	Dyspnea
			7X5 cm	Middle mediastinum	*	57/F	Dyspnea
2013	Walz PC, *et al*[8]	Ectopic mediastinal goiter successfully managed via cervical approach: case report and review of the literature.	3x2 cm	Anterior mediastinum	Cervical incision	31/M	Dysphagia
2013	Kim S-Y[9]	A case of right paratracheal ectopic thyroid mimicking metastasis on CT and 18F-FDG PET CT.	*	Middle mediastinum	*	67/M	Asymptomatic
2014	Lee WS, *et al*[10]	A 7.3×5.3×3.5-cm heterotopic thyroid in the posterior mediastinum in a patient with situs inversus totalis	7.3x5.3 cm	Posterior mediastinum	Thoracotomy	62/F	Asymptomatic
2018	Tay WL, *et al*[11]	Video-assisted thoracoscopic surgery (VATS) resection of a right paratracheal ectopic thyroid: a case report	4.1x5.4 cm	Middle mediastinum	VATS	62/F	Neck pain
2018	Metere A, *et al*[12]	Diagnosis and management of a mediastinal ectopic thyroid laying on the right bronchus: case report and review of literature.	6x8 cm	Middle mediastinum	Cervical incision+Partial sternotomy	63/M	Asymptomatic

[a]Ectopic thyroid tissue; *Not mentioned in the article; M: Male, F: Female

CONCLUSION

In conclusion, ETTs are extremely rare causes of mediastinal masses, but they must be considered in the differential diagnosis of all mediastinal masses. Surgical excision must be applied in proper cases due to the risk of compression of neighboring structures and malignant transformation. We recommend the use of VATS in appropriate patients because of its described benefits.

ACKNOWLEDGMENT

None

Conflict of interest statement: Authors declare that there is no conflict of interest in this study.

Author contribution: Guntug Batihan and Kenan Can Ceylan conceived of the presented idea, Seyda Ors Kaya contributed to the final manuscript. All authors provided critical feedback and helped shape the research and manuscript.

REFERENCES

1. Gamblin TC, Jennings GR, Christie DB, Thompson WM, Dalton ML. Ectopic thyroid. Ann Thorac Surg 2003; 75(6):1952-1953.
2. Kawakami M, Ito K, Yoshimura K, Tanaka H. A case of mediastinal goiter. Auris Nasus Larynx 2004; 31(2):183-187.
3. Bodner J, Lottersberger CA, Kirchmayr W, Schmid T. Ectopic mediastinal thyroid adenoma. Eur J Cardiothorac Surg 2004; 26:211-212.
4. de Perrot M, Fadel E, Mercier O, Farhamand P, Fabre D, Mussot S, *et al*. Surgical management of mediastinal goiters: when is a sternotomy required? Thorac Cardiovasc Surg 2007; 55(1):39-43.
5. Karapolat S, Bulut I. Ectopic posterior mediastinal thyroid: a case report. Cases J 2008; 1:53.
6. Demirhan R, Onan B, Oz K, Keser SH, Gul AE, Onan IS. Posterior mediastinal ectopic thyroid: an unusual cause for dysphagia. Ann Thorac Surg 2009; 88(2):656-659.

7. Guimaraes MJ, Valente CM, Santos L, Baganha MF. Ectopic thyroid in the anterior mediastinum. J Bras Pneumol 2009; 35(4):383-387.
8. Walz PC, Iwenofu OH, Essig GF. Ectopic mediastinal goiter successfully managed via cervical approach: case report and review of the literature. Head Neck 2013; 35(3):E94-97.
9. Kim SY. A case of right paratracheal ectopic thyroid mimicking metastasis on CT and 18F-FDG PET CT. Open J Med Imaging 2013; 3:82-85.
10. Lee WS, Kim YH, Chee HK, Hwang JJ, Lee SA, Lee JH, *et al*. A 7.3×5.3×3.5-cm heterotopic thyroid in the posterior mediastinum in a patient with situs inversus totalis. J Thorac Dis 2014; 6(5):E39-E42.
11. Tay WL, Hwang JS, Ong BH. Video-assisted thoracoscopic surgery (VATS) resection of a right paratracheal ectopic thyroid: a case report. The Journal of Visualized Surgery 2018; 4:6.
12. Metere A, Giacomo TD, Vergine M, Biffoni M, Giacomelli L. Diagnosis and management of a mediastinal ectopic thyroid laying on the right bronchus: case report and review of literature. BMC Surg 2018; 18(1):19.

Case Report

Gastrointestinal Stromal Tumor (GIST) present as a cystic epigastric mass: Case report

Sarah Qassim, Khaild Al-Yaqout, Ali Al-Daham
Department of Surgery, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait

Kuwait Medical Journal 2022; 54 (1): 111 - 114

ABSTRACT

Gastrointestinal stromal tumors (GIST) are the 3rd most common mesenchymal tumors. This case report is one of the rare presentations of a cystic GIST. It starts when a 57-year-old male complained of abdominal pain and mass. Several investigations were performed, including an abdominal ultrasound which showed an abdominal cystic lesion 5cm in size. A contrast-enhanced computed tomography scan of the abdomen was done and revealed the same finding with uncertain origin. Hence, magnetic resonance cholangiopancreatography and endoscopic ultrasound were performed and showed a cystic mass originating from the pancreas. Fine needle aspiration showed gastrointestinal stromal tumor. The patient underwent an 8cm mass resection of the gastric body via laparotomy. Immuno-histology study showed GIST. After that, the patient recovered well with no recurrence in follow-up. Gastrointestinal stromal tumors are commonly presented as a solid lesion, and cystic appearance is rare and can be misdiagnosed as pancreatic pseudocyst.

KEY WORDS: gastrointestinal tract, mesenchymal tumors, oncology

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common subtype of mesenchymal neoplasms of the gastrointestinal tract with a prevalence of less than 1%[1]. GISTs typically occur in older adults, with a male predominance above 50 years of age, median age of 60-65 patient age and rarely under the age of 40[2]. They are most commonly located in the stomach, followed by the small intestine, colon and rectum, and esophagus; with incidence of 60%, 20%, 5% and less than 5% respectively[3]. Initial patient evaluation should include a computed tomography (CT) scan and endoscopic ultrasound (EUS) might be of additional value to rule out neoplastic cells[3]. Cystic based GIST are uncommon, as the majority are submucosal in origin; this case study represents a GIST with cystic changes.

CASE REPORT

A 57-year-old gentleman presented with epigastric and right upper quadrant pain of two months duration. The pain was intermittent, radiating to the left side with no aggravating or relieving factors. The patient also gave a history of chronic diarrhea of six months duration with no blood or mucus discharge. There was no nausea, vomiting, loss of appetite or weight. His abdomen was soft with no tenderness and epigastric mass was felt. The laboratory investigations were within accepted range. The patient had an abdominal ultrasound, which showed irregular thickened wall with rounded cystic structure 5x7 cm. CT scan of the abdomen showed left hypochondriac central mass. Tumor Markers CEA, Ca 125, Ca 19.9, Ca 15.3, AFP were all within normal range.

Magnetic resonance cholangiopancreatography showed a cystic mass measuring 7x8x9 cm with irregular thickened wall seen in the left para-pancreatic area, around its tail, splenic hilum and retro-stomach. The mass had almost rugae like anterior wall and it is inseparable from the greater curve of stomach. The impression was a left upper quadrant abdominal mass, more in favor of exophytic gastric tumor (GIST) (Figure 1).

Address correspondence to:
Sarah Qassim, Department of Surgery, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait. Tel: +965 66447299; E-mail: sarahqassim89@gmail.com

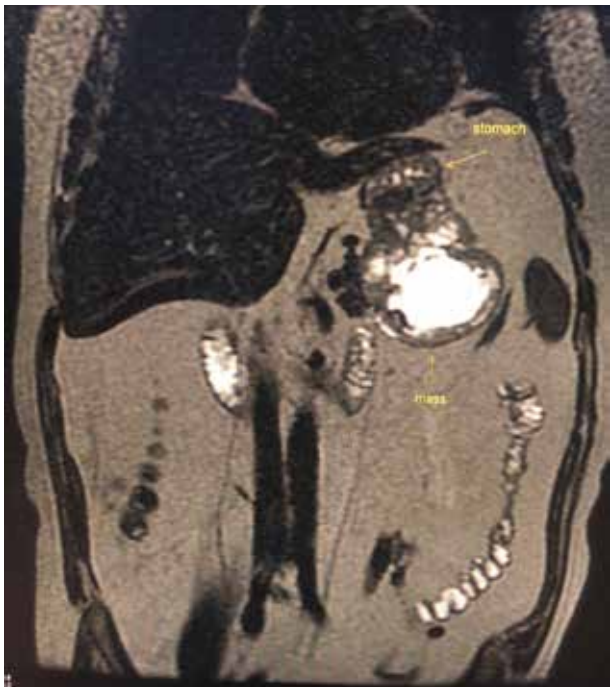


Fig 1: Endoscopic ultrasound. Compression noted at the greater curvature.

EUS was performed and an external compression was noticed at the greater curvet at 40 cm from the incisors. Difficult to assess its origin, but it was most likely arising from the tail of pancreas. Largest diameter 8x6.5 cm lesion was cystic in nature with nodular components and thickened walls. The largest nodule 2.4x0.7cm. The thickened wall diameter measured 3.6 cm, single septum identified. Lesion was doppler negative. It was hypo/isoechoic in nature and anechoic of the cystic component. Three passes were performed and samples were taken; 65 cc of serosanguinous material was drained.

The impression was that the lesion is cystic in nature with nodular component and thickened wall suggestive of possible malignant transformation (Figure 2). Fine needle aspiration cytology (FNAC) showed a positive CD117, DOG1 and negative S-100, which conclude a GIST. At first, a diagnostic laparoscopy was performed and a mass was noted behind the stomach. However, mass origin couldn't be identified via laparoscopy and conversion to laparotomy was done after failure of progression. In laparotomy, a pedunculated gastric mass from

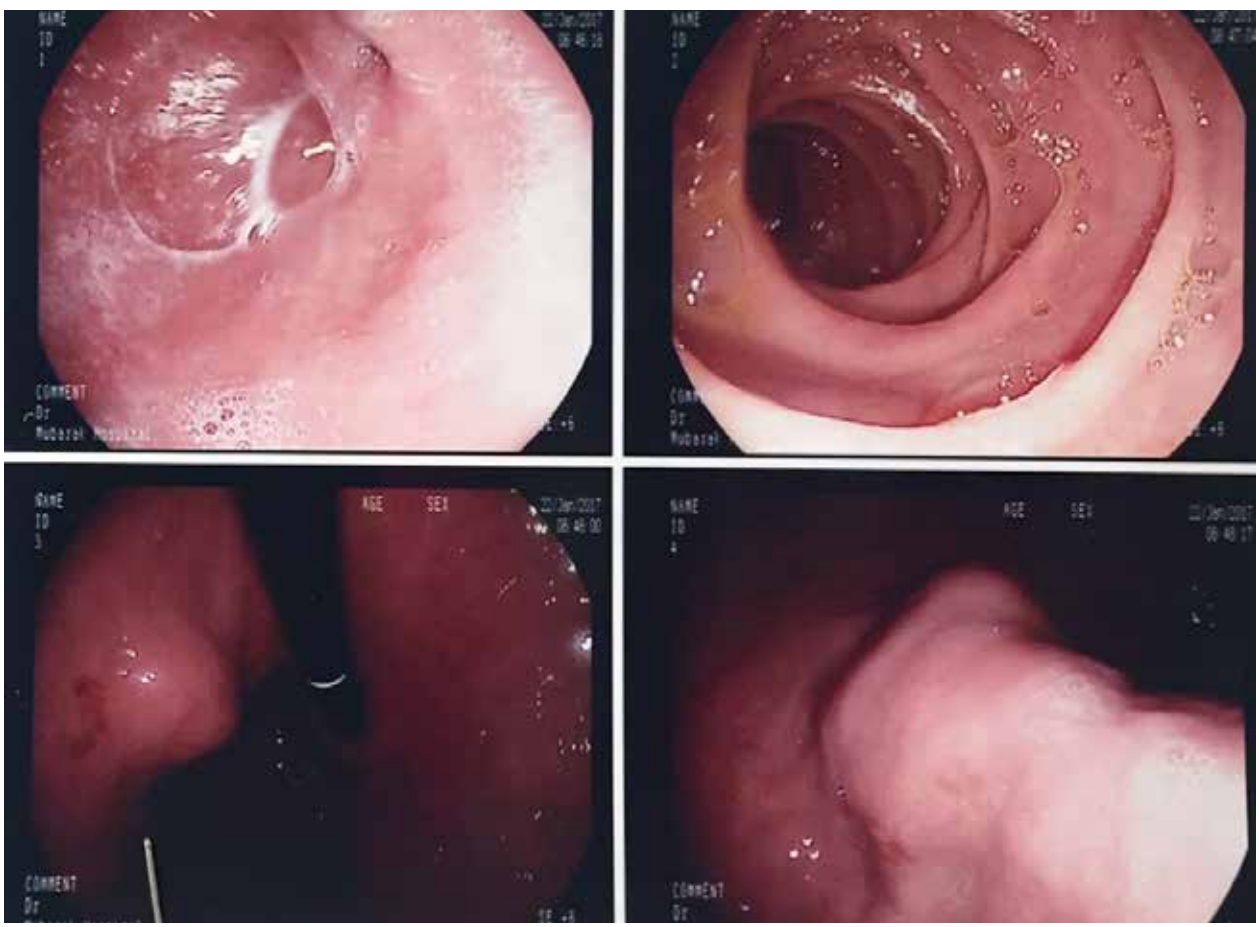


Fig 2: Magnetic resonance cholangiopancreatography. A cystic mass noted, retro gastric 7x8x9cm.

posterior wall of the stomach was identified and wedge resection with 2cm margin was performed. Histopathology of the gastric mass showed a GIST, grade 1, (T3 Nx Mx). Tumor size was 8.5 at greatest diameter, unifocal, spindle cell subtype, 1/50 HPF mitotic rate, low risk with negative margins. Immuno-histopathology showed positive CD117, DOG1 and negative CD34+, SMA (focal+), S100 and Desmin.

The operation was uneventful with high recovery rate. Case was discussed with a multidisciplinary team of radiologist, histopathologist, surgeon and oncologist; in which, only follow up was advised with no need of adjuvant therapy. On follow up, patient was symptom free with no recurrence of tumor on further investigation.

DISCUSSION

GISTs are the most common sarcomas of the gastrointestinal tract. They can occur from esophagus to rectum, but most commonly have been found in the stomach[4]. GISTs originated from intestinal cell of Cajal (ICCs). GISTs are the only tumors that express both c-Kit and CD34 as the development of ICCs and other stem cells are dependent on SCF-KIT oncogene. Also, ICCs are located in and near the circular muscle layers of the gastrointestinal tract, and GIST usually originate from the submucosa and muscularis propria and present as solid tumors[5]. Mostly, patients experience melena due to central necrosis in the lesion and others are usually symptomatic if the lesion is 5 cm or larger[6]. In this case, the patient experienced only diffuse abdominal pain and mass. CT scan is the gold standard method, and with the agnetic resonance cholangiopancreatography and EUS-guided FNAC, a cystic pancreatic mass with a malignant transformation was revealed. However, EUS-guided fine-needle aspiration did not reflect the tumor subtype and mitotic ratio, and thus proper management and prognosis cannot be achieved via FNAC result[7]. Exophytic stromal tumors with cystic changes have been previously reported; however, they are rarely observed and during preoperative diagnosis, these masses may be misdiagnosed as duodenal, pancreatic or liver cyst, duplication cyst, diverticulum or even a metastatic lesion from a primary liver or pancreatic tumor[8-9]. The patient underwent a diagnostic laparoscopy that revealed a gastric mass from the posterior wall of the stomach. The surgery was converted to upper midline laparotomy in which wedge resection of the pedunculated mass was done. Histopathology of the resected lesion showed a grade 1 GIST, spindle subtype with mitotic rate of 1/50 HPF positive CD117. So, an accurate diagnosis and prognosis of the lesion is only done after surgical resection. GISTs are relatively rare tumors that require a multimodal approach to management. Surgery remains the definitive treatment and is recommended for primary disease (tumors ≥2 cm). This is followed by tumor classification into low or high risk of malignancy according to tumor size, mitotic count and location. The introduction of imatinib will improve the clinical outcome of metastatic GIST[10]. For that, a multidisciplinary team was conducted, in which the patient will be followed by the surgical and ontological team for the progression of the disease.

CONCLUSION

Most GISTs are solid tumors and cystic change is uncommon. Preoperatively, an intra-abdominal cyst may be considered pancreatic in origin. Resection of the mass is the standard treatment and with malignant lesion, imatinib is prescribed.

Take home message:

- GISTs are solid tumors, and they can present as a cystic lesion.
- Considering GIST as a differential diagnosis of a cystic lesion.
- Appropriate diagnosis and management of GIST is resection of lesion. So, EUS-guided FNAC is not the gold standard for diagnosis.

ACKNOWLEDGMENT

Author's Contribution: Sarah Qassim, the corresponding author, has written the case report and the co-authors have collected the recourses and patient consent. The authors read and approved the final manuscript.

Conflict of interest: None

REFERENCES

1. Zhao X, Yue C. Gastrointestinal stromal tumor. J Gastrointest Oncol 2012; 3(3):189-208.
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors. Gastroenterol Clin North Am 2013; 42(2):399-415.
3. Beham AW, Schaefer I-M, Schüler P, Cameron S, Ghadimi BM. Gastrointestinal stromal tumors. Int J Colorectal Dis 2012; 27(6):689-700.
4. Sun K-K, Xu S, Chen J, Liu G, Shen X, Wu X. Atypical presentation of a gastric stromal tumor masquerading as a giant intraabdominal cyst: a case report. Oncol Lett 2016; 12(4):3018-3020.
5. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, *et al*. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998; 279(5350):577-580.
6. Chen X, Lv H, Zhang W, Cao J. Large cystic-based gastrointestinal stromal tumor: A case report. Oncol Lett 2014; 7(3):846-848.

7. Ricci R, Chiarello G, Attili F, Fuccio L, Alfieri S, Persiani R, *et al*. Endoscopic ultrasound-guided fine needle tissue acquisition biopsy samples do not allow a reliable proliferation assessment of gastrointestinal stromal tumours. Dig Liver Dis 2015; 47(4):291-295.
8. Zhu C-C, Liu Y, Zhao G. Exophytic gastrointestinal stromal tumor with cystic changes: a case report. Oncol Lett 2014; 7(5):1427-1429.
9. Hamza AM, Ayyash EH, Alzafiri R, Francis I, Asfar S. Stromal tumour masquerading as a cyst in the lesser sac. BMJ Case Rep 2016; 2016:bcr2016215479.
10. Blay JY, von Mehren M, Blackstein ME. Perspective on updated treatment guidelines for patients with gastrointestinal stromal tumors. Cancer 2010; 116(22):5126-5137.

Case Report

Ipsilateral synchronous renal cell carcinoma: Papillary and chromophobe

Yasemen Adali[1], Tugba Toyran[2], Ozge Ertener[1]
[1]Department of Pathology, Izmir Economy University Faculty of Medicine, Izmir, Turkey
[2]Department of Pathology, Adana State Hospital, Adana, Turkey

Kuwait Medical Journal 2022; 54 (1): 115 - 118

ABSTRACT

Synchronous renal tumors are the general name of multiple tumors with bilateral or unilateral location which are less frequently seen. Here, we present a case of papillary renal cell carcinoma (pRCC) and chromophobe renal cell carcinoma (chRCC) as a rare entity in a single kidney.

A 41-year-old woman underwent a radical nephrectomy for a mass with an 11 cm diameter localized in the lower left pole. Macroscopic examination revealed a 10.5x9.5 cm sized tumor and one more tumor 1 cm away from this tumor sized 1.7x1.2 cm. The histopathological and immunohistochemical features of the two tumors were evaluated and were diagnosed as chRCC and pRCC.

Synchronous renal tumors are rare. Generally one component of renal synchronous tumors reported in the literature is usually clear cell renal cell carcinoma, which is the most frequently seen renal cell carcinoma type of all. We present this case because of it's uniqueness.

KEY WORDS: chromophobe, papillary, renal cell carcinoma, synchronus renal tumor

INTRODUCTION

Renal cell carcinoma (RCC)[1], which accounts for about 2% to 3% of all cancers, originates from renal tubular epithelium and contains a group of tumors that have different morphological and genetic characteristics that vary in prognosis[2]. The most common histological subtypes of RCC are clear cell RCC (ccRCC), constituting 80-90% of the cases, and papillary RCC (pRCC) which comprise 10-15%[2]. Other RCCs include chromophobe renal cell RCC (chRCC), collecting duct carcinoma, multilocular cystic clear cell renal cell neoplasm of low malignant potential (mcccRCNlmp) and medullary carcinoma[3]. RCCs are more common in men and usually seen from middle age onwards. The most common clinical symptoms are hematuria, flank pain and palpable mass, although asymptomatic cases can also be observed.

Synchronous renal tumors are the general name of multiple tumors with bilateral or unilateral location, which can be sporadic or syndromic. Bilateral synchronous sporadic RCC was reported at 3-4.2% among RCCs[4]; two different synchronous and ipsilateral renal tumors are reported in the literature in the range of 0.5-5.4%[5,6]. Synchronous renal tumors, as with bilateral pRCCs, may be associated with chronic kidney disease or may be related to genetic predisposition such as hereditary familial RCC syndrome[7]. Histological subtypes of RCC have different clinical progression patterns and respond to different treatments[2]. In synchronous renal tumors, histological subtyping is very important, as the prognosis is determined by the more aggressive tumor[8]. Here, we present the presence of pRCC and chRCC as a rare entity in a single kidney.

Address correspondence to:

Yasemen Adali, MD, Department of Pathology, Izmir Economy University Faculty of Medicine, Izmir, Turkey. Tel: +90 5063437199; E-mail: yasemenadali@hotmail.com. ORCID: 0000-0002-8004-7364

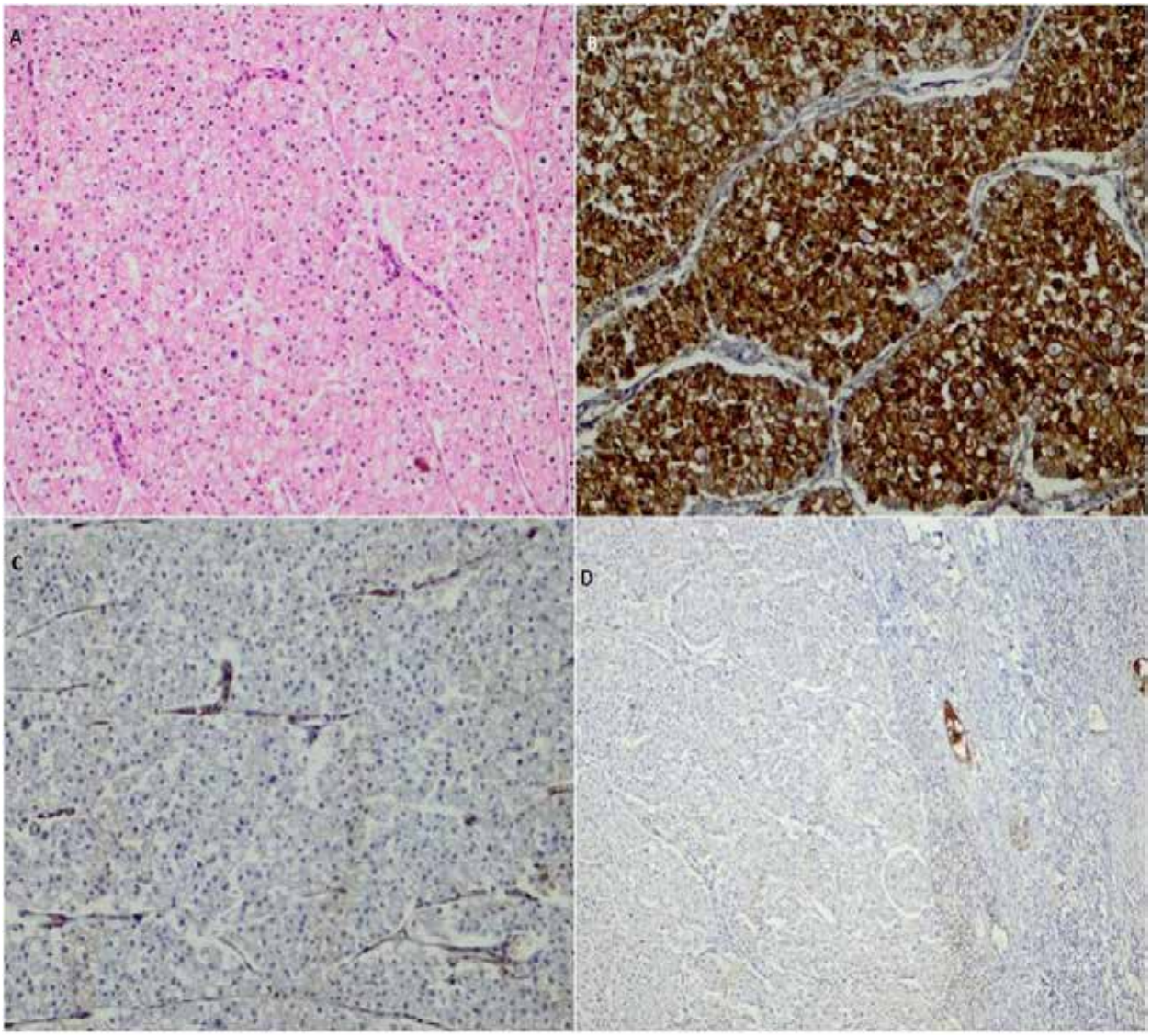


Fig 1: (A) Neoplastic cells of 10.5x9.5 cm sized tumor showing pale cytoplasm and perinuclear halo (H&E, 200x); **(B)** Neoplastic cells of 10.5x9.5 cm sized tumor showing immunohistochemical cytokeratin 7 positivity (Cytokeratin 7, 200x); **(C)** Neoplastic cells of 10.5x9.5 cm sized tumor showing immunohistochemical vimentin negativity (Vimentin, 100x); **(D)** Neoplastic cells of 10.5x9.5 cm sized tumor showing immunohistochemical CD10 negativity (CD10, 100x).

CASE REPORT

A 41-year-old woman was admitted to hospital with left side pain, nausea and fever for three days. The laboratory tests were normal. Computerized tomography revealed a 11 cm diameter mass localized in the lower left pole. The patient underwent a radical nephrectomy.

Macroscopically, the left kidney measured 18.5x12x6.5 cm with perirenal fat. The attached adrenal gland measured 5.5x3.5x1 cm. The cut surface showed a tan-brownish coloured tumor with a size of 10.5x9.5 cm located in the lower left pole and focal hemorrhagic areas. In addition, 1 cm away from this tumor, a 1.7x1.2 cm sized, yellow coloured tumor is observed.

On microscopic examination, the larger tumour revealed hemorrhage and necrosis. Architecturally, the tumor is composed of large solid islands and trabeculae. Most of the tumor cells had pale cytoplasm, prominent cell borders, irregular nuclear membranes and some tumor cells had a small nucleus with a perinuclear halo (Fig 1A). Tumor cells stained positively with pancytokeratin and cytokeratin 7 [Fig 1B] and negative for vimentin (Fig 1C), CD10 (Fig 1D) and AMACR by immunohistochemical examination.

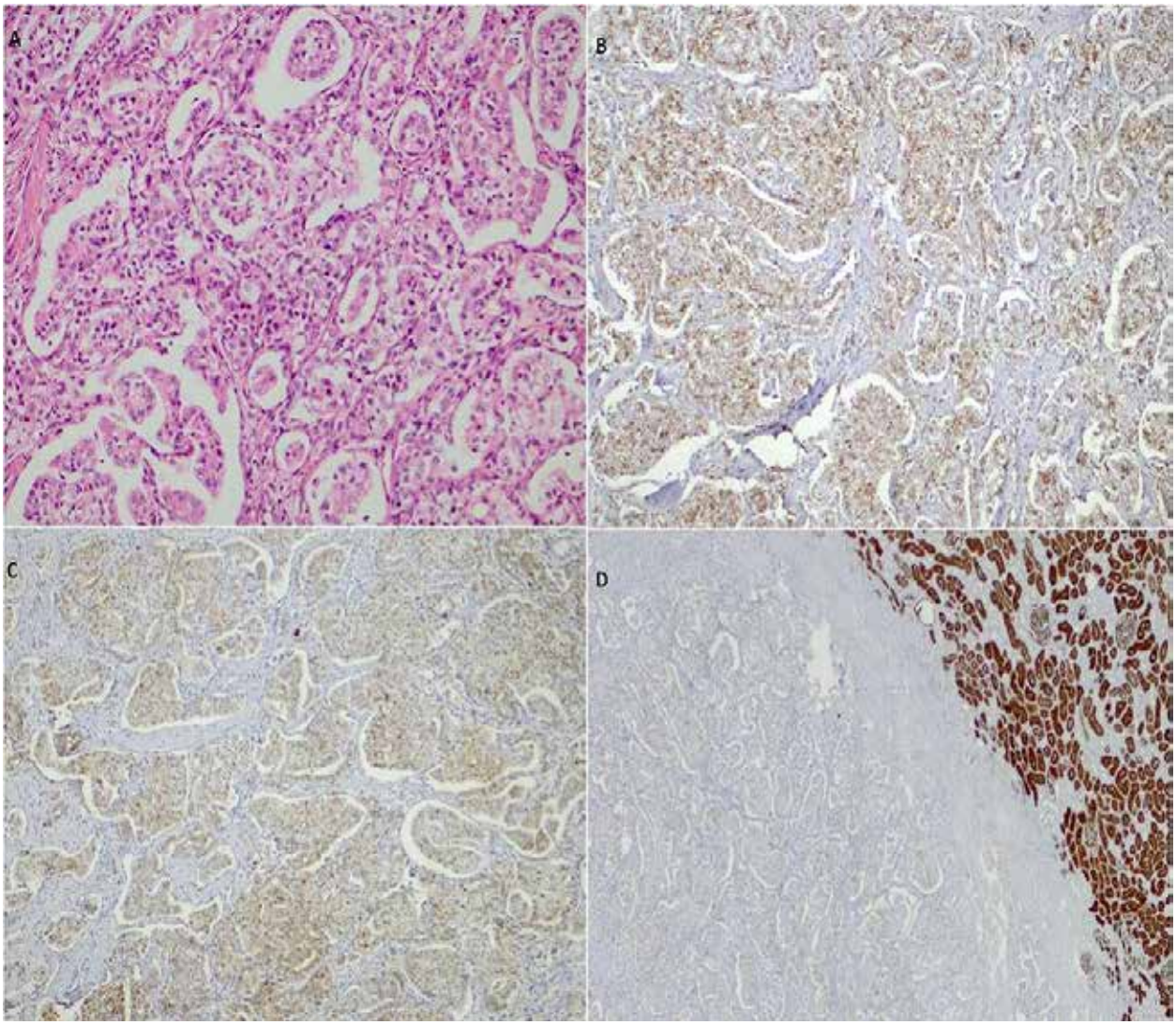


Fig 2: (A) Neoplastic cells of tumor sized 1.7x1.2 cm showing papillary architecture (H&E, 200x); **(B)** Neoplastic cells of tumor sized 1.7x1.2 cm showing immunohistochemical vimentin positivity (Vimentin, 100x); **(C)** Neoplastic cells of tumor sized 1.7x1.2 cm showing immunohistochemical AMACR positivity (AMACR, 100x); **(D)** Neoplastic cells of tumor sized 1.7x1.2 cm showing immunohistochemical CD 10 negativity with CD 10 positive normal renal tissue (CD 10, 100x).

The smaller tumor consists of cells arranged around long papillary structures with micropapillary and fibrovascular cores and shows solid areas (Fig 2A). Tumor cells showed elongated eosinophilic cytoplasm with irregular, basally located vesicular nuclei (Fig 2A). Tumor cells were immunohistochemically positive with pancytokeratin, vimentin (Fig 2B), cytokeratin 7 and AMACR (Fig 2C); and negative staining with CD10 (Fig 2D).

When the morphological and immunohistochemical features of the two tumors were considered, they were diagnosed as chRCC and pRCC.

DISCUSSION

Histopathological subtypes of RCCs are an important factor that determines the prognosis, and it is very important to make the correct histologic typing. Therefore clinical, macroscopic, microscopic, histochemical and immunohistochemical analysis must be evaluated together as well as cytogenetic features[9].

Synchronous renal tumors are reported in approximately 10% of radical nephrectomy specimens[10]. Bilateral and ipsilateral tumor associations are reported. Common ipsilateral synchronous tumours include ccRCC and chRCC[8], ccRCC and pRCC[11], ccRCC and mcccRCNlmp[12], ccRCC and transitional cell carcinoma[13]. In most of the tumors reported as synchronous in the literature, one of the tumors usually shows ccRCC characteristics. The difference of our case is that one of the tumors was pRCC and the other was chRCC.

pRCC is generally encapsulated by a fibrous capsule, yellow-brown in color and has a granular appearance macroscopically. It may have hemorrhagic and necrotic areas, as well as pseudocystic changes. Multifocality and bilaterality are more frequent in pRCC compared to other RCC histological subtypes. pRCC is microscopically divided into two subgroups, type 1 and type 2. Immunohistochemically, pRCCs stain positive with cytokeratin 7, CD10, vimentin, AMACR, RCCma. Type 2 pRCCs stain less with cytokeratin 7, while cytokeratin 20 is more frequently stained.

chRCCs generally have a better prognosis than ccRCC and pRCC. In addition, it is seen equally in men and women. Macroscopically, the mean diameter of these tumors are 8 cm and they are usually tan-brownish in colour with a central fibrous scar. Microscopically, tumor cells in chRCC are arranged in large trabeculae and solid islands. In some cases, tubulocystic structures may be predominant.

CONCLUSION

In conclusion, as in many tumors, one of the most important factors affecting prognosis is histological type of tumor. We would like to emphasize that the typing of synchronous renal tumors is important for both pathologists and clinicians.

ACKNOWLEDGMENT

This case report is presented as poster presentation in 26. National Pathology Congress & 7. Cytopathology Congress, Belek- Antalya/ Turkey, November 2016

Author contributions: Yasemen Adali and Tugba Toyran examined and reported the macroscopy of the case. Yasemen Adali, Ozge Ertener and Tugba Toyran made the definitive diagnosis. All authors discussed the case and contributed to the final manuscript.

Conflict of Interest: The authors declare that they have no conflict of interest.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66(1):7-30.
2. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, *et al*. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015; 67(5):913-924.
3. Protocol for the Examination of Specimens from Patients with Invasive Carcinoma of Renal Tubular Origin. 2017 College of American Pathologists (CAP), (Accessed June 2017, at https://cap.objects.frb.io/protocols/cp-kidney-17protocol-4011.pdf)
4. Grimaldi G, Reuter V, Russo P. Bilateral non-familial renal cell carcinoma. Ann Surg Oncol 1998; 5(6):548-552.
5. Harlow BL, Klaassen Z, Holzman S, Reinstatler L, Franken AA, Kavuri SK, *et al*. Multiple discordant histology after nephrectomy: descriptive analysis and outcomes. Clin Genitourin Cancer 2016; 14(2):e171-e175.
6. Crispen PL, Lohse CM, Blute ML. Multifocal renal cell carcinoma: clinicopathologic features and outcomes for tumors</¼4 cm. Adv Urol 2008; 2008:518091.
7. Breda A, Lucarelli G, Rodriguez- Faba O, Guirado L, Facundo C, Bettochi C, *et al*. Clinical and pathological outcomes of renal cell carcinoma (RCC) in native kidneys of patients with end-stage renal disease: along-term comparative retrospective study with RCC diagnosed in the general population. World J Urol 2015; 33(1):1-7.
8. Chughtai A, Shafqat K, Anwar MF, Chughtai AS. Synchronous ipsilateral renal tumors. J Coll Physicians Surg Pak 2018; 28(6):S110-S111.
9. Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, *et al*. ISUP Renal Tumor Panel. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am J Surg Pathol 2013; 37(10):1469-1489.
10. Rosin A, Bauer JJ, Costible RA. Surgical implications of multicentricity in renal cell carcinoma. Mil Med 2000; 165(9):670-671.
11. Ustuner M, Yaprak B, Teke K, Ciftci S, Kart M, Yildiz K, *et al*. Coexisting papillary and clear renal cell carcinoma in the same kidney. Case Rep Urol 2014; 2014:575181.
12. Raspollini MR, Castiglione F, Cheng L, Montironi R, Lopez-Beltran A. Synchronous clear cell renal cell carcinoma and multilocular cystic renal cell neoplasia of low malignant potential: A clinico-pathologic and molecular study. Pathol Res Pract 2016; 212(5):471-474.
13. Atilgan D, Uluocak N, Parlaktas BS. Renal cell carcinoma of the kidney with synchronous ipsilateral transitional cell carcinoma of the renal pelvis. Case Rep Urol 2013; 2013:194127.

Case Report

First report of t(1;9)(q21;q34) in Fanconi anemia as a preceeding chromosomal aberration before leukemia development

Sureyya Bozkurt[1], Sule Unal[2], Fatma Gumruk[2]
[1]Department of Medical Biology, Faculty of Medicine, Istinye University, Istanbul, Turkey
[2]Department of Pediatric Hematology, Hacettepe University Ankara,Turkey

Kuwait Medical Journal 2022; 54 (1): 119 - 122

ABSTRACT

Patients with Fanconi anemia (FA) tend to develop various hematologic and solid tumors. Cytogenetic abnormalities such as translocations of chromosome 1q, monosomy 5 and 7, trisomy 10, gains of 3q and t(8;21) have been reported in patients with FA who developed hematological malignancies. Since survival is low after the development of leukemia in FA patients, the follow-up for leukemia progression is very important. For this reason, cytogenetic anomalies that can be used as biomarkers in the development of leukemia are needed. Herein, we describe a patient with FA who developed acute myeloid leukemia with der(9)t(1;9)(q21;q34) for the first time.

KEY WORDS: acute myeloid leukemia, childhood leukemia, chromosomal abnormalities, Fanconi anemia, rare translocation.

INTRODUCTION

Fanconi anemia (FA) is a rare, autosomal recessively and less commonly X-linked disease characterized by congenital physical abnormalities, such as short stature, thumb and radius deformities, peculiar facies, skin hyperpigmentation including café au lait spots, organ malformations, in addition to chromosomal instability, progressive bone marrow failure and cancer susceptibility[1].

The risk for myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and solid tumors of the head and neck region and genitourinary system have been reported as dramatically increased compared to general population[2]. The reason of higher cancer predisposition of FA patients is related to defects in the DNA repair pathway and chromosomal instability[3,4]. Patients with FA have an approximately 500-fold increased risk of developing AML[5]. Cytogenetic abnormalities such as translocations of chromosome 1q, monosomy 5, 7, trisomy 10, gains of 3q, dup(1)(q12-q24), inv(7)(p11pter) and t(8;21) have been reported in patients with FA who developed hematological malignancies[6,7].

Herein, we present a 29-year-old male with FA who developed t(1;9)(q21;q34) progressed to AML. t(1;9)(q21;q34) has not been previously reported in patients with FA as a chromosomal abnormality relevant to AML development.

CASE REPORT

A 29-year-old male who was diagnosed with FA at one-year of age due to bilateraly absent thumbs, hyperpigmentation, café au lait spots, microcephaly, microphtalmia, short stature and cleft palate is presented. There was no consanguinity between parents, and diepoxybutane test from peripheral blood lymphocytes was positive. The patient developed mild thrombocytopenia at 15 years of age (hemoglobin: 13.1 g/dl, hematocrit: 37.3%, mean corpuscular volume: 100.5 fl, white blood cell: $5.7x10^9$/L, platelet $130x10^9$/L). During the follow-up, thrombocytopenia deepened (at 29 years of age,

Address correspondence to:
Sureyya Bozkurt PhD, Department of Medical Biology, Faculty of Medicine, Istinye University, Maltepe Mahallesi. Edirne Çırpıcı yolu. No:9 Zeytinburnu. Istanbul, Turkey. Tel: +850 2836000; Mob: 05373180565; E-mail: sureyyabozkurt8@gmail.com

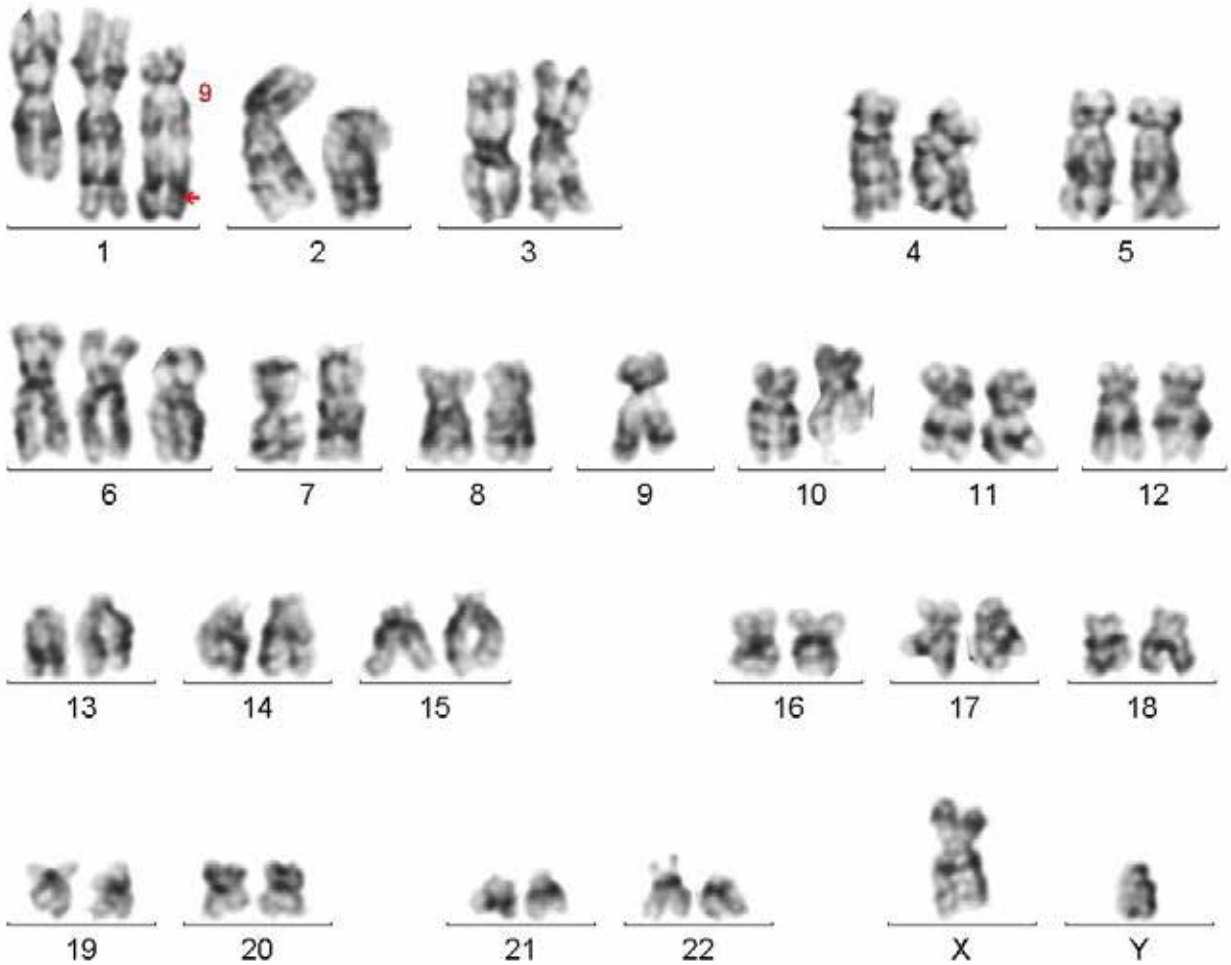


Fig 1: Karyotype from bone marrow aspirate prior to leukemia development 47,XY,der(1),der(9)t(1;9)(q21;q34),+6.

hemoglobin: 10.2 g/dl, hematocrit: 30.3%, mean corpuscular volume: 88 fl, white blood cell: $5.5x10^9$/L, platelet $20x10^9$/L). Bone marrow aspiration was done annually in order to follow for clonal evolution and last bone marrow at the age of 29 revealed that cellularity of 80% with megaloblastic dysplastic changes were present and blast cell ratio of 3%. Cytogenetic analysis from bone marrow aspirate was performed and the karyotype was identified as 46,XY,der(1),der(9)t(1;9)(q21;q34)[12]/47,sl,+6[8] (Figure 1). Translocation between chromosome 1 and 9 found in 12 metaphasis and also trisomy 6 in addition to these abnormalities was found in 8 metaphasis. A diagnosis of MDS was established; no matched family donor was present and unrelated donor search was initiated. During the subsequent follow-up visits, the patient was severely thrombocytopenic and received thrombocyte transfusions related to epistaxis. By the 3rd month of this bone marrow evaluation, the hemogram revealed hemoglobin: 8.1 g/dl, white blood cell: $75x10^9$/L, platelet:$16x10^9$/L and peripheral blood smear revealed 70% blasts. Bone marrow aspiration was repeated and revealed AML in a bone marrow biopsy with cellularity of 90%. Erythroid and myeloid lineages revealed dysplastic findings. The blasts and immature cells made up 20% of all cellular blood elements and in addition to dysplastic changes, since the blast percentage was higher in the peripheral blood compared to bone marrow, AML transformation from MDS was suspected. Karyotype from this bone marrow sample exibited 46,XY,der(1),der(9)t(1;9)(q21;q34)[20]. Translocation between chromosomes 1 and chromosomes 9 was found in all metaphasis similar to the previous karyotype; however, trisomy 6 was absent in this subsequent bone marrow which revealed leukemia diagnosis. Piperacillin-tazobactam antibiotherapy was begun due to fever. At the same time idarubicin-ara-c chemotherapy was begun. However, the patient developed neutropenic fever and deceased after septic shock.

DISCUSSION

Herein, we describe a patient with FA who developed AML with der(9)t(1;9)(q21;q34) for the first time. This chromosomal aberration has been previously reported in two adult patients at diagnosis of de-novo AML-M7 and chronic myeloid leukemia[8,9]. der(9)t(1;9)(q21;q34) is an unbalanced translocation resulted in trisomy of long arm of chromosome 1.

Since survival is low after the development of leukemia in FA patients, the follow-up for leukemia progression is very important. Although the clinical significance of the presence of cytogenetic clones is controversial in FA patients, recent studies have suggested that clonal chromosomal alterations may be a marker of leukemia development[10]. Therefore, determining the prognostic value of chromosomal abnormalities in FA patients could be important for evaluation of treatment options and clinical benefits[11], and the report of these rare aberrations which have relevance to MDS or leukemia is crucial.

The gain of 1q which occurs as a result of unbalanced 1q anomalies is frequently seen in FA patients[12]. Partial or total increase of long arm of chromosome 1 that is particularly the consequence of unbalanced translocations, are associated with myeloproliferative disorders[13-14]. We also determined the gain of 1q as a result of der(9)t(1;9)(q21;q34) in our patient, who developed AML in the background of FA.

This case reports the first Fanconi anemia patient showing der(9)t(1;9)(q21;q34) translocation which occurs seldomly. The possible fusion gene resulting from der(9)t(1;9)(q21;q34) has not yet been identified. However, it is stated that trisomy 1q may contribute to the pathogenesis of the disease. Previously, it has been published that the genes carried in the 1q21-q23 region of the chromosome 1 may contribute to the development of myeloid malignancies as in the anomaly we have detected. The ABL gene is present in the q34 region of chromosome 9. A possible contribution of this gene may be considered as a factor to the development of AML[15-16].

Additionally, trisomy 6 with der(9)t(1;9)(q21;q34) in 8 metaphasis was seen in a previous bone marrow aspirate prior to leukemia progression, however it was absent at leukemia diagnosis. The mechanism of the oncogenic role of trisomy 6 in hematologic malignancies is unknown but the gene dosage effect, with the extra copies of the gene as a result of trisomy 6 leading to overexpression may be the underlying mechanism[17].

CONCLUSION

It is a major concern to predict which patients would proceed to leukemia in leukemia prone disorders, including inherited bone marrow failure syndromes. The patients with FA have increased risk of leukemia development and 30% of FA patients develop a type of a hematological malignancy before 40 years of age. The current approach to follow the patients with FA for leukemia progression is obtaining bone marrow aspirates and karyotype analyses annualy. However, there is limited data on which karyotypes are specific for MDS or predictive for imminent leukemia. Since FA is a disorder with increased chromosomal breakages, these patients are prone to develop translocations. However, not all of these translocations are clonal and have malignancy potential. This report is important since it attracts attention to a leukemia precedent chromosomal aberration.

ACKNOWLEDGMENT

Authors declare that they have no conflict of interest. Patient's informed consent was recevied from his family.

REFERENCES

1. Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev 2010; 24(3):101-122.
2. Kottemann MC, Smogorzewska A. Fanconi anaemia and the repair of Watson and Crick DNA crosslinks. Nature 2013; 493(7432):356-363.
3. Pradhan A, Ustiyan V, Zhang Y, Kalin TV, Kalinichenko VV. Forkhead transcription factor FoxF1 interacts with Fanconi anemia protein complexes to promote DNA damage response. Oncotarget 2016; 7(2):1912-1926.
4. de Latour RP, Soulier J. How I treat MDS and AML in Fanconi anemia. Blood 2016; 127(24):2971-2979.
5. Alter BP, Giri N, Savage SA, Peters JA, Loud JT, Leathwood L, *et al*. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. Br J Haematol 2010; 150(2):179-188.
6. Tonnies H, Huber S, Kuhl JS, Gerlach A, Ebell W, Neitzel H. Clonal chromosomal aberrations in bone marrow cells of Fanconi anemia patients: gains of the chromosomal segment 3q26q29 as an adverse risk factor. Blood 2003; 101(10):3872-3874.
7. Hussain S, Adil SN. Rare cytogenetic abnormalities in acute myeloid leukemia transformed from Fanconi anemia – a case report. BMC Res Notes 2013; 6:316.
8. Huret JL, Ahmad M, Arsaban M, Bernheim A, Cigna J, Desangles F, *et al*. Atlas of genetics and cytogenetics in oncology and haematology in 2013. Nucleic Acids Res 2013; 41:D920-924.
9. Mitelman F, Johansson B, Mertens F. Mitelman database of chromosome aberrations and gene fusions in cancer. http://cgap.nci.nih.gov/Chromosomes/Mitelman. 2017. Accessed April 25, 2019.

10. Mehta PA, Harris RE, Davies SM, Kim M-O, Mueller R, Lampkin B, *et al*. Numerical chromosomal changes and risk of development of myelodysplastic syndrome-acute myeloid leukemia in patients with Fanconi anemia. Cancer Genet Cytogenet 2010; 203(2):180-186.
11. Quentin S, Cuccuini W, Ceccaldi R, Nibourel O, Pondarre C, Pages M-P, *et al*. Myelodysplasia and leukemia of Fanconi anemia are associated with a specific pattern of genomic abnormalities that includes cryptic RUNX1/AML1 lesions. Blood 2011; 117(15):161-170.
12. Rochowski A, Olson SB, Alonzo TA, Gerbing RB, Lange BJ, Alter BP. Patients with Fanconi anemia and AML have different cytogenetic clones than de novo cases of AML. Pediatr Blood Cancer 2012; 59(5):922-924.
13. Borges ML, Capela de Matos RR, Amaral BD, *et al*. Molecular cytogenetic approach to characterize novel and cryptic chromosome abnormalities in childhood myeloid malignances of Fanconi anemia. J Pediatr Hematol Oncol 2017: 39:85-91.
14. Zamecnikova A, Al Bahar S. 1q translocations (unbalanced) in myeloid malignancies. Atlas Genet Cytogenet Oncol Haematol 2013; 17:845-848.
15. Zamecnikova A, Al Bahar S. der(9)t(1;9)(q11-12;q34). Atlas Genet Cytogenet Oncol Haematol 2016; 20(10):531-533.
16. Caramazza D, Hussein K, Siraguso S, Pardanani A, Knudson RA, Ketterling RP, *et al*. Chromosome 1 abnormalities in myeloid malignancies: a literature survey and karyotpe-phenotype associations. Eur J Hematol 2010; 84(3):191-200.
17. Mohamed AN, Varterasian ML, Dobin SM, Mc Connell TS, Wolman SR, Rankin C, *et al*. Trisomy 6 as a primary karyotypic aberration in hematologic disorders. Cancer Genet Cytogenet 1998; 106(2):152–155.

Case Report

Breast pseudo angiomatous stromal hyperplasia (PASH): A case series assessing local recurrence

Amal Abdullah Abdulkareem
Breast & Endocrine Unit, General Surgery Department, College of Medicine, King Saud University, Saudi Arabia

Kuwait Medical Journal 2022; 54 (1): 123 - 126

ABSTRACT

Pseudo angiomatous stromal hyperplasia (PASH) is a benign breast lesion rarely presented as palpable lesion. It's a myofibroblastic proliferation of the breast, which represents localized form of stromal overgrowth with hormonal etiology (primarily progesterone). Microscopically, PASH consists of a network of slit-like spaces lined by myofibroblasts that resembles vascular space. It's not true vascular space; it is the disruption and separation of stromal collagen fibers, not like low grade angiosarcoma sarcoma, which is characterized by anastomotic vascular channels with invasion into breast parenchyma. It's important to differentiate it histologically from low grade angiosarcoma. PASH lacks the invasive features with no destruction of mammary epithelial structures. It is not a premalignant lesion and is common in gynecomastia. Core-needle biopsy is accurate. Mimicking low grade angiosarcoma histologically may lead to unnecessary radical surgery. Surgical excision is the treatment for localized lesions. This prospective study was conducted to assess the local recurrence rate post-surgical excision with rarity of PASH as palpable breast lesion. Only 3 cases were collected and followed up for variable duration; the longest was 5 years. None of them developed local recurrence post-surgical excision.

KEY WORDS: hyperplasia, PASH, Pseudoangiomatous, recurrence, stromal

INTRODUCTION

Pseudo angiomatous stromal hyperplasia (PASH) of the breast, first described in 1986[1-3], is an uncommon benign breast disease. Only 109 cases have been reported since its initial description till 2005[2]. PASH is an incidental finding in about 23% of breast biopsy specimens. It commonly occurs in premenopausal and postmenopausal women on hormonal replacement therapy (primarily progesterone)[1,4-5] and is extremely common in gynecomastia[1-2,6-7]. PASH can be presented as a diffuse enlargement of the breast during pregnancy[1].

PASH can form a circumscribed mass ranging in size from 1-15 cm in greatest diameter[1]; it is important to differentiate it histologically from low grade angiosarcoma and phyllodes tumor[1,5,8]. PASH represents a localized form of stromal overgrowth with a hormonal etiology (primarily progesterone)[4]. Stromal cells were positive for ER, PR receptors and negative CD31, supporting the diagnosis of PASH[9-10]. it can present as peau-de-orange skin changes mimicking inflammatory breast carcinoma[11]. It can range from focal non-significant microscopic to dominant palpable mass, progressive breast enlargement associated with engorgement, cyclic pain can respond to tamoxifen[8-9]. It can also present as tumorous PASH involving both breasts, causing breast enlargement[9]. The definitive diagnosis of tumorous PASH relies on histopathological evaluation[9]. Radiologically, PASH exhibits poorly defined irregular border which can be classified as BI-RAD 4 suspicions lesion[9]. Mammograms are non-specific[5] and magnetic resonance imaging is not adequately studied[3]. Fine needle aspiration produces a cellular specimen; some of the lesion can grow, raising a clinical concern of malignancy[9]. Characterized as dens a cellular collagen

Address correspondence to:
Dr. Amal Abdullah Abdulkareem, CABS (Arab Board of General Surgery), Breast & Endocrine Unit, General Surgery Department, College of Medicine, King Saud University, P.O. Box: 11472, Saudi Arabia. Tel: +966 556651691; E-mail: aabdulkareem@ksu.edu.sa

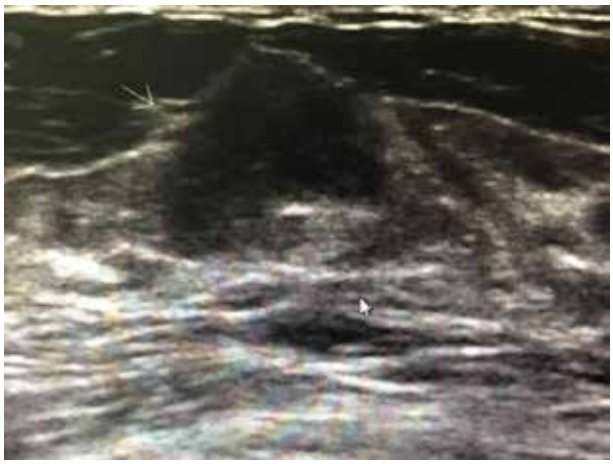


Fig 1: PASH in left breast ultrasound forming an oval mass 1.6X1 cm with no acoustic shadow (Case 1)

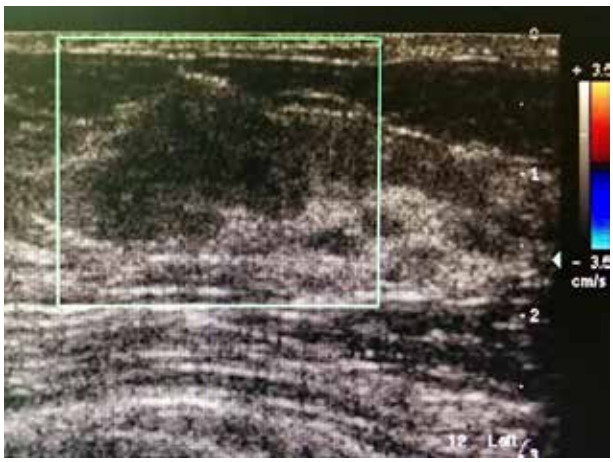


Fig 2: Doppler ultrasound of left breast mass with no vascular activity (Case 1)

stroma and slender spindle cell proliferation forming slit like structure[1,7,9-10]. If not surgically excised, it grows over time[12].

CASE REPORT

Case 1

A 58-year-old female patient with a positive family history of breast carcinoma (her sister) complained of small left breast mass for few months. Left breast exam showed 1x1 cm mass at 1 o' clock position.

Breast ultrasound (Fig 1), doppler ultrasound (Fig 2) and mammogram (Fig 3) was done. Dense breast was reported as BI RAD 4. Core needle biopsy was done and reported as stromal fibrosis is the predominant feature with no malignant cell.

Wide local excision was done for the patient. Post-operative histopathology report revealed no malignant cell fibrocystic mastopathy with pseudo angiomatous stromal hyperplasia (PASH). Patient had a follow up for 5 years to assess local recurrence, with no evidence of any local recurrence.

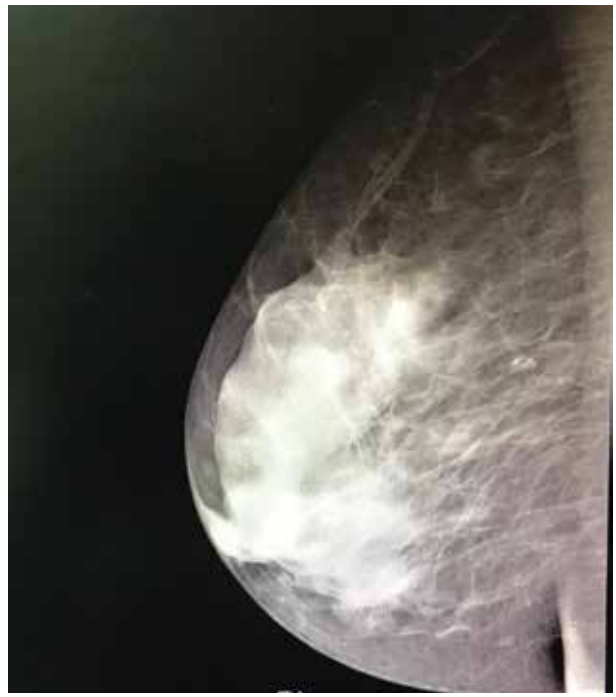


Fig 3: Mammogram of left breast, dense breast tissue reported as BI-RAD 4 (Case 1)

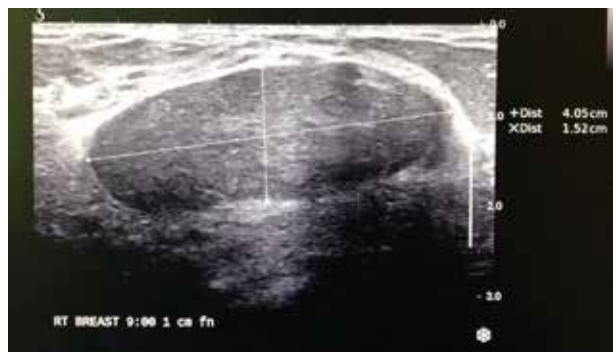


Fig 4: PASH from benign looking oval mass of 4x1.5 cm in right breast ultrasound (Case 2)

Case 2

A 35-year-old female complained of right breast mass for 3 years, which was increasing in size. Breast ultrasound was done (Fig 4). Initial breast ultrasound showed benign looking oval mass with no acoustic shadow. Follow up ultrasound after 6 months showed an increase in size (Fig 5), as did the Doppler breast ultrasound (Fig 6). Patient was advised to have core needle biopsy, which showed a fibroepithelial lesion consist with PASH. Surgical excision was done for the patient. Post-operative diagnosis revealed a 4x3 cm rounded mass of 19 grams. The outer surface is gray

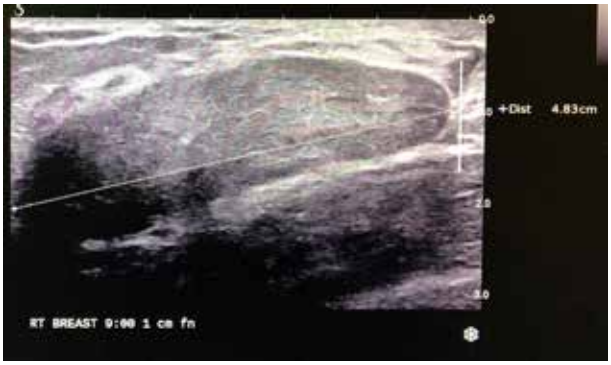


Fig 5: Right breast ultrasound after 6 months follow-up shows a benign looking mass PASH, size increased to 4.8 cm (Case 2)

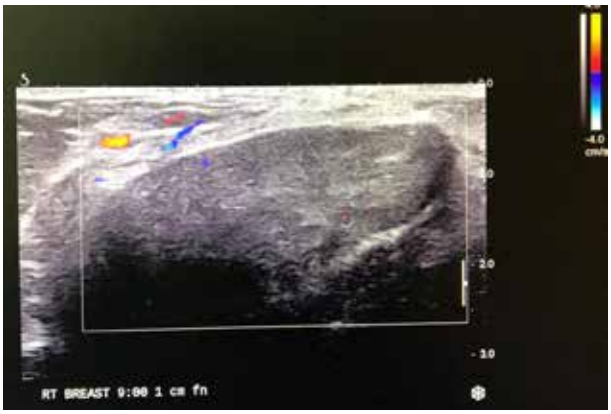


Fig 6: PASH in Doppler ultrasound showing no increase in vascularity (Case 2)

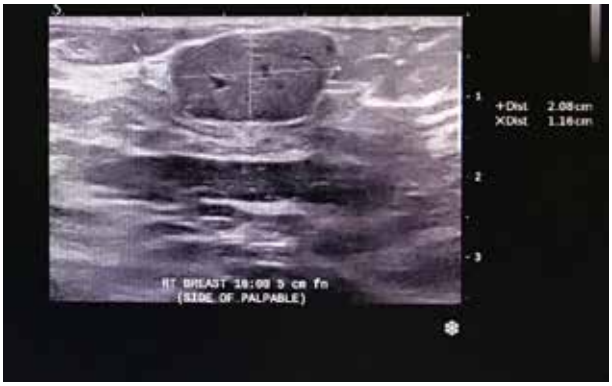


Fig 7: RT breast mass 2x1cm (PASH) by ultrasound (Case 3)

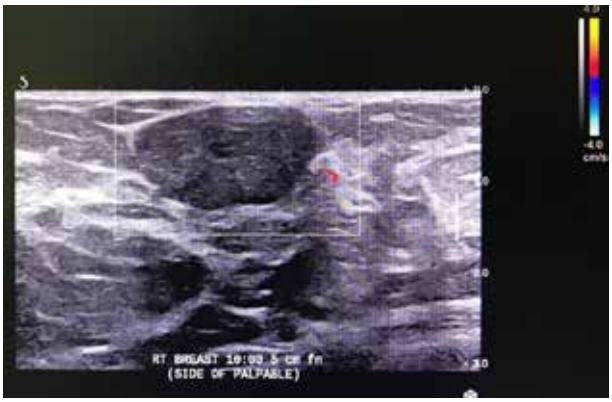


Fig 8: Doppler ultrasound of RT breast mass showing no vascular activity (Case 3)

and histology was consistent with usual ductal hyperplasia in background of PASH. Patient had her follow-up for 6 months with no local recurrence and is still under follow-up.

Case 3

A young 33-year-old woman complained of right breast mass for 4 years, which increased in size during her last pregnancy. Right breast ultrasound (Fig 7) and Doppler breast ultrasound (Fig 8) both reported as intermediate breast mass BI-RAD 4. Core needle biopsy showed hyaliniyzed fibroadenoma with focal of PASH. Lumpectomy was done for the patient and the post-operative histopathology was consistent with hyaliniyzed fibroadenoma with focal of PASH. Patient had follow-up for 1 year with no local recurrence.

RESULTS

Three cases of PASH had complete excision with no local recurrence in variable duration of follow up as indicated in Table 1.

DISCUSSION

PASH is a benign breast disease rarely presented as a palpable lesion. Less than 200 cases have been described in the literatures[3]. It may present as a rubbery single circumscribed mass with size ranging from 1-12 cm and is not considered as premalignant[3]. The incidental finding of microscopic PASH in breast biopsy is not uncommon[13]. Management depends clinically on factors which include the size of the lesion and severity of the symptoms. For incidental focal lesion, no treatment is required[9]. In the 1st case, patient

Table 1: Local recurrence rate in relation to duration of follow up, age and size of PASH

Case no	Age	Size of PASH	Duration of follow up	Local recurrence percentage
1	58 y	1.3x1 cm	5 years	0
2	35 y	4x3 cm	6 months	0
3	33 y	2.7x1.6 cm	One year	0

PASH: pseudo angiomatous stromal hyperplasia

had a small lesion, but mammogram report was BI-RAD 4 and with positive family history of carcinoma, the breast mass was biopsied and excised. PASH presenting as mass can grow fast. For case 2, the mass was benign looking by ultrasound, but the size increased after a six-month interval, and was hence biopsied and excised. PASH growth from 1 cm to 5 cm in a period of six months was observed by Kweon Yoo *et al* in his reported case[6,10,13-14]. Surgical excision is adequate in majority of cases[9].

PASH is a benign lesion of complex anastomosing, slit-like spaces (simulating vascular channels, hence the term "pseudoangiomatous")[3], mimicking low grade angiosarcoma[3]. Histological examination is mandatory for definitive diagnosis to avoid unnecessary radical surgery[3]. Radiology ultrasound and mammogram are non-specific[3]. PASH in mammogram is mostly reported as BI-RAD 4, as in case 1, whose mammogram reported BI-RAD 4, but the lesion was oval and demonstrated no posterior acoustic shadow by ultrasound. MRI is not adequately studied in PASH[3]. FNA often produces a cellular specimens[3]. Core needle biopsy is accurate. The presence of spindle cell is similar to those seen in phyllodes tumor and desmoid tumor[3]. Surgical excision is the treatment of choice for localized lesion. Some authors recommend 1-2 cm margin. Diffuse PASH may require mastectomy and tamoxifen may cause tumor regression[7].

Management by wide local excision is the treatment of choice. It should be considered for symptomatic patients with enlarging lesion. Non-surgical management is for patients who refuse surgery, have breast pain. Breast enlargement can be treated with Tamoxifen, however, long-term use may not be ideal[3]. The recurrence rate in literature was 15-22%[3], which may indicate incomplete excision.

CONCLUSION

PASH is a benign breast lesion rarely presented as palpable mass. Surgical excision is the treatment of choice for a localized form of PASH. No local recurrence after complete excision.

ACKNOWLEDGMENT

Our thanks to Prof. Abdelazeem Eldawlatly for his wise advice and everlasting encouragement, as well as to my colleagues; Prof. Abdullah Aldohayan for his endless support and encouragement during the process of the preparation of this series case report; and lastly, to all my loved ones and others for their emotional and moral support.

Financial support and sponsorship: The study was not sponsored by any agency.

Conflict of interest: None.

REFERENCES

1. Joshi M, Reddy SJ, Nanavidekar M, Russo JP, Russo AV, Pathak R. Core biopsies of the breast: diagnostic pitfalls. Indian J Pathol Microbiol 2011; 54(4):671-682.
2. Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, *et al*. Psuodoanguomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. Breast J 2012; 18(3):242-247.
3. Jaunoo SS, Thrush S, Dunn P. Pseudoangiomatous stromal hyperplasia (PASH): a brief review. Int J Surg 2011; 9(1):20-22.
4. Anderson C, Ricci A Jr, Pedersen CA, Cartun RW. Immunocytochemical analysis of estrogen and progesterone receptors in benign stromal lesions of the breast. Evidence for hormonal etiology in pseudoangiomatous hyperplasia of mammary stroma. Am J Surg Pathol 1991; 15(2):145-149.
5. Vo QD, Koch G, Girard JM, Zamora L, de Joliniere JB, Khomsi F, *et al*. A case report: Pseudoangiomatous stromal hyperplasia tumor presenting as a palpable mass. Front Surg 2015; 2:73.
6. Siedman JD, Borkowski A, Aisner SC, Sun CC. Rapid growth of pseudoangiomatous hyperplasia of mammary stroma in axillary gynecomastia in an immunosuppressed patient. Arch Pathol Lab Med 1993; 117(7):736-738.
7. The Ohio State University: Wexner Medical Center. C2002-2019, PathologyOutlines.com, Inc. Available from: http://www.pathologyoutlines.com/topic/breastpash.html. Accessed on - 20 May 2019
8. Pruthi S, Reynolds C, Johnson RE, Gisvold JJ. Tamoxifen in the management of pseudoangiomatous stromal hyperplasia. Breast J 2001; 7(6):434-439.
9. Dai H, Connor C, Cui W, Gatewood J, Fan F. Bilateral diffuse tumurous pseudoangiomatous stromal hyperplasia: a case of bilateral mastectomy in a 29-year-old woman. Case Rep Pathol 2014; 2014:250608.
10. Yoo K, Woom OH, Yong HS, Kim A, Ryu WS, Koo BH, *et al*. Fast-growing pseudoangiomatous stromal hyperplasia of the breast: report of a case. Surgery Today 2007; 37(11):967-970.
11. Ibrahim RE, Sciotto CG, Weidner N. Pseudoangiomatous hyperplasia of mammary stroma. Some observations regarding its clinicopathologic spectrum. Cancer 1989; 63(6):1154-1160.
12. Polger MR, Denison CM, Lester S, Meyer JE. Pseudoangiomatous stromal hyperplasia: mammographic and sonographic appearances. AJR Am J Roentgenol 1996; 166(2):349-352.
13. Holloway TL, Jataoi I. Tumorous PASH presenting as rapid unilateral breast enlargement. Mayo Clinic Proceedings 2013;, 88(7):e75.
14. Sasaki Y, Kamata S, Saito K, Nishikawa Y, Ogawa J. Pseudoangiomatous stromal hyperplasia (PASH) of the mammary gland: report of a case. Surg Today 2008 ;38(4):340-343.

Case Report

Unusual pathology of sphenopalatine foramen; Sphenopalatine-choanal polyp

Abdulmoniem Mohammed Alshwareb[1,2], Ahmed Hassan A Alhasan[3], Nada Ali Alshaikh[4]
[1]Saudi Board of Otolaryngology Head and Neck surgery (SBORL-HNS)
[2]Department of Otolaryngology Head & Neck Surgery, Dammam Medical Complex, Dammam, KSA
[3]College of medicine, University of Jeddah, Jeddah, KSA
[4]National university of Singapore. Department of Otolaryngology Head & Neck Surgery, Dammam Medical Complex, Dammam, KSA

Kuwait Medical Journal 2022; 54 (1): 127 - 132

ABSTRACT

Choanal polyps are benign unilateral nasal lesions originating from the lateral nasal wall and extending into the choana with a single stalk. Commonly they are antrochoanal polyp. To the best of our knowledge, there is no reported case of choanal polyp originating from sphenopalatine foramen. We present this report of a very rare case of sphenopalatine-choanal polyp from the otolaryngology department, Dammam Medical complex, Saudi Arabia.

A 25-year-old man presented with right sided nasal blockage. Endoscopic view showed polypoidal mass posterior to basal lamella and medical to middle turbinate of the right side and occupying the nasopharynx reaching the choana on the left. Computed tomography scan with contrast revealed non-enhancing soft tissue density in the right nasal cavity dorsal half extending into the choana with widening and hyperostosis of the right sphenopalatine foramen. The polyp was adequately removed by endoscopic endonasal approach. Histopathology revealed benign inflammatory polyp. Follow-up up to 24 months showed no evidence of disease recurrence.

Sphenopalatine-choanal polyp is a very rare clinical entity. It can be sufficiently managed by endoscopic approach. Exclusion of other lesions (*e.g.* juvenile nasopharyngeal angiofibroma, infiltrating nasopharyngeal carcinoma) is substantially important.

KEY WORDS: antrochoanal polyp, functional endoscopic sinus surgery, inflammatory polyp, juvenile nasopharyneal angiofibroma, sphenochoanal polyp

INTRODUCTION

Choanal polyps are benign unilateral nasal lesions originating from the lateral nasal wall and extending into the choana with a single stalk[1]. Three types of choanal polys can be identified; antrochoanal, sphenochoanal, and ethmochoanal[2]. The most common type is antrochoanal polyp followed by sphenochoanal polyp[2]. It has been reported that choanal polyps histologically originate from the recovery process of sinusitis, in which there is expansion of mucinous cyst as a result of the obstruction and rupture of the mucous gland[3]. The aim of this report is to present a very rare case of choanal polyp originating from the sphenopalatine foramen.

CASE REPORT

A 25-year-old healthy male presented to rhinology clinic with a chief complaint of right progressive nasal obstruction of one-year duration. It was accompanied by thick mucoid bloody nasal discharge, hyposmia, and headache which was exacerbated by leaning forward. He is a non-smoker and there was no industrial exposure to carcinogenic substance. Examination with a 0° nasal endoscope of the right nasal cavity revealed a polypoidal pinkish mass with smooth surface originating from lateral nasal wall posterior and medial to the middle turbinate. There was mucoid discharge around the mass (Figure 1A). Endoscopic view of the left nasal cavity showed the

Address correspondence to:
Abdulmoniem M Alshwareb, MD, Box 38974, Dhahran 31942, Saudi Arabia. Tel: +966 548841255; E-mail: abdulmoneim@hotmail.com

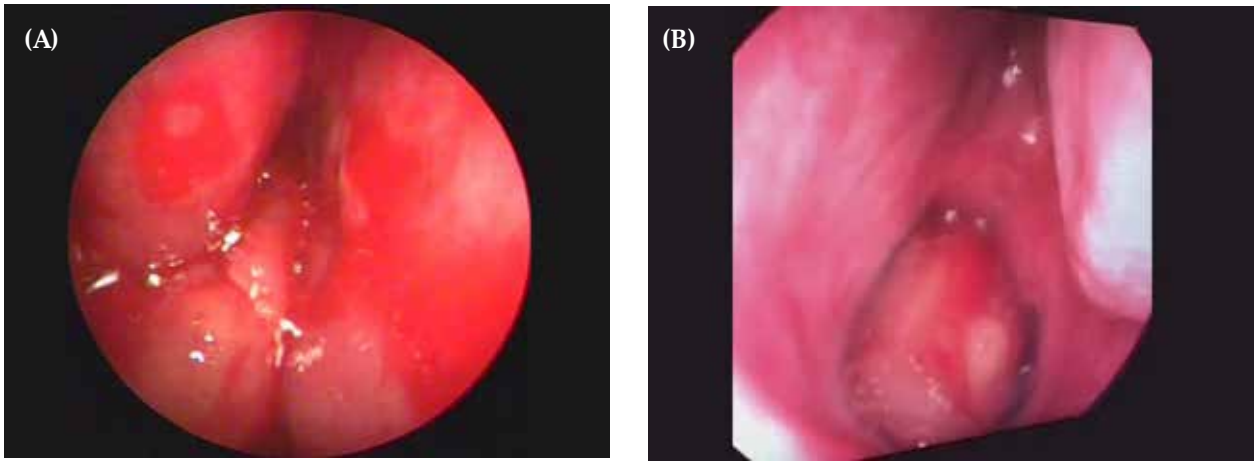


Fig 1: 0° Endoscopic view of: **(A)** the right nasal cavity showing polypoidal pinkish mass originating from lateral nasal wall posterior to basal lamella and medial to middle turbinate. **(B)** Endoscopic view of left nasal cavity showing the mass occupying the nasopharynx and blocking the entire left choana.

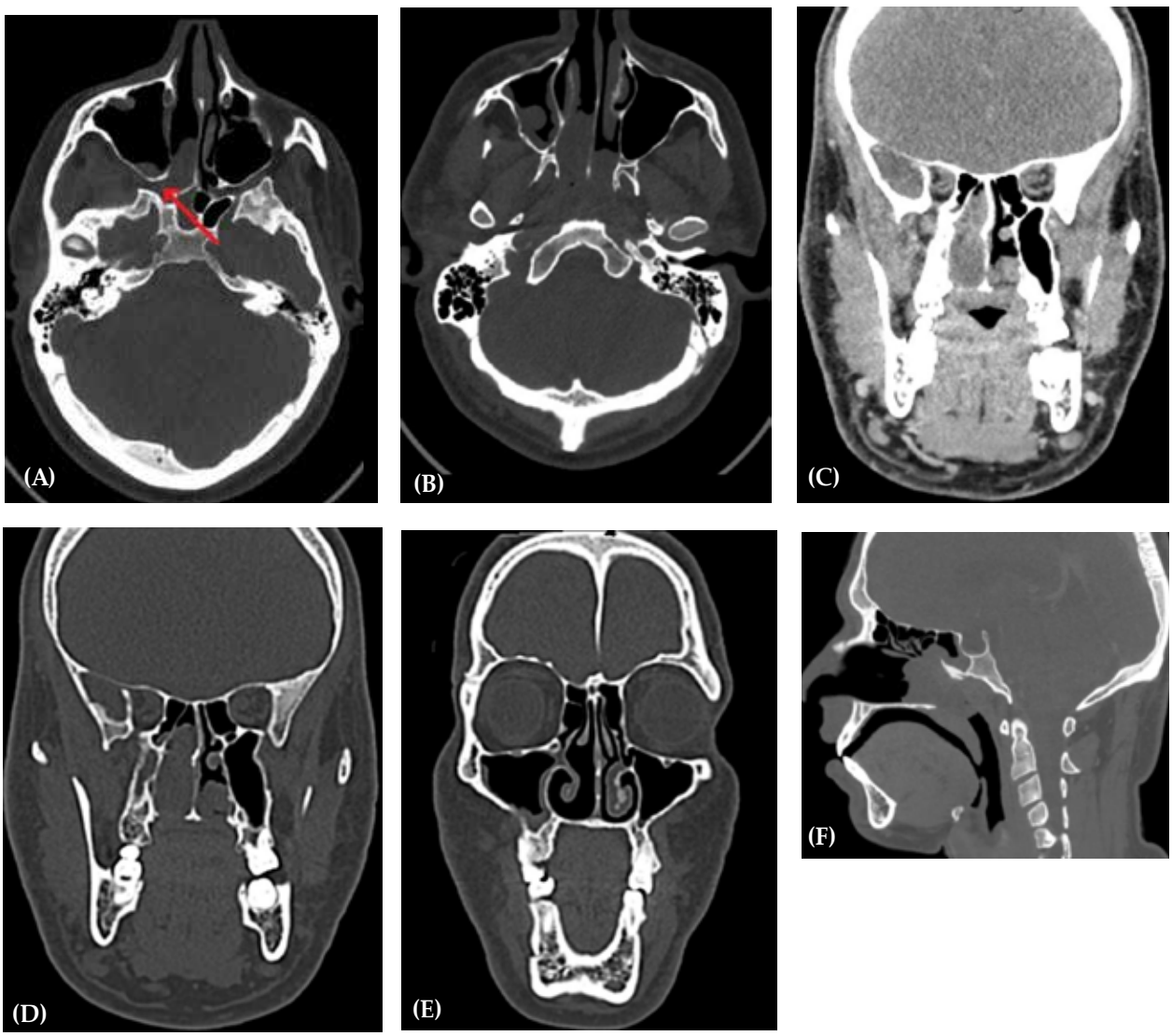


Fig 2: Computed tomography scan with contrast revealed non-enhancing soft tissue density in posterior end of the right nasal cavity extending into both choana with widening and hyperostosis of the right sphenopalatine foramen (red arrow) (A,B,C,D). Ipsilateral maxillary and sphenoid sinuses are only partially opacified (E,F).

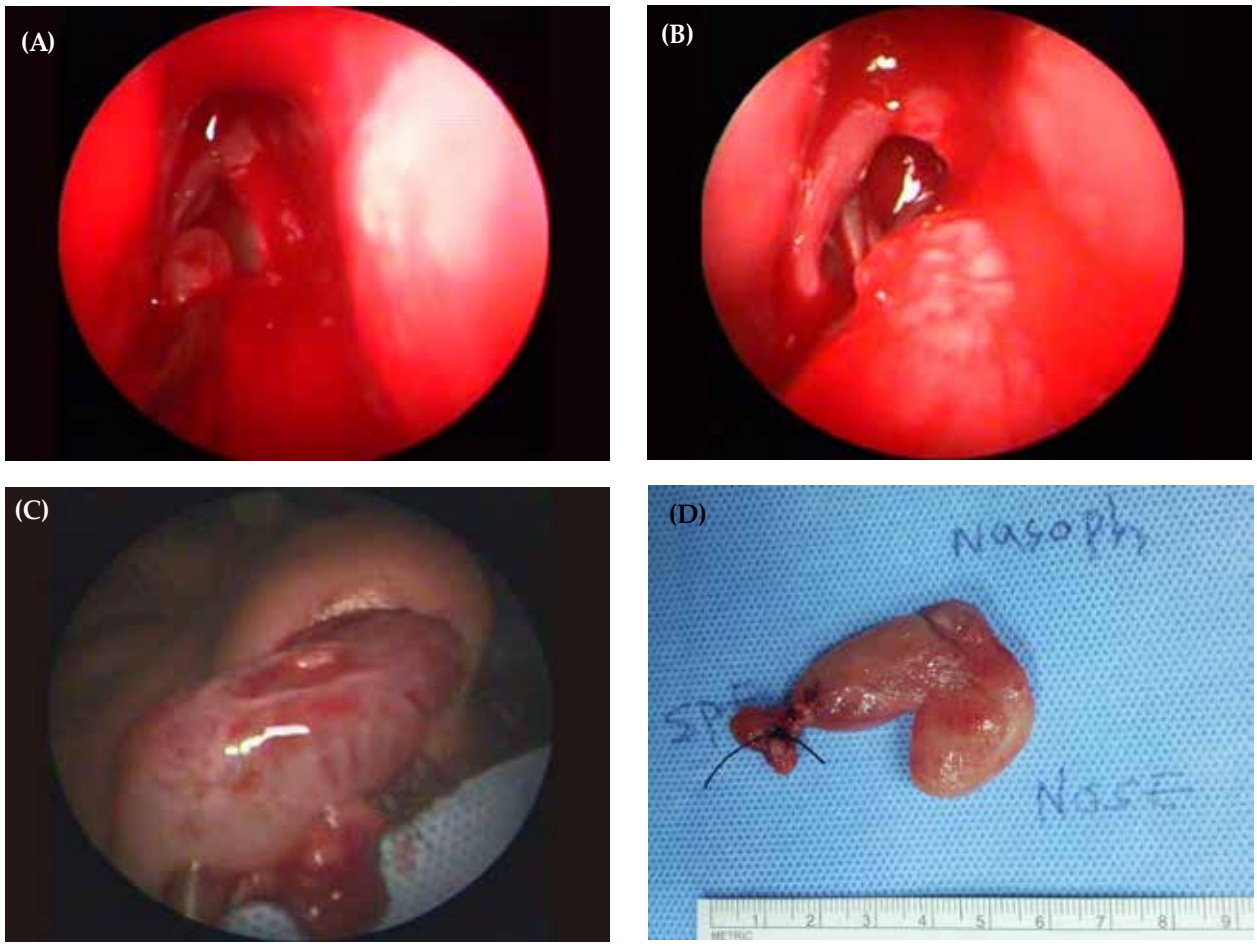


Fig 3: A and B show endoscopic enbloc resection of mass with its attachment in lateral nasal wall at the vicinity of sphenopalatine foramen. C and D show the mass during and after delivery [SPF: sphenopalatine foramen on the left; Nasoph: nasopharynx; NOSE: nasal cavity on the right].

mass filling the nasopharynx and fully obstructing the right choana (Figure 1B). Throat and rest of ear, nose, and throat examination was clear. There were no palpable neck nodes.

Computed tomography scan with contrast revealed non-enhancing homogenous soft tissue density in the posterior aspect of the right nasal cavity extending into both choana with widening and hyperostosis of the right sphenopalatine foramen. It also showed polypoidal thickening and partial opacification of right maxillary and sphenoid sinuses while rest of paranasal sinuses appeared clear (Figure 2A-F).

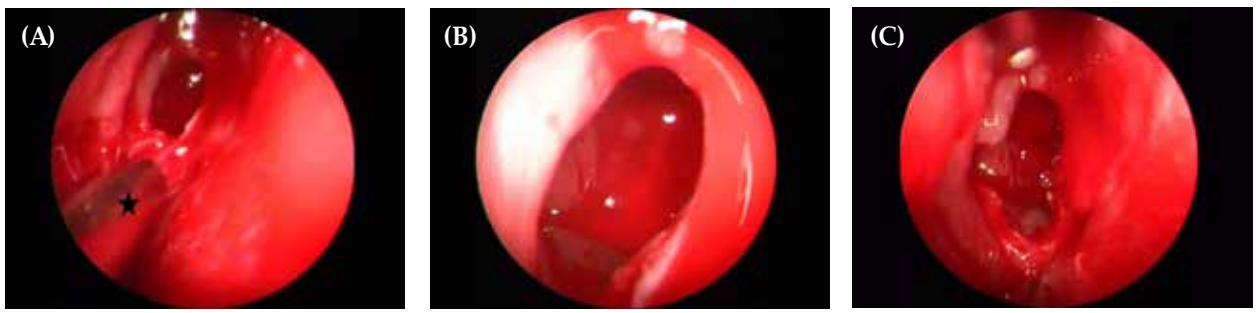


Fig 4: **(A)** Endoscopic view of sphenoid osteum after resection of polyp demonstrating its large size relative to suction tip (marked with asterisks). **(B)** Close-up view of right sphenoid sinus ostium. **(C)** Right sphenoidotomy: inferior and lateral lips of ostium were resected and sent for histopathology.

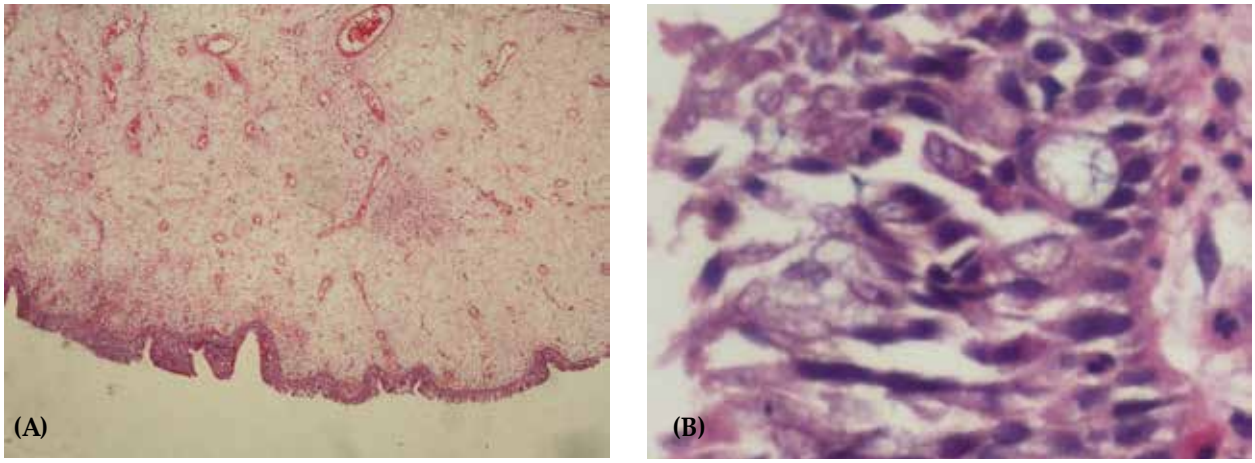


Fig 5: (A) Polypoid formation (40x), **(B)** Mostly lined by respiratory epithelium (cilliated pseudostratified columnar epithelium).

The polyp was managed surgically. Intra-operative finding was right nasal mass originating from lateral nasal wall posterior to basal lamella of middle turbinate and specifically from the sphenopalatine foramen and extending superiorly to the anterior face of the sphenoid sinus causing blockage of the ostium. Sphenoid osteum was noted to be significantly widened. The mass was protruding anteriorly into the nasal cavity medial to the middle turbinate and posteriorly filling the right choana, the nasopharynx, and the left choana. There was no accessory maxillary sinus ostium. The polyp was managed by endoscopic enbloc resection (Figure 3A-D). Endoscopic surgery also included right uncinectomy, middle meatus antrostomy and sphenoidotomy (Figure 4A-C). The polyp was sent for histopathology. A swab from middle meatus was sent for culture and sensitivity.

Histopathology revealed polypoidal edematous core, infiltrated by acute and chronic inflammatory cells and few eosinophils with respiratory lining epithelium mostly, but also showed areas of squamous metaplasia (Figure 5A-B, Figure 6A-D). No evidence of infection or malignancy was found.

The final diagnosis was made as a sphenopalatine-choanal polyp; choanal polyp originating from sphenopalatine foramen.

Patient was started on co-amoxiclav for two weeks as culture and sensitivity result showed *Moraxella species* and *Streptococcus pneumonia*.

Two weeks post-operatively, patient reported resolution of symptoms; nasal obstruction was resolved. He was sleeping comfortably and had no headache. Endoscopic examination showed clear cavity, mild congestion, with no evidence for residual mass. At two-year follow-up, there was no evidence for recurrence of the polyp on endoscopic examination.

DISCUSSION

Choanal polyp is defined as a benign solitary soft tissue mass mostly originating from sinuses and which protrude into the choana causing choanal obstruction[4]. The origin of these polyps is mostly from maxillary sinus. In rare, atypical cases, the origin of these polyps can be from sphenoid or ethmoid sinuses[5]. In this report, we presented a case of unusual origin of choanal polyp where the stalk was found to protrude from the lining of the sphenopalatine foramen. Literature review showed no such previously reported origin of naso-choanal polyps.

Choanal polyps usually occur in children and young adults[6]. About 50% of reported cases of sphenochoanal polyps were in children[7].

The presentation of choanal polyps is commonly unilateral nasal obstruction with occasional ear symptoms, headache and nasal discharge[8]. On examination, the polyp will be pinkish in color, smooth in surface, obstructing the nasal cavity, protruding into the choana and commonly filling the nasopharynx with occasional decent into the oropharynx. Differential diagnosis may include antrochoanal polyp, juvenile angiofibroma, hypertrophied adenoid, Thornwaldt cyst, pituitary tumour, lymphoma, and nasopharyngeal carcinoma[9]. Nasal endoscopies with computed tomography imaging or magnetic resonance imaging are ideal for diagnosing choanal polyp. Contrast study is indicated to exclude vascular tumor, especially in our reported case where the origin is from the sphenopalatine foramen.

Clinician have divided these polyps into inflammatory which is more common, and non-inflammatory[10]. In this case, histopathology findings showed inflammatory cells infiltration of the mass. Histopathologic diagnosis is important to rule out neoplastic pathology[11]. The gold standard treatment

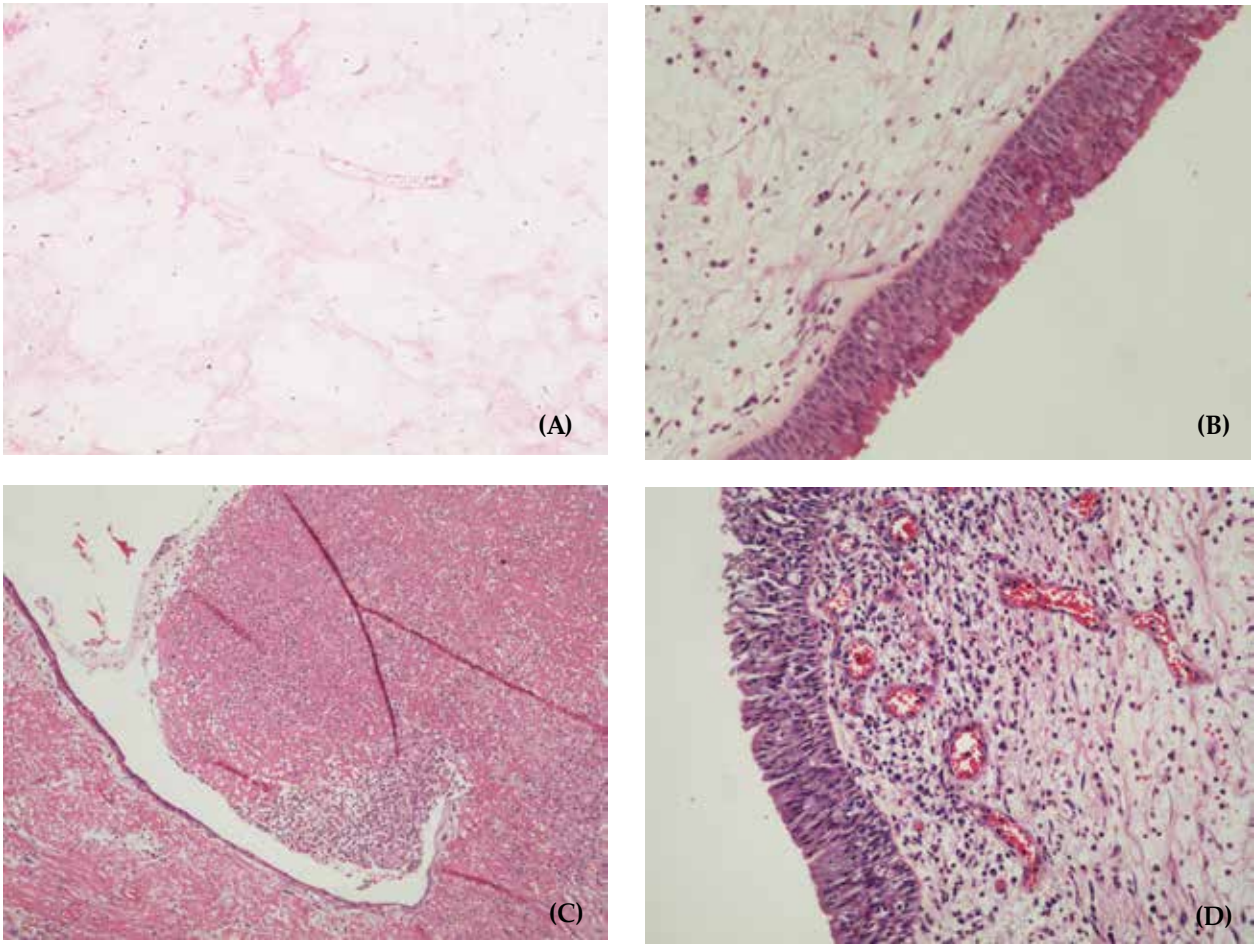


Fig 6: Polyp core. **(A)** Shows oedematous core (myxoid type) with lack of cellularity. **(B)** Shows lining by squamous metaplasia with keratin on surface of epithelium. **(C)** Shows focal ulceration evident by fibrin background (clot) & leukocytes infiltration. **(D)** Shows chronic inflammation.

of all types of choanal polyps is surgery through endoscopic endonasal approach[12]. Complete surgical excision of choanal polyp with resection of the pedicle of origin in order to reduce risk for recurrence is the standard recommended management. Endoscopic approach provides excellent result with lower rate of complications, morbidity, length of stay and recurrence[13].

CONCLUSION

Sphenopalatine-choanal polyp is a very rare clinical entity. It can be sufficiently managed by endoscopic approach. Exclusion of other lesions such as juvenile nasopharyngeal angiofibroma and nasopharyngeal carcinoma is substantially important.

ACKNOWLEDGMENT

Author contribution: Abdulmoniem Mohammed Alshwareb prepared the first draft of this manuscript, selected and edited figures, and prepared figure legends, and edited and reviewed the final manuscript. Ahmed Hassan A Alhasan prepared the first worded draft. Nada Ali Alshaikhis the supervising author who provided guidance and directions and reviewed the first worded draft.

Conflict of interest: None.

Source of support: None.

REFERENCES

1. Slirola R. Choanal polyps. Acta Otolaryngol 1966; 61:42-48.
2. Yariktaş M, Doğru H, Döner F, Tüz M, Yasan H. Choanal polyp originating from the inferior turbinate presenting as nasal polyposis. Kulak Burun Bogaz Ihtis Derg 2006; 16(1):37-40.
3. Mills CP. Secretary cysts of the maxillary antrum and their relation to the development of antrochoanal polyp. J Laryngol Otol 1959; 73(5):324-334.

4. Soh KBK, Tan KK. Sphenochoanal polyps in Singapore: diagnosis and current management. Singapore Med J 2000; 41:1848-1887.
5. Ileri F, Koybasioglu A, Uslu S. Clinical presentation of a sphenochoanal polyp. Eur Arch Otorhinolaryngol 1998; 255(3):138-139.
6. Yaman H, Yilmaz S, Karali E, Guclu E, Ozturk O. Evaluation and management of antrochoanal polyps. Clin Exp Otorhinolaryngol 2010; 3(2):110-114.
7. Tosun F, Yetiser S, Akcam T, *et al*. Sphanochoanal polyp: endoscopic surgery. Int J Pediatr Otorhinolaryngol 2001; 58:87-90.
8. Dadaş B, Yilmaz O, Vural C, Caliş AB, Turgut S. Choanal polyp of sphenoidal origin. Eur Arch Otorhinolaryngol 2000; 257(7):379-381.
9. Ken Y, Ho SY, Yanagisawa E. Endoscopic view of a sphenochoanal polyp. Ear, Nose & Throat Journal 2000; 79:546-548.
10. Bist SS, Kumar R, Varshney S, Bisht M. Isolated sphenochoanal polyp: a rare clinical entity. Indian Journal of Otolaryngology Head Neck Surg 2007; 59(1):56-57.
11. de Jesus EPF, Goto EY, Marone SAM, Zagati LL, Haddad A, Portes KP, *et al*. Sphenochoanal polyp – case report and literature review. Int Arch Otorhinolaryngol 2005; 9(4):314-318.
12. Cook PR, Davis WE, McDonald R, McKinsey JP. Antrochoanal polyps: a review of 33 cases. Ear Nose Throat J 1993; 72(6):401-402.
13. Tysome JR, Saleh HA. Sphenochoanal polyp presenting with concomitant nasal polyps. Ear Nose Throat J 2007; 86(1):50-52.

Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2022; 54 (1): 133 - 135

Progesterone: A Unique Hormone with Immunomodulatory Roles in Pregnancy

Raj Raghupathy[1], Julia Szekeres-Bartho[2 3 4 5]

[1]Department of Microbiology, Faculty of Medicine, Kuwait University, Safat 13110, Kuwait.
[2]Department of Medical Biology and Central Electron Microscope Laboratory, Medical School, University of Pécs, 7624 Pécs, Hungary.
[3]National Laboratory for Human Reproduction, University of Pécs, 7624 Pécs, Hungary.
[4]János Szentágothai Research Centre, University of Pécs, 7624 Pécs, Hungary.
[5]MTA-PTE Human Reproduction Scientific Research Group, University of Pécs, 7624 Pécs, Hungary.

Int J Mol Sci. 2022 Jan 25;23(3):1333. doi: 10.3390/ijms23031333.

Progesterone is well known for its numerous endocrinologic roles in pregnancy but is also endowed with fascinating immunomodulatory capabilities. It can downregulate the induction of inflammatory reactions, the activation of immune cells and the production of cytokines, which are critical mediators of immune responses. These features appear to be critical to the success of pregnancy, given the ability of maternal immune reactivity to interfere with pregnancy and to contribute to several pregnancy complications. This review summarizes the contribution of maternal immune effectors in general, and cytokines in particular, to pregnancy complications such as recurrent miscarriage, pre-eclampsia and preterm labor; it describes the promise offered by supplementation with progesterone and the oral progestogen dydrogesterone, as well as the progesterone-induced blocking factor in the prevention and/or treatment of these serious complications.

Case Report: Conservative Non-operative Management of a Neonate With Torted Wandering Spleen

Maha Bourusly[1], Mariam Ayed[2], Zainab Bahzad[3]
[1]Pediatric Hematology Oncology Department, National Bank Kuwait Specialized Children Hospital, Kuwait City, Kuwait.
[2]Neonatal Department, Farwaniya Hospital, Kuwait City, Kuwait.
[3]Pediatric Department, Farwaniya Hospital, Kuwait City, Kuwait.

Front Pediatr. 2022 Jan 28;9:791932. doi: 10.3389/fped.2021.791932. eCollection 2021.

BACKGROUND
The management of wandering spleen (WS) with torsion, a rare pathological condition, is currently unclear. Most patients with this disorder are treated with surgical interventions, such as splenectomy or splenopexy.

CASE PRESENTATION
A newborn female presented with low hemoglobin (10.8 mg/L) and high total serum bilirubin (193

μmol/L) at 3 h of life. A palpable mass was observed during her physical examination, and a magnetic resonance imaging scan of the abdomen confirmed the presence of an infarcted WS with torsion. Upon conservative management with oral antibiotic prophylaxis, careful observation, and repeated follow-ups, the infant remained clinically stable. At 2 years of age, she had normal complete blood count, and a repeat technetium study revealed two splenunculi/splenules in the splenic bed.

CONCLUSION

Most patients with WS are treated surgically with splenectomy or splenopexy. Non-operative management may be a feasible treatment option in select cases with infarcted WS and may allow the natural process of autosplenectomy to occur.

A prospective study of switching asthma patients from a Fixed-Dose Combination (FDC) Inhaled Corticosteroid [ICS]/Long-Acting Beta Agonist [LABA] therapy delivered by Dry Powder Inhaler (DPI) to ICS/LABA delivered by pressurised Metered Dose Inhaler (pMDI)

Mona Al-Ahmad[1], David Webb[2]

[1]Microbiology Department, Faculty of Medicine, Kuwait University, Department Allergy, Al-Rashed Allergy Centre, Kuwait. Electronic address: mona.alahmad@ku.edu.kw.

[2]Houghton House Group, Johannesburg, South Africa. Electronic address: dawebb@mweb.co.za.

Respir Med. 2022 Feb 12;194:106771. doi: 10.1016/j.rmed.2022.106771. Online ahead of print.

BACKGROUND

Previous real-world studies have suggested that in comparison to a dry powder inhaler (DPI), the rate of critical errors is lower with a pressurised metered dose inhaler (pMDI), and inhaled corticosteroid/long-acting bronchodilator (ICS/LABA) delivered by pMDI is more likely to achieve asthma control.

OBJECTIVES

To evaluate the acceptability, efficacy, safety and cost-effectiveness of switching asthma patients from an ICS/LABA DPI to an ICS/LABA pMDI in a real-world population in Kuwait.

METHODS

This was a 12-month, observational, nonblinded, prospective, real world study. Patients with asthma for ≥1 year with 2 or more asthma exacerbations in the last year were assigned to either switch to ICS/LABA pMDI, or to continue with ICS/LABA DPI.

RESULTS

A total of 239 patients were treated with either ICS/LABA pMDI (Switch cohort; n = 119) or ICS/LABA DPI (Maintenance cohort; n = 120). The majority of patients (99/119; 83.2%) in the Switch cohort remained on ICS/LABA pMDI over 12 months of follow-up. Both cohorts experienced an improvement in their FEV1 levels, with mean values in the Switch group reaching normal levels (>80% predicted). On average, at 3 and 12 months, the Switch cohort had significantly better FEV1 values than patients in the Maintenance cohort (p = 0.001). At 12 months, the proportion of patients with controlled asthma increased in the Switch group, but did not change significantly in the Maintenance group.

CONCLUSIONS

In patients with asthma symptoms that are not well controlled with an ICS/LABA DPI, switching to an ICS/LABA pMDI provides an alternative choice that may improve asthma control.

Detecting spontaneous retroperitoneal hemorrhage using a modified RUSH protocol: a case report

Zouheir Ibrahim Bitar[1], Ragab Desouky Elshabasy[2], Mohamed Jaber Mohsen[3], Ossama Sajeh Maadarani[4], Mahmoud Mostafa Elzoueiry[5], Mohamed Refaat Gohar[6]

[1]Critical Care Unit, Ahmadi Hospital, Kuwait Oil Company, PO Box 46468, 64015 Fahahil, Kuwait. Electronic address: zbitar2@hotmail.com.

[2]Critical Care Unit, Ahamdi Hospital, Kuwait Oil Company, Kuwait. Electronic address: Relshabasy@kockw.com.

[3]Critical Care Unit, Ahamdi Hospital, Kuwait Oil Company, Kuwait. Electronic address: momohsen@kockw.com.

[4]Critical Care Unit, Ahmadi Hospital, Kuwait Oil Company, PO Box 46468, 64015 Fahaheel, Kuwait.

[5]Critical Care Unit, Internal Medicine Dept, Ahmadi Hospital, Kuwait.

[6]Specialist Internal Medicine, Ahmadi Hospital, KOC, Kuwait. Electronic address: Mgohar@kockw.com.

Int J Surg Case Rep. 2022 Feb 12;92:106830. doi: 10.1016/j.ijscr.2022.106830. Online ahead of print.

INTRODUCTION

Bleeding in the retroperitoneal space is a serious complication. Hypovolemia and shock develop late after losing a large volume of blood. However, point of care ultrasound (POCUS) examinations in adult patients with shock do not include the retroperitoneal space.

CASE PRESENTATION

We present the case of a 74-year-old male with ischemic heart disease on dual antiplatelet. He developed vague abdominal pain and hemoglobin drop without overt bleeding source until he developed shock. Modified POCUS examination that included the retroperitoneal space detected the bleeding source and confirmed later by computerized tomography of the abdomen. The case was managed conservatively.

CLINICAL DISCUSSION

The risk factors associated with the formation of spontaneous retroperitoneal hematomas are age above 70 years and dual antiplatelet therapy. The initial integration of point-of-care ultrasound into the assessment of shocked patients leads to an earlier and accurate initial diagnosis with a clear patient care plan. POCUS should include the retroperitoneal space examination in every patient presenting with shock.

CONCLUSION

In patients with unexplained hemorrhagic shock, a modified POCUS protocol could help by including an examination of the retroperitoneal space in the assessment.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2022; 54 (1): 136 - 141

1250th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Mar 02, 2022
United Arab Emirates, Abu Dhabi
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2022/UAE/1/ICMBPS/

1274th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Mar 02, 2022
Germany, Berlin
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/Germany/2/ICRAMS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Mar 03, 2022
United States, Texas, Houston
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/18499/ICRAMMHS/

World **Disability & Rehabilitation** Conference (WDRC)
Mar 03, 2022
India, Nellore, Andhra Pradesh
Email: papers.asar@gmail.com
Event Website: http: //asar.org.in/Conference/27095/WDRC/

International Conference on **Medical and Health Sciences** (ICMHS)
Mar 05, 2022
United States, Boston
Email: papers.scienceplus@gmail.com
Event Website: http: //scienceplus.us/Conference/18656/ICMHS/

1100th International Conference on **Pharma and Food** (ICPAF)
Mar 07, 2022
Turkey, Antalya
Conference Inquiry Email ID: info@academicsera.com
Conference Website: http: //academicsera.com/Conference2022/Turkey/2/ICPAF/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Mar 08, 2022
New Zealand, Christchurch
Conference Inquiry Email ID: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/11189/ICHCG/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Mar 09, 2022
Singapore, Singapore
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/18684/ICRAMMHS/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Mar 09, 2022
Qatar, Doha
Email: info.gsrd@gmail.com
Event Website: http: //gsrd.co/Conference2022/3/Qatar/ICMPH/

1233rd International Conference on **Science, Health and Medicine** (ICSHM)
Mar 10, 2022
Spain, Madrid
Email: info@iser.co
Event Website: http: //iser.co/Conference2022/Spain/1/ICSHM/

International Conference on **Cardiology and Diabetes** (ICCD)
Mar 11, 2022
United Arab Emirates, Dubai
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/126/ICCD/

1244th International Conference on **Medical and Biosciences** (ICMBS)
Mar 12, 2022
Oman, Muscat
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2022/Oman/1/ICMBS/

International Conference on Recent Advances in **Medical Science** (ICRAMS)
Mar 14, 2022
United States, San Francisco
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/US/21/ICRAMS/

1247th International Conference on **Medical and Biosciences** (ICMBS)
Mar 16, 2022
Switzerland, Zurich
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2022/Switzerland/1/ICMBS/

1108th International Conference on **Sports Nutrition and Supplements** (ICSNS)
Mar 17, 2022
United States, Denver
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2022/USA/4/ICSNS/

1109th International Conference on **Pharma and Food** (ICPAF)
Mar 19, 2022
United Kingdom, Oxford
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2022/UK/1/ICPAF/

1272nd International Conferences on **Medical and Health Science** (ICMHS)
Mar 20, 2022
Turkey, Istanbul
Email: info@theires.org
Event Website: http: //theires.org/Conference2022/Turkey/2/ICMHS/

International Conference on **Oncolytic Virus Therapeutics** (ICOVT)
Mar 21, 2022
United Kingdom, London
Email: info.conferenceonline@gmail.com
Event Website: http: //www.conferenceonline.net/Conference/271/ICOVT/

International Virtual Conference on **COVID-19** and its Effect (IVCCE)
Mar 23, 2022
Japan, Tokyo
Email: info.conferenceonline@gmail.com
Event Website: http: //www.conferenceonline.net/Conference/269/IVCCE/

5th Boston MSK **MRI Course**, Dubai
Mar 25, 2022
United Arab Emirates, Dubai
Email: info@radiologycourses.org
Event Website: https: //www.radiologycourses.org/

International Conference on **Oncolytic Virus Therapeutics** (ICOVT)
Mar 27, 2022
United States, New York
Email: info.conferenceonline@gmail.com
Event Website: http: //www.conferenceonline.net/Conference/272/ICOVT/

1277th International Conferences on **Medical and Health Science** (ICMHS)
Mar 28, 2022
Kuwait, Kuwait City
Email: info@theires.org
Event Website: http: //theires.org/Conference2022/Kuwait/1/ICMHS/

1260th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Mar 30, 2022
Canada, Montreal
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2022/Canada/2/ICRAMHS/

International Conference on **Obesity, Weight Management and Nutrition Research** (ICOBWN)
Mar 30, 2022
India, Kochi, Kerala
Email: info.irfsr@gmail.com
Event Website: http: //irfsr.com/Conference/1405/ICOBWN/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Apr 02, 2022
United Arab Emirates, Dubai
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/10792/ICMEP/

1282nd International Conferences on **Medical and Health Science** (ICMHS)
Apr 05, 2022
Australia, Sydney
Email: info@theires.org
Event Website: http: //theires.org/Conference2022/Australia/2/ICMHS/

International Conference on Recent advancement in **Medical Education, Nursing, and Health Sciences** (ICRAMNH)
Apr 07, 2022
Japan, Kobe
Email: info.irfconference@gmail.com
Event Website: http: //irfconference.org/Conference/12304/ICRAMNH/

International Conference on **Cell and Tissue Science** (ICCTS)
Apr 09, 2022
United States, San Jose
Email: info@conferencefora.org
Event Website: http: //conferencefora.org/Conference/30791/ICCTS/

1299th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Apr 12, 2022
Morocco, Marrakesh
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/Morocco/1/ICRAMS/

1288th International Conferences on **Medical and Health Science** (ICMHS)
Apr 14, 2022
Saudi Arabia, Jeddah
Email: info@theires.org
Event Website: http: //theires.org/Conference2022/SaudiArabia/4/ICMHS/

International Conference on Recent Advances in **Medical Science** (ICRAMS)
Apr 15, 2022
United States, Massachusetts
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/US/32/ICRAMS/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Apr 15, 2022
Switzerland, Bern
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/11794/ICHCG/

1127th International Conference on **Pharma and Food** (ICPAF)
Apr 16, 2022
United States, New York
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2022/USA/6/ICPAF/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Apr 17, 2022
United States, Kansas City
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/11927/ICMEP/

International Conference on Recent Advances in **Medical Science** (ICRAMS)
Apr 18, 2022
United States, Atlanta
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/US/34/ICRAMS/

1279th International Conference on **Medical and Health Sciences** (ICMHS)
Apr 18, 2022
United Kingdom, London
Email: info@iserd.co
Event Website: http: //iserd.co/Conference2022/UK/2/ICMHS/

1259th International Conference on **Science, Health and Medicine** (ICSHM)
Apr 20, 2022
Italy, Rome
Email: info@iser.co
Event Website: http: //iser.co/Conference2022/Italy/1/ICSHM/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Apr 22, 2022
Turkey, Ankara
Email: info.gsrd@gmail.com
Event Website: http: //gsrd.co/Conference2022/4/Turkey/2/ICMPH/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Apr 24, 2022
Italy, Rome
Email: papers.issrd@gmail.com
Event Website: http: //issrd.org/Conference/12566/ICMPB/

International Conference on **Cell and Tissue Science** (ICCTS)
Apr 26, 2022
United Arab Emirates, Al Ain
Email: info@conferencefora.org
Event Website: http: //conferencefora.org/Conference/31087/ICCTS/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Apr 27, 2022
Japan, Kawasaki
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/12443/ICHCG/

1309th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Apr 28, 2022
Kuwait, Kuwait City
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/Kuwait/1/ICRAMS/

World Conference on **Pharma Industry and Medical Devices** (WCPIMD)
Apr 28, 2022
Saudi Arabia, Mecca
Email: info.iferp@gmail.com
Event Website: http: //iferp.org/Conference/6099/WCPIMD/

International Conference on **Oncolytic Virus Therapeutics** (ICOVT)
Apr 30, 2022
China, Beijing
Email: info.conferenceonline@gmail.com
Event Website: http: //www.conferenceonline.net/Conference/293/ICOVT/

1288th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
May 01, 2022
United Arab Emirates, Dubai
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2022/UAE/4/ICMBPS/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
May 01, 2022
United States, New York
Email: papers.issrd@gmail.com
Event Website: http: //issrd.org/Conference/12332/ICMPB/

International Conference on **Medical and Health Sciences** (ICMHS)
May 02, 2022
Canada, Montreal
Email: papers.academicsconference@gmail.com
Event Website: http: //academicsconference.com/Conference/19945/ICMHS/

1314th International Conference on Recent Advances in **Medical Science** (ICRAMS)
May 05, 2022
Australia, Sydney
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/Australia/3/ICRAMS/

International Conference on **Cell and Tissue Science** (ICCTS)
May 05, 2022
Netherlands, Rotterdam
Email: info@conferencefora.org
Event Website: http: //conferencefora.org/Conference/31274/ICCTS/

1315th International Conference on Recent Advances in **Medical Science** (ICRAMS)
May 06, 2022
Lebanon, Beirut
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/Lebanon/1/ICRAMS/

1140th International Conference on **Pharma and Food** (ICPAF)
May 07, 2022
Japan, Tokyo
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2022/Japan/4/ICPAF/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
May 11, 2022
India, Navi Mumbai, Maharashtra
Email: papers.issrd@gmail.com
Event Website: http: //issrd.org/Conference2022/5/NaviMumbai/ICMPB/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
May 13, 2022
United Arab Emirates, Dubai
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/18836/ICRAMMHS/

1274th International Conference on **Science, Health and Medicine** (ICSHM)
May 14, 2022
United Arab Emirates, Dubai
Email: info@iser.co
Event Website: http: //iser.co/Conference2022/UAE/5/ICSHM/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
May 16, 2022
China, Beijing
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/18947/ICRAMMHS/

1291st International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
May 16, 2022
United States, New York
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2022/USA/7/ICRAMHS/

1189th International Conference on **Food Microbiology and Food Safety** (ICFMFS)
May 17, 2022
United States, Denver
Email: info@theires.org
Event Website: http: //theires.org/Conference2022/USA/8/ICFMFS/

World Conference on **Pharma Industry and Medical Devices** (WCPIMD)
May 19, 2022
Malaysia, Kuching
Email: info.iferp@gmail.com
Event Website: http: //iferp.org/Conference/5896/WCPIMD/

1300th International Conference on **Medical and Health Sciences** (ICMHS)
May 21, 2022
Czech Republic, Prague
Email: info@iserd.co
Event Website: http: //iserd.co/Conference2022/CzechRepublic/1/ICMHS/

1301st International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
May 21, 2022
Italy, Venice
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2022/Italy/2/ICMBPS/

490th International Conference on **Sports Nutrition and Supplements** (ICSNS)
May 26, 2022
Slovakia, Bratislava
Email: info.wrfase@gmail.com
Event Website: http: //wrfase.org/Conference2022/5/Slovakia/ICSNS/

1153rd International Conference on **Pharma and Food** (ICPAF)
May 27, 2022
United Arab Emirates, Abu Dhabi
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2022/UAE/4/ICPAF/

International Conference on **Medical, Medicine and Health Sciences** (ICMMH)
Jun 05, 2022
Turkey, Istanbul
Email: contact.iierd@gmail.com
Event Website: http: //iierd.com/Conference/1637/ICMMH/

International Conference on **Medical and Biological Engineering** (ICMBE)
Jun 08, 2022
Singapore, Singapore
Email: papers.techno@gmail.com
Event Website: http: //technoarete.com/Conference/6899/ICMBE/

International Conference on **Nutrition & Health** (ICNH)
Jun 08, 2022
India, Puducherry
Email: papers.asar@gmail.com
Event Website: http: //asar.org.in/Conference/30512/ICNH/

International Conference on **Obesity and Chronic Diseases** (ICOCD)
Jun 10, 2022
France, Paris
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/106/ICOCD/

Hands-on Advanced **Cardiovascular CT Angiogram** Course towards Level 2 Cardiac CT
Jun 18, 2022
United Arab Emirates, Dubai Healthcare City
Email: info@radiologycourses.org
Event Website: https: //www.radiologycourses.org/

International Conference on **Science, Health and Medicine** (ICSHM)
Jun 20, 2022
Canada, Vancouver
Email: info@iser.co
Event Website: http: //iser.co/Conference2022/Canada/27/ICSHM/

1309th International Conference on **Medical and Biosciences** (ICMBS)
Jun 23, 2022
United States, Miami
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2022/USA/8/ICMBS/

World Conference on **Pharma Industry and Medical Devices** (WCPIMD)
Jun 25, 2022
United Arab Emirates, Sharjah
Email: info.iferp@gmail.com
Event Website: http: //iferp.org/Conference/6052/WCPIMD/

International Conference on **Cardiology and Diabetes** (ICCD)
Jun 26, 2022
United States, Washington DC
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/74/ICCD/

International Research Conference on **COVID-19 and its Impact** on Mental Health (IRCCIMH)
Jun 29, 2022
India, Puducherry
Email: info.researchconferences@gmail.com
Event Website: http: //researchconferences.in/Conference/2404/international-research-conference-on-covid-19-and-its-impact-on-mental-health/

1320th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Jul 01, 2022
United Arab Emirates, Dubai
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2022/UAE/5/ICRAMHS/

International Conference on **Medical and Health Sciences** (ICMHS)
Jul 02, 2022
United Kingdom, Glasgow
Email: papers.scienceplus@gmail.com
Event Website: http: //scienceplus.us/Conference/20597/ICMHS/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Jul 06, 2022
Australia, Adelaide
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/13530/ICHCG/

International Conference on **Medical, Medicine and Health Sciences** (ICMMH)
Jul 09, 2022
United Kingdom, George Town
Email: contact.iierd@gmail.com
Event Website: http: //iierd.com/Conference/1729/ICMMH/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Jul 15, 2022
Switzerland, Bern
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/13635/ICMEP/

1325th International Conference on **Medical and Biosciences** (ICMBS)
Jul 17, 2022
United States, Denver
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2022/USA/10/ICMBS/

International Conference on **Nursing Ethics and Medical Ethics** (ICNEME)
Jul 17, 2022
United States, New York
Email: info.wrfase@gmail.com
Event Website: http: //wrfase.org/Conference2022/7/USA/ICNEME/

International Video Conference on **Healthcare** (IVCH)
Jul 28, 2022
Turkey, Istanbul
Email: info.conferenceonline@gmail.com
Event Website: http: //www.conferenceonline.net/Conference/387/IVCH/

WHO-Facts Sheet

1. Dioxins and their effects on human health
2. Food additives
3. Microcephaly
4. Road traffic injuries
5. Poliomyelitis

Compiled and edited by
Vineetha E Mammen

Kuwait Medical Journal 2022; 54 (1): 142 - 151

1. DIOXINS AND THEIR EFFECTS ON HUMAN HEALTH

KEY FACTS

- Dioxins are a group of chemically-related compounds that are persistent environmental pollutants (POPs).
- Dioxins are found throughout the world in the environment and they accumulate in the food chain, mainly in the fatty tissue of animals.
- More than 90% of human exposure is through food, mainly meat and dairy products, fish and shellfish. Many national authorities have programmes in place to monitor the food supply.
- Dioxins are highly toxic and can cause reproductive and developmental problems, damage the immune system, interfere with hormones and also cause cancer.
- Due to the omnipresence of dioxins, all people have background exposure, which is not expected to affect human health. However, due to the highly toxic potential, efforts need to be undertaken to reduce current background exposure.
- Prevention or reduction of human exposure is best done via source-directed measures, i.e. strict control of industrial processes to reduce formation of dioxins.

Background

Dioxins are environmental pollutants. They belong to the so-called "dirty dozen" - a group of dangerous chemicals known as persistent organic pollutants (POPs). Dioxins are of concern because of their highly toxic potential. Experiments have shown they affect a number of organs and systems.

Once dioxins enter the body, they last a long time because of their chemical stability and their ability to be absorbed by fat tissue, where they are then stored in the body. Their half-life in the body is estimated to be 7 to 11 years. In the environment, dioxins tend to accumulate in the food chain. The higher an animal is in the food chain, the higher the concentration of dioxins.

The chemical name for dioxin is: *2,3,7,8-tetrachlorodibenzo para dioxin (TCDD)*. The name "dioxins" is often used for the family of structurally and chemically related *polychlorinated dibenzo para dioxins (PCDDs)* and *polychlorinated dibenzofurans (PCDFs)*. Certain dioxin-like polychlorinated biphenyls (PCBs) with similar toxic properties are also included under the term "dioxins". Some 419 types of dioxin-related compounds have been identified but only about 30 of these are considered to have significant toxicity, with TCDD being the most toxic.

Sources of dioxin contamination

Dioxins are mainly by-products of industrial processes but can also result from natural processes, such as volcanic eruptions and forest fires. Dioxins are unwanted by-products of a wide range of manufacturing processes including smelting, chlorine bleaching of paper pulp and the manufacturing of some herbicides and pesticides. In terms of dioxin release into the environment, uncontrolled waste incinerators (solid waste and hospital waste) are often the worst culprits, due to incomplete burning. Technology is available that allows for controlled waste incineration with low dioxin emissions.

Although formation of dioxins is local, environmental distribution is global. Dioxins are found throughout the world in the environment. The highest levels of these compounds are found in some

Address correspondence to:
Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: http://www.who.int/

soils, sediments and food, especially dairy products, meat, fish and shellfish. Very low levels are found in plants, water and air.

Extensive stores of PCB-based waste industrial oils, many with high levels of PCDFs, exist throughout the world. Long-term storage and improper disposal of this material may result in dioxin release into the environment and the contamination of human and animal food supplies. PCB-based waste is not easily disposed of without contamination of the environment and human populations. Such material needs to be treated as hazardous waste and is best destroyed by high temperature incineration in specialised facilities.

Dioxin contamination incidents

Many countries monitor their food supply for dioxins. This has led to early detection of contamination and has often prevented impact on a larger scale. In many instances dioxin contamination is introduced via contaminated animal feed, e.g. incidences of increased dioxin levels in milk or animal feed were traced back to clay, fat or citrus pulp pellets used in the production of the animal feed,

Some dioxin contamination events have been more significant, with broader implications in many countries.

In late 2008, Ireland recalled many tons of pork meat and pork products when up to 200 times the safe limit of dioxins were detected in samples of pork. This led to one of the largest food recalls related to a chemical contamination. Risk assessments performed by Ireland indicated no public health concern. The contamination was traced back to contaminated feed.

In 1999, high levels of dioxins were found in poultry and eggs from Belgium. Subsequently, dioxin-contaminated animal-based food (poultry, eggs, pork) were detected in several other countries. The cause was traced to animal feed contaminated with illegally disposed PCB-based waste industrial oil.

Large amounts of dioxins were released in a serious accident at a chemical factory in Seveso, Italy, in 1976. A cloud of toxic chemicals, including TCDD, was released into the air and eventually contaminated an area of 15 square kilometres where 37 000 people lived.

Extensive studies in the affected population are continuing to determine the long-term human health effects from this incident.

TCDD has also been extensively studied for health effects linked to its presence as a contaminant in some batches of the herbicide Agent Orange, which was used as a defoliant during the Vietnam War. A link to certain types of cancers and also to diabetes is still being investigated.

Although all countries can be affected, most contamination cases have been reported in industrialized countries where adequate food contamination monitoring, greater awareness of the hazard and better regulatory controls are available for the detection of dioxin problems.

A few cases of intentional human poisoning have also been reported. The most notable incident is the 2004 case of Viktor Yushchenko, President of the Ukraine, whose face was disfigured by chloracne.

Effects of dioxins on human health

Short-term exposure of humans to high levels of dioxins may result in skin lesions, such as chloracne and patchy darkening of the skin, and altered liver function. Long-term exposure is linked to impairment of the immune system, the developing nervous system, the endocrine system and reproductive functions.

Chronic exposure of animals to dioxins has resulted in several types of cancer. TCDD was evaluated by the WHO's International Agency for Research on Cancer (IARC) in 1997 and 2012. Based on animal data and on human epidemiology data, TCDD was classified by IARC as a "known human carcinogen". However, TCDD does not affect genetic material and there is a level of exposure below which cancer risk would be negligible.

Due to the omnipresence of dioxins, all people have background exposure and a certain level of dioxins in the body, leading to the so-called body burden. Current normal background exposure is not expected to affect human health on average. However, due to the high toxic potential of this class of compounds, efforts need to be undertaken to reduce current background exposure.

Sensitive groups

The developing fetus is most sensitive to dioxin exposure. Newborn, with rapidly developing organ systems, may also be more vulnerable to certain effects. Some people or groups of people may be exposed to higher levels of dioxins because of their diet (such as high consumers of fish in certain parts of the world) or their occupation (such as workers in the pulp and paper industry, in incineration plants, and at hazardous waste sites).

Prevention and control of dioxin exposure

Proper incineration of contaminated material is the best available method of preventing and controlling exposure to dioxins. It can also destroy PCB-based waste oils. The incineration process requires high temperatures, over 850°C. For the destruction of large amounts of contaminated material, even higher temperatures - 1000°C or more - are required.

Prevention or reduction of human exposure is best

done via source-directed measures, i.e. strict control of industrial processes to reduce formation of dioxins as much as possible. This is the responsibility of national governments. The Codex Alimentarius Commission adopted a Code of Practice for Source Directed Measures to Reduce Contamination of Foods with Chemicals (CAC/RCP 49-2001) in 2001. Later in 2006 a Code of Practice for the Prevention and Reduction of Dioxin and Dioxin-like PCB Contamination in Food and Feeds (CAC/RCP 62-2006) was adopted.

More than 90% of human exposure to dioxins is through the food supply, mainly meat and dairy products, fish and shellfish. Therefore, protecting the food supply is critical. In addition to source-directed measures to reduce dioxin emissions, secondary contamination of the food supply needs to be avoided throughout the food chain. Good controls and practices during primary production, processing, distribution and sale are all essential in the production of safe food.

As indicated through the examples listed above, contaminated animal feed is often the root-cause of food contamination.

Food and feed contamination monitoring systems must be in place to ensure that tolerance levels are not exceeded. It is the responsibility of feed and food producers to assure safe raw materials and safe processes during production, and it is the role of national governments to monitor the safety of food supply and to take action to protect public health. When contamination is suspected, countries should have contingency plans to identify, detain and dispose of contaminated feed and food. The affected population should be examined in terms of exposure (for example, measuring the contaminants in blood or human milk) and effects (for example, clinical surveillance to detect signs of ill health).

What should consumers do to reduce their risk of exposure?

Trimming fat from meat and consuming low fat dairy products may decrease the exposure to dioxin compounds. Also, a balanced diet (including adequate amounts of fruits, vegetables and cereals) will help to avoid excessive exposure from a single source. This is a long-term strategy to reduce body burdens and is probably most relevant for girls and young women to reduce exposure of the developing fetus and when breastfeeding infants later on in life. However, the possibility for consumers to reduce their own exposure is somewhat limited.

What does it take to identify and measure dioxins in the environment and food?

The quantitative chemical analysis of dioxins requires sophisticated methods that are available only in a limited number of laboratories around the world. The analysis costs are very high and vary according to the type of sample, but range from over US$ 1000 for the analysis of a single biological sample to several thousand US dollars for the comprehensive assessment of release from a waste incinerator.

Increasingly, biological (cell- or antibody) -based screening methods are being developed, and the use of such methods for food and feed samples is increasingly being validated. Such screening methods allow more analyses at a lower cost, and in case of a positive screening test, confirmation of results must be carried out by more complex chemical analysis.

WHO activities related to dioxins

WHO published in 2015 for the first time estimates of the global burden of foodborne disease. Dioxins' effects on fertility and on thyroid function were considered in this context, and only considering these 2 endpoints shows that this exposure can contribute significantly to foodborne disease burden in some parts of the world.

Reducing dioxin exposure is an important public health goal for disease reduction. To provide guidance on acceptable levels of exposure, WHO has held a series of expert meetings to determine a tolerable intake of dioxins.

In 2001, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) performed an updated comprehensive risk assessment of PCDDs, PCDFs, and "dioxin-like" PCBs.

In order to assess long- or short-term risks to health due to these substances, total or average intake should be assessed over months, and the tolerable intake should be assessed over a period of at least 1 month. The experts established a provisional tolerable monthly intake (PTMI) of 70 picogram/kg per month. This level is the amount of dioxins that can be ingested over lifetime without detectable health effects.

WHO, in collaboration with FAO, through the Codex Alimentarius Commission, has established a 'Code of Practice for the Prevention and Reduction of Dioxin and Dioxin-like PCB Contamination in Foods and Feed'. This document gives guidance to national and regional authorities on preventive measures.

WHO is also responsible for the Global Environment Monitoring System's Food Contamination Monitoring and Assessment Programme. Commonly known as GEMS/Food, the programme provides information on levels and trends of contaminants in food through its network of participating laboratories in over 50 countries around the world. Dioxins are included in this monitoring programme.

WHO also conducted periodic studies on levels of dioxins in human milk. These studies provide an assessment of human exposure to dioxins from all sources. Recent exposure data indicate that measures introduced to control dioxin release in a number of developed countries have resulted in a substantial reduction in exposure over the past 2 decades. Data from developing countries are incomplete and do not allow yet a time-trend analysis.

WHO is continuing these studies in collaboration with the United Nations Environmental Programme (UNEP), in the context of the 'Stockholm Convention', an international agreement to reduce emissions of certain persistent organic pollutants (POPs), including dioxins. A number of actions are being considered to reduce the production of dioxins during incineration and manufacturing processes. WHO and UNEP are undertaking global breast milk surveys, including in many developing countries, to monitor trends in dioxin contamination across the globe and the effectiveness of measures implemented under the Stockholm Convention.

Dioxins occur as a complex mixture in the environment and in food. In order to assess the potential risk of the whole mixture, the concept of toxic equivalence has been applied to this group of contaminants.

WHO has established and regularly re-evaluated toxic equivalency factors (TEFs) for dioxins and related compounds through expert consultations. WHO-TEF values have been established which apply to humans, mammals, birds and fish.

2. FOOD ADDITIVES

KEY FACTS

- Food additives are substances added to food to maintain or improve its safety, freshness, taste, texture, or appearance.
- Food additives need to be checked for potential harmful effects on human health before they can be used.
- The Joint FAO/WHO Expert Committee on Food Additives (JECFA), is the international body responsible for evaluating the safety of food additives.
- Only food additives that have been evaluated and deemed safe by JECFA, on the basis of which maximum use levels have been established by the Codex Alimentarius Commission, can be used in foods that are traded internationally.

What are food additives?

Substances that are added to food to maintain or improve the safety, freshness, taste, texture, or appearance of food are known as food additives. Some food additives have been in use for centuries for preservation – such as salt (in meats such as bacon or dried fish), sugar (in marmalade), or sulfur dioxide (in wine).

Many different food additives have been developed over time to meet the needs of food production, as making food on a large scale is very different from making them on a small scale at home. Additives are needed to ensure processed food remains safe and in good condition throughout its journey from factories or industrial kitchens, during transportation to warehouses and shops, and finally to consumers.

The use of food additives is only justified when their use has a technological need, does not mislead consumers, and serves a well-defined technological function, such as to preserve the nutritional quality of the food or enhance the stability of the food.

Food additives can be derived from plants, animals, or minerals, or they can be synthetic. They are added intentionally to food to perform certain technological purposes which consumers often take for granted. There are several thousand food additives used, all of which are designed to do a specific job in making food safer or more appealing. WHO, together with FAO, groups food additives into 3 broad categories based on their function.

Flavouring agents

Flavouring agents – which are added to food to improve aroma or taste – make up the greatest number of additives used in foods. There are hundreds of varieties of flavourings used in a wide variety of foods, from confectionery and soft drinks to cereal, cake, and yoghurt. Natural flavouring agents include nut, fruit and spice blends, as well as those derived from vegetables and wine. In addition, there are flavourings that imitate natural flavours.

Enzyme preparations

Enzyme preparations are a type of additive that may or may not end up in the final food product. Enzymes are naturally-occurring proteins that boost biochemical reactions by breaking down larger molecules into their smaller building blocks. They can be obtained by extraction from plants or animal products or from micro-organisms such as bacteria and are used as alternatives to chemical-based technology. They are mainly used in baking (to improve the dough), for manufacturing fruit juices (to increase yields), in wine making and brewing (to improve fermentation), as well as in cheese manufacturing (to improve curd formation).

Other additives

Other food additives are used for a variety of reasons, such as preservation, colouring, and sweetening. They are added when food is prepared, packaged, transported, or stored, and they eventually become a component of the food.

Preservatives can slow decomposition caused by mould, air, bacteria, or yeast. In addition to maintaining the quality of the food, preservatives help control contamination that can cause foodborne illness, including life-threatening botulism.

Colouring is added to food to replace colours lost during preparation, or to make food look more attractive.

Non-sugar sweeteners are often used as an alternative to sugar because they contribute fewer or no calories when added to food.

WHO response

Evaluating the health risk of food additives

WHO, in cooperation with the Food and Agriculture Organization of the United Nations (FAO), is responsible for assessing the risks to human health from food additives. Risk assessment of food additives are conducted by an independent, international expert scientific group – the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

Only food additives that have undergone a JECFA safety assessment, and are found not to present an appreciable health risk to consumers, can be used. This applies whether food additives come from a natural source or they are synthetic. National authorities, either based on the JECFA assessment or a national assessment, can then authorize the use of food additives at specified levels for specific foods.

JECFA evaluations are based on scientific reviews of all available biochemical, toxicological, and other relevant data on a given additive – mandatory tests in animals, research studies and observations in humans are considered. The toxicological tests required by JECFA include acute, short-term, and long-term studies that determine how the food additive is absorbed, distributed, and excreted, and possible harmful effects of the additive or its by-products at certain exposure levels.

The starting point for determining whether a food additive can be used without having harmful effects is to establish the acceptable daily intake (ADI). The ADI is an estimate of the amount of an additive in food or drinking water that can be safely consumed daily over a lifetime without adverse health effects.

International standards for the safe use of food additives

The safety assessments completed by JECFA are used by the joint intergovernmental food standard-setting body of FAO and WHO, the Codex Alimentarius Commission, to establish levels for maximum use of additives in food and drinks. Codex standards are the reference for national standards for consumer protection, and for the international trade in food, so that consumers everywhere can be confident that the food they eat meets the agreed standards for safety and quality, no matter where it was produced.

Once a food additive has been found to be safe for use by JECFA and maximum use levels have been established in the Codex General Standard for Food Additives, national food regulations need to be implemented permitting the actual use of a food additive.

How do I know which additives are in my food?

The Codex Alimentarius Commission also establishes standards and guidelines on food labelling. These standards are implemented in most countries, and food manufacturers are obliged to indicate which additives are in their products. In the European Union, for example, there is legislation governing labelling of food additives according to a set of pre-defined "E-numbers". People who have allergies or sensitivities to certain food additives should check labels carefully.

WHO encourages national authorities to monitor and ensure that food additives in food and drinks produced in their countries comply with permitted uses, conditions and legislation. National authorities should oversee the food business, which carries the primary responsibility for ensuring that the use of a food additive is safe and complies with legislation.

3. MICROCEPHALY

KEY FACTS

- Microcephaly is a condition where a baby is born with a small head or the head stops growing after birth.
- Microcephaly is a rare condition. One baby in several thousand is born with microcephaly.
- The most reliable way to assess whether a baby has microcephaly is to measure head circumference 24 hours after birth, compare the value with WHO growth standards, and continue to measure the rate of head growth in early infancy.
- Babies born with microcephaly may develop convulsions and suffer physical and learning disabilities as they grow older.
- There are no specific tests to determine if a baby will be born with microcephaly, but ultrasound scans in the third trimester of pregnancy can

sometimes identify the problem.
- There is no specific treatment for microcephaly.

Microcephaly is a condition where a baby has a head size much smaller compared with other babies of the same age and sex. Head size is an important measurement to monitor a child's brain growth. The severity of microcephaly ranges from mild to severe. Microcephaly can be present at birth (congenital) or may develop postnatally (acquired).

Scope of the problem

Microcephaly is a rare condition. Reported estimate incidence of microcephaly has wide variation due to the differences in the definition and target population.

Increased number or clustering of cases of microcephaly have been reported in context of outbreaks of Zika virus infection. The most likely explanation of available evidence is that Zika virus infection during pregnancy is a cause of congenital brain abnormalities including microcephaly.

In addition to microcephaly, a range of manifestations of varying severity has been reported among newborns that were exposed to Zika virus in utero. These include malformations of the head, seizures, swallowing problems, hearing and sight abnormalities. Other outcomes associated with Zika virus infection in utero may involve miscarriages and stillbirths. Together, this spectrum is referred to as 'congenital Zika virus syndrome.'

Diagnosis

Early diagnosis of microcephaly can sometimes be made by fetal ultrasound. Ultrasounds have the best diagnosis possibility if they are made at the end of the second trimester, around 28 weeks, or in the third trimester of pregnancy. Often diagnosis is made at birth or at a later stage.

Babies should have their head circumference measured in the first 24 hours after birth and compared with WHO growth standards. The result will be interpreted in relation to the gestational age of the baby, and also the baby's weight and length. Suspected cases should be reviewed by a paediatrician, have brain imaging scans, and have their head circumference measured at monthly intervals in early infancy and compared with growth standards. Doctors should also test for known causes of microcephaly.

Causes of microcephaly

There are many potential causes of microcephaly, but often the cause remains unknown. The most common causes include:
- infections during pregnancy: toxoplasmosis (caused by a parasite found in undercooked meat), Campylobacter pylori, rubella, herpes, syphilis, cytomegalovirus, HIV and Zika;
- exposure to toxic chemicals: maternal exposure to heavy metals like arsenic and mercury, alcohol, radiation, and smoking;
- pre- and perinatal injuries to the developing brain (hypoxia-ischemia, trauma);
- genetic abnormalities such as Down syndrome; and
- severe malnutrition during fetal life.

Based on a systematic review of the literature up to 30 May 2016, WHO has concluded that Zika virus infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly; and that Zika virus is a trigger of Guillain-Barré syndrome.

Signs and symptoms

Many babies born with microcephaly may demonstrate no other symptoms at birth but go on to develop epilepsy, cerebral palsy, learning disabilities, hearing loss and vision problems. In some cases, children with microcephaly develop entirely normally.

Treatment and care

There is no specific treatment for microcephaly. A multidisciplinary team is important to assess and care for babies and children with microcephaly. Early intervention with stimulation and play programmes may show positive impacts on development. Family counselling and support for parents is also extremely important.

WHO response

WHO has been working closely with countries affected by Zika virus and related complications on the investigation of and response to the outbreak since mid-2015.

The Strategic Response Framework and Joint Operations Plan outlines steps that WHO is taking with partners to respond to Zika and potential complications.
- Working closely with affected countries on the Zika outbreak investigation and response and on the unusual increase in microcephaly cases.
- Engaging communities to communicate the risks associated with Zika virus disease and how they can protect themselves.
- Providing guidance and mitigating the potential impact on women of childbearing age and those who are pregnant, as well as families affected by Zika virus.
- Helping affected countries strengthen care for pregnant women and the families of children born with microcephaly.

- Investigating the reported increase in microcephaly cases and the possible association with Zika virus infection by bringing together experts and partners.
- Describing the full spectrum of congenital Zika virus syndrome, which may evolve, as part of the WHO Zika virus research agenda.

4. ROAD TRAFFIC INJURIES

KEY FACTS

- Approximately 1.3 million people die each year as a result of road traffic crashes.
- The United Nations General Assembly has set an ambitious target of halving the global number of deaths and injuries from road traffic crashes by 2030 (A/RES/74/299)
- Road traffic crashes cost most countries 3% of their gross domestic product.
- More than half of all road traffic deaths are among vulnerable road users: pedestrians, cyclists, and motorcyclists.
- 93% of the world's fatalities on the roads occur in low- and middle-income countries, even though these countries have approximately 60% of the world's vehicles.
- Road traffic injuries are the leading cause of death for children and young adults aged 5-29 years**.**

Every year the lives of approximately 1.3 million people are cut short as a result of a road traffic crash. Between 20 and 50 million more people suffer non-fatal injuries, with many incurring a disability as a result of their injury.

Road traffic injuries cause considerable economic losses to individuals, their families, and to nations as a whole. These losses arise from the cost of treatment as well as lost productivity for those killed or disabled by their injuries, and for family members who need to take time off work or school to care for the injured. Road traffic crashes cost most countries 3% of their gross domestic product.

Who is at risk?

Socioeconomic status

More than 90% of road traffic deaths occur in low- and middle-income countries. Road traffic injury death rates are highest in the African region. Even within high-income countries, people from lower socioeconomic backgrounds are more likely to be involved in road traffic crashes.

Age

Road traffic injuries are the leading cause of death for children and young adults aged 5-29 years.

Sex

From a young age, males are more likely to be involved in road traffic crashes than females. About three quarters (73%) of all road traffic deaths occur among young males under the age of 25 years who are almost 3 times as likely to be killed in a road traffic crash as young females.

Risk factors

The Safe System approach: accommodating human error

The Safe System approach to road safety aims to ensure a safe transport system for all road users. Such an approach takes into account people's vulnerability to serious injuries in road traffic crashes and recognizes that the system should be designed to be forgiving of human error. The cornerstones of this approach are safe roads and roadsides, safe speeds, safe vehicles, and safe road users, all of which must be addressed in order to eliminate fatal crashes and reduce serious injuries.

Speeding

- An increase in average speed is directly related both to the likelihood of a crash occurring and to the severity of the consequences of the crash. For example, every 1% increase in mean speed produces a 4% increase in the fatal crash risk and a 3% increase in the serious crash risk.
- The death risk for pedestrians hit by car fronts rises rapidly (4.5 times from 50 km/h to 65 km/h).
- In car-to-car side impacts the fatality risk for car occupants is 85% at 65 km/h.

Driving under the influence of alcohol and other psychoactive substances

- Driving under the influence of alcohol and any psychoactive substance or drug increases the risk of a crash that results in death or serious injuries.
- In the case of drink-driving, the risk of a road traffic crash starts at low levels of blood alcohol concentration (BAC) and increases significantly when the driver's BAC is ≥ 0.04 g/dl.
- In the case of drug-driving, the risk of incurring a road traffic crash is increased to differing degrees depending on the psychoactive drug used. For example, the risk of a fatal crash occurring among those who have used amphetamines is about 5 times the risk of someone who hasn't.

Nonuse of motorcycle helmets, seat-belts, and child restraints

- Correct helmet use can lead to a 42% reduction in the risk of fatal injuries and a 69% reduction in the risk of head injuries.

- Wearing a seat-belt reduces the risk of death among drivers and front seat occupants by 45 - 50%, and the risk of death and serious injuries among rear seat occupants by 25%.
- The use of child restraints can lead to a 60% reduction in deaths.

Distracted driving

There are many types of distractions that can lead to impaired driving. The distraction caused by mobile phones is a growing concern for road safety.

- Drivers using mobile phones are approximately 4 times more likely to be involved in a crash than drivers not using a mobile phone. Using a phone while driving slows reaction times (notably braking reaction time, but also reaction to traffic signals), and makes it difficult to keep in the correct lane, and to keep the correct following distances.
- Hands-free phones are not much safer than hand-held phone sets, and texting considerably increases the risk of a crash.

Unsafe road infrastructure

The design of roads can have a considerable impact on their safety. Ideally, roads should be designed keeping in mind the safety of all road users. This would mean making sure that there are adequate facilities for pedestrians, cyclists, and motorcyclists. Measures such as footpaths, cycling lanes, safe crossing points, and other traffic calming measures can be critical to reducing the risk of injury among these road users.

Unsafe vehicles

Safe vehicles play a critical role in averting crashes and reducing the likelihood of serious injury. There are a number of UN regulations on vehicle safety that, if applied to countries' manufacturing and production standards, would potentially save many lives. These include requiring vehicle manufacturers to meet front and side impact regulations, to include electronic stability control (to prevent over-steering) and to ensure airbags and seat-belts are fitted in all vehicles. Without these basic standards the risk of traffic injuries – both to those in the vehicle and those out of it – is considerably increased.

Inadequate post-crash care

Delays in detecting and providing care for those involved in a road traffic crash increase the severity of injuries. Care of injuries after a crash has occurred is extremely time-sensitive: delays of minutes can make the difference between life and death. Improving post-crash care requires ensuring access to timely prehospital care, and improving the quality of both prehospital and hospital care, such as through specialist training programmes.

Inadequate law enforcement of traffic laws

If traffic laws on drink-driving, seat-belt wearing, speed limits, helmets, and child restraints are not enforced, they cannot bring about the expected reduction in road traffic fatalities and injuries related to specific behaviours. Thus, if traffic laws are not enforced or are perceived as not being enforced it is likely they will not be complied with and therefore will have very little chance of influencing behaviour.

Effective enforcement includes establishing, regularly updating, and enforcing laws at the national, municipal, and local levels that address the above mentioned risk factors. It includes also the definition of appropriate penalties.

What can be done to address road traffic injuries

Road traffic injuries can be prevented. Governments need to take action to address road safety in a holistic manner. This requires involvement from multiple sectors such as transport, police, health, education, and actions that address the safety of roads, vehicles, and road users.

Effective interventions include designing safer infrastructure and incorporating road safety features into land-use and transport planning, improving the safety features of vehicles, improving post-crash care for victims of road crashes, setting and enforcing laws relating to key risks, and raising public awareness.

WHO response

Providing technical support to countries

WHO works across the spectrum in countries, in a multisectoral manner and in partnership with national and international stakeholders from a variety of sectors. Its objective is to support Member States in road safety policy planning, implementation and evaluation.

In addition, WHO collaborates with partners to provide technical support to countries. For example, WHO is currently collaborating with the Bloomberg Initiative for Global Road Safety (BIGRS) to reduce fatalities and injuries from road traffic crashes in targeted low- and middle-income countries and cities.

In 2017, WHO released *Save LIVES a road safety technical package* which synthesizes evidence-based measures that can significantly reduce road traffic fatalities and injuries. *Save LIVES: a road safety technical package* focuses on **S**peed management, **L**eadership, **I**nfrastructure design and improvement, **V**ehicle safety standards, **E**nforcement of traffic laws and post-crash Survival.

The package prioritizes 6 strategies and 22

interventions addressing the risk factors highlighted above, and provides guidance to Member States on their implementation to save lives and meet the road safety target of halving the global number of deaths and injuries from road traffic crashes by 2020.

Coordinating the Decade of Action for Road Safety

WHO is the lead agency – in collaboration with the United Nations regional commissions – for road safety within the UN system. WHO chairs the United Nations Road Safety Collaboration and serves as the secretariat for the Decade of Action for Road Safety 2011– 2020. Proclaimed through a UN General Assembly resolution in 2010, the Decade of Action was launched in May 2011 in over 110 countries, with the aim of saving millions of lives by implementing the Global Plan for the Decade of Acton.

WHO also plays a key role in guiding global efforts by continuing to advocate for road safety at the highest political levels; compiling and disseminating good practices in prevention, data collection and trauma care; sharing information with the public on risks and how to reduce these risks; and drawing attention to the need for increased funding.

Monitoring progress through global status reports

WHO's *Global status report on road safety 2018* presents information on road safety from 175 countries. This report is the fourth in a series and provides an overview of the road safety situation globally. The global status reports are the official tool for monitoring the Decade of Action.

5. POLIOMYELITIS

KEY FACTS

- Polio (poliomyelitis) mainly affects children under 5 years of age.
- 1 in 200 infections leads to irreversible paralysis. Among those paralysed, 5% to 10% die when their breathing muscles become immobilized.
- Cases due to wild poliovirus have decreased by over 99% since 1988, from an estimated 350 000 cases then, to 33 reported cases in 2018.
- As long as a single child remains infected, children in all countries are at risk of contracting polio. Failure to eradicate polio from these last remaining strongholds could result in as many as 200 000 new cases every year, within 10 years, all over the world.
- In most countries, the global effort has expanded capacities to tackle other infectious diseases by building effective surveillance and immunization systems.

Symptoms

Polio is a highly infectious disease caused by a virus. It invades the nervous system, and can cause total paralysis in a matter of hours. The virus is transmitted by person-to-person spread mainly through the faecal-oral route or, less frequently, by a common vehicle (for example, contaminated water or food) and multiplies in the intestine. Initial symptoms are fever, fatigue, headache, vomiting, stiffness of the neck and pain in the limbs. 1 in 200 infections leads to irreversible paralysis (usually in the legs). Among those paralysed, 5% to 10% die when their breathing muscles become immobilized.

People most at risk

Polio mainly affects children under 5 years of age.

Prevention

There is no cure for polio, it can only be prevented. Polio vaccine, given multiple times, can protect a child for life.

Global caseload

Wild poliovirus cases have decreased by over 99% since 1988, from an estimated 350 000 cases in more than 125 endemic countries then, to 33 reported cases in 2018.

Of the 3 strains of wild poliovirus (type 1, type 2, and type 3), wild poliovirus type 2 was eradicated in 1999 and no case of wild poliovirus type 3 has been found since the last reported case in Nigeria in November 2012.

WHO Response

Launch of the Global Polio Eradication Initiative

In 1988, the Forty-first World Health Assembly adopted a resolution for the worldwide eradication of polio. It marked the launch of the Global Polio Eradication Initiative (GPEI), spearheaded by national governments, WHO, Rotary International, the US Centers for Disease Control and Prevention (CDC), UNICEF, and later joined by additional key partners including the Bill & Melinda Gates Foundation and Gavi, the Vaccine Alliance. This followed the certification of the eradication of smallpox in 1980, progress during the 1980s towards elimination of the poliovirus in the Americas, and Rotary International's commitment to raise funds to protect all children from the disease.

Progress

Overall, since the GPEI was launched, the number of cases has fallen by over 99%.

In 1994, the WHO Region of the Americas was certified polio-free, followed by the WHO Western

Pacific Region in 2000 and the WHO European Region in June 2002. On 27 March 2014, the WHO South-East Asia Region was certified polio-free, meaning that transmission of wild poliovirus has been interrupted in this bloc of 11 countries stretching from Indonesia to India. This achievement marks a significant leap forward in global eradication, with 80% of the world's population now living in certified polio-free regions.

More than 18 million people are able to walk today, who would otherwise have been paralysed. An estimated 1.5 million childhood deaths have been prevented, through the systematic administration of vitamin A during polio immunization activities.

Opportunity and risks: an emergency approach

The strategies for polio eradication work when they are fully implemented. This is clearly demonstrated by India's success in stopping polio in January 2011, in arguably the most technically-challenging place, and polio-free certification of the entire South-East Asia Region of WHO occurred in March 2014.

Failure to implement strategic approaches, however, leads to ongoing transmission of the virus. Endemic transmission of wild poliovirus is continuing to cause cases in border areas of Afghanistan and Pakistan. Failure to stop polio in these last remaining areas could result in as many as 200 000 new cases every year, within 10 years, all over the world. That is why it is critical to ensure polio is eradicated completely, once and for all.

Future benefits of polio eradication

Once polio is eradicated, the world can celebrate the delivery of a major global public good that will benefit all people equally, no matter where they live. Economic modelling has found that the eradication of polio would save at least US$ 40–50 billion, mostly in low-income countries. Most importantly, success will mean that no child will ever again suffer the terrible effects of lifelong polio-paralysis.