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Review Article

Meniscal tears and chondral damages profile in patients with anterior cruciate ligament injury

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ABSTRACT

Anterior cruciate ligament (ACL) injuries are common and are usually associated with concomitated knee joint structure injuries such as meniscal injuries. Understanding the pattern of these injuries and the long-term consequence of these injuries is important. ACL injury causes knee joint laxity, meniscal injury, quadricep muscle wasting and weakness, chondral damage and abnormal knee kinetic eventually leading to early knee joint osteoarthritis. Understanding the pattern of concurrent meniscal pathology with ACL-deficient knee in the population is important to establish awareness programs, preventive measures and early treatment protocols.

KEY WORDS: anterior cruciate ligament, chondral damage, meniscal tear, osteoarthritis

INTRODUCTION

Knee joint injuries are regular public and athletes' problems necessitating medical attention. Of these injuries, anterior cruciate ligament (ACL) injuries are of huge concern in practice. In a systematic review, the annual national population incidence rates range from 0.01% to 0.05% in several countries[1]. These injuries are unusually found isolated, rather they are frequently associated with other intra-articular injuries, with meniscal pathology being the most common. This association is well described in the literature[2-20], nevertheless the pattern of meniscal tear is still controversial. In acute ACL rupture, meniscal tears are found in 16-82% of the cases. However, in chronic ACL insufficiency, 96% of the cases have meniscal tears[4].

Another intra-articular pathology of interest when considering ACL associated injuries is chondral damage. It is found in 16-46% of cases with acute ACL injury[13]; besides it is found to increase in frequency and severity with delayed anterior cruciate ligament reconstruction (ACLR)[8-12,21]. Increase in meniscal tears increases the likelihood of cartilage damage and vice versa[9,22]. According to Outerbridge classification, the cartilage damage is classified as: grade 1 (softening and fibrillation); grade 2 (superficial changes); grade 3 (deep changes and no exposed bone); and grade 4 (exposed bone)[23-26]. It was found that high Outerbridge grades (3-4) are more frequently found in patients with previous history of medial or lateral meniscectomy[14]. The International Cartilage Repair Society has adopted a classification system for cartilage injury and repair, which is also frequently in use[19,26-27].

The menisci are crescent-shaped fibrocartilage structures which cover about two-thirds of the articular surface. The lateral meniscus is more circular, smaller and more mobile than the medial meniscus. They are relatively considered as avascular structures with a limited blood supply to the peripheral zone reaching 10-30% only. Menisci are essential structures for the normal function and well-being of the knee joint. The menisci have primary and secondary functions. Their primary function is to aid proper load transmission. This is done through increasing the congruency and contact area of the tibiofemoral joint, in order to decrease the contact stress to the articular cartilage. The secondary functions are shock absorption, stability, lubrication, nutrition and proprioception to the knee joint[20,28].

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LITERATURE REVIEW

Meniscal tear is a common cause of significant morbidity in orthopedics practice. The annual global incidence is around 60-70 per 100,000. Its peak incidence is 21-30 years in males and 11-20 years in females, with male to female ratio of 4:1. The dynamic basis for meniscal tears are combined abnormal axial overloading and twisting forces at the knee joint. The symptoms of meniscal tears include pain, swelling at the knee joints and mechanical symptoms. These are locking, catching, grinding and giving away[20,28].

Acute traumatic event to the knee can result in either an isolated meniscal tear or meniscal tear in conjunction with ACL injury. However, chronic ACL insufficiency can lead to secondary meniscal tears by repetitive traumatic attacks of instability. Unstable knee gives an uncontrolled environment to equalize the tension between the two menisci. This subjects one of them to abnormal overloading tensile force. Thus, meniscal tears are classified to acute and degenerative tears. Snoeker *et al*[29] did a systematic review with meta-analysis to study the risk factors of meniscal tears. They found that there is strong evidence that playing soccer and rugby increases the risk of acute meniscal tears. They also found that age above 60 years, male gender, work related kneeling and squatting and climbing stairs of more than 30 flights are strongly associated with increased risk for degenerative tears. Sitting for more than 2 hours per day significantly reduces the risk for degenerative meniscal tears. Moreover, both patients with early or overt osteoarthritis are more vulnerable to degenerative meniscal tears[30].

The profile of ACL injury in association with meniscal pathology differs with mode and velocity of injury. For instance, in western countries, ACL injuries are often due to low velocity injuries, mainly sport-related. However, in developing countries, high velocity injuries, namely road traffic accidents and occupational injuries, are responsible for many ACL injuries[3].

In literature, the mode of injury is classified into sporting activity, non-sporting activity and non-activity. Sporting activity is further classified to contact and non-contact activity[20]. Sport-related ACL injuries are frequently studied. It was found that the pattern of meniscal pathology significantly differs with various types of sports. Granan *et al*[31] found that when compared with soccer, skiing, American football and basketball are more likely to result in isolated ACL injuries, multi-ligamentous and lateral meniscal tears, respectively. This difference is best explained by the different bio-mechanical forces applied to the knee joint during these sports activities.

ACL being the primary knee joint stabilizer, its absence increases the number of instability episodes. These episodes could be reduced by avoiding high demand contact sports and prevented by ACLR. Therefore, early ACLR is recommended to decrease the chances of collateral damage to the meniscus and cartilage[2-3,28,32]. Ultimately, this will reduce the disability, cost of treatment and exposure to more invasive treatment. Likewise, the quality of life, degree of productivity and level of efficiency will improve post ACLR[33-35].

Knee functional stability could be restored successfully by ACLR, but the associated meniscal and chondral damage will persist in majority of the cases even after treatment. The residual meniscal and cartilage damage increases the long-term consequences, *i.e.*, premature and progressive osteoarthritis[8,21,30]. The prevalence of osteoarthritis is higher in patients with ACL injury compared with general population[36-37]. Some studies showed that the risk of development of osteoarthritis is reduced by ACLR[38-39], but stronger evidences suggested that ACLR has no protective role against the development of osteoarthritis[30,40]. Additionally, patients with concomitant meniscal tears with ACL injuries are found to have a greater risk of developing osteoarthritis compared with patients with isolated ACL injuries[36,40].

Meniscal injuries can present as medial, lateral or bi-meniscal. In acute ACL injuries, lateral meniscal tears are more common than medial meniscal tears[2,6,12,20]. Some studies showed the opposite, where medial meniscus is more commonly torn in acute ACL injuries[4-5,7]. Al Saran *et al*[4] published one of these studies. Their findings were justified by three major points, first being that patients with medial meniscal tears were significantly older than those with lateral and bi-meniscal tears. Second, they mentioned that their population is known to have a higher rate of genu-varus. Third, some of the cases of meniscal pathology were diagnosed by magnetic resonance imaging, which has a lower sensitivity in diagnosing lateral meniscal tears[4,20,41]. Chronic ACL insufficiencies are more frequently found to be accompanied by medial meniscus tears[3,7-8,11-12,15,20]. These differences were attributed to the anatomical variation between the two menisci. In ACL-deficient knee, the medial meniscus acts as the main stabilizer of the knee joint by restricting anterior tibial translation since it is firmly attached to the tibial plateau. Adopting this new function increases the tension on the medial meniscus, making it more liable to be damaged in patients with chronic ACL insufficiency[4-5,20].

The patterns of meniscal tears in patients with ACL insufficiency are usually studied based on independent

variables to find out the reason behind their variation. These variables are age, gender, body mass index, mode of injury, velocity of injury, time from injury to surgery and number of instability episodes.

The effect of age on the pattern of meniscal tears in conjunction with ACL injury is debatable. In general, increasing age rises the rate of meniscal tears[8,19-20]. Some studies showed that patients with medial meniscal tears were significantly older than those with lateral meniscal tears[4,7,19]. This was attributed to age-related arthritic changes, while others found that there was no statistical association with age[3]. Likewise, age was found to increase the chance of developing chondral lesions in patients with ACL injury[6,16,19].

The majority of male patients undergoing ACL reconstructive surgery were between the ages of 15-45 years, whereas females were between 15-25 years[8,42]. Chhadia *et al*[8] found that female patients with ACL injury were younger than male patients, and they had surgery at shorter interval compared to male patients. Male gender was found to be associated with high rates of lateral meniscal tears, medial meniscal tears and chondral lesions in patients with ACL injuries[6,8,10,19]. This dissimilarity is due to the fact that men were significantly older and their time to surgery was longer. In addition, they had a high-energy initial injury and/or higher frequencies of instability episodes.

Body mass index, when studied as continuous or categorical variable, was found to increase the probability of chondral lesion in patients with ACL injury[6,16]. Kluczynski *et al*[6] found that obesity is a negative predictor of medial meniscal tears. The association between obesity and valgus deformity is well established[43]. This malalignment causes less stress to the medial compartment of the knee. This hypothesis could explain their finding.

Time to surgery is considered to be the most significant factor for intra-articular pathology occurrence discrepancy. The longer the period, the higher the incidence of meniscal tears and cartilage damages[3,7-12,17,19]. Most of the studies found that increased time to surgery leads to a significant increase in the medial meniscal tears compared to lateral and bi-meniscal tears[7-8,11-12,15,18-19]. These findings were also reproducible in a juvenile population[19]. Some studies showed that lateral meniscal tears remained fairly steady[7-8] and others found that they increased considerably with increased time to surgery[3,11,19].

After shining a light on the significance of time from injury to surgery, it is of high importance to say that the exact safe waiting time to perform ACLR is still controversial. Despite that, it is generally agreed that the sooner the reconstruction, the better the outcome. It was demonstrated in many studies that secondary pathology following ACL injury increased significantly with delay in ACLR of more than 12 months[7-8,11,19,29,44]. Sri-Ram *et al*[19] have further refined the time to surgery to be within five months, seeing that the risk of secondary pathology increased dramatically on a monthly basis after five months.

Kluczynski *et al*[6] studied the number of instability episodes as a predictor of meniscal tears and chondral lesions. They found that with increasing instability episodes, there were higher rates of medial meniscal tears. This finding was also significant when adjusted for time from injury to surgery. On the other hand, time from injury to surgery was not found to be a significant predictor of medial meniscal tears when adjusted for number of instability episodes. This means that the number of instability episodes may be a more accurate predictor of medial meniscal tears in ACL injured patients.

The goal of meniscal treatment is to eliminate pain, retain some of the pre-injury activity level and reduce pre-mature knee joint degeneration. During arthroscopy, the course of action with meniscal tears entails surgical treatment, *i.e.* partial meniscectomy or meniscal repair, or non-surgical treatment. Chhadia *et al*[8] studied meniscal repair rates in association with time to surgery, age and gender. They found that with increased time to surgery, there is a decrease in medial meniscal repair rate. This was possibly due to the fact that delay in surgery caused extensive damage to the menisci beyond the level of repair. Therefore, these patients will require meniscectomy, which is considered as a very strong predictor for developing osteoarthritis in the future[20,30,32,40,45]. This finding suggests that early ACLR would help to increase the rate of meniscal repair to further restore the normal knee mechanics and preserve knee joint integrity. In the long-term, this intervention would decrease the risk of future development of osteoarthritis.

CONCLUSION

Anterior cruciate ligament injury is a great source of morbidity and disability since it causes knee joint laxity, meniscal injury, quadricep muscle wasting and weakness, chondral damage and abnormal knee kinetic, eventually leading to knee joint osteoarthritis. Understanding the pattern of concurrent meniscal pathology with ACL-deficient knee in the population will help both the patients and the care providers. The patients will be more aware of the associated risk factors, to empower the prevention measures of the aforementioned complications. The care providers' perpetration could be improved in handling these issues. This could be implied by focusing their effort on patient health education, preventive training and early intervention.

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Original Article

May the length of the surgical midurethra be longer than the anatomical midurethra? A prospective anatomic study

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ABSTRACT

Objective: To compare the mesh location to the anatomic mid-urethra in midurethral sling (MUS) patients with successful results, and find out if there is a difference in the lengths of the surgical and anatomic mid-urethra
Design: Prospective study
Settings: Tertiary University Hospital
Subjects: Seventy-two successfully treated stress incontinence patients via transobturatory tape operation
Intervention: In this study, all cases with successful results were prospectively phone called, and a translabial ultrasonographic examination was performed.
Main outcome measures: The length of the urethra and the suburethral mesh, the distance from the bladder neck and external urethral meatus to the edges of the mesh, the deviation of the midpoint of mesh from the midpoint of the urethra, and the posterior urethrovesical angle were all measured.
Results: The study group consisted of 72 females. The midpoint of the meshes was at the exact midpoint of the urethra without any deviation only in six patients, and it was deviated in 66 patients. Meshes were in the borders of the midurethra in 41 patients, and meshes were partially slipping out of the anatomic mid-urethral borders at different rates in a total of 25 patients. Slipping from the distal and proximal edges of the midurethra was 2.1-26.7% (13.2±7.6%) and 2.4-30% (12.3±11%) of the midurethral lengths of patients, respectively.
Conclusions: In this anatomical study, the distribution of the zone where the mesh is localized shows that to achieve a successful result, the targeted anatomic region of the urethra is longer than the mid one-third of the urethra.

KEY WORDS: anatomic midurethra, surgical midurethra, transobturator tape

INTRODUCTION

The surgical treatment of stress urinary incontinence (SUI) is successfully maintained by transobturator midurethral sling (MUS) surgeries over a decade. The short and medium-term results are well understood after many clinical trials[1,2]. The mesh is aimed to localize just under the mid one-third of the urethra during MUS. After understanding the "integral theory", this concept has become more important[3].

The location of the mesh under the midurethra is crucial for the success and complication rates of MUS. Anatomically, the midurethra is the mid one-third of the urethra. This part is the high-pressure region of the urethra[4]. The aim of this study is to evaluate the exact location of the mesh under the urethra with translabial ultrasonography and to compare the mesh position to the anatomic midurethra in MUS patients with favorable results, and find out if there is a difference in the lengths of surgical and anatomic midurethra. This is an anatomic definition study.

SUBJECTS AND METHODS

Between September 2011 and April 2016, a total of 96 transobturator tape (TOT) surgeries were performed at the Department of Urology, Medicine Faculty of Ahi Evran University. In this study, after an ethical board approval, all cases with successful results were prospectively phone called for a translabial ultrasonographic examination to evaluate the relationship of the mesh to the surrounding structures

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after surgery. Written informed consent was obtained from the study participants.

Patients who had had TOT operation with a successful surgical outcome were included in this study. Patients who had another urogynecological surgery simultaneously or with unsuccessful surgical outcome were excluded from the study. Patients without SUI, emptying problem, extrusion of the mesh or erosion of the urethra were accepted as surgical success. Objective success was defined as a negative cough stress test with a postvoiding residual urine volume <100 ml assessed with suprapubic ultrasonography, and objective success was assessed three months after the surgery. Subjective success was assessed with Urogenital Distress Inventory Six short form (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7)[5]. The number of patients with a failure of TOT was low, so a comparison was not made between the successful and the unsuccessful patients.

Surgical technique

The same surgical team performed the surgical procedures. The method of the operation was based on Delorme's definition[6]. A polypropylene and monofilament mesh was used with an outside-in technique to all patients under spinal anesthesia. The Foley catheter was removed on the first postoperative day. After measuring postvoiding residual volume with suprapubic ultrasonography, patients were discharged.

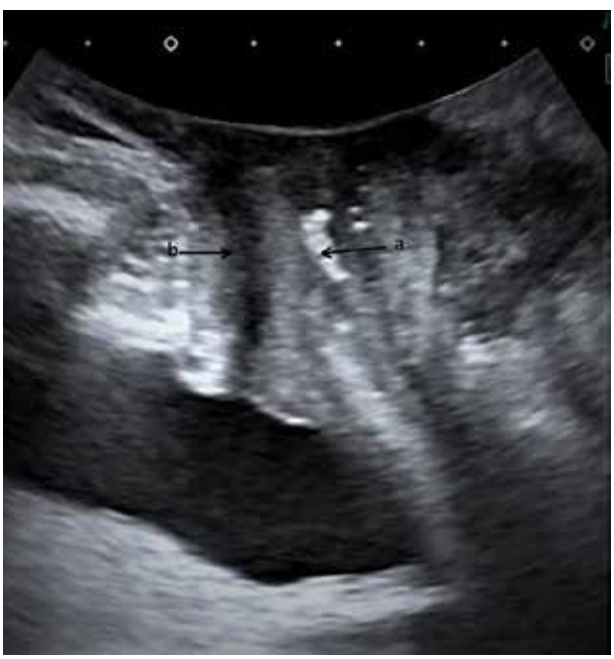

Fig 1: The TLUSG view of the midurethral mesh **a)** the sagittal view of the echogenic midurethral mesh, **b)** the sagittal view of the urethra.

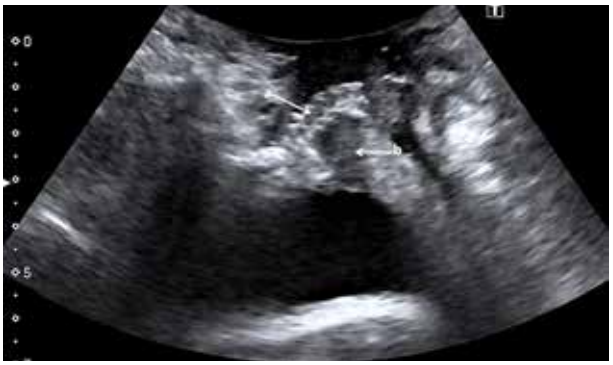

Fig 2: The TLUSG view of the midurethral mesh **a)** the horizontal view of the midurethral mesh, **b)** the horizontal view of the urethra.

Technique of translabial ultrasonography

A high-resolution ultrasound (Toshiba Aplio 500, Tokyo, Japan) was used for the procedure. The procedure was performed with a 3.5 Mhz convex transducer, and B-mode images were received. Emptying the bowel before the procedure was recommended to the patients. Translabial ultrasonography (TLUSG) were conducted with a moderately full bladder in all patients[7]. Supine position with flexed knees and abducted thigh was used during the ultrasonographic evaluation.

Patients were covered for privacy. The transducer was covered and placed in the midsagittal position. This technique enables to view the symphysis pubis, urethra, bladder neck, vagina, rectum and suburethral mesh (Figure 1, 2). An experienced radiologist performed TLUSG. After measuring the length of the urethra and the suburethral mesh, the distance from the bladder neck and external urethral meatus to the edges of the mesh was measured. The anatomical mid-urethra was measured as the mid one-third of the urethral length. Patients with favorable surgical results were examined to clarify whether all the meshes are in the boundaries of the anatomic mid-urethra or not. The deviation of the midpoint of mesh from the midpoint of the urethra was measured. After calculating the deviation of midpoint of the mesh from midpoint of the urethra in "mm", the deviation "percentage" was measured (100 x the deviation of midpoint of the mesh from midpoint of the urethra in mm / the mid one-third of the urethral length) because the length of the urethra was different in each patient. The width of the mesh, the distance from the urethral mucosa and vaginal mucosa to the mesh were also measured. All measurements were made in mm (Figure 3). The posterior urethrovesical angle was measured as the angle between the line parallel to the proximal urethra and the bladder trigone during resting and Valsalva maneuver. The average of this angle after two different measurements was calculated.

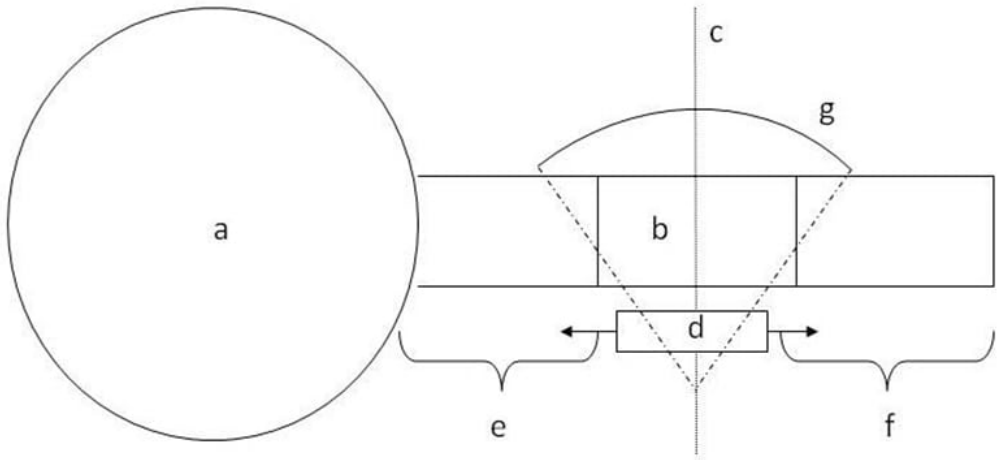

Fig 3: The definitions of the parameters that measured by TLUSG **a)** bladder, **b)** the length of the anatomic midurethra, **c)** midurethral point, **d)** the length of the midurethral mesh, **e)** the distance between the bladder neck and proximal end of the midurethral mesh, **f)** the distance between the external urethral meatus and distal end of the midurethral mesh, **g)** the deviation of the meshes in successful cases after TOT (possible surgical midurethra).

Statistical analysis

In this study, Statistical Package for Social Sciences version 21.0 Software for Windows (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA) was used for statistical analysis. The normality of distribution assumption was tested with Kolmogorov-Smirnov test. Data are expressed as mean±SD. One sample *t* test was used for continuous variables. Pearson's correlation was used for comparative statistics. In all tests, $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Baseline data and patient characteristics were given in Table 1. Seventy-five of the 96 patients met the inclusion criteria and a phone call reached these 75 patients. The midurethral mesh was folded onto itself under the urethra in three patients, but despite this situation, these three patients did not have SUI. Mesh was in "U" shape and not straight under the urethra in these patients, and the results were favorable. The relationship between mesh and urethra was not measured in these patients. The positional relationship of mesh and urethra was measured in 72 patients. The study group consisted of 72 females between the ages of 26 and 81 (mean: 54.5±10.5) years.

The urethral lengths ranged between 29 and 53 mm (mean: 41.8±5.7 mm). The distance from the bladder neck to the proximal edge of the mesh was between 9 and 25 mm (mean: 17.1±3.2 mm). The distance from external urethral meatus to the distal edge of the mesh was between 10 and 24 mm (mean: 15.8±3.7 mm).

The length of the midurethra (mid one-third of the urethra) was between 9.6 and 17.6 mm (mean 13.9±1.9). The midpoint of the mesh was at the exact midpoint of the urethra without any deviation only in six patients and was deviated in 66 patients. Despite the deviation from the midpoint of the anatomic midurethra, meshes were in the borders of anatomic midurethra in 41 patients. The mesh was found to be partially slipping out of the anatomic midurethral borders at different rates in a total of 25 patients. Distal slipping was detected in 17, and proximal slipping was detected in eight patients. Distal slipping was between 0.33 and 4.33 mm (mean: 1.83±1.17 mm), and proximal slipping was between 0.3 and 3.3 mm (mean: 1.41±1.03 mm) from the distal or proximal borders of the anatomic midurethra. Slipping from the distal and proximal edges of the midurethra was 2.1-26.7% (mean: 13.2±7.6%) and 2.4-30% (mean: 12.3±11%) of the midurethral lengths of patients, respectively (Table 2).

Table 1: Characteristics of the patients and meshes

Characteristics of the patients and meshes	GROUP min-max (mean±SD)
Patients' age	26-81 (54.5±10.5)
Urethral length	29-53 mm (41.8±5.7)
Midurethral length	9.6-17.6 mm (13.9±1.9)
Bladder neck to prox edge of mesh	9-25 mm (17.1±3.2)
External meatus to distal edge of mesh	10-24 mm (15.8±3.7)
Deviation percentage proximally	7.5-45.2% (25.6±13.8 %)
Deviation percentage distally	2.4-30% (12.3±11 %)

Table 2: Patients with slipping of the meshes out of the anatomic midurethra

Number of patients and details of measurement	Distal slipping of meshes out of anatomic midurethra	Proximal slipping of meshes out of anatomic midurethra
Patient number (n)	17	8
From the edge of the mesh (mm)	0.33-4.33 mm (1.83±1.17)	0.3-3.3 mm (1.41±1.03)
From the edge of the mesh (%)	2.1-26.7% (13.2±7.6)	2.4-30% (12.3±11%)

The distance between the midpoint of the mesh and the midpoint of the urethra ranged between -6 and +6 mm (proximal deviation from the midpoint of the urethra was accepted as a minus, and the distal deviation was taken as a plus). The deviation percentage of the mesh from mid point of the midurethra was -7.5 to -45.2% (mean: 25.6±13.8%) proximally and 13.6 to 46.2% (mean: 25.7±10.3%).

The distance from urethral mucosa to mesh was between 1.5 and 5 mm (mean: 2.7±1.2 mm). The distance from mesh to the vagina was between 2 and 4 mm (mean: 3±0.6 mm).

Nineteen patients had mixed urinary incontinence preoperatively. Both urge and stress incontinence improved in eight of these patients after MUS. De-novo urgency was seen in two patients. The difference of the urethrovesical angle between resting and Valsalva maneuver was between 10° and 45° (mean: 19.6°±8.4°). The correlation between the difference of the urethrovesical angle (rest and Valsalva) and the deviation percentage of the midpoint of mesh from the midpoint of the urethra were done via Pearson's correlation analysis. The correlation between the deviation percentages of the proximally located meshes and the difference of the urethrovesical angle was statistically insignificant (P=0.059, r=-0.297). The correlation between the deviation percentages of the distally deviated meshes and the difference of the urethrovesical angle was statistically insignificant (P=0.30, r=-0.205).

The preop UDI-6 short form score was between 8 and 12 (mean: 9.36±1.03), and postop score was between 1 and 3 (mean: 1.94±0.80; P <0.01). The preop IIQ-7 score was between 12 and 19 (mean: 16.67±2.00), and postop score was between 0 and 4 (mean: 1.43±1.11; P <0.01). The postoperative follow-up period was between 3 and 53 months (mean: 31.5±13).

DISCUSSION

SUI, defined as ''the involuntary leakage of urine on exertion, sneezing or coughing'', is present in 10-39% of women[8,9]. Although there are multiple treatment modalities like physical therapies, pessaries and bulking agents, MUS surgeries have become standardized surgical techniques for the treatment of SUI[10]. The long-term satisfaction success rates of MUS surgeries are as high as 80%[11]. MUS is as valid as retropubic colposuspensions and pubovaginal slings. However, MUS is more advantageous because of shorter operation times and lower complication rates[12].

In the historical background, different parameters such as insertion of the pubococcygeal muscle at the level of midurethra, urethral hypermobility, the suburethral hammock are accepted as the pathophysiological explanations of SUI[13]. According to the integral theory, pubourethral ligaments, the pubococcygeus muscle, and the suburethral vaginal hammock maintain the continence. The failure of any of these components results in incontinence[3]. The maximal urethral closure in a continent woman is obtained at the midurethra. Understanding the importance of the midurethra had brought the identification of midurethral sling surgeries[14]. The success of MUS surgeries has been verified in the literature[15].

The term "midurethra" defines the mid one-third of the urethral length anatomically. The aim of placing a mesh during the MUS surgery is to emplace the mesh under the mid one-third of the urethra. For a satisfactory result, this is obligatory. In this study, the postoperative location of the mesh was investigated by TLUSG in cases with successful results, and patients with favorable surgical results were examined to clarify whether all the meshes are in the boundaries of the anatomic midurethra or not.

According to the results of this study, the midpoint of the mesh was at the exact midpoint of the urethra without any deviation only in six patients and was deviated in 66 patients. Despite the deviation from the midpoint of the anatomic midurethra, meshes were in the borders of the anatomic midurethra in 41 patients. The mesh was found to be partially slipping out of the anatomic mid-urethral borders at different rates in a total of 25 patients. When the partial slipping of the mesh was calculated from distal or proximal edges of the anatomic midurethra, distal slipping was 2.1-26.7% (mean: 13.2±7.6), and proximal slipping was 2.4-30% (12.3±11) of the midurethral lengths of patients. Although the mesh in these patients was exiting the borders of the anatomic midurethra, the results of the surgeries were successful. It is understood that the surgical midurethra may be longer than the anatomic mid-urethra.

The location of the midurethral sling can affect the results of the surgical treatment of SUI[16]. It has been reported in the literature that slings located too proximal to the bladderneck can cause failure. In this study, the mesh locations of successful cases were examined, and the number of unsuccessful cases is not sufficient for a comparison of the mesh locations of successful and unsuccessful cases. Therefore, a cutoff value can not be determined for the borders of the surgical mid-urethra, but it can be concluded that it is longer than the anatomic mid-urethra.

According to the integral theory, urethral hypermobility is one of the causes and important factors of SUI[3,17]. There are some methods to evaluate the urethral mobility. Q-Tip test, visual urethral mobility examination, and pelvic ultrasonography are some of them[18-20]. Changes in retrovesical or posterior urethrovesical angle on TLUSG can define the urethral mobility[21]. In this study, we examined the difference of the urethrovesical angles between resting and Valsalva with TLUSG, postoperatively. There was no correlation between the difference of the urethrovesical angles (rest and Valsalva) and the deviation percentage of the midpoint of mesh from the midpoint of the urethra proximally or distally in patients with satisfactory results after MUS surgery. In the literature, it is advocated that urethrovesical angle does not indicate the urethral mobility, and the urethral motion profile is a better way to assess the urethral mobility[22,23]. The posterior urethrovesical angles were not evaluated with TLUSG before the surgeries, and the comparison of the improvement of urethrovesical angle difference could not be assessed in this study.

Nineteen patients had mixed urinary incontinence preoperatively. These patients were evaluated with urodynamic studies preoperatively. Both urge and stress incontinence improved in eight of these patients after MUS. The mechanism of MUS is to improve the urethral occlusion. As mentioned in the literature, stress induced urgency may heal after MUS, and this is the explanation of the improvement of urge incontinence after MUS[24].

During a TOT surgery, an objective calculation is not performed in the course of the positioning of the mesh under the mid one third of the urethra, and the mesh is placed with a sense of proportion by the surgeon. In this study, the mesh was found to be partially slipping out of the anatomic mid-urethral borders at different rates in a total of 25 patients. Although the mesh in these patients was exiting the boundaries of the anatomic midurethra, the results of the surgeries were successful.

CONCLUSION

In this study, the distribution of the zone where the mesh is localized shows that to achieve a successful result, the targeted anatomic region of the urethra is longer than the mid one-third of the urethra. This study is an anatomic definition study. It is more accurate to categorize the mid-urethra as anatomic and surgical. The number of unsuccessful cases was not sufficient for a comparison of the mesh locations of successful and unsuccessful cases. Therefore, a cutoff value could not be determined for the borders of the surgical mid-urethra.

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Conflict of interest: None

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Original Article

Relationship between laterality and clinicopathological characteristics in patients with breast cancer: A retrospective cross-sectional study

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ABSTRACT

Objectives: To compare the incidence of right- and left-sided breast cancer (BC) according to the age at diagnosis, sex, involved quadrants, grade, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) status.
Design: A retrospective cross-sectional study
Setting: A tertiary university hospital in Riyadh, Saudi Arabia
Subjects: We included 142 patients diagnosed with invasive breast carcinoma between January 2017 and December 2018.
Interventions: No intervention was performed.
Main outcome measures: Demographic data were collected from the hospital's medical records. Information on the diagnoses and ER/PR/HER-2 status was obtained by reviewing the patients' histopathological and immunohistochemistry reports, and the fluorescence in situ hybridization (FISH) report for the HER-2 patients, respectively.
Results: Unilateral and bilateral BCs were detected in 93% and 7% of the patients, respectively. Overall, 74 (52%) patients had left-sided and 58 (41%) had right-sided BC. The age range in both groups was 45-54 years. Both right-sided (53%) and left-sided (46%) BCs were most common in the upper outer quadrant. Surprisingly, all HER-2 equivocal cases on immunohistochemistry that were amplified on FISH were left-sided BCs. There was no significant relationship between laterality and tumor grade. Compared to right-sided and bilateral tumors, left-sided tumors were more likely to be ER-negative, PR-negative and HER-2-negative.
Conclusions: Newly diagnosed BC patients could have both left and right-sided BC. Interestingly, all equivocal HER-2 cases on immunohistochemistry that were amplified on FISH were left-sided BCs. Hence, the primary tumor location may be considered when systematically evaluating and screening BC patients.

KEY WORDS: breast cancer, incidence, invasive ductal carcinoma, tumor location

INTRODUCTION

Breast cancer is one of the most frequent cancers in women worldwide, including in Saudi women, with a prevalence of 21.8%[1,2]. Globally, it is the ninth leading cause of cancer-related deaths according to the most recent survey of cancer-related mortalities[3]. Ibrahim *et al* predicted that over the next few decades, the breast cancer rate in Saudi Arabia will substantially increase as the cancer burden grows[4]. This predicted increase can be attributed to the growth and aging of the Saudi population. In 2010, 1,473 (27.4%) of the 5,378 incident cancer cases in Saudi Arabia were breast cancers. Further, it the most common newly diagnosed malignancy in Saudi women, with approximately 930 new cases annually[1,5]. The continuous increase in the incidence of breast cancer-related death is partly due to late detection and an advanced stage at presentation. Thus, screening and early diagnosis of breast cancer remains a critical issue among young Saudi women.

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It has been consistently reported that women are more likely to be diagnosed with cancer in the left breast than in the right[5-10]. Although the consistency of this finding may reflect etiologic factors that are not yet recognized or understood, it already has important clinical implications which guide the public to focus on the highly prevalent site of breast cancer during self-examination. Hence, the primary tumor location must be taken into consideration while systematically evaluating patients with breast cancers.

Radiation therapy has been found to be useful in reducing the necessity of mastectomies. However, the mortality risk in breast cancer patients treated with radiotherapy has increased because of ischemic heart disease, with cardiac deaths occurring more frequently in patients with left-sided breast cancers[11,12]. This study aimed to compare the incidence of right- and left-sided breast cancer in relation to the age at diagnosis, sex, involved quadrants, grade, expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) status.

SUBJECTS AND METHODS

This was a retrospective cross-sectional study carried out in a university tertiary hospital. We reviewed the medical records of all breast cancer patients who were newly diagnosed between January 2017 and December 2018. A total of 373 patients were excluded because of non-invasive cancer diagnoses, other non-carcinoma histology or unspecified malignancy. Data on the age at diagnosis, sex, laterality of breast cancer, involved quadrants, grade, and hormonal and HER-2 status were collected for 142 invasive breast carcinoma patients. The researchers were blinded to the histopathological data, comprising routine hematoxylin and eosin-stained slides and immunohistochemically stained slides for analyzing the expression of ER (ER: SP1; rabbit monoclonal primary antibody; Ventana), PR (PR: 1E2; rabbit monoclonal primary antibody; Ventana), and HER-2/neu (HER-2/neu: 4B5; rabbit monoclonal primary antibody; Ventana). The results of the immunohistochemical staining were evaluated and scored according to the American Society of Clinical Oncology/College of American Pathologists' guidelines[13,14]. Fluorescence in situ hybridization (FISH) was performed for all HER-2/neu-equivocal cases.

Categorical variables were summarized as frequency counts and percentages. The chi-square test was used to compare the relationship between right- and left-sided breast cancers with the other variables. All statistical analyses were performed using SPSS® version 15 (SPSS Inc., IBM, Armonk, NY, USA). A *P*-value <0.05 was considered statistically significant.

This study was approved by the relevant Institutional Review Board. The need for informed patient consent was waived due to the retrospective nature of this study. None of the patients could be identified in the course of the study or through the publication of results.

RESULTS

Patient characteristics

Overall, 132 (93%) and 10 (7%) patients had unilateral and bilateral breast cancer, respectively. Further, 74 (52%) patients had left-sided breast cancer, and 58 (41%) had right-sided breast cancer. The left to right laterality ratio (LRR) was 1.26, with no significant difference (*P*=0.740). Of the 142 patients, two were men and both had unilateral male breast cancer. One had left-sided breast cancer and the other one had right-sided breast cancer (LRR of 1.00). Of the 140 women, 130 had a unilateral disease; 73 (56.2%) had left-sided breast cancer and 57 (43.8%) had right-sided breast cancer (LRR of 1.28).

Relationship between laterality and clinicopathological characteristics

Surprisingly, all HER-2 equivocal cases on immunohistochemistry amplified on FISH were left-sided breast cancer cases. There was no significant difference in the age at diagnosis between the patients with left-sided and right-sided breast cancers. Both left-sided (37%) and right-sided (29%) breast tumors had the highest incidence among patients aged 45–54 years (*P*=0.640 and *P*=0.052, respectively). Both left-sided (46%) and right-sided (53%) breast cancers were also most frequent in the upper outer quadrant with no significant difference in the tumor

Table 1: Hormone receptor and HER-2 status based on the breast tumor location

Variable	Location			*P*-value
	Right-sided n (%)	Left-sided n (%)	Bilateral n (%)	
ER expression				0.872
Positive (n = 109)	44 (40.4)	59 (54.1)	6 (5.5)	
Negative (n = 30)	13 (43.0)	16 (53.0)	1 (4.0)	
PR expression				0.967
Positive (n = 93)	38 (40.9)	50 (53.8)	5 (5.4)	
Negative (n = 46)	19 (41.0)	25 (54.0)	2 (5.0)	
HER-2 status				0.172
0 (n = 43)	16 (37.0)	25 (58.0)	2 (5.0)	
1+ (n = 33)	14 (42.4)	14 (42.4)	5 (15.2)	
2+ (n = 37)*	15 (40.5)	22 (59.5)	0 (0)	
3+ (n = 26)	12 (46.2)	13 (50.0)	1(3.8)	

ER: estrogen receptor; PR: Progesterone receptor; HER-2: human epidermal growth factor receptor 2

*Equivocal HER-2 breast cancer cases were further evaluated using fluorescence in situ hybridization. Five cases were amplified, all of which were left-sided tumors.

location between both groups (*P*=0.50). There was no significant relationship between laterality and tumor grade (*P*=0.60), although patients with bilateral breast cancers were more likely to have advanced tumors (60%) than those with left-sided (51%) or right-sided (49%) breast cancers. Compared to patients with right-sided or bilateral tumors, those with left-sided tumors were more likely to have ER-negative (53%, 43% and 4%, respectively), PR-negative (54%, 41% and 5%, respectively), and HER-2-negative (58%, 37%, and 5%, respectively) tumors. However, none of these differences were significant (*P*=0.872, *P*=0.967 and *P*=0.172, respectively) (Table 1).

DISCUSSION

This retrospective analysis indicated that left-sided breast cancers were 11% more common than right-sided ones. A study on laterality conducted in the United States between 1973 and 2010, comprising approximately 1.2 million patients in the Surveillance, Epidemiology and End Results program suggested that left-sided breast cancer has been predominant for several decades[15]. Our results support this trend on a smaller and a more limited scale. Surprisingly, all the cases of equivocal HER-2 on immunohistochemistry that were HER-2 amplified on FISH were left-sided breast cancer cases. Previous studies have shown that left-sided breast cancers were more frequently identified than right-sided breast cancers by a marginal 5%, regardless of race/ethnicity, age or stage at diagnosis[1,5,16]. It is evident from various studies that left breast tumors are more common than right breast tumors[1,5,16]. This may be attributed to the fact that the left breast is usually larger than the right one as argued by Sughrue and Brody. However, this does not explain variations in the laterality ratio among breast quadrants[16]. Alternatively, this predominance raises the possibility of breastfeeding side preferences by mothers. This could explain why the laterality ratio among women was greater than one in our study, whereas that among men was exactly one[16]. Another potential explanation is that right-handed women tend to check for tumors in their left breasts more frequently[17].

This study did not examine the relationship between breast cancer and immune functions. Therefore, the role played by the immune system still needs to be analyzed since immune functions diminish with increasing age. In this study, patients aged between 45 and 54 years accounted for majority of the patients diagnosed with left-sided breast cancers (37%) and right-sided breast cancers (29%). Hence, middle-aged patients are more likely to develop breast cancer than any other age group in our population in accordance with previous reports[1,2,5].

Regarding the involved quadrant, the upper outer quadrant was the most commonly involved quadrant in both left-sided (46%) and right-sided (53%) tumors, with no significant difference in tumor location. Although tumor location is not a proven prognostic factor of cancer-specific survival, several studies have concluded that tumors in the medial and lower sites of the breast were related to poor survival outcomes[18,19]. In addition, breast cancer location is an important factor in predicting metastasis. Although the internal mammary chain involvement is not routinely investigated for lymph node metastasis from breast cancer, undetected involvement of these lymph nodes contributes to higher mortality rates, even in early-stage breast cancer[18,19]. Furthermore, internal mammary chain metastasis depends on the tumor location within the breasts. A higher prevalence of internal mammary chain metastasis was noted in tumors of the internal half of the breasts, especially in those in the lower internal quadrant[20]. There was no significant relationship between laterality and breast cancer grade (*P*=0.60). However, patients with bilateral breast cancers tended to have more advanced tumors (60%) than those with left-sided (51%) or right-sided (49%) breast cancers. This could be because bilateral breast cancers tend to be discovered late or ignored by the patient, resulting in more advanced disease at presentation. In terms of hormonal receptors and HER-2 status, left-sided tumors were more likely to be triple negative tumors than right-sided or bilateral tumors.

This study has limitations; its sample size was small, and it was a single center study. Additional prospective studies on the laterality of breast cancer at our institution and other institutions are needed to validate our results and explore associations between tumor sidedness and clinicopathological factors.

CONCLUSION

All equivocal HER-2 cases on immunohistochemistry that were HER-2 amplified on FISH were left-sided breast cancer cases. This could change the management of breast cancer. There were no significant differences in age at diagnosis, sex, involved quadrants, grade, expression of hormonal receptors, or HER-2 status between the right- and left-sided breast cancer patients.

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Original Article

Outcomes of retrograde intrarenal surgery after previous SWL failure

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ABSTRACT

Objectives: To evaluate whether previous shock wave lithotripsy (SWL) failure affects the outcomes of retrograde intrarenal surgery for renal pelvis stones between 1-2 cm or not
Design: Retrospective study
Settings: Tertiary University Hospital
Subjects: Eighty-seven patients with renal pelvis stones between 1-2 cm
Intervention: Shock wave lithotripsy and retrograde intrarenal surgery was performed for renal pelvis stones.
Main outcome measures: In group 1, all patients were primary cases, and in group 2, SWL treatment had been performed to all patients and had failed. The medical records were assessed on the aspect of primary and secondary end points of the study. The primary end point of this study was the surgical success rate on the first postoperative day. Secondary end points were fluoroscopy time, lithotripsy duration and time of the surgery peroperatively, and the surgical success and stone-free situation at the end of the first month, postoperatively.
Results: The mean lithotripsy duration was significantly longer in group 2 (35.06±4.40 min; P <0.05). Surgical success was obtained in 45 (88.2%) patients in group 1 and in 30 (83.3%) patients in group 2 (P=0.51). The stone-free rates were 94.1% and 91.7% in groups 1 and 2 respectively one month after the procedures (P=0.65). The fluoroscopy time was significantly longer in group 2 (P <0.01).
Conclusion: It has determined that SWL failure results in a longer duration of surgery, longer fluoroscopy time, and does not affect the surgical success of retrograde intrarenal surgery.

KEY WORDS: kidney stone, retrograde intrarenal surgery, SWL failure

INTRODUCTION

Today, minimally invasive surgery has been used routinely in the treatment of renal stones with high success rates. High success rates of shock wave lithotripsy (SWL), percutaneous nephrolithotripsy (PCNL) and retrograde intrarenal surgery (RIRS) have been proven in a number of studies[1].

A diameter of 20 mm is the accepted critical size for a kidney stone for the selection of treatment procedure. Sequence of treatment recommendations for all kidney stones except the lower pole stones are firstly SWL, and secondarily endourological procedures.

In the case of unsuccessful results with interventions, a second treatment session can be planned with either the same approach or using another treatment. RIRS is usually used in the treatment of renal stones smaller than 20 mm[2]. This approach can be used in primary cases as well as unsuccessful cases after PCNL or extracorporeal SWL, or in the case of residual fragments after treatment.

Although the shock waves are focused on the stone during SWL, the surronding tissues may also be affected. This may cause the impaction of the stone, and it inceases the fragility of the surronding epithelium. In this study, we evaluate whether previous SWL affects the outcomes of RIRS for renal pelvis stones between 1-2 cm or not.

SUBJECTS AND METHODS

A total of 87 patients with renal pelvis stones between 1-2 cm were treated via RIRS at the Department of Urology, Medicine Faculty of Ahi Evran University

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between April 2014 and June 2016. After ethics board approval, patients' medical records were reviewed retrospectively.

Patients younger than 18-years-old, with a history of open or endosurgical intervention from the same renal unit, with calyx stones or renal pelvis stones <10 mm and >20 mm were excluded from the study. Double-J catheter inserted patients for passive dilatation of the ureter before the surgery were also excluded. Primary cases and patients with a history of SWL failure with a renal pelvis stone between 10 and 20 mm were included in this study.

Patient groups, patient and stone size evaluation

Consecutive patients were divided into two groups. In group 1, all patients were primary cases and did not have any intervention for the stone, and in group 2, SWL treatment had been performed on all patients and had failed. There were 51 and 36 patients in groups 1 and 2, respectively.

All patients were evaluated through urine analysis, urine culture, blood biochemical parameters, a plain abdominal radiograph of the kidney-ureter and bladder (KUB) and non-contrast abdominal computerized tomography (CT) before surgery. The stones above the ureteropelvic junction (UPJ) and in the renal pelvis were accepted as the renal pelvis stone. The localization, length, width and depth of the stone and hydronephrosis were all assessed on abdominal CT. Stone size was measured for the greatest length, width and depth on abdominal CT preoperatively. Stone volume was calculated using an ellipsoid algebra formula ($\pi \times$ length $\times$ width $\times$ depth $\times$ 0.167)[3]. Skin-to-stone distance was measured as defined by Pareek G *et al*[4]. Largest cross-sectional stone area was used to measure the stone density on CT (Hounsfield units (HU)). Radiological assessment was performed by a radiologist.

Patients were reevaluated on the first postoperative day and one month after the surgery with KUB films and ultrasonography for detecting the residual stone fragments and hydronephrosis. Patients with residual fragments >3 mm were accepted as a surgical failure. Patients with stone-free status or with residual fragments ≤3 mm were accepted as surgical successes. The primary end point of this study was the surgical success rate on the first postoperative day. Secondary end points were fluoroscopy time, lithotripsy duration and time of the surgery peroperatively and the surgical success and stone-free situation at the end of the first month postoperatively.

SWL and surgical technique

SWL was performed with a shock wave lithotripter (MULTIMED ClassicTM, ELMED, Turkey) system by a staff urologist. Diclofenac sodium 75 mg/3 ml was injected intramuscularly to the patients for the analgesia before the procedure. Antibiotic prophylaxis was not used regularly. 3000 (1.0-1.5 Hz) shocks were performed under fluoroscopic guidance for each patient for one session routinely. Localization control of the stone was performed after every 500 shocks. Ultrasound gel was used for acoustic coupling regularly. SWL failure was defined as the absence of any change on the stone on KUB radiograph after SWL. Patients were considered to have SWL failure if the stone was not fragmented at the end of one week after the third session.

The surgeries were performed by the same surgical team. After administering a prophylactic wide spectrum antibiotic, a semirigid ureteroscopy was conducted on all patients under general anesthesia. Semirigid 7.5 and 9.5 Fr ureterorenoscopes (Richard Wolf, Knittlingen, Germany) were used for ureteroscopy to visualize and dilate the ureter under lithotomy position. Two different hydrophilic guidewires were inserted during semirigid ureterorenoscopy into the renal pelvis under multidirectional C-arm fluoroscopy; one for insertion of ureteral access sheath and the other for safety. In the case of stone impaction, the hydrophilic guidewire was left under the stone in the upper ureter. Ureteral access sheath (inner diameter 9.5 Fr and 35-45 cm) was routinely inserted into the renal unit under fluoroscopy before flexible ureterorenoscopy. It was left in the upper ureter and was not passed UPJ. Ureteral orifice dilatation with a balloon dilatator was not routinely performed, but used when it was necessary. We used continuous irrigation with 0.9% NaCl and a manual irrigation pump system when there were difficulties in maintaining the visualization. 272 μm reusable laser fibers were used with holmium:YAG laser (Sphinx 30 Minimally Invasive Surgical Laser, LISA laser, Pleasanton, CA, USA) lithotripter and the lithotripsy was performed with 0.5J/20Hz for dusting and 1J/30 Hz for popcorn settings in both groups. A 7.5 Fr flexible ureterorenoscope (FlexX2, Karl Storz, Tuttlingen, Germany) was used for RIRS. Eventually, a double-J catheter was placed for two to four weeks. Finally, patients were re-evaluated on the day and one month after the surgery.

Statistical analysis

Statistical Package for Social Sciences version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA) were used for statistical analysis. The results were given as mean±standard deviation. Normality of distribution was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Kurtosis and Skewness values were also analyzed. In this study, Pearson's Chi-squared

test was used for the comparison of categorical values. Independent samples t-test was used for the analysis of the normally distributed parametric data. P <0.05 was considered as statistically significant.

RESULTS

The baseline data and clinical characteristics

The baseline data and clinical characteristics of this study are given in Table 1. The groups were similar in both age (P=0.65) and gender (P=0.50; Table 1).

The mean stone area was 1.64±0.75 cm^2 in group 1 and 1.59±0.64 cm^2 in group 2. There was no statistically significant difference between the groups regarding the area of the stone (P=0.74). The mean stone burden was 1.06±0.65 cm^3 in group 1 and 1.08±0.68 cm^3 in group 2. There was no difference between the groups for stone burden (P=0.87). The time interval between SWL and RIRS was 13.4±3.5 days. The skin-to-stone distance was 11.5±2.1 cm in group 2. The stone density was 782±150 HU and 824±130 HU in groups 1 and 2 respectively (P=0.178).

Primary and secondary endpoints

Surgical success was obtained in 45 (88.2%) patients in group 1 and 30 (83.3%) patients in group 2. Although the success rate was higher in group 1, the difference between the groups was not statistically significant (P=0.51). The stone-free rates were 94.1% and 91.7% in groups 1 and 2 respectively, one month after the procedures (P=0.65).

It was determined that stone size was statistically significant for surgical success in both groups (P <0.01). There were impacted stones in three (5.9%) patients in group 1 and 11 (30.6%) patients in group 2 (P <0.01).

The mean lithotripsy duration was 32.25±5.92 min in group 1, and it was significantly longer, 35.06±4.40 min in group 2 (P <0.05). The mean duration of the surgery was 74.21±6.83 min in group 1, and 74.91±6.25 min in group 2, without any significant difference in between (P=0.62). The fluoroscopy time was 95.49±19.01 sec in group 1, and 116.16±26.13 sec in group 2. The difference between the groups was statistically significant (P <0.01).

Residual stone fragments were seen in 19 (37.3%) patients in group 1, consisting of 13 (25.5%) patients with clinically insignificant, six (11.8%) patients with clinically significant fragments. In group 2, a total of 12 (33.4%) patients had residual stones, consisting of six (16.7%) patients with clinically insignificant, and six (16.7%) patients with clinically significant fragments.

Table 1: Baseline data and clinical characteristics

Baseline data and clinical characteristics	Group 1	Group 2	P
Gender (n)			0.50
Male	28 (55%)	18 (50%)	
Female	23 (45%)	18 (50%)	
Total	51	36	
Age (years)			0.65
Male			
min	27	27	
max	64	72	
Mean±SD	44.6±10.8	44±13.2	
Female			
min	26	28	
max	77	70	
Mean±SD	45.2±13.2	47.3±13.2	
Stone size (mm^3)			0.87
Stone volume (mm^3)	0.27-2.93	0.42-3.77	
min-max (mean±SD)	(1.06±0.65)	(1.08±0.68)	
Surgical success rates in groups [n(%)]			
Successful	45 (88.2%)	30 (83.3%)	0.51
Unsuccessful	6 (11.8%)	6 (16.7%)	0.51
Auxillary procedures for clinically significant fragments [n(%)]			0.65
Extracorporeal shock wave lithotripsy	1(2%)	-	
Retrograde intrarenal surgery	2(3.9%)	3(8.3%)	
Total	3(5.9%)	3(8.3%)	
Spontaneous passage	3(5.9%)	3(8.3%)	
Lithotripsy time (min)			<0.05
Mean±SD (min-max)	32.25±5.92 (20-50)	35.06±4.40 (25-45)	
Operation time (min)			0.62
Mean±SD (min-max)	74.21±6.83 (62-90)	74.91±6.25 (68-88)	
Fluoroscopy time (sec)			<0.01
Min-max (Mean±SD)	60-142 (95.49±19.01)	79-182 (116.16±26.13)	
Postoperative 1st month stone free rates	94.1%	91.7%	0.65

All patients that had clinically insignificant stones in study groups were stone free, one month after surgery. When clinically significant stones were taken into consideration, it was determined that three (5.9%) patients were stone-free in group 1, and three (8.3%) patients were stone-free in group 2, one month after surgery.

Complications

One (2%) of three patients with treatment failure after one month had SWL, and two (3.9%) had re-do RIRS in group 1, and all three (8.3%) patients with treatment failure had re-do RIRS in group 2.

Minor postoperative complications such as postoperative fever, bleeding not requiring transfusion, and laceration were seen in eight (15.7%) patients in group 1, and in seven (19.4%) patients in group 2. The groups were similar for complication rates (P=0.64). None of the patients had a more severe complication than a Clavien-Dindo grade II.

The mean hospital stay was 23.94±10.26 hours in group 1 and 25.88±12.39 hours in group 2 (P=0.42). The mean follow-up periods were 7.4±3.3 and 7.6±3.4 months in groups 1 and 2, respectively.

DISCUSSION

Renal stones had been treated with quite invasive methods in the past. However, currently, renal stones are being successfully treated with minimally traumatic surgical approaches. Percutaneous nephrolithotomy, RIRS and SWL are minimally invasive techniques that are being performed successfully in the treatment of renal stones. The cutoff value for planning minimally invasive surgery for the treatment of renal stones has been determined as two cm[5]. Treatment approach is determined regarding the size and the localization of the stone. Currently, the technological facilities of the clinics may be regarded as a parameter to choose the treatment option. The presence of different treatment options and their high success rates force both patients and surgeons to use the least damaging minimally invasive surgery in the treatment.

In the case of treatment failure with the initial treatment option, either the same treatment option or the others are used for second-line or salvage treatment. Obesity, stone density, calculus size and hydronephrosis are the risk factors for SWL failure[6]. It has been reported that SWL may fail if the body mass index of the patient is over 30 kg/m^2, and the stone density is greater than 800[7-9]. Stone-skin distance is another predictor of SWL failure[10]. In group 2, the skin-to-stone distance was 11.5±2.1 cm and the stone density was 824±130 HU. The threshold of the stone-skin distance was argued in the literature. A stone-to-skin distance >9 - 10 cm is a cutoff measure for predicting the SWL failure[11]. A calculus >750 HU is 10.5 times more prone to need ≥3 SWL sessions[4]. Patient compliance, skin-to-stone distance and the stone density are possible causes of the failure of SWL in group 2.

Although the shock waves are focused on the stone during SWL, they may affect urothelium, kidney parenchyma and other surrounding tissues. In this instance, the stones may get impacted into the affected urothelium after SWL failure, and the edema that occurs in the epithelium may cause increased fragility of the tissues. RIRS and PCNL are treatment alternatives for patients that had failure after SWL. In the literature, it has been reported that SWL failure does not have any adverse effect on a subsequent PCNL treatment[12,13]. RIRS is the other treatment option in case of SWL failure. However, does impaction of the stone during SWL, and formation of edema in urothelium and increased the fragility of the tissues affect the outcomes of RIRS for renal pelvis stones between 1-2 cm after SWL failure?

RIRS has taken its place among the second-line treatment options in the treatment of renal stones smaller than two cm in size owing to its successful outcomes and low complication rates[14]. Success rates of RIRS have been reported between 65% and 96% in the literature[15,16]. The discrepancy in the success rates may be related to the presence of patients with renal abnormalities among the patients included in the studies, and variations in the size and the numbers of the stones. In this study, the success rates were 88.2% in group 1 and 83.3% in group 2. Although the success rate was lower in the group that had RIRS after SWL failure, the difference between the groups was not statistically significant. A study published in 2006 reported that success rates were lower, complication rates were higher, and hospital stay was longer in patients that had RIRS after SWL failure[17]. In our study, we did not find any significant difference between two groups for success rates, complication rates or hospital stay. It was determined that the stones failed after SWL treatment were impacted more frequently. This situation could complicate the situation for reaching the renal unit or resulted in poor vision quality when RIRS was performed subsequently in those patients.

Impacted stones are defined as the stones that stay unchanged in the same position, do not let a guide-wire to pass calculus, and cause obstruction with non-visualization of the contrast on the other side of the stone on intravenous urography[18]. In this study, the absence of any passage to the proximal side of the stone under fluoroscopy or direct vision, and inability to move the stone on renoscopy were regarded as impacted stone. There are five sites along the upper urinary tract where stones are more prone to become

impacted. These sites are minor and major calyx system, pelviureteric junction, the iliac crossing of the ureter, ureterovesical junction and vesical orifice. In our study, the position of the stones was determined by an experienced radiologist and the impacted stones were extending to the pelviureteric junction and the UPJ was the impaction site. There were impacted stones in 5.9% of the patients in group 1 and in 30.6% in group 2. The shock wave spreads in the fluid around the stone and generates a peripheral force on the calculus. This force causes a tensile stress in the stone. Furthermore, this force influences the surrounding tissues. It has been reported that there may be acute histological changes such as fibrosis, diffuse interstitial fibrosis, calcium and hemosiderin deposits after SWL[19]. Although those histopathological changes that occur after SWL might have caused impaction of the stones in the case of an SWL failure, it may be that impacted renal stones are less likely to respond to SWL. Further studies are needed to understand this. High impacted stone rate and impaired vision caused a significantly longer fluoroscopy time in group 2 (P <0.01).

The quality of vision is essential for a safe and effective surgery in flexible renoscopy. The factors that affect the quality of vision are the use of a flexible digital renoscope, good circulation of irrigation fluid, bleeding, the settings of the laser used for fragmentation (dusting (0.5J / 20Hz), and popcorn-effect/laser-burst (1J / 30Hz). According to morphologic studies, shock waves can rupture blood vessels and harm surrounding renal tubules during SWL[19]. The mean duration for fragmentation of the stone was 32.25±5.92 min in group 1 and 35.06±4.40 min in group 2. This may be due to the fragility of the renal tissues owing to SWL, bleeding during surgery due to this weakness and resulting in impaired vision, and adhesion of the stone to the surrounding structures.

Important complications including severe ureteral complications, sepsis, bleeding and perforation have been reported after RIRS in the literature. It was found that the lithotripsy duration was longer, and impacted stone rate was higher in patients that had RIRS after SWL. It was determined that a longer lithotripsy time, higher impacted stone rate, and easier deterioration of the vision quality did not increase complication rate in this group. The groups were not different for complication rates, and none of the patients had a complication more severe than the Clavien-Dindo grade II, in groups.

SWL failure results in impaired vision and a longer duration of surgery during RIRS. Also, it results in a longer fluoroscopy time for RIRS. Although the histopathological changes that occur after SWL might have caused impaction of the stones in the case of an SWL failure, it may be that impacted renal stones are less likely to respond to SWL.

Limitations of this study were the retrospective design and a relatively small sample size.

CONCLUSON

In this study, it has determined that SWL failure does not affect the surgical success of the RIRS. RIRS can be performed safely to the renal pelvis stones between 1-2 cm after SWL failure.

Compliance with ethical standards

This study has been performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The authors' have no financial disclosure for this study. Informed consents were obtained from all participants included in the study.

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Conflict of interest: None

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Original Article

Causes of lethal blunt injuries: Autopsy study

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ABSTRACT

Objective: To investigate the cause of blunt traumatic death and the injury profile that may contribute to the medical interventions
Design: Retrospective study
Setting: Firat University, School of Medicine, Elazig, Turkey
Subject: Patients (n=368) who had died due to blunt trauma for three years and who had undergone autopsy were included in the study.
Intervention: None
Main outcome measures: Demographic data, injury mechanism, detailed injury profile, medical records, autopsy report, Injury Severity Score (ISS) and Revised Trauma Score (RTS), cause of death and place of death were recorded. Preventable deaths were determined by using World Health Organization criteria.
Results: Mean age of the patients was 44.7±23.3 years and the majority were male (78.8%). Mean ISS was 38.1±13.9; mean RTS was 3.9±2.6. The most common cause of death was multiple fatal injuries (40.5%), followed by head trauma (32.1%) and hemorrhage (17.1%). Half of the deaths (49.7%) occurred at the site or within the first one hour and 64.7% of the patients died within the first 24 hours. The total preventable/potentially preventable mortality rate was 12.8%, and the most common cause of these deaths was hemorrhage.
Conclusions: In our study, we found that fatal blunt traumas were mostly caused by traffic accidents, and half of the patients died at the scene or within the first hour after trauma. The most common cause of blunt traumatic deaths was multiple fatal injuries, whereas hemorrhage was the leading cause of preventable deaths.

KEY WORDS: injuries, non-penetrating, postmortem examination

INTRODUCTION

In particular, traumas are the primary cause of death in the young population and continue to be one of the most important causes of death and disability worldwide[1-3]. Detecting the cause of traumatic deaths and preventable deaths contributes to the reduction of mortality and morbidity due to trauma as well as improving trauma care[4]. Detailed information about the injury profile and cause of death can be obtained from traumatic deaths occurring within the hospital. However, a significant portion of traumatic deaths occur before the patients are hospitalized[5-7]. The autopsy after traumatic deaths provides detailed information about the type and the severity of the injury, and the cause of death[4]. Research published on this subject generally focuses on the deaths during the transfer to the hospital and in the hospital, while there are only limited studies which evaluate the mortality at the scene of death[8]. In our study, we aimed to contribute to the medical interventions by investigating the cause of death and the injury profile in the death scene, emergency service, intensive care unit, operating room and hospital wards for a three-year duration.

MATERIALS AND METHODS

Local ethics committee approval was obtained for the study (2018:03-11). All patients who died due to blunt trauma and underwent autopsy in the forensic department of our hospital were included in the study during the three years. Autopsy was performed by forensic medicine expert. The data were recorded retrospectively. Demographic data, injury mechanism, detailed injury profile, medical records, autopsy

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Table 1: Definitions of preventability for death

Preventability	Definitions
Preventable death	• Injuries and sequelae considered survivable • Death could have been prevented if appropriate steps had been taken • Frank deviations from standard of care that, directly or indirectly, caused patient's death • Statistically, probability of survival greater than 50%, or Injury Severity Score (ISS) below 20
Potentially preventable death	• Injuries and sequelae severe but survivable • Death potentially could have been prevented if appropriate steps had been taken • Evaluation and management generally appropriate • Some deviations from standard of care that may, directly or indirectly, have been implicated in patient's death • Statistically, probability of survival 25–50% or ISS between 20 and 50
Non-preventable	• Injuries and sequelae non-survivable even with optimal management • Evaluation and management appropriate according to accepted standards • If patient had co-morbid factors, these were major contributors to death • Statistically, probability of survival less than 25% or ISS above 50

report, Injury Severity Score (ISS) and revised trauma score (RTS), cause of death and place of death were recorded. By following the World Health Organization criteria, the causes of death were divided into three groups as preventable, potentially preventable and non-preventable by a committee consisting of emergency physicians and forensic medicine expert (Table 1)[9]. Penetrating trauma, intoxication, hanging, burns and frost-related deaths were excluded from the study. SPSS 22 (SPSS, Inc., Chicago, IL, USA) was used for the data analysis. Descriptive statistics were calculated as mean±SD, median (min-max) or number (percentage) as appropriate.

RESULTS

During the three-year study period, 368 patients met the inclusion criteria. The mean age of the patients was 44.7±23.3 years. Most of the patients were male (78.8%). The majority of fatalities were suffered from a traffic accident. The mean ISS and RTS were 38.1 (min:16, max:75) and 3.9 (min:0, max:7.84), respectively. Alcohol levels were determined in 5.7% of the cases. Table 2 shows the demographic data of all patients and the mechanism of injury.

Table 2: Characteristics of patients and mechanism of injury

Characteristics	n (%)
Patient demographics	
Sex	
Female	78 (21.2%)
Male	290 (78.8%)
Mean age (years)	44.7±23.3
Mechanism of injury	
Motor vehicle accident	151 (41.0%)
Auto versus pedestrian	113 (30.7%)
Fall	75 (20.4%)
Assault	7 (1.9%)
Animal related injuries	7 (1.9%)
Television related injuries	4 (1.1%)
Other	11 (3%)
Alcohol	21 (5.7%)
Mean RTS	3.9±2.6
Mean ISS	38.1±13.9

RTS: Revised Trauma Score; ISS: Injury Severity Score

Table 3: Causes of death of blunt trauma

Causes	n (%)
Multiple lethal injuries	149 (40.5)
Head injury + hemorrhage	126 (34.2)
Head injury + Spinal cord injury	2 (0.5)
Head injury + Airway/ventilation problems	4 (1.1)
Hemorrhage + Airway/ventilation problems	9 (2.5)
Head injury + Hemorrhage + Airway/ventilation problems	8 (2.2)
Head injury	118 (32.1)
Hemorrhage	63 (17.1)
MOF/ARDS/sepsis/PE	33 (8.9)
Spinal cord injury	5 (1.4)

MOF: multiorgan failure; ARDS: acute respiratory distress syndrome; PE: pulmonary embolism

Multiple lethal injuries were the most frequent cause of death, followed by head injury and hemorrhage, respectively. Causes of death are listed in Table 3.

While head trauma was observed in the patients most frequently, it was followed by thorax and abdomen trauma, respectively. Head trauma was present in 78.5% of the patients and 20.1% of them had isolated head trauma. Seventeen of 215 patients with thoracic trauma and four of 159 patients with abdominal trauma had isolated injuries. Table 4 shows the distribution of injury to an anatomical region.

Half of the deaths occurred at the scene or within the first hour after the trauma (n=183, 49.7%). The most common accompanying trauma to the patients who died on the scene or within the first hour was, in order, head (n=147, 80.3%), thorax (n=128, 69.9%) and abdomen (n=104, 56.8%) trauma. The majority of 63 patients with vascular injury (n=58, 84%) died on the scene or within the first hour. The temporal distribution of measurements according to the accompanying trauma is given in Table 5.

Table 4: Distribution of injury to the anatomical region

Anatomic regions	n (%)
Head n (%)	289 (78.5)
Subarachnoid hemorrhage	231 (62.8)
Skull fracture	219 (59.5))
Brain contusion/laceration/hemorrhage	168 (45.7)
Subdural hematoma	124 (33.7)
Brain edema	121 (32.9)
Epidural hematoma	37 (10.1)
Thorax n (%)	215 (58.4)
Rib fracture	202 (54.9)
Lung contusion	170 (46.2)
Hemothorax	151 (41)
Pneumothorax	77 (20.9)
Cardiac injuries	35 (9.5)
Traumatic asphyxia	10 (2.7)
Abdomen n (%)	159 (43.2)
Intraperitoneal hemorrhage	119 (32.3)
Liver	95 (25.8)
Splen	80 (21.7)
Retroperitoneal hemorrhage	43 (11.7)
Renal	21 (5.7)
Diafram	12 (3.3)
Bowel	12 (3.3)
Bladder	6 (1.6)
Stomach	6 (1.6)
Pancreas	2 (0.5)
Extremities n (%)	143 (38.9)
Upper extremity	102 (27.7)
Lower extremity	84 (22.8)
Vertebra n (%)	92 (25)
Cervical	36 (9.8)
Thoracal	48 (13.3)
Lomber	31 (8.4)
Vascular n (%)	69 (18.8)
Thoracic aorta	33 (9)
Abdominal aorta	25 (6.8)
Renal artery/vein	17 (4.6)
Subclavian artery	5 (1.4)
Jugular artery/vein	4 (1.1)
Axillar artery/vein	3 (0.8)
Pulmonary artery/vein	3 (0.8)
Iliac artery	3 (0.8)
Inferior vena cava	2 (0.5)
Splenic artery	2 (0.5)
Femoral artery	2 (0.5)
Portal vein	1 (0.3)
Pelvic ring	51 (13.9)
Spinal cord	49 (13.3)
Neck	39 (10.6)

64.7% (n=238) of the patients died within 24 hours following the trauma. Of the patients who died within the first 24 hours, 180 (75.6%) had head trauma, 166 (69.7%) had thoracic trauma, 134 (56.3%) had abdominal and 65 (27.3%) had a vascular injury.

Died on the scene

One hundred and thirty-nine patients (37.8%) died on the scene. The most common cause of death in the scene was multiple fatal injuries (n=77, 55.4%), followed by head trauma (n=39, 28.1%) and hemorrhage (n=21, 15%). The most common accompanying trauma was traumatic head trauma (n=114, 82%). There were aortic injuries in 28 patients and cardiac injuries in 27 patients. Mean ISS value of the patients was 44.81±15.8.

Died in Emergency Service

Of the 48 patients (13%) who died in the emergency service, 30 were administered as having a cardiopulmonary arrest. Mean ISS of the patients was 38.3±12.8, mean RTS was 0.99±1.9. Twenty patients had multiple fatal injuries, 15 had a hemorrhage, and 13 had died due to head trauma. Thoracic trauma (n=36) was the most common cause of death in the emergency service, followed by head trauma (n=33) and abdominal trauma (n=31). Five patients had an aortic injury, and five patients had a cardiac injury.

Died in hospital

The number of patients who died in the intensive care unit (ICU), operating room (OR) or hospital wards were 181 (49.2%). Thirteen of these patients had a cardiopulmonary arrest in the emergency service and were taken to OR or ICU as a result of the successful resuscitative procedure. Mean ISS value of the patients was 32.9±10; mean RTS was 4.8±2.1. The most common cause of death was the head injury (n=66, 36.5%), followed by multiple injuries (n=52, 28.7%) and multiorgan failure (MOF) / acute respiratory distress syndrome (ARDS) / sepsis / pulmonary embolism (PE) (n=33, 18.2%). The causes of death corresponding to the localization of traumatic deaths are shown in Figure 1.

Table 5: Temporal distribution of deaths associated with accompanying trauma

Time	Head trauma (n)	Thoracic trauma (n)	Abdominal trauma (n)	Vascular injury (n)	Pelvic trauma (n)	Spinal cord injury (n)	Limb trauma (n)
Scene	114	98	79	45	13	26	60
0-1 h	33	30	25	13	3	2	10
1-6 h	24	26	19	3	13	6	18
6-24 h	9	12	11	4	6	2	6
1-3 d	33	17	11	2	6	1	17
3-30 d	71	31	13	2	9	10	29
30 d	5	1	1	0	1	2	3

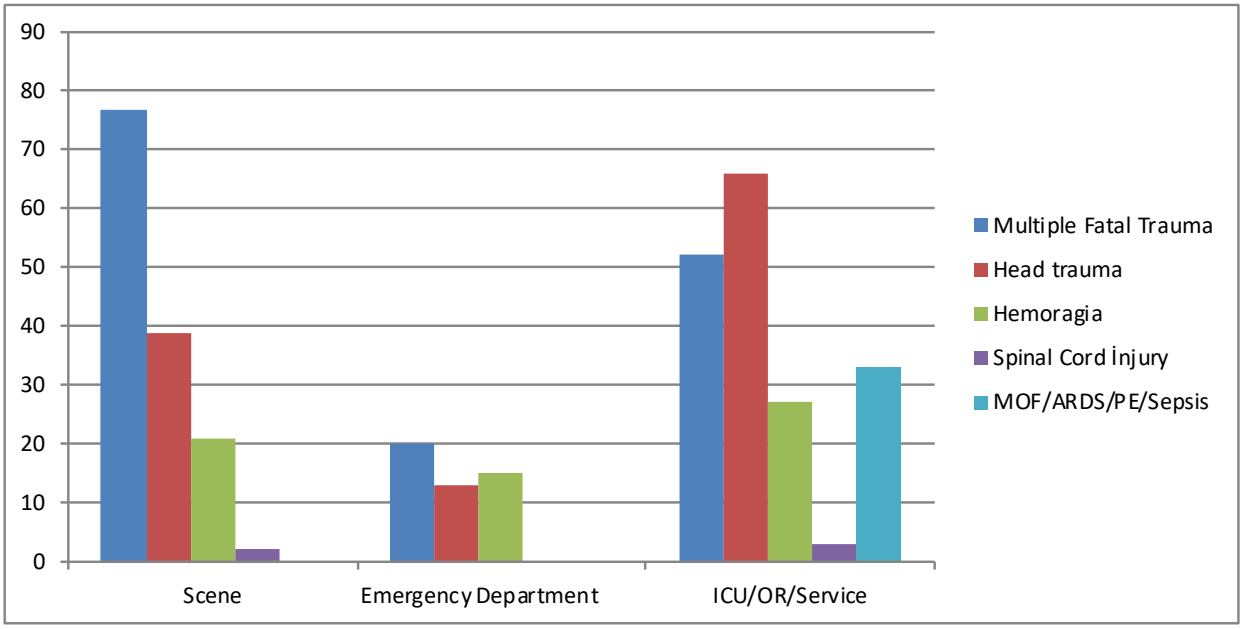

Fig 1: Causes of death in relation to the localization of traumatic deaths

Prevention of deaths

Of the deaths, 87.2% (n=321) were non-preventable deaths, and almost half of them (43.3%) died at the scene. The rate of total preventable/potentially preventable mortality was 12.8% (n=47) (potentially preventable deaths: 11.7%, preventable deaths: 1.1%). Preventable/potentially preventable deaths were most frequently associated with haemorrhage (n=19, 40.4%) and followed by multiple injuries (n=15, 31.9%), MOF / ARDS / sepsis / PE (n=10, 21.3%) and head trauma (n=3, 6.4%). When the mistakes in preventable/potentially preventable deaths are examined, airway obstruction and aspiration were present in two patients with head trauma and one patient with thoracic trauma due to failure in providing adequate airway protection prior to hospitalization. There was an error in the management of three patients who were unstable due to bleeding. Two of these patients were transferred from a different hospital, and one was sent to the radiology unit. Sixteen patients had delay in bleeding control. Three patients had a missed diagnosis in clinical evaluation. Cardiac tamponade in one patient, intracranial hemorrhage in one patient, and intrabdominal injury in one patient were missed diagnosis.

DISCUSSION

Trauma is responsible for more than 5 million deaths worldwide[10] and is still a significant cause of death, despite advances in trauma care[6,11]. It is very important to recognize fatal injuries quickly and to be treated as soon as possible to prevent traumatic deaths.

In this study, the mean age of the patients was 44.7±23.3 years and the majority of the cases were male (78.8%) in accordance with the literature[2,6,12-15]. Mean RTS was 3.9±2.6 and mean ISS was 38.1±13.9. The most common cause of injury was traffic accidents, followed by injuries related to falling. Consistent with our study, the most common cause of trauma in many studies was related to traffic accidents, and it was followed by fall[3,6,12,14,16,17].

In our study, the most common cause of death was multiple fatal injuries, followed by head trauma and hemorrhage. While Gruen *et al*[18] found similar results in our study, central nervous system injuries were the most common cause of death in some studies[5,8,16]. In our study, the majority of multiple fatal injuries were accompanied by central nervous system injuries. Central nervous system injuries are the main cause of death in trauma patients and this is followed by hemorrhage[4,15]. In accordance with the literature, head trauma was the most common injury in 78% of the cases[4,12,16,19]. The second most frequent injury were the injuries of the thorax and abdomen.

Trauma-related deaths are affected by the time and place of the injury, the cause of injury, the age of the person and the injured body area[15]. In our study, half of the patients died within the first hour after the incident and 65% died within the first 24 hours after the trauma. Similarly, most of the deaths were reported within the first 24 hours in the previous studies[6,15]. In our study, 38% of deaths took place on the scene. This rate is affected by many factors such as trauma systems, geographical features, injury severity and injury mechanism. Pre-hospital mortality rate can be as high as 66%[5]. In their studies, Wilson *et al*[2], Durusu *et al*[17] and Eyi *et al*[3] found the rate of death on the scene

as 22.8%, 52.46%, 56.7%, respectively. Furthermore, Søreide *et al*[16] and Kleber *et al*[19] showed that 43% and 59%, respectively, of the deaths due to blunt trauma occurred before the hospitalization. These deaths are usually caused by unsurvivable injuries[13,20]. In our study, the rate of ISS of the deaths occurred on the scene was 44.8, and these were with severe injuries, and more than half of the patients had fatal two or more injuries.

Of the 48 patients who died in the emergency service, 30 were administered as cardiopulmonary arrest. Mean ISS of the patients was 38, and mean RTS was 0.99 with serious injuries. The most common causes of injury were, in order, thoracic trauma (n=36), head trauma (n=33) and abdominal trauma (n=31). The most common cause of death was multiple, fatal injury, hemorrhage and head trauma, respectively. Söderlund *et al* identified the average ISS value of the 115 trauma patients who died in the emergency service as 34.6[21].

The mean ISS of the 181 patients admitted to the ICU or hospital wards was 32.9, and the RTS was 4.8. Thirteen of these patients had a cardiopulmonary arrest in the emergency service and were taken to OR or ICU as a result of the successful resuscitative procedure. The most common cause of death in these patients was head trauma, followed by multiple injuries and MOF / ARDS / sepsis / PE. In our study, the mortality rate related to MOF / ARDS / sepsis / PE was 8.9%, while Saar *et al*[5] reported as 2.2%, Kleber *et al*[19] reported 10.5% and Trajano *et al*[15] reported 17.1%.

Besides being an indicator of the quality of trauma care, the rate of preventable mortality and the analysis of preventable errors in these deaths provide a basis for studies aimed at improving the quality of trauma care[17,22]. However, due to the variability in the methods used to identify preventable deaths, it is difficult to evaluate results by comparing with the literature[23]. Furthermore, identification is affected by many factors such as geographic localization of the area where the trauma occurs, urban/rural areas, and the complexity of the trauma system[24]. Preventable traumatic mortality rates have been reported to range between 1-45%[12]. The total preventable mortality rate in our study was 12.8% (1.1% preventable, 11.7% potentially preventable). In the article, Settervall *et al*, where they reviewed 24 different studies, found the mean preventable mortality rate to be 10.7% (range: 0.4% to 39.6%)[25]. Wilson *et al*[2], who examined 500 traumatic deaths in their study, found the preventable mortality rate as 14%. Schoeneberg *et al*[26], examined 193 deaths within the hospital and found the preventable mortality rate as 20.3%. Vähäaho *et al*[7] found 12% of 130 traumatized patients in the hospital, Kleber *et al*[19] of 15.2%, while Sanddal *et al*[24] found a rate of 6.7% in the study where they investigated 434 deaths. In a study conducted in our country in 2008, 747 traumatic deaths were investigated, Durusu *et al*[17] reported preventable mortality rate as 4.15% and potentially preventable mortality as 16.2%. In the study of 592 traumatic deaths between 2011 and 2012, Eyi et al[3] reported a preventable mortality rate of 4.1% and a preventive mortality rate of 14.5%.

Hemorrhage is the leading cause of preventable deaths in trauma patients[27]. In our study, we found that preventable/potentially preventable deaths were most commonly associated with hemorrhage (40%) in accordance with the literature[7,8,22,26]. Davis *et al* found that 28.5% of the deaths were potentially preventable deaths; hemorrhage was the leading cause in 54.1% of these deaths, 10.3% was with the hemorrhage, and the other major cause was neurotrauma in their study of 512 deaths before arrival to the hospital[8]. In their study of 2081 traumatic death, Teixeira *et al* found that preventable deaths were most commonly caused by hemorrhage (39.2%), and followed by Multiple Organ Dysfunction Syndrome (27.5%)[22]. In their study of 2594 in-hospital death, Gruen *et al* found that the major problem in the patient management was in control of hemorrhage (28%) and this was followed by the problems in airway management (16%) and inadequate management of the unstable patient (14%)[18]. Schoeneberg *et al* reported that the most common mistake in trauma care was related to hemorrhage control, and the other serious mistake was related to airway control[26]. The most common mistake in our study was related to hemorrhage control. In our study, there were mistakes in unstable patient management in three patients and airway management in three patients.

CONCLUSION

In conclusion, in our study, we observed that the most common cause of fatal blunt trauma was traffic accidents and half of these deaths occurred at the scene or within the first hour after trauma. The primary cause of blunt traumatic deaths was multiple fatal injuries followed by head trauma. The significant proportion of multiple injuries were accompanied by head trauma. Hemorrhage was the most common cause of preventable deaths. It is necessary to focus on the prevention of injury to reduce deaths occurring on the scene. Early access to patients, rapid transport, early evaluation and early treatment including the surgery to control the hemorrhage and airway integrity will help to reduce these mortality rates.

Limitations

Since this study was a retrospective study, there were deficiencies in the recording of some data. Pre-hospital medical records and treatments, and the time

records of arrival of the ambulance team after the incident were missing.

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Original Article

Knowledge, attitudes, and practices of medical interns toward COVID-19 in Saudi Arabia: a cross sectional survey, April-May 2020

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ABSTRACT

Objectives: This article reports medical interns' knowledge, attitude and practice (KAP) toward COVID-19 prevention measures in the Kingdom of Saudi Arabia (KSA).
Design: We conducted a cross-sectional online survey. The questionnaire included 10 questions each to assess knowledge and attitudes, and seven questions to assess practice. We did descriptive analyses to report KAP and performed *t*-test or ANOVA, and multi-variable logistic regression analyses to investigate socio-demographic determinants of KAP.
Setting: All regions in the KSA
Subjects: Medical interns from all medical colleges in the KSA were invited to participate
Intervention: Not applicable
Main outcome Measure: Attitude about COVID-19 was assessed as positive (≥90% correct responses), moderate (80-90% correct) or poor (< 80% correct); whereas knowledge and practice were assessed as excellent, good or poor respectively for ≥90%, 75%-90%, and <75% correct responses.
Results: Our results suggest that 24% of medical interns rely on social media, television, or friends as primary source of COVID-19 information. The prevalence of positive attitude, excellent knowledge and excellent/good practices are 55.2%, 38% and 24%, respectively. Graduating from government universities are associated with higher odds of excellent knowledge [Odds Ratio (OR): 3.87; 95% Confidence Interval (CI): 1.05-14.22] and positive attitude [OR: 4.84 (1.28-18.23)]. Interns from the west [OR: 2.35 (1.05-5.23)] and north [OR: 3.2 (1.32-7.75)] regions have higher odds of excellent/good practice compared to the central region.
Conclusions: Our findings reveal gaps in KAP among medical interns. Medical interns in the KSA are not deployed as front-line health workers to combat COVID-19. However, community transmission of COVID-19 makes it critical to improve KAP of medical interns toward COVID-19 prevention measures.

KEY WORDS: attitude, COVID-19, knowledge, medical interns, Saudi Arabia

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a new highly infectious viral disease of the respiratory system and is caused by novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[1]. The outbreak of COVID-19 was first reported in late December 2019 in Wuhan, China. Later, it spread in other parts of China and throughout the world. Consequently, the World Health Organization (WHO) declared it a pandemic on March 11, 2020[1]. The primary mode of transmission

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of the virus causing COVID-19 is respiratory droplets and contact routes[2]. Limited evidence suggests that there is also a possibility of fecal-oral transmission[3]. Severe COVID-19 patients are more contagious than mild ones. However, asymptomatic infected persons can also shed infectious virus[4]. Incubation period of SARS-Cov-2 is between 2-14 days with a median of 5 days[5]. The most common clinical manifestations of COVID-19 are fever, fatigue, cough, myalgia and dyspnea, while the less common manifestations are sputum production, headache, diarrhea and hemoptysis[6]. To date, there are several effective vaccines against COVID-19, but treatment options are still experimental. COVID-19 patients are currently managed with supportive care and antibiotics to counter secondary bacterial infections[7].

In Saudi Arabia, the first COVID-19 case was confirmed on March 2, 2020. As of June 26, 2020, the outbreak of COVID-19 was reported in all regions of the kingdom with 170,639 confirmed cases, 1428 deaths and 117,882 recoveries[8].

Healthcare professionals often come at close, repeated and or prolonged contact with diagnosed or undiagnosed COVID-19 patients[9]. Therefore, they are at a higher risk of getting infection. Globally, many healthcare professionals have already been infected with SARS-CoV-2 while treating patients[10]. High rates of SARS-CoV-2 infections among healthcare professionals might be due to a lack of adherence to safety guidelines, including a lack of access to or use of appropriate personal protective equipment (PPE)[11]. In this context, ensuring safety of healthcare professionals is of prime importance for continued quality healthcare services and to control further spread of the disease[9]. To prevent disease transmission in healthcare settings, the WHO recommends the use of contact and droplet precautions by healthcare professionals while treating COVID-19 patients. WHO also recommends the correct use of PPE, including choosing the right PPE for the setting, correctly putting on, removing and disposing of the PPE. In addition, healthcare professionals must adhere to hand hygiene and other infection prevention and control measures correctly[10].

Although healthcare professionals are at a higher risk of getting infection, previous studies with healthcare professionals showed that there were gaps in knowledge and attitude toward Middle East Respiratory Syndrome (MERS) and other emerging infectious diseases in Saudi Arabia[12-14] and Severe Acute Respiratory Syndrome in Taiwan[15]. Another hospital-based study in Riyadh, Saudi Arabia reported good knowledge and attitude, but poor practices toward MERS among healthcare professionals[16].

To facilitate the management of the COVID-19 outbreak in Saudi Arabia, there is an urgent need to understand the awareness of COVID-19 among the healthcare professionals, including medical interns, at this critical moment. To our knowledge, ours is the first study in Saudi Arabia to assess medical interns' knowledge, attitude and practices (KAPs) toward COVID-19. The aim of this study was to evaluate the medical interns' KAPs toward COVID-19 prevention measures and investigate its socio-demographic determinants in the kingdom of Saudi Arabia during the COVD-19 outbreak period in 2020. Our findings are expected to inform the authorities to organize necessary educational programs for the medical interns to ensure best practice in controlling the COVID-19 epidemic in the kingdom.

SUBJECTS AND METHODS

Study design, sampling and population

We conducted a cross-sectional survey of KAPs toward COVID-19 prevention measures of medical interns in Saudi Arabia. Medical interns are the trainee doctors who have successfully completed medical schooling and are engaged in a year of additional training at hospitals before residency. They do not get the graduation certificate until they successfully finish this internship year. Due to the lockdown and other restriction measures imposed in Saudi Arabia to control the COVID-19 epidemic, we employed a convenient, non-probability sampling technique to enroll medical interns who meet the inclusion criteria. Medical interns from all over the Kingdom of Saudi Arabia (KSA) who completed their study from any public, private or foreign medical colleges recognized by the Saudi Ministry of Education were eligible to participate in the survey. Medical interns who were not training in either a public or private hospital in Saudi Arabia during the survey were excluded from the study. Characteristics of the participants are presented in Table 1. Two hundred and sixty-one intern medical doctors from all over Saudi Arabia participated in this study. However, 11 respondents were dropped from further analysis because of incomplete responses. Among them, 64% were aged between 20 and 25 years, 60% were male, about 90% were single and over 90% were Saudi. Most medical interns (86%) were graduated from government universities in Saudi Arabia and the rest were graduated from private universities in Saudi Arabia or from any foreign universities, and 97.6% of the interns were training in public hospitals (Table 1).

Data collection

We developed a structured online survey using an online survey administration application, the Google forms. We distributed the link of the questionnaire to the medical interns in Saudi Arabia via social media like WhatsApp, Twitter and Facebook. We promoted

Table 1: Characteristics of the participants, KAP of medical interns toward COVID-19, cross-sectional survey, KSA, April-May 2020

Variables	Frequency (%)
Age	
20-25 years	160 (64.0)
25-30 years	86 (34.4)
30-35 years	4 (1.6)
Gender	
Male	150 (60.0)
Female	100 (40.0)
Marital status	
Single	224 (89.6)
Married	26 (10.4)
Nationality	
Saudi	227 (90.8)
Non-Saudi	23 (9.2)
University	
Government	215 (86.0)
Private	26 (10.4)
Foreign	9 (3.6)
Region	
Central (Riyadh & Qassim)	103 (41.2)
Eastern	22 (8.8)
West (Mecca & Medina)	50 (20.0)
North (Hail, Jouf, Tabuk & Northern borders)	34 (13.6)
South (Asir & Najran)	41 (16.4)
Employer	
Government hospital	244 (97.6)
Private hospital	6 (2.4)

our online survey through our professional networks. In addition, we advertised our survey through the medical interns' social media groups. We collected data between April and May 2020. Prior to data collection, we pre-tested the questionnaire in a convenience sample of 20 medical interns. These interns were not included in our final survey. Following pretesting, we made minor modification of the questionnaire to improve clarity and understanding of the questions by the interns.

The questionnaire and variables

The questionnaire we used consisted of two parts. The first part includes sociodemographic information of the participants- age in years, gender, nationality, area of residence, marital status, name of the university and type of the training hospital. These sociodemographic variables were treated as explanatory variables. The second part consists of the questions to assess the medical interns' KAP about COVID-19 prevention measures. This section is developed following the WHO and Saudi Ministry of Health guidelines on the prevention and control of COVID-19. KAP of medical interns toward COVID-19 were used as dependent variables.

Ten questions were used to assess knowledge. Knowledge questions covered symptoms, transmission mode and prevention strategies of COVID-19. Correct response had a value of 1, wrong response had a value of -1 and do not know response had a value of 0 (knowledge aggregated score ranged from -10 to 10 points). We classified medical interns' overall knowledge as excellent if the score (percent correct out of the 10 questions) was between 90 and 100% (knowledge score of +8 to +10 points), moderate if the score was between 75 and 90% (knowledge score of +5 to +7.99 points), and poor if the score was less than 75% (knowledge score of <+5 points). Attitude towards COVID-19 was evaluated using 10 questions. Responses were graded on a 3-point Likert scale; an agreement scale ranging from 1 for positive attitude to -1 for negative attitude (attitude aggregated score ranged from -10 to 10 points). We classified the medical interns' attitude as positive if the score (percent of positive attitude out of the 10 questions) was between 90 and 100% (attitude score of +8 to10 points), moderate if the score was between 80 and 90% (attitude score of + 6 to +7.99 points) and negative if the score was less than 80% (attitude score of -10 to 5.99 points). In addition, we assessed practice using seven questions regarding preventive measures as well as source of knowledge about COVID-19. Good practice was awarded 1 point, while bad practice was awarded -1 point (practice aggregated scores were ranged from -7 to 7 points). We classified medical interns' overall practice as excellent if the score (percent adherence to the seven practices) was between 90 and 100% (practice score of +5.6 to +7 points), good if the score was between 75 and 90% (practice score of +3.5 to +5.5 points), and poor if the score was less than 75% (practice score of -7 to + 3.49 points).

Data management and analysis

Data were downloaded and coded in an Excel file. Later, the Excel data file was converted to IBM SPSS Statistics 20. Two hundred and sixty-one medical interns submitted the online form but during data cleaning, 11 participants were identified with incomplete information, hence had removed them from further analysis. We did descriptive analysis of all categorical data and reported both frequency and percentage. We analyzed and reported prevalence of excellent knowledge, positive attitude and excellent/good practice in percentage with 95% confidence interval. We computed and reported mean and standard deviation for total and subgroups' KAP score. We performed *t*-test or ANOVA to analyze the relationship between the dependent (KAP), and explanatory (sociodemographic characteristics of the participants) variables. Mean differences were considered statistically significant if $P<0.05$. In addition, we performed multi-variable logistic regression analysis to investigate the sociodemographic determinants of KAP. We reported adjusted OR with

Table 2: Knowledge of medical interns toward COVID-19, cross-sectional survey, KSA, April-May 2020

Knowledge items (correct response)	Correct Freq. (%)	Incorrect Freq. (%)	Don't know Freq. (%)
Fever, dry cough, muscle ache, shortness of breath, and fatigue are the main symptoms of COVID-19 (yes)	240 (96.0)	8 (3.2)	2 (0.8)
GI symptoms can be part of the COVID-19 symptoms (yes)	162 (64.8)	55 (22.0)	33 (13.2)
Elderly, immunocompromised, pregnant, and people with chronic illness are at higher risk of developing severe disease and complications if infected (yes)	248 (99.2)	1 (0.4)	1 (0.4)
SARS-CoV-2 is transmitted through respiratory droplets via direct contact with infected person or indirect contact with contaminated surfaces (yes)	153 (61.2)	81 (32.4)	16 (6.4)
Airborne transmission is possible for SARS-CoV-2 in general context (no)	155 (62.0)	80 (32.0)	15 (6.0)
Washing hands with soap and water or rubbing hands with alcohol-based sanitizer reduce chances of getting infected with SARS-CoV-2 (yes)	248 (99.2)	1 (0.4)	1 (0.4)
Hand hygiene must be practiced after blowing your nose, coughing or sneezing; visiting a public place; touching surfaces outside of the home or money; before, during and after caring for a sick person and before and after eating (yes to all events)	154 (61.6)	96 (38.4) *	0
Minimal hand washing time with soap and water (40-60 seconds)	184 (73.6)	66 (26.4)	0
Minimal hand sanitizing time using alcohol-based hand sanitizer (20-30 seconds)	168 (67.2)	82 (32.8)	0
Minimum social distancing between two persons (1-2 meter)	235 (94.0)	15 (6.0)	0

*said no to at least one of the events

95% CI. We considered the differences as statistically significant for a two-tailed test if $P<0.05$. For multivariable logistic regression analyses, the dependent variables excellent knowledge, positive attitude, and excellent/good practice were coded as 1 and the other categories of KAP were coded as 0. Proportions of the medical interns with excellent practice were too low. Therefore, we re-coded practice as excellent/good (1) versus poor (0). The explanatory variables in the models included age groups (20-25 years vs 25-30 years), nationality (Saudi vs non-Saudi), gender (male vs female), marital status (single vs currently married), type of university (private or foreign vs government) and the regions (central, east, west, north and south).

Ethical issues

We received ethical approval from the subcommittee of Health Research Ethics, Deanship of Scientific Research, Qassim University, Saudi Arabia. First page of the online survey form included informed consent statements. Proceeding further by the interns implied their consent for participation. We informed the participants about the purpose of the survey, approximate time to complete the survey and guaranteed anonymity and confidentiality. It was made clear that participating or not participating in this survey will not affect their internship in any way.

RESULTS

Knowledge

To evaluate knowledge, we posed key questions on COVID-19 symptoms, vulnerable groups, and mode of transmission and prevention strategies. We found that nearly all the medical interns (99.2%) correctly identify the population vulnerable to COVID-19 and know the importance of hand hygiene to reduce the chance of getting the infection. However, only 61.6% can report all the events require practicing of hand hygiene. Most of them (96%) know the main manifestations of the disease, and 64.8% know that GI symptoms can be part of the COVID-19 symptoms. Among the interns, 94% recognizes that 1-2 meters is the minimum social distancing between two persons to prevent transmission; 61.2% of the interns correctly report that respiratory droplets via direct contact with infected persons or indirect contact with surfaces contaminated by the virus are the mode of transmission of the virus causing COVID-19; while 62% correctly report that airborne transmission of SARS-CoV-2 is not possible in general contexts. We found that the proportion of medical interns know the minimum time required for hand washing using soap and water and hand sanitizing using alcohol-based hand sanitizer are 73.6% and 67.2%, respectively (Table 2).

Based on their total knowledge score, we classified the interns as having excellent, good or poor knowledge. We found that the mean knowledge score of the interns is 6.1±2.7 on a scale of -10 to 10 and only 38% (32.2-44.2) of the interns has excellent knowledge with a score of at least 90%. Figure 1 presents a histogram of total knowledge scores. To investigate the mean differences in knowledge score between groups, we did *t*-test or ANOVA. We found that Saudi interns and interns graduated from Saudi public universities has significantly higher knowledge score compared to non-Saudi interns and interns graduated from private or foreign universities, respectively (Table 3).

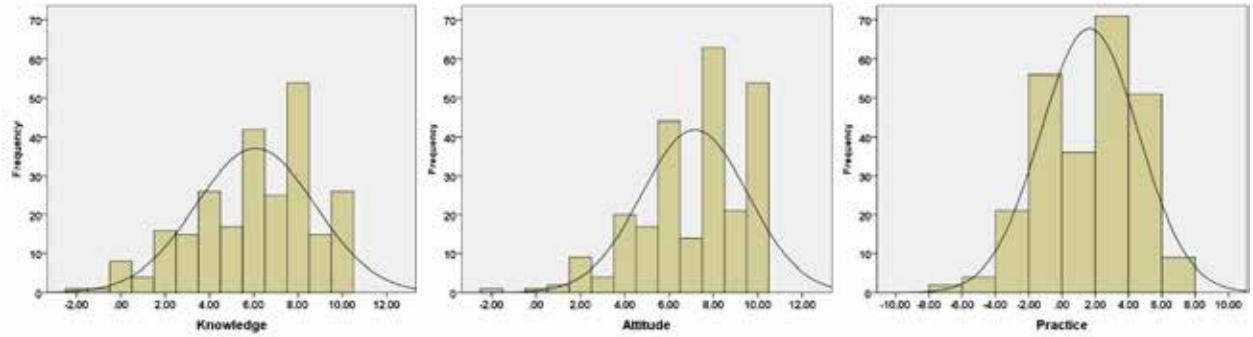

Fig 1: Histogram displaying distribution of the medical interns' total knowledge, attitude, and practice scores

We performed multivariable logistic regression analysis to investigate the socio-demographic determinants of COVID-19 knowledge among medical interns. We found that the odds of excellent knowledge among interns graduated from Saudi public universities are 3.87 (95% CI: 1.05-14.22) times the odds of interns graduated from Saudi private universities or foreign universities, adjusting for the effect of other variables included in the model. However, there are no significant differences in COVID-19 knowledge between age groups, gender, marital status, nationality and region (Table 4).

Attitude

We posed statements to assess medical interns' attitudes toward COVID-19 prevention strategies and their beliefs and awareness regarding the strategies being implemented by their hospital. Regarding declaring recent travel history, 92% of the interns think that they should declare their recent travel history before rejoining work, even if they do not have any COVID-19 symptom. Regarding asymptomatic virus carrier, 90% believe that they can be a virus carrier, even if they do not have fever or cough. Findings suggest that 73% of the interns rightly think that they do not need to wear N95 mask at work all the time to avoid getting infected with SARS-CoV-2. Among the medical interns, 97% believe that appropriate social distancing can reduce their risk of getting infected or infecting others with SARS-CoV-2, and 92% of the medical interns think they should stay home, isolate themselves, and inform their superior if they develop

Table 3: Knowledge, attitude, and practices of medical interns toward COVID-19 in KSA, cross-sectional survey, April-May 2020

Variables	Knowledge		Attitude		Practice	
	Score^	Excellent	Score^	Positive	Score^	Excellent/good
	Mean (SD)	Percent (95% CI)	Mean (SD)	Percent (95% CI)	Mean (SD)	Percent (95% CI)
Total	6.1 (2.7)	38.0 (32.2-44.2)	7.2 (2.4)	55.2 (48.9-61.3)	1.7 (2.9)	24.0 (19.1-29.7)
Age						
20-25 years	6.1 (2.8)	37.5 (30.3-45.3)	7.3 (2.5)	61.9 (54.1-69.1)	1.6 (2.9)	24.4 (18.3-31.7)
25-30 years	6.2 (2.5)	38.9 (29.3-49.4)	6.9 (2.2)	43.3 (33.4-53.8)	1.8 (2.9)	23.3 (15.7-33.3)
Nationality						
Saudi	6.3 (2.6) *	40.5 (34.3-47.1)	7.1 (2.4)	53.7 (47.2-60.2)	1.7 (2.9)	24.7 (19.5-30.7)
Non-Saudi	3.9 (2.7) *	13.0 (4.1-34.3)	7.6 (2.1)	69.6 (47.9-85.1)	1.4 (2.9)	17.4 (6.5-38.9)
Gender						
Male	6.0 (2.8)	39.3 (31.8-47.4)	7.1 (2.5)	53.3 (45.3-61.2)	1.5 (3.0)	22.0 (16-29.4)
Female	6.2 (2.6)	36.0 (27.1-46.0)	7.3 (2.3)	58.0 (48.0-67.3)	1.8 (2.8)	27.0 (19.1-36.6)
Marital status						
Single	6.0 (2.7)	37.1 (31.0-43.6)	7.2 (2.4)	55.8 (49.2-62.1)	1.7 (2.9)	23.7 (18.5-29.7)
Married	6.4 (2.2)	46.2 (28.0-65.4)	6.9 (2.5)	50.0 (31.3-68.7)	1.4 (3.4)	26.9 (13.2-47.2)
University*						
Private/ foreign	4.5 (2.5) *	14.3 (6.0-30.4)	6.7 (2.3)	48.6 (32.5-65)	1.7 (2.9)	22.9 (11.7-39.8)
Government	6.3 (2.6) *	41.9 (35.4-48.6)	7.2 (2.4)	56.3 (49.5-62.8)	1.7 (2.9)	24.2 (18.9-30.4)
Region						
Central	6.2 (2.6)	37.9 (29-47.7)	7.3 (2.2)	56.3 (46.5-65.6)	1.1 (2.9)	16.5 (10.5-25.1)
East	6.1 (2.6)	31.8 (15.6-54.0)	6.8 (2.9)	54.5 (33.6-74.0)	1.5 (2.7)	18.2 (6.8-40.4)
West	6.7 (2.5)	44.0 (30.8-58.1)	7.2 (2.2)	58.0 (43.8-70.9)	2.3 (2.3)	32.0 (20.5-46.2)
North	5.4 (3.2)	32.4 (18.7-49.9)	6.8 (2.9)	55.9 (38.8-71.6)	2.4 (3.1)	38.2 (23.4-55.6)
South	5.7 (2.7)	39.0 (25.3-54.8)	7.2 (2.3)	48.8 (33.8-64)	1.8 (3.1)	24.4 (13.5-40.0)

*Mean difference is significant for a two-tailed test at p <0.001.
^Knowledge and attitude was scored on a scale of -10 to 10, while practice was scored on scale of -7 to 7.

Table 4: Determinants of KAP toward COVID-19 among medical interns, multivariable logistic regression analyses, cross-sectional survey, KSA, April-May 2020

Variables	Knowledge OR (95% CI)	Attitude OR (95% CI)	Practice OR (95% CI)
Age			
20-25 years	1	1	1
> 25 years	0.96 (0.54-1.7)	0.51 (0.29-0.9)	0.94 (0.49-1.82)
Gender			
Male	1	1	1
Female	0.81 (0.46-1.4)	1.06 (0.6-1.85)	1.29 (0.68-2.45)
Marital status			
Single	1	1	1
Married	1.6 (0.68-3.78)	1 (0.42-2.36)	1.14 (0.44-2.96)
Nationality			
Saudi	1	1	1
Non-Saudi	0.63 (0.12-3.26)	6.92 (1.44-33.22) *	0.58 (0.12-2.83)
University			
Private or foreign	1	1	1
Government	3.87 (1.05-14.22) *	4.84 (1.28-18.23) *	0.66 (0.2-2.24)
Region			
Central (Riyadh & Qassim)	1	1	1
Eastern	0.85 (0.3-2.37)	0.92 (0.35-2.41)	1.17 (0.35-3.92)
West (Mecca & Medina)	1.31 (0.64-2.67)	1.27 (0.62-2.62)	2.35 (1.05-5.23) *
North (Hail, Jouf, Tabuk & Northern borders)	0.64 (0.28-1.48)	0.87 (0.39-1.94)	3.2 (1.32-7.75) *
South (Asir & Najran)	0.77 (0.35-1.68)	0.73 (0.34-1.57)	1.8 (0.71-4.54)

* Significant at P <0.05

fever or cough even if they have not been exposed to COVID-19 patients or recently returned from a travel. 97% of the interns believe that quarantining suspected COVID-19 cases for 14 days can reduce the spread of the infection. Regarding prevention strategies in place in hospital, 72% of interns believe that their hospitals have taken all the necessary protective measures to protect healthcare providers and patients from getting infected with SARS-CoV-2. Our results suggest that 94% of the interns think that it is their social responsibility to protect public health by following the government's recommendations to control the spread of COVID-19. The least proportion of positive attitude are regarding the interns' awareness about the measures taken by their hospitals to address COVID-19 pandemic (61.2%) as well as visual triage checklist from the Saudi Ministry of Health for COVID-19 patients (62%) (Table 5).

Based on their total attitude score, we classified the interns as having positive, moderate or negative attitude. We found that the mean attitude score of the interns is 7.2±2.4 on a scale of -10 to 10 and only 55.2 (95% CI: 48.9-61.3) of the interns has positive attitude with a score of at least 90%. Figure 1 presents a histogram of total attitude scores. To investigate the mean differences in total attitude score between groups, we did *t*-test or ANOVA. Mean differences in total

Table 5: Attitude of medical interns toward COVID-19, cross-sectional survey, KSA, April-May 2020

Attitude items (positive attitude)	Positive Freq. (%)	Negative Freq. (%)	Don't know Freq. (%)
I don't need to declare recent travel history before rejoining work if I have no symptoms (disagree)	229 (91.6)	17 (6.8)	4 (1.6)
I can't be a virus carrier if I don't have symptoms of fever or cough (disagree)	226 (90.4)	22 (8.8)	2 (0.8)
I need to wear N95 mask at work all time to avoid getting infected with SARS-CoV-2 (no)	182 (72.8)	50 (20.0)	18 (7.2)
I think social distancing can reduce my chances of getting infected or infecting others with SARS-CoV-2 (yes)	242 (96.8)	6 (2.4)	2 (0.8)
I should stay home, isolate myself, and inform my superior if I have fever or cough even if I have not been exposed to COVID-19 patients or recently returned from travel (yes)	230 (92.0)	10 (4.0)	10 (4.0)
I think quarantine of suspected COVID-19 cases for 14 days can reduce the spread of the infection (yes)	243 (97.2)	3 (1.2)	4 (1.6)
I believe that my hospital has taken all the necessary protective measures to protect healthcare providers and patients from getting infected with SARS-CoV-2 (yes)	179 (71.6)	35 (14.0)	36 (14.4)
I fell that I have social responsibility to protect public health by following the government's recommendations to control the spread of COVID-19 (yes)	236 (94.4)	8 (3.2)	6 (2.4)
I am aware about visual triage checklist from the Saudi Ministry of Health for COVID-19 patients (yes)	155 (62.0)	71 (28.4)	24 (9.6)
I am aware about the measures taken by my hospital to address COVID-19 pandemic (yes)	153 (61.2)	63 (25.2)	34 (13.6)

Table 6: Practices of medical interns toward COVID-19, cross-sectional survey, KSA, April-May 2020

Practice items (good practice)	Good Freq. (%)	Bad Freq. (%)
I have been practicing social distancing and avoiding going out unnecessarily (yes)	230 (92.0)	20 (8.0)
I have been more vigilant about washing my hands (yes)	228 (91.2)	22 (8.8)
I have got fitted for N95 mask (yes)	83 (33.2)	167 (66.8)
No, I didn't want to	-	27 (10.8)
No, I don't have access to fitting test/hospital doesn't have N95 masks	-	83 (33.2)
No, I have a beard and I didn't want to shave it	-	24 (9.6)
No (other reasons)	-	33 (13.2)
I attended training on hand hygiene during COVID-19 pandemic (yes)	174 (69.6)	76 (30.4)
I attended training on wearing and removing face mask (or N95 mask) and gloves safely during COVID-19 pandemic (yes)	127 (50.8)	123 (49.2)
I attended training on performing nasopharyngeal swab safely (yes)	50 (20.0)	200 (80.0)
I have obtained knowledge about COVID-19 pandemic mainly from official websites of Saudi MoH, WHO, CDC or other international societies, and hospital resources (website, emails, and posters)	190(76.0)	60 (24.0) *

attitude score between different socio-demographic groups are not significant (*P*>0.05) (Table 3).

We performed multivariable logistic regression analysis to investigate the socio-demographic determinants of medical interns' attitude toward COVID-19 prevention strategies. We found that the odds of positive attitude among non-Saudi interns are 6.92 (1.44-33.22) times the odds of positive attitude among Saudi interns, given that the effect of all other variables in the model are held constant. In addition, the odds of positive attitude among the interns graduated from Saudi public universities are 4.84 (1.28-18.23) times the odds of positive attitude among the interns graduated from Saudi private universities or foreign universities, adjusting for the effect of other variables included in the model. However, there are no significant differences in attitude toward COVID-19 prevention strategies between age groups, gender, marital status and region (Table 4).

Practices

To assess medical interns' practices, we posed seven questions. We found that among the interns, 92% practice social distancing and avoid going out unnecessarily; 91% became more vigilant about washing their hands. However, only 33% of the interns have got fitted for N95 mask. Regarding improving knowledge, we found that 70%, 51% and 20% of the interns respectively attended training on hand hygiene, safely wearing and removing face masks or N95 mask and gloves and taking nasopharyngeal swab safely. We also found that 76% of the interns use official websites of the Saudi ministry of health, WHO or other international societies, hospital resources including website, emails and posters as their primary source of information on COVID-19, while others were relying on social media, newspaper and television, friends or family (Table 6).

Based on their total practice score, we classified the interns as having excellent, good or poor practice. We found that the mean practice score of the interns is 1.7±2.9 on a scale of -7 to 7 and only 24% (95% CI: 19.1-29.7) of the interns has excellent or good practice with a score of at least 75%. Figure 1 presents a histogram of total practice scores. To investigate the mean differences in total practice score between groups, we did *t*-test or ANOVA. Mean differences in total attitude score between different socio-demographic groups are not significant (*P*>0.05) (Table 3).

We performed multivariable logistic regression analysis to investigate the socio-demographic determinants of medical interns' practice toward COVID-19 prevention strategies. We found that the odds of excellent/good practice in the west region (Mecca and Medina) are 2.35 (95% CI: 1.05-5.23) times the odds of excellent/good practice in the central region (Riyadh and Qassim), given that the effect of all other variables in the model are held constant. In addition, the odds of excellent/good practice in the North (Hail, Jouf, Tabuk & Northern borders) region are 3.2 (95% CI: 1.32-7.75) times the odds of excellent/good practice in the central region, adjusting for the effect of other variables included in the model. However, there is no significant difference (*P*>0.05) in practice toward COVID-19 prevention strategies between age groups, gender, marital status, type of university and nationality (Table 4).

DISCUSSION

COVID-19 is a rapidly evolving global health crisis. Healthcare professionals are at the forefront of the COVID-19 outbreak response. Hence, their risk of infection is greater than the general population[17]. Therefore, it is vital that healthcare professionals have adequate KAP regarding diagnosis, treatment and prevention of COVID-19. Here, we assessed the KAP

of medical interns toward COVID-19 prevention in KSA. Our results reveal that there are gaps in KAP of medical interns training in KSA regarding COVID-19 prevention. To the best of our knowledge, this is the first study in KSA to assess medical interns' KAP regarding COVID-19. Our results have implications for the relevant authorities in KSA.

Healthcare professionals' good KAP in complying with precautionary measures help to create awareness among patients and the general population[18]. Medical interns in KSA are not deployed as frontline healthcare professionals to combat COVID-19. However, evidence suggests that there are high chances of having undiagnosed COVID-19 patient contact at some point of time in healthcare settings[19]. Therefore, they are at risk of contracting and spreading the infection. Evidence suggests that non-frontline healthcare workers have lower confidence in protecting themselves from the virus[20]. On the other hand, frontline healthcare workers receive greater material support and care from the health systems, and they are more confident in their ability to protect themselves from the virus[21].

Knowledge forms positive attitudes and promotes positive behaviors[22]. Our results suggest gaps between the current evidence on COVID-19 and the depth of knowledge among medical interns- particularly about the mode of transmission, the events that require practicing hand hygiene, and minimum time required to disinfect hands with soap and water or with alcohol-based hand sanitizer. However, over 99% interns know the population most vulnerable to COVID-19 infection and complications. This is much higher than that reported in Vietnam, where only 79% of hospital healthcare workers correctly identified the vulnerable population[23]. Over 99% of the interns know that washing hands with soap and water or rubbing hands with alcohol-based sanitizer reduce chances of getting infected with SARS-CoV-2. This finding is consistent with that reported by Huynh *et al* in Vietnam among hospital health workers[23]. We found that 96% of medical interns in KSA know the main symptoms of COVID-19, which is higher than the proportion reported among hospital health workers in other countries[23,24]. We found that 61% of the interns know the mode of transmission of SARS-CoV-2. This proportion is higher than the proportion (39%) reported by a global online survey among doctors and allied health workers[25], but lower than the proportion (98%) of dental practitioners, as reported by another multinational online survey involving participants from all the continents[26]. Studies from other countries also reported a similar proportion (62-67%), such as among medical students in India[27] and among hospital healthcare workers in Vietnam[23].

We found that the vast majority (97%) of the interns have a positive attitude towards the efficacy of quarantine of suspected COVID-19 cases for 14 days in reducing the spread of the infection. A lower percentage (66%) was reported among hospital healthcare workers in Vietnam[23]. In addition, most of the medical interns (92%) positively believe that there is a need to declare recent travel history before rejoining work even if having no symptoms. This agrees with the findings reported by Bhagavathula *et al*[25]. Similarly, healthcare workers in Henan, China[20] believe that visitors with any close contact with a confirmed case or recent travel to an area with community transmission should disclose their exposure history. Most medical interns in KSA are positive toward staying home, isolating him/herself, and informing his/her superior if having fever or cough even if they have not been exposed to COVID-19 patients or recently returned from a travel. This agrees with a Vietnam study[23], where 98% of health workers accept isolation in health facilities if getting COVID-19 exposure. More than two-thirds of the medical interns in KSA (73%) rightly think that there is no need to wear N95 mask at work all time to avoid getting infected with SARS-CoV-2. This is in line with the findings of Modi *et al* in India[27]. In Uganda[24], 17% of healthcare workers believe that wearing general medical masks is not protective against COVID-19 contrary to findings by Ng *et al*[28], which showed adequate protection. In addition, WHO recommends rational use of masks and other PPE in both healthcare and community settings[10]. The surprising negative attitude of our studied group was about participants' awareness about the measures taken by their hospitals to address COVID-19 pandemic as well as visual triage checklist from the Saudi Ministry of Health for COVID-19 patients. This indicates the importance of improved communication and training provisions and materials on COVID-19 by the hospitals to strengthen preventive strategies including raising awareness of health workers including medical interns.

This study found that over 90% of the medical interns in the KSA reports that they are proactively practicing social distancing or avoiding going out unnecessarily and practicing hand hygiene more vigilantly than any previous time. Similar findings are also reported among hospital healthcare workers in Uganda[24]. However, our findings suggest gaps in getting fitted for N95 mask, attending training on performing nasopharyngeal swab, hand hygiene and safe use of masks. It is important to note that one-third of the interns reported that the reason behind not getting fitted for N95 mask is not having access to fitting test or their hospital didn't provide them with N95 masks. Healthcare professionals come in

close contact with different patients. Hence, at the time of epidemic, they have a higher risk of exposure to infected cases and are at higher risk of getting an infection. In this regard, the COVID-19 epidemic offers a unique opportunity to the Saudi ministry of health to provide all health settings with the required PPE for the healthcare workers to protect their safety and control the spread of the infection in the healthcare settings.

For prevention and control of infectious disease in healthcare settings, healthcare workers should place a high value on safely putting on, removing and disposing PPE[29]. When removing contaminated PPE such as gowns, gloves, medical masks and face shield in high-risk settings, it is necessary to follow strict safety regulations to prevent further contamination and spread of infection[29]. However, we found that only half of the medical interns in KSA attended training on wearing and removing face mask (or N95 mask) and gloves safely during the COVID-19 pandemic. Kumar *et al*[30] reported that 89% of healthcare workers in an orthopedic surgery setting in Pakistan believe that they know the proper steps of wearing a surgical face mask; however, only 35% performed well in answering the procedural questions. Another study in India reported that only 45% healthcare workers are aware of the correct procedure for the application of a mask/respirator[27]. A study with healthcare workers in China suggests that careful removal of PPE is positively associated with higher education level and work experience[20]. Therefore, hospital administration should arrange repetitive training and demonstrated competency in putting on and removing PPE for healthcare workers[29], specially targeting novices like medical interns.

One of the very vital practices to prevent transmission of COVID-19 from patients to patients, patients to healthcare workers and vice versa is hand hygiene. Hand hygiene must be practiced after blowing nose, coughing or sneezing; visiting a public place; touching surfaces outside of the home or money; before, during and after caring for a sick person; and before and after eating. We found that only 62% correctly identified all presented events that require practice of hand hygiene. In contrary, only 70% attended training on hand hygiene during COVID-19 pandemic. Having good handwashing technique is not a COVID-19-specific skill. Unlike knowledge about COVID-19 (which they would not have been taught previously), they should have known how to properly wash hands. Therefore, these results can also inform the medical colleges regarding the general preparedness of their graduates for facing a situation of heightened use of PPE, handwashing, etc. Medical education units should assess how they could enhance their educational content with these skill sets (not just hand washing, but proper placement, removal and disposal of PPE).

Our findings reveal that although a majority of the interns rely on formal websites and resource for COVID-19 information, 24% relies on social media, newspaper, television, friends or family for the same. Use of social media and informal networks is evident among healthcare workers in other countries too[23-25]. This finding has implications for the Saudi ministry of health and hospitals. It is important to consider a variety of channels, including official websites and social media, to update and disseminate knowledge and learning materials about this epidemic. Overall, our findings show that the prevalence of excellent or good practice among medical interns in KSA is only 24%. This gap in practice might be attributable to their lack of experience and not being deployed to treat COVID-19 patients directly. Studies suggest that good practice is associated with age of the healthcare workers[24], work experience, working time[20] and qualification[24]; all of which are deficient among medical interns.

Regarding overall KAP, our results suggest that prevalence of excellent knowledge, positive attitude and excellent/good practice among medical interns are 38%, 55% and 24%, respectively. This is much lower than the prevalence estimate reported by studies conducted in other countries[18,20,23,24,26,30]. However, in our study, interns responded greater or similar proportion of correct answers. Low prevalence of excellent KAP in our study is largely attributable to the methodological differences in calculating total KAP between our study and the other. We used more criteria of scoring. In our study, negative score was given for wrong answers, whereas in other studies wrong answer received zero. These stricter scoring criteria contributed to lower total knowledge score in our study. We argue that it is vital to give negative score when assessing KAP of healthcare professionals. Since poor KAP of healthcare professional may lead to catastrophic consequences. Knowledge of COVID-19 is evolving every day; this perhaps explains the knowledge gaps regarding COVID-19 among healthcare professionals globally. Health authorities must regularly update information and disseminate up-to-date information to all healthcare professionals including medical interns.

Our multivariable logistic regression analysis suggests significant association between knowledge and the type of graduating medical colleges, and attitude and the type of medical colleges. Medical interns graduated from government colleges are more likely to have excellent knowledge and positive attitude

toward COVID-19 prevention and control measures than interns from private or foreign colleges. This could be attributable student recruitment strategies, quality of faculty, resources, and overall academic environment in governmental colleges. However, this needs further investigation since only 14% of the participants were from private or foreign medical colleges. Our findings also suggest that non-Saudi medical interns are more likely to have a positive attitude toward COVID-19 prevention measures compared to Saudi interns. This might be attributable to perceived lack of support from friends and family in times of a personal crisis when living in a foreign country without or with only immediate family members. Regarding practice, our result suggests significant association between region and excellent/good practice. Medical interns from the west (Mecca and Medina) and the north (Hail, Jouf, Tabuk & Northern borders) regions are more likely to have excellent/good practice than the interns from the central region (Riyadh and Qassim). During the time of data collection, west and north regions were the worst hit by COVID-19 than the central and other regions of KSA. This perhaps explains the more careful practice of the interns from west and north region. Other studies found that the most significant associated factors with KAP scores were age of the healthcare workers (more than 40 years with knowledge and practice), qualification (holding a diploma with practice)[24], occupation (pharmacists with knowledge and attitude)[23] or working experiences and job category (5-9 years of experience and frontline status with attitude and practice)[20].

Our study findings should be interpreted with caution because of its methodological limitations. Given the lockdown measures in KSA and the urgent need to know the COVID-19 KAP status of this neglected healthcare professional group, we did a rapid online survey using the popular social media to recruit participants. Nevertheless, the study participants were from all over KSA, thus, generalization of the results is possible. One of the primary limitations of measuring "attitude" and "practice" is that of an expectation bias that result from self-report of desired attitude and behaviors. Therefore, there is a possibility that the self-assessment of attitude and adherence to good practices among our study participants may be over-reported.

CONCLUSIONS

Our findings have highlighted the gaps in KAP among medical interns toward COVID-19 prevention. Although, medical interns are not deployed to treat COVID-19 patients in KSA, community transmission in all regions of KSA implies that they are also at risk of exposure while treating non-COVID-19 or undiagnosed COVID-19 patients. Knowledge of COVID-19 is rapidly developing; hence it is the responsibility of the hospital authority to keep prevention protocol up-to-date and communicate up-to-date information to all healthcare workers, including medical interns.

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Original Article

Risk adapted strategy for choosing the right drug for antibiotic prophylaxis in percutaneous nephrolithotomy

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ABSTRACT

Objective: To create risk groups and compare the effectiveness of ceftriaxone and cefazolin for prophylaxis according to these risk groups
Design: Retrospective study
Setting: Department of Urology, Health Sciences University, Bozyaka Training and Research Hospital, Turkey
Subjects: A total of 671 patients who underwent percutaneous nephrolithotomy (PCNL) for renal stones between January 2014 and July 2018 were included in the present retrospective study. Two hundred and twenty-three of the patients were given cefazolin, whereas 448 were given ceftriaxone as antibiotic prophylaxis. High-risk patients were defined as having ≥2 cm stone diameter plus one of the following: operation duration ≥120 min, multiple puncture (≥2), recurrent urinary tract infection history, stone culture positivity or renal pelvic urine culture positivity. All patients were followed up for systemic inflammatory response syndrome (SIRS) criteria postoperatively.
Interventions: Percutaneous nephrolithotomy
Main outcome measures: SIRS
Results: Of all patients, 188 (28%) were in high risk group and 483 (72%) were in low risk group. No statistically significant difference was found between cefazolin and ceftriaxone group for SIRS in all patients and in low-risk group. However, in high-risk group, SIRS rates were significantly higher in cefazolin group compared to ceftriaxone group (P=0.001).
Conclusions: A risk adapted approach is important for selecting the type of antibiotic for prophylaxis in PCNL. In the present study, we found that ceftriaxone is superior to cefazolin in terms of post PCNL SIRS only in high-risk patients.

KEY WORDS: antibiotic prophylaxis, cefazolin, ceftriaxone, percutaneous nephrolitholithotomy, systemic inflammatory response syndrome

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) has become the standard treatment modality for renal stones >2cm, since the first renal calculi extraction through a percutaneous nephrostomy was defined in 1976 by Fernström *et al*[1]. Since, infectious complications are common after PCNL, the European Association of Urology and American Urology Association guidelines recommend antibiotic prophylaxis for all patients undergoing PCNL. The American Urology Association guidelines recommend 1st/2nd generation cephalosporin, aminoglycoside with metronidazole or clindamycin, ampicillin/sulbactam, fluoroquinolone; whereas European Association of Urology guidelines recommend 2nd/3rd generation cephalosporin, trimethoprim-sulfamethoxazole, fluoroquinolone or aminopenicillin with a β-lactamase inhibitor for antibiotic prophylaxis in PCNL[2,3]. However, the optimal timing, dosing and duration of antibiotic prophylaxis is still under debate. The other important point is choosing the right antibiotic regimen for the patient. Several studies compared the different antibiotic regimens in PCNL patients and found no difference[4,5]. We know from previous studies that there are some preoperative and intraoperative risk factors for infectious complications after PCNL[6,7]. None of

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the previous studies on antibiotic prophylaxis have stratified the PCNL patients according to risk factors for infectious complications. The aim of the present study is to compare the effectiveness of ceftriaxone and cefazolin for prophylaxis in PCNL patients according to risk groups for infectious complications.

SUBJECTS AND METHODS

A total of 671 patients who underwent PCNL for renal stones between January 2014 and July 2018 were included in the recent study. Two antibiotic regimen were used (cefazolin 1gr IV, ceftriaxone 1gr IV) as antibiotic prophylaxis for PCNL at different time periods in our clinic. Two hundred and ten of the patients were given cefazolin, whereas 461 were given ceftriaxone as antibiotic prophylaxis. Antibiotic prophylaxis was given as a single dose intravenously at anesthesia induction and continued until the time of nephrostomy removal. Data were gathered from electronic records of patients retrospectively. PCNL procedure is performed as told before[6]. Risk stratification of the patients was made according to the common parameters that have proven to impact post-PCNL infectious complications in different studies[6,7]. High-risk patients were defined as having ≥2 cm stone diameter plus one of the following: operation duration ≥120 min, multiple puncture (≥2), recurrent urinary tract infection history, stone culture positivity or renal pelvic urine culture positivity. All patients were followed up for systemic inflammatory response syndrome (SIRS) criteria[8] postoperatively. All procedures were performed in accordance with the ethical standards of the institutional 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.

Operation technique

All PCNLs were performed in a tertiary referral center by two experienced surgeons (IHB and TD). All patients were evaluated with computerized tomography preoperatively. All procedures were performed under general anesthesia in prone position. All accesses were performed by surgeons under fluoroscopy guidance and amplatz dilatators used for dilatation. The operation duration was calculated after the patient turned to prone position. The patients' demographic characteristics, stone burden, number of tracts and location, operation time, fluoroscopy time, presence of residual stones and estimated blood loss were recorded in all patients postoperatively.

Statistical analysis

For the evaluation of the relationship between the two categorical variables, Chi-square analysis was used. Linear relationship between continuous variables was calculated using Pearson's coefficient of correlation. Kolmogorov Smirnov test was used for determination of the relevance of a normal distribution. Mann Whitney U test was applied for evaluating the two paired groups. Mean±standard deviation, frequency and percentage values are given as descriptive statistics. For analyses of the data, SPSS ver. 18 (SPSS Inc., Chicago, IL, USA) was used and $P < 0.05$ was accepted as significant.

RESULTS

According to the risk stratification criteria described above, 188 (28%) of the patients were in high-risk group and 483 (72%) were in the low-risk group. Mean patient age was 47.76±13.03 (range 8-82) years and 47.19±12.95 (range 14-82) years and mean stone size was 891.09±620.06 (range 314-2951.6) and 373.31±390.79 (range 34.54-2869.2) mm^2 for high-risk group and low-risk group, respectively. Two groups were similar for age, body mass index, sex distribution, stone density, operation laterality and Clavien score for complications. The most common bacteria isolated from stone cultures were *E.coli*, followed by *Pseudomonas* spp and *Proteus* spp. However, *Pseudomonas* spp was the most common bacteria isolated from renal pelvic urine culture, followed by *E.coli* and *Proteus* spp. The preoperative and postoperative data were summarized in Table 1. In cefazolin group, 60 (28.6%) patients were in high-risk and 150 (71.4%) were in low-risk; whereas in ceftriaxone group, 128 (27.8%) were in high-risk and 333 (72.2%) were in low-risk (Table 2). The demographical data according to the given antibiotic was shown in Table 2. The mean stone burden of the cefazolin and ceftriaxone given patients were 584.39 ± 599.84 and 488.31 ± 478.35 for all patients, 959.34±729.51 and 859.10±561.82 for high-risk subgroup. No statistically significant difference was found between the two groups for stone burden, both in all patients and in high-risk subgroups (P=0.075 and P=0.303, respectively).

No statistically significant difference was found between cefazolin and ceftriaxone group for SIRS (P=0.056) in all patients. Also, in low-risk patients, there was no statistically significant difference between cefazolin and ceftriaxone group for SIRS (P=0.716). In high-risk group, SIRS rates were significantly higher in cefazolin group compared to ceftriaxone group (P=0.001) (Table 3).

DISCUSSION

Preoperative antibiotic prophylaxis is recommended to all patients undergoing PCNL despite a negative baseline urine culture because it significantly reduced the rate of postoperative fever and other complications[9]. There are several drugs recommended for antibiotic prophylaxis in PCNL,

Table 1: Demographic characteristics of all patients

Variable	High-risk group (n=188)	Low-risk group (n=483)	*P*
Postoperative SIRS			0.004
(+)	31	42	
(-)	157	441	
Preoperative antibiotic			0.829
Cefazolin	60	150	
Ceftriaxone	128	333	
Age (years)	50(8-82)	48(14-82)	0.388
BMI (kg/m^2)	26.1(17.3-43.3)	26.1(16-43)	0.562
Sex			0.472
Female	67(35.6%)	158(32.7%)	
Male	121(64.4%)	325(67.3%)	
Previous SWL			0.003
(+)	21(11.2%)	101(20.9%)	
(-)	167(88.8%)	379(79.1%)	
Stone type			<0.001
Staghorn	104(55.3%)	85(17.6%)	
Not Staghorn	84(44.7%)	398(82.4%)	
Stone density (HU)	1120(400-1824)	1000(170-3200)	0.077
Stone size (mm^2)	623.3(314-2951.6)	266.9(34.5-2869.2)	<0.001
Operation laterality			0.959
Right	93(49.5%)	240(49.7%)	
Left	95(50.5%)	243(50.3%)	
Blood transfusion			<0.001
(-)	165(87.8%)	458(94.8%)	
(+)	23(12.2%)	25(5.2%)	
Clavien score			0.053
0	141(75%)	390(80.8%)	
1	22(11.7%)	45(9.3%)	
2	16(8.5%)	19(3.9%)	
3	8(4.3%)	20(4.1%)	
4	1(0.5%)	8(1.7%)	
5	0	1(0.2%)	
Residual stone			0.010
(-)	140(74.5%)	398(82.4%)	
(+)	42(22.3%)	64(13.3%)	
Clinically insignificant*	6(3.2%)	21(4.3%)	
Operation duration	120(30-300)	90(30-300)	<0.001
Access number			<0.001
1	150(79.8%)	455(94.2%)	
2	37(19.7%)	26(5.4%)	
3	1(0.5%)	2(0.4%)	
Access location			<0.044
Upper calyx	11(5.9%)	31(6.4%)	
Middle calyx	70(37.2%)	163(33.7%)	
Lower calyx	107(56.9%)	287(59.4%)	
Renal pelvis	0	2(0.4%)	
Hospitalization time (days)	4(2-15)	3(1-47)	<0.001
Preoperative urine culture			<0.001
(+)	26(13.8%)	14(2.9%)	
(-)	162(86.2%)	469(97.1%)	
Stone culture			<0.001
(+)	46(24.5%)	33(6.8%)	
(-)	142(75.5%)	450(93.2%)	
RPUC			0.130
(+)	10(94.7%)	14(2.9%)	
(-)	178(5.3%)	469(97.1%)	

SIRS: systemic inflammatory response syndrome; BMI: body mass index; SWL: shock wave lithotripsy; HU: Hounsfield unit; RPUC: renal pelvic urine culture

*The term clinically insignificant residual fragment implies ≤4mm

Table 2: Demographic characteristics of patients according to given antibiotic

Variable	Cefazolin (n=210)	Ceftriaxone (n=461)	*P*
Postoperative SIRS			0.056
(+)	30(14.3%)	43(9.3%)	
(-)	180(85.7%)	418(90.7%)	
Risk stratification			0.829
High risk group	60(28.6%)	128(27.8%)	
Low risk group	150(71.4%)	333(72.2%)	
Age (years)	50(20-82)	47(8-77)	0.096
Sex			0.191
Female	63(30.0%)	162(35.1%)	
Male	147(70.0%)	299(64.9%)	
Previous SWL			0.003
(+)	52(24.8%)	70(15.2%)	
(-)	158(75.2%)	391(84.8%)	
Stone type			0.732
Staghorn	61(29.0%)	128(27.8%)	
Not staghorn	149(71.0%)	333(72.2%)	
Stone size (mm^2)	329.7 (70.7-2512)	319.5 (34.5-2951.6)	0.075
Operation laterality			0.171
Right	96(45.7%)	237(51.4%)	
Left	114(54.3%)	224(48.6%)	
Use of catheter			<0.001
None	4(1.9%)	2(0.4%)	
Ureteric catheter	172(81.9%)	351(76.1%)	
DJ catheter	10(4.8%)	57(12.4%)	
Nephrosthomy catheter	0	17(3.7%)	
Re-entry	24(11.4%)	34(7.4%)	
Blood transfusion			0.673
(-)	193(91.9%)	429(93.0%)	
(+)	17(8.1%)	32(7.0%)	
Clavien score			0.036
0	135(64.3%)	396(85.7%)	
1	41(19.5%)	26(5.6%)	
2	20(9.5%)	15(3.3%)	
3	10(4.8%)	18(3.9%)	
4	4(1.9%)	5(1.1%)	
5	0	1(0.2%)	
Residual stone			<0.001
(-)	146(69.5%)	392(85.0%)	
(+)	48(22.9%)	58(12.6%)	
Clinically insignificant	16(7.6%)	11(2.4%)	
Operation duration (minute)	110(40-230)	90(30-300)	<0.001
Access number			0.033
1	182(86.7%)	423(91.8%)	
2	28(13.3%)	35(7.6%)	
3	0	3(0.7%)	
Access location			0.581
Upper calyx	11(5.2%)	33(7.1%)	
Middle calyx	72(34.3%)	161(34.9%)	
Lower caliyx	127(60.5%)	265(57.5%)	
Renal pelvis	0	2(0.5%)	
Hospitalization time (days)	3(1-13)	3(1-47)	0.145
Preoperative urine culture			0.158
(+)	8(3.8%)	32(6.9%)	
(-)	202(96.2%)	429(93.1%)	
Stone culture			0.656
(+)	23(11.0%)	56(12.1%)	
(-)	187(89.0%)	405(87.9%)	
Renal pelvic urine culture			0.180
(+)	11(5.2%)	13(2.8%)	
(-)	199(94.8%)	448(97.2%)	

SIRS: systemic inflammatory response syndrome; SWL: shock wave lithotripsy; HU: hounsfield unit

Table 3: Comparison of SIRS positivity between cefazolin and ceftriaxone according to risk groups

Patient group	Cefazolin	Ceftriaxone	*P*
All patients			0.056
SIRS (+)	30(14.3%)	43(9.3%)	
SIRS (-)	180(85.7%)	418(90.7%)	
Low risk group			0.716
SIRS (+)	12(8%)	30(9%)	
SIRS (-)	138(92%)	303(91%)	
Total	150	333	
High risk group			0.001
SIRS (+)	18(30%)	13(10.2%)	
SIRS (-)	42(70%)	115(89.8%)	
Total	60	128	

SIRS: systemic inflammatory response syndrome

however no clear recommendations have been made for choosing which antibiotic in which condition.

Many different criteria and endpoints were used in the previous studies investigating the post-PCNL infectious complications. Mostly postoperative fever[10-13] was used as an end point and less commonly SIRS[14,15], sepsis[16] and septic shock were used[17]. Fever at immediate post-operative period may not be a sign of infection. Post-operative fever was reported as 39.8% within the postoperative 24 h of PCNL, however it was reduced to 13% after 1st post-operative day[14]. In the former study, it was concluded that fever after 1st postoperative day is more likely to be of bacterial origin and thus can be used to predict post operative infection. In the present study, we used SIRS criteria[8] as an end point.

Preoperative factors including positive preoperative urine culture, stone size and intraoperative factors including operative time, multiple punctures, positive renal pelvic urine culture and positive stone culture are the most common factors which are known to be associated with SIRS or postoperative fever[6,7]. PCNL for larger stones generally carries higher risk of complication, and moreover it was reported that renal calculi greater than 20 mm have greater risk of carrying infectious agents compared to 20 mm or less[18].

There is only one randomized controlled trial comparing antibiotic prophylaxis (single dose, 1g, intravenous cefotaxime) with placebo[19]. No statistically significant difference was detected, however the power of this study is too low due to the limited number of patients. Some authors proposed extended antibiotic prophylaxis to prevent postoperative infectious complications. Mariappan *et al* studied one week of ciprofloxacin before PCNL, whereas Bag *et al* studied one week of nitrofurantoin before PCNL[20,21]. In both studies, authors concluded that extended antibiotic prophylaxis before PCNL significantly reduces upper tract infection and urosepsis.

Only a few studies investigated the superiority of one antibiotic over the other in terms of prophylaxis before PCNL[4,5]. Demirtas *et al* compared ciprofloxacin with ceftriaxone for the prophylaxis with the end point of SIRS[5]. They compared the duration of prophylaxis besides the effectiveness of both drugs. In that study, no statistically significant difference was found between the two antibiotics in terms of SIRS. Although they didn't stratify the patients into risk groups for infectious complications, when analyzed in detail in patients with higher stone burden, longer operative time and multiple access, higher rates of SIRS was present in ciprofloxacin group compared to ceftriaxone group.

Seyrek *et al* compared sulbactam-ampicillin and cefuroxime for the prophylaxis of PCNL[4]. Additionally, they also investigated the duration of antibiotic prophylaxis. They concluded that cefuroxime and sulbactam-ampicillin have similar efficiency to prevent infectious complications after PCNL. They randomized the patients, no risk groups for infectious complications were defined and thus the possible difference in the efficacy of both drugs in the risk group is unknown.

Widespread use of broad-spectrum antibiotics may lead to increase in antibiotic resistance in the population. Thus, it is important to choose the best fit drug for the patient rather than giving the same antibiotic to all. In this regards, the infectious risk of the patients undergoing PCNL should be determined and they should be stratified into risk groups, and the type of antibiotic should be chosen accordingly.

Our study is different from the others, that we defined a risk group for infectious complications and compared the efficacy of cefazolin and ceftriaxone in between low risk and high-risk groups. Similar to previous studies[4,5], no statistically significant difference was found between the two antibiotics for SIRS in all patients in the present study. When the patients were divided into risk groups, SIRS rates were similar in low-risk group for cefazolin and ceftriaxone, whereas SIRS rate was significantly higher in high risk group for cefazolin compared to ceftriaxone.

Limitations of the present study include its retrospective design, lack of a standardized risk group definition in the literature and inadequate data about the resistance rates for the used antibiotics in our institution.

CONCLUSION

A risk adapted approach is important for selecting the type of antibiotic for prophylaxis in PCNL. In patients with larger stones, urinary tract infection history and if the estimated operation time is long and

multiple access is planned, a wide spectrum antibiotic should be chosen for prophylaxis. In the present study, we found that ceftriaxone is superior to cefazolin in terms of post PCNL SIRS in high-risk patients.

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Author's contribution: Ibrahim H Bozkurt designed the study, and wrote and edited the manuscript; Ismail Basmaci and Anil Eker collected the data; Ertugrul Sefik designed the study, collected the data and edited the manuscript; Serdar Celik and Tansu Degirmenci analysed the data.

Conflict of interest: None

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Original Article

Evaluation of the postoperative analgesic efficacy of a catheter placed into the pectoral region using an open technique in patients undergoing modified radical mastectomies, a clinical trial

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ABSTRACT

Objectives*:* The aim of this study was to examine the effects of local anesthetics delivered through a catheter inserted in the pectoral and axillary nerves using an open technique to treat persistent post-mastectomy pain syndrome (PPMPS).
Design: A randomized, prospective, clinical study
Setting: Istanbul University- Cerrahpasa, Cerrahpasa School of Medicine, Istanbul, Turkey
Subject: Eighty-six adult females aged 18-80 years who underwent modified radical mastectomy (MRM)
Interventions: At the end of the surgery, group I was infused with 100 mg tramadol. Group II had a peripheral block catheter placed in the pectoral area just before closing the surgical area.
Main outcome measures: All patients were evaluated for postoperative 1-24 hr visual analog scores (VAS), mean arterial pressure, heart rate, postoperative nausea and vomiting (PONV), and additional analgesic requirements. Motor and sensorial block levels were examined.
Results*:* The immobile and mobile VAS scores at all time intervals, PONV scores, and 90th day median VAS scores were lower in group II than in group I (P<0.001, P<0.01, P<0.001, P<0.01, respectively). More patients used additional analgesic in group I than in group II (P<0.0001).
Conclusions: Local anesthesia given through a peripheral block catheter placed on the brachial plexus in patients undergoing MRM may be effective in preventing PPMPS.

KEY WORDS: brachial plexus, modified radical mastectomy, peripheral block, persistent post-mastectomy pain syndrome, postoperative pain

INTRODUCTION

Breast cancer occurs in 1 out of every 8 women in the world and is generally prevalent in the young adult population. Breast cancer causes psychological problems due to organ loss, fear of death and separation from the family. The anxiety caused by these problems may cause additional pain in the perioperative period, as well as hemodynamic instability (tachycardia, hypertension, etc.)[1]. Surgery by radical mastectomy or axillary curettage (also referred to as modified radical mastectomy (MRM)) is the main treatment choice, but it is frequently accompanied by persistent post-mastectomy pain syndrome (PPMPS) in 20-40% of patients. Postoperative radiotherapy is a further contributor to the persistence of pain. PPMPS can develop within a short time or at different times after surgery. When this pain occurs later than three months after surgery, it is defined as neuropathic pain[2].

A painless period during and after mastectomy may prevent the development of PPMPS. Therefore,

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effective perioperative pain treatment can increase the quality of life after surgery and facilitate a return to normal life. Many techniques have been tested for post-mastectomy pain treatment, including thoracic epidural blocks, wound infiltration blocks, intercostal blocks, and pectoral nerve block (PECS). However, none of these techniques is fully successful in pain treatment for a number of reasons[3]. For example, the inadequacy of imaging techniques or inexperience of the practitioner may result in application of drugs to the wrong area. These techniques are also invasive, so ultrasound should be used to avoid complications, but every clinic may not be adequately equipped with ultrasound equipment[4].

In the present study, our primary aim was to investigate the effect of local anesthetics given through a catheter inserted into the pectoral and axillary nerves by an open technique for the treatment of early postoperative pain. Our secondary aim was to determine the benefits of this open catheter placement technique in preventing the development of PPMPS.

SUBJECTS AND METHODS

This randomized prospective clinical study was conducted on 86 American Society of Anesthesiologists Physical Status I-II (ASA) adult females between 18-80 years of age who were scheduled to undergo MRM. The study was approved by the Ethics Committee of Istanbul University- Cerrahpasa, Cerrahpasa School of Medicine (No: 83045809/604.01) and written informed consent was obtained from all patients. The study was registered with the www.clinicaltrials.gov protocol registration system (NCT03204708). Patients with a history of local anesthetic allergy or anticoagulant use, patients with central or peripheral nerve diseases, and male patients were excluded from the study. The study was conducted between April 2016 and February 2017.

Patients were taken to the preoperative anesthesia room, where a 20 G intravenous cannula was secured on the dorsum of the hand contralateral to the breast to be operated on. An infusion of balanced electrolyte solution was started at a rate of 2 ml/kg/h, and premedication was achieved with 0.03 mg/kg iv midazolam. The patients were taken to the operation room and connected to standard monitors (peripheral oxygen saturation, electrocardiography and non-invasive blood pressure). Anesthesia was induced with 2 mg/kg propofol and 2 μg/kg fentanyl. Following the start of hypnosis, 0.6 mg/kg rocuronium was administered and endotracheal intubation was performed. Anesthesia was maintained with 2% sevoflurane in a 40% oxygen/air mixture in a 4 L fresh gas flow. Patients were ventilated in the pressure-controlled mode at 7 cm H_2O positive end-expiratory pressure with a 1:2 inspiratory to expiratory ratio, respiratory rate between 10 and 12, a preset airway pressure of 12-14 cm H_2O to achieve $ETCO_2$ values between 32 and 36 mm Hg, and a tidal volume of 7 ml/kg. When systolic arterial pressure and heart rate increased 20% from the initial values, an additional iv. dose of 50 μg fentanyl was given.

Patients were randomized into two groups 45 minutes prior to the end of the surgery using a computer-based application (https://www.randomizer.org/). At 20 minutes prior to the end of the surgery, patients in group I (n=43) were infused with 100 mg tramadol in 100 ml 0.9% NaCl in 5-10 minutes. Patients in group II had a peripheral block catheter (Contiplex® D, BBraun, Germany) placed in the pectoral area by the surgeon general at the end of the surgery (20 minutes before extubation), but just before closing the surgical area. Catheterization was done by the same surgeon (Mehmet Velidedeoğlu) in all patients. The catheter was directed from the skin and pectoralis major muscle in the infraclavicular region near the acromion, inside the breast tissue, through a 20 G needle. The tip of the catheter was inserted and placed under the lateral one-third of the clavicle, passing through axillary vein. The catheter was advanced 3 cm above the clavicle in accordance with the axillary vein trace. This is the area where the nerves split from brachial plexus to innervate the breast and axillary region. The lateral and medial pectoral nerves, thoracodorsal nerve, nervus thoracicus longus, nervus intercostabrachialis, and 2-6 latero-anterior cutaneous intercostal nerves split from brachial plexus, just below the area we placed the pectoral catheter (Figure 1). No additional surgical incision was used for this intervention. After surgery closure, about 20 minutes before extubation, patients in group II received a bolus dose of a mixture of 20 ml 0.25% bupivacaine and 10 ml 1% lidocaine.

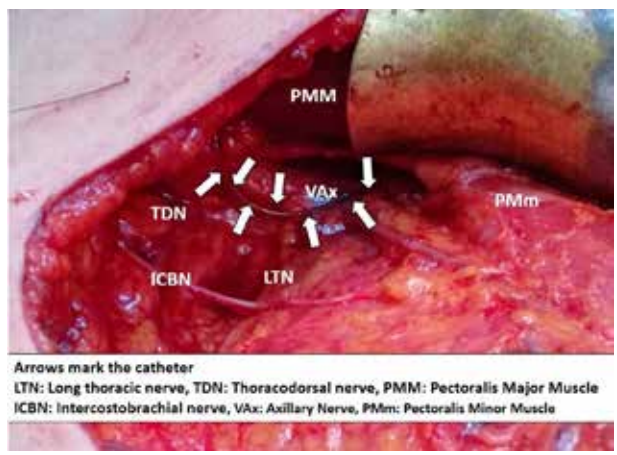

Fig 1: Catheter placement in the pectoral area

Patients in both groups were extubated with 0.15 mg/kg atropine and 0.03 mg/kg neostigmine when their spontaneous breathing effort was adequate and then taken to the post anesthesia care unit. Patients were released to the ward when their Aldrete scores were 9 or above. Further evaluations included the postoperative 1st, 6th, 12th and 24th hour visual analog scale (VAS) scores, temperature, mean arterial pressure, heart rate, postoperative nausea and vomiting (PONV), and additional analgesic requirements. Motor and sensorial block levels (pinprick test) were examined postoperatively at 1st hour. When the VAS scores were 4 or higher in group I, 50 mg dexketoprophen trometamol in 100 ml 0.9% NaCl was administered as a rescue analgesic, and the administration was recorded. When the VAS scores were 4 or higher in group II, the patients were administered a mixture of 5 ml of 0.5% bupivacaine and 5 ml 0.9% NaCl through the catheter.

Subsequently, at the 24th postoperative hour, the catheter was removed slowly, after the dressing was opened by the surgeon who had placed the catheter.

On the 90th postoperative day, patients were called by telephone and queried regarding VAS scores of the area of scar and shoulder or arm at rest and movement at the time of the call, burning and evoked pain, and edema in the arm. Any additional analgesic usage or complaints were noted. If VAS scores were >3 during rest and movement at the time of the call, the patient was considered to have PPMPS.

Statistical analysis

For the Shapiro-Wilk test, the normality audit was conducted using a histogram, Q-Q plot and box plot. The data were input as the mean and standard deviation. The variables that showed normal distributions between the two groups were analyzed using an independent samples t-test, and the variables not normally distributed were analyzed using the Mann-Whitney U test. The normal variables were evaluated using a chi-squared test with the Yates correction and Fisher's exact probability test. The significance was two-tailed, with a cutoff point of P <0.05. All analyses were conducted using NCSS 10 statistical software (2015, NCSS, LLC, Kayaville, UT, USA).

The number of patients included in the study was determined based on an expectation that the VAS pain score reduction rate would be 25% between the two groups, according to the results of a prior study[5]. Based on a type I error of 5% (two-tailed), a type II error of 20% (80% power), and a VAS reduction rate of 25% in the catheter group when compared to the iv analgesia group, a total of 43 patients were considered ideal for each group for evaluating postoperative acute pain and PPMPS. Taking into account the fact that a certain number of patients would be excluded from this study, we decided to include 45 patients in each group.

Table 1: Demographic data

Demographic data	Group I (n=43)	Group II (n=43)	*P*
Age (year±SD)	52.1±10.9	51.9±9.6	>0.05
BMI (kg/m²±SD)	24.8±1.6	25.1±1.9	>0.05
ASA I/II (n)	22/11	23/12	>0.05

ASA: American Society of Anesthesiologists physical status; BMI: body mass index; SD: standard deviation; n: number

Table 2: Acute pain, hemodynamic parameters, PONV and additional analgesic requirement according to groups

Groups	Parameters	1st hour	6th hour	12th hours	24th hours
Group I (n=43)	VAS immobile	4.1±0.3	4.0±0.6	4.3±0.4	3.8±0.5
	VAS mobile	5.3±0.2	5.2±0.5	5.3±0.6	4.3±0.6
	Mean Art Press (mmHg)	76.7±38.0	65.4±27.4	68.9±26.3	60.3±28.5
	Heart rate (beat/min)	88.4±23.6	80.6±42.7	83.5±33.6	70.4±32.3
	PONV	2.1±0.2	1.4±0.4	0	0
	Add. Analg (n)	20	18	13	0
Group 2 (n=43)	VAS immobile	2.2±0.2**	2.4±0.5**	2.3±0.7**	0±0.4***
	VAS mobile	3.7±0.5**	3.1±0.3**	2.8±0.6**	1.3±0.7***
	Mean Art Press (mmHg)	70.4±34.9*	65.8±25.8	65.5±34.2	60.8±21.4
	Heart rate(beat/min)	80.5±26.8*	75.7±27.4*	75.4±35.4*	72.5±28.3
	PONV	0***	0***	0	0
	Add. Analg (n)	0***	0***	0***	0***

All data are given as ±SD.
VAS: visual analog scale; PONV: postoperative nause and vomiting; Add analg: number of patients required additional analgesic; SD: standard deviation; n: number
*P<0.05 group I compared to group II.
**P<0.01 group I compared to group II.
***P<0.001 group I compared to group II.

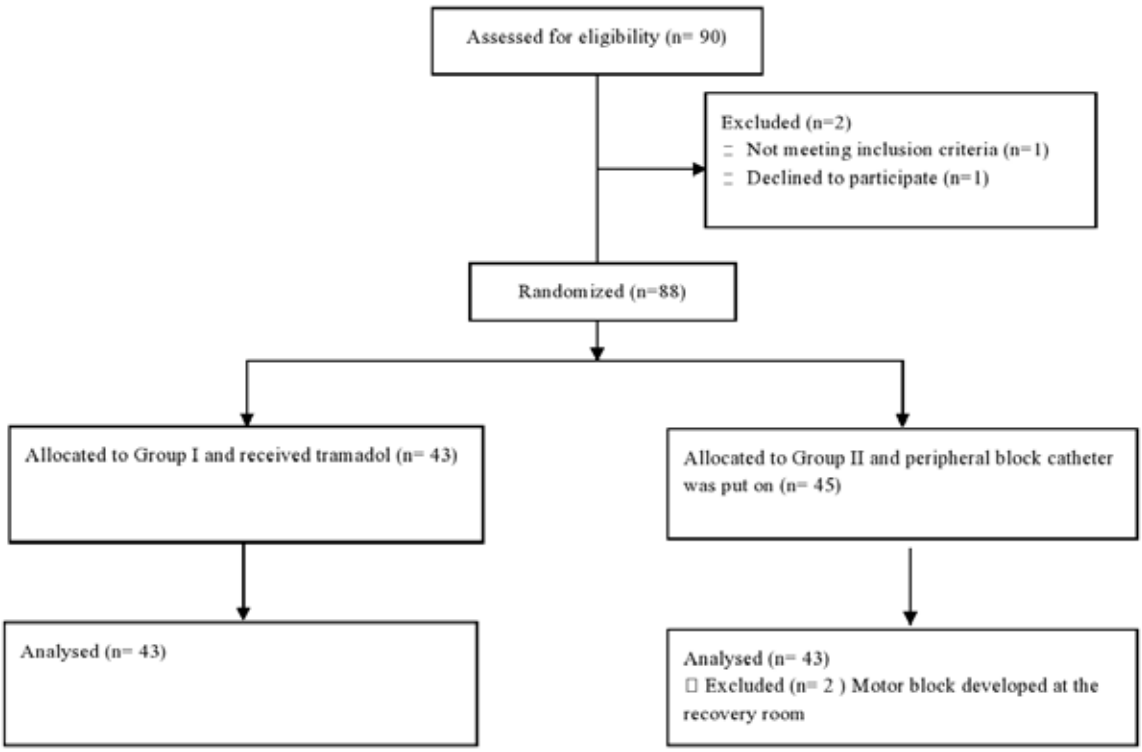

Fig 2: Consort flow diagram of the study

RESULTS

No significant differences were observed between the two groups in terms of demographic data and ASA scores (Table 1).

The immobile and mobile VAS scores were lower in group II than in group I for all time intervals (P<0.001, P<0.01, respectively; Table 2).

The mean arterial pressure was lower at the 1st hour in group II than in group I (P<0.05, Table 2). Heart rates at the 1st, 6th and 12th hours were lower in group II than in group I (P<0.05, Table 2).

The PONV scores were lower at the 1st and 6th hours in group II than in group I (P<0.001, Table 2). The PONV scores at other times were similar in both groups. Additional analgesic requirements were lower in group II than in group I (P<0.001, Table 2).

The 90th day median VAS scores when mobile and immobile were lower in group II than in group I (P<0.001, Table 3). The number of patients diagnosed as having PPMPS and requiring additional analgesic was higher in group I than in group II (P<0.0001) (Table 3). The occurrence of edema in the arm was similar in both groups (Table 3).

The sensorial block at 1st hour after the operation was at level of T1-T8 in 18 patients (40%), T1-T10 in 10 patients (22.2%), T2-T8 in 15 patients (33.3%), and T2-T4 in 2 patients (4.4%) (Table 4). In two patients in group II, a motor block developed in the forearm and elbow and their catheters were removed in the postoperative unit. These two patients were not included in the final evaluation (Figure 2).

Table 3: VAS, PPMPS, edema and analgesic requirement at 90th day according to groups

VAS scores	Group I (n=43)	Group II (n=43)	*P*
VAS mobile (±SD)	4.2±1.1	1.1±0.2	<0.001
VAS immobile (±SD)	5.4±1.6	1.2±0.6	<0.001
PPMPS (n)	13	0	<0.0001
Edema (n)	0	0	>0.05
Add Analg (n)	15	0	<0.0001

VAS: visual analog scale; PPMPS: persistent post-mastectomy pain syndrome; n: number; SD: standard deviation; Add analg: number of patients required additional analgesic

Table 4: Pin prick and motor block levels of group II at 1st hour after the operation (n=45)

Pin prick and motor block	Dermatomes involved			
	T1-T8	T1-T10	T2-T8	T2-T4
Pin prick (n) (%)	18 (40.0%)	10 (22.2%)	15 (33.3%)	2 (4.4%)
Motor block (n) (%)	0	2 (4.4%)	0	0

n: number of patients; T: thoracic.

DISCUSSION

This study describes the first use of an open catheter insertion technique through to the brachial plexus in the operation area of MRM. In this technique, the peripheral nerve catheter is placed under the clavicle on the axillary vein tracing and on the clavipectoral fascia so that it falls outside the nerve sheath and into the division part of the brachial plexus. A local anesthetic drug delivered from the inserted catheter then spread downward through the hole of the catheter due to gravity. With this spread, the block consists of the lateral and medial pectoral nerves, the upper subscapular nerve (T4), the intercostabracial nerves, and the nervus thoracicus longus (T8), which are the nerves in the area of axillary curettage performed during MRM[6]. In our study, our aim was to increase the efficacy of the drug by delivering a large volume. In addition, this block, with the intercostabracial nerves originating in the T2 cutaneous sensory nerve, constitutes a sensorial block that includes the upper inner arm, the axilla, and the upper outer quadrant of the breast. The cutaneous sensorial branch of T2 is also the nerve responsible for phantom pain (occurring in 17.4% of patients) and the burning-stinging after mastectomy[7,8].

Today, several postoperative analgesia techniques are used following MRM. These techniques include intravenous analgesia, but central and peripheral nerve blocks are the most preferred ones. Epidural analgesia is the gold standard in the treatment of postoperative analgesia; however, its use in breast surgery is still limited. The reason for this is the hemodynamic changes that arise due to the large volume of local anesthetic that must be used for effective analgesia[9,10].

The PECS blocks described by Blanco are now widely used. In fact, the region of the PECS I and II blocks is similar to the block area we provided in the current study[6]. An ultrasonography device is required for PECS blocks, and this necessitates a physician competent with this device[6]. By contrast, our technique requires no ultrasonography, because the catheter is visible in the surgical area during insertion. Consequently, our technique carries little risk of complications and failure of insertion or of application of the drug to the wrong area. In addition, inserting the catheter takes only a few seconds, so the duration of anesthesia is shortened.

In our study, the patients in group II had lower VAS scores and required no additional analgesics. These group II patients were also more stable hemodynamically. No PONV was observed in group II, whereas group I patients displayed PONV at the 1st and 6th postoperative hours. The pain scores and additional analgesic requirements at the 1st, 6th and 12th hours were also higher in the group I patients. We preferred lidocaine as an initial local anesthetic for the rapid onset of the block applied to group II, and we added bupivacaine as a long-acting analgesic. Therefore, the analgesic effect of the block had a rapid onset, as well as a long duration. The VAS scores and additional analgesic requirements were higher in group I at the 90th day, and more patients in group I developed PPMPS.

Thomas *et al*[11] gave ropivacaine by an infiltration technique in one group after surgery in their prospective randomized controlled triple-blind study of 60 patients undergoing MRM. They gave 20 ml of ropivacaine to the fascia on the serratus anterior and 10 ml to the fascia between the pectoralis major and minor at the level of the third rib (PECS II). In their control group, the same techniques were applied, but saline was infiltrated into the same regions. They found that the pain scores and analgesic requirements were significantly lower in the patients administered ropivacaine and PECS II than in the control group. This technique by Thomas *et al*[11] was similar to ours in terms of making the block from the open surgical field. However, the infiltration of the block and the type of local anesthetic used were different. Thomas *et al*[11] also did not focus on PPMPS development in their study.

Razek *et al*[12] in their study published in 2018 compared PECS and a serratus anterior intercostal plane block (SIPB) applied to the fascia between the serratus anterior and the intercostal external muscles for the treatment of intra- and postoperative pain in breast surgery. Their prospective clinical study showed that both techniques, in combination with general anesthesia, provide sufficient analgesia for post-mastectomy pain with or without axillary curettage. They also showed that the SIPB was more successful than PECS for the treatment of postoperative pain. In SIPB, the local anesthetic drug is introduced between the serratus anterior and the external intercostal muscles using ultrasonography. Therefore, the drug is given through the location where the brachial plexus is not separated into anterior and posterior branches and the block level is between T2-T9. In addition, the thoracic longus and thoracodorsal nerves in this region are blocked and a sensorial block develops.

In our study, we placed the catheter before the branching of the brachial plexus and a block extending up to T8 developed. Therefore, the level of analgesia in our block technique is similar to the level of analgesia achieved by the PECS and SIPB techniques. The advantage of our technique was that we made the block under direct visualization to reduce intervention-related failure rate. When we consider that not every

clinic has readily available ultrasound equipment, this is a major benefit of our procedure.

One of the limitations of our study is that we did not infuse the local anesthetic from the peripheral catheter. If we perform local anesthetic infusion in future, we might provide longer postoperative pain treatment with safer borders. A second limitation is that we did not survey our patients for chronic pain. In future, we could query the patients about chronic pain by examining their VAS scores beyond 90 days and subsequent to radiotherapy treatments.

CONCLUSION

In conclusion, we suggest that analgesia provided by local anesthesia given through a peripheral block catheter placed on the brachial plexus in patients undergoing MRM may be effective in the treatment of post-mastectomy pain and for prevention of PPMPS. Further randomized prospective clinical studies are needed to confirm this possibility.

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Author contribution: All authors contributed to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafted the work or revised it critically for important intellectual content; gave final approval of the version to be published; and have agreed 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.
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Original Article

Total ischemia time and delayed graft function in recipients of deceased donor kidney transplant: a single center experience

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ABSTRACT

Objectives: Delayed graft function (DGF) is a well-known complication following kidney transplant. Ischemia time is one of several factors known to contribute to its development. The unique set up of the transplant service in Kuwait helps to achieve a shorter ischemia time than average compared to many other programs. We aim to study the association between the total ischemia time (TIT) and DGF, as well as other related common risk factors in this set up.
Design: A single-center retrospective medical records review
Setting: Kuwait Organ Transplant Center
Subjects: All recipients of brain-dead deceased donor kidney transplant from January 2016 to December 2021
Intervention: No intervention
Main outcome measures: The effect of TIT on developing DGF was studied, as well as other risk factors of DGF related recipients and donors.
Results: A total of 180 kidney transplant recipients were included. DGF rate was 33% for the entire period with a significant decrease in the rate over the years, along with a significant decrease in the median TIT. Compared to TIT of less than 6 hours, increasing the time to 6-8 or 8-10 hours can result in over 3x the risk of DGF ($P<0.05$).
Conclusions: Since DGF is a multi-factorial event, having a shorter TIT than average was not enough to result in a very low DGF rate. However, we demonstrated that even within the generally considered short ischemia times, to achieve shorter than 6 hours can potentially reduce DGF significantly.

KEY WORDS: delayed graft function, ischemia time, kidney transplant

INTRODUCTION

Delayed graft function (DGF) is one of the feared early complications of kidney transplant due to its known implication on graft survival[1]. It also results in a longer hospital stay and added costs[2]. Though there are different definitions for it, the most widely used one is the need for dialysis in the first week following a kidney transplant.

It is a multi-factorial event with several implicated risk factors on both donor and recipient sides as well as perioperative factors. Donor-related factors include donation after brain or cardiac death, age, body mass index (BMI), ischemia time, race and gender[3]. On the recipient side, these factors include gender, age, BMI, diabetes, history of previous transplant, panel reactive antibody and pretransplant dialysis[3].

Once a transplant patient is affected by DGF, treatment options are limited and not very effective[4], though some studies suggest that a full recovery from DGF can improve the outcome[5]. Due to that, the focus has always been more on preventing or decreasing its risk. On the other hand, the shortage of organs and pressure from long waiting lists, with its associated risk of mortality, have pushed many programs towards utilizing marginal grafts with higher risks of DGF.

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Table 1: Baseline recipients' data

Recipients' factors	Total	DGF		OR	95%CI	*P*-value
		No	Yes			
Number of patients	180	121	59			
Gender						
Male	116 (64.4)	72 (59.5)	44 (74.6)	1	0.25 - 0.99	0.049*
Female	64 (35.6)	49 (40.5)	15 (25.4)	0.50		
Age	40.8 ± 14.8 (39)	40.2 ± 14.5 (39)	42.0 ± 15.5 (39)	1.01	0.99 - 1.03	0.459
BMI						
<25	77 (43.5)	55 (45.8)	22 (38.6)	1		0.663
25-30	60 (33.9)	39 (32.5)	21 (36.8)	1.35	0.65 - 2.78	0.422
>30	40 (22.6)	26 (21.7)	14 (24.6)	1.35	0.60 - 3.05	0.475
Diabetes mellitus						
No	127 (71.3)	88 (72.7)	39 (68.4)	1	0.62 - 2.45	0.554
Yes	51 (28.7)	33 (27.3)	18 (31.6)	1.23		
HTN						
No	33 (18.5)	24 (19.8)	9 (15.8)	1	0.57 - 3.06	0.518
Yes	145 (81.5)	97 (80.2)	48 (84.2)	1.32		
Waiting time	646.3 ± 607.9 (460)	561.8 ± 513.1 (406.5)	815.3 ± 739.3 (582)	1.0007	1.0001 - 1.0012	X0.012*

*P<0.05; **P<0.01; ***P<0.001
DGF: delayed graft function; OR: odds ratio; CI: confidence interval; BMI: body mass index; HTN: hypertension

The kidney transplant program in Kuwait is the first such program among the Arabian Gulf countries, with the first kidney transplant performed in February 1979. The program was dependant mainly on living related donation. However, over the past two decades, there have been more deceased donation from brain-dead donors, leading to almost half of all transplanted kidneys in some of the recent years coming from deceased donors. All kidney transplants in Kuwait take place in a single dedicated center with reasonably short travel distance from all the general hospitals in the country, where the donor surgeries take place. Furthermore, almost always, when both kidneys from the same donor are utilized, both recipients' surgeries take place simultaneously in two different operating rooms.

In view of this, we aimed to look at the rate of DGF in Kuwait over the past six years among recipients of deceased donor kidney transplant. In addition, different contributing factors were analyzed comparing the two groups of patients (DGF vs no DGF), with more focus on the effect of the total ischemia time (further dividing this time into cold and warm ischemia time was not available).

SUBJECTS AND METHODS

All recipients who had deceased donor kidney transplant in Kuwait at Hamid Al-Essa Organ Transplant Center between January 2016 and December 2021 were included in this study. All the required clinical and laboratory data were retrieved from transplant database and patients' medical charts after approval from the Institutional Review Board. Patients with missing pre-transplant and day 7 serum creatinine values, or those who died within the first week post-transplant, were excluded.

Definitions

DGF was defined as the need for dialysis during the first week post-transplant. Immediate graft function was defined as a drop of serum creatinine by 70% or more on day 7 compared to the pre-transplant value, while those who didn't achieve that were considered to have a slow graft function. Extended criteria donor was defined as any donor 60 years of age or more, or a donor between 50 and 59 years of age with at least two of the following: cerebrovascular cause of death, history of hypertension, or terminal creatinine >1.5 mg/dL (132.6 μmol/L). Total ischemia time (TIT) is the time from cross clamping the abdominal aorta in the donor surgery, till the time of reperfusion of the donor kidney in the recipient surgery.

Immunosuppression

Induction immunosuppression is done with basiliximab for recipients with less than 4 HLA mismatch. Those with 4 or more mismatches are induced with antithymocyte globulin. Maintenance immunosuppression consists of steroids, tacrolimus, and mycophenolate mofetil (or mycophenolic acid). Steroids are omitted in cases of zero mismatch.

Statistical analysis

The data were analysed using the Statistical Package for the Social Science (SPSS version 21.0). Descriptive analysis for continuous variables was

Table 2: Donors' data

Donors' factors	Total	DGF		OR	95%CI	*P*-value
		No	Yes			
Number of patients	180	121	59			
Gender					1.02 - 4.92	0.045*
Male	149 (82.8)	105 (86.8)	44 (74.6)	1		
Female	31 (17.2)	16 (13.2)	15 (25.4)	2.24		
Age	43.1 ± 9.3 (43)	42.8 ± 9.3 (43)	43.7 ± 9.4 (44)	1.01	0.98 - 1.05	0.501
Type					0.81 - 5.12	0.129
SCD	159 (88.3)	110 (90.9)	49 (83.1)	1		
ECD	21 (11.7)	11 (9.1)	10 (16.9)	2.04		

*P<0.05; **P<0.01; ***P<0.001
DGF: delayed graft function; OR: odds ratio; CI: confidence interval; SCD: standard criteria donors; ECD: expanded criteria donors

computed, e.g., mean and standard deviation, and median and interquartile range. Categorical variables were presented as frequency tables. Binary logistic regression models were used to explore the association between covariates and DGF. Results are presented as odds ratios, 95% confidence intervals and *P*-value. *P*-value was calculated using Chi-square (χ^2) test; a *P*-value <0.05 was considered as statistically significant in all analysis.

RESULTS

During the study period, 189 deceased donor kidney transplant were performed in the Organ Transplant Center. One recipient passed away within the first 7 days post-transplant and the medical charts of eight recipients (4%) were missing, 6 of them were from the year 2017. These nine recipients were excluded and the rest of the 180 recipients were included in the analysis. The incidence of DGF in our cohort was 33% (59 recipients out of 180). Males represented almost 2/3 of all recipients (64%) and they were twice more likely to get DGF (P<0.05). Recipient age was not associated with any increased risk of DGF and a similar finding was seen with regard to the BMI. Neither the history of diabetes, nor the history of hypertension were associated with DGF. The only other studied recipient related factor to have a statistically significant association with DGF was the waiting time before transplant with a median waiting time of 582 days for the DGF group, compared to 406.5 days for the no DGF group (Table 1).

In terms of donor related factors, only gender was found to be associated with DGF. Female donors were twice as likely to result in DGF. For the donor type (standard criteria donors (SCD) and expanded-criteria donors (ECD)), there was a trend toward more DGF with ECD donors, though it did not reach statistical significance. However, it has to be noted that only 21 (11.7%) donors in the 6-year period were considered to be ECD (Table 2).

Table 3 shows the association of the TIT with DGF for 158 recipients out of the 180 included in the study (this was missing for the other 22 recipients). Ischemia time was divided into five different categories. Those who had TIT between 6-8 hours and 8-10 hours were 3x and 3.4x respectively more likely to develop DGF compared to the ones who had less than 6 hours of TIT. Only 19 (12%) and 17 (11%) of the recipients had TIT of 10-12 hours and more than 12 hours respectively, and both categories did not result in a statistically significant difference.

Table 3: Association between DGF event and TIT

TIT categories	Total	DGF		OR	95%CI	*P*-value
		No	Yes			
Number of patients	158	107	51			
TIT						0.142
<6	39 (24.7)	32 (29.9)	7 (13.7)	1		
6-8	50 (31.6)	30 (28.0)	20 (39.2)	3.05	1.13 - 8.24	0.028*
8-10	33 (20.9)	19 (17.8)	14 (26.5)	3.37	1.16 - 9.82	0.026*
10-12	19 (12.0)	13 (12.1)	6 (11.8)	2.11	0.59 - 7.49	0.248
>12	17 (10.8)	13 (12.1)	4 (7.8)	1.41	0.35 - 5.63	0.630

*P<0.05; **P<0.01; ***P<0.001
DGF: delayed graft function; OR: odds ratio; CI: confidence interval; TIT: total ischemia time

Fig 1: Graft function according to years

Over the 6-year period, there was a trend towards less DGF cases per year. The highest rate was seen in 2016 and 2018, reaching up to 50%, whereas the lowest rate was seen in 2020 with less than 17% DGF cases and the highest rate of immediate graft function at 67.7% (Fig 1). When TIT was also plotted against the years (Fig 2), a similar trend of lower median ischemia time was observed, with the lowest point been in 2020 and the highest in 2016 (P=0.03).

DISCUSSION

DGF is a significant complication of kidney transplant, especially from deceased donors. Rates in the more recent literature vary between 20-40% in

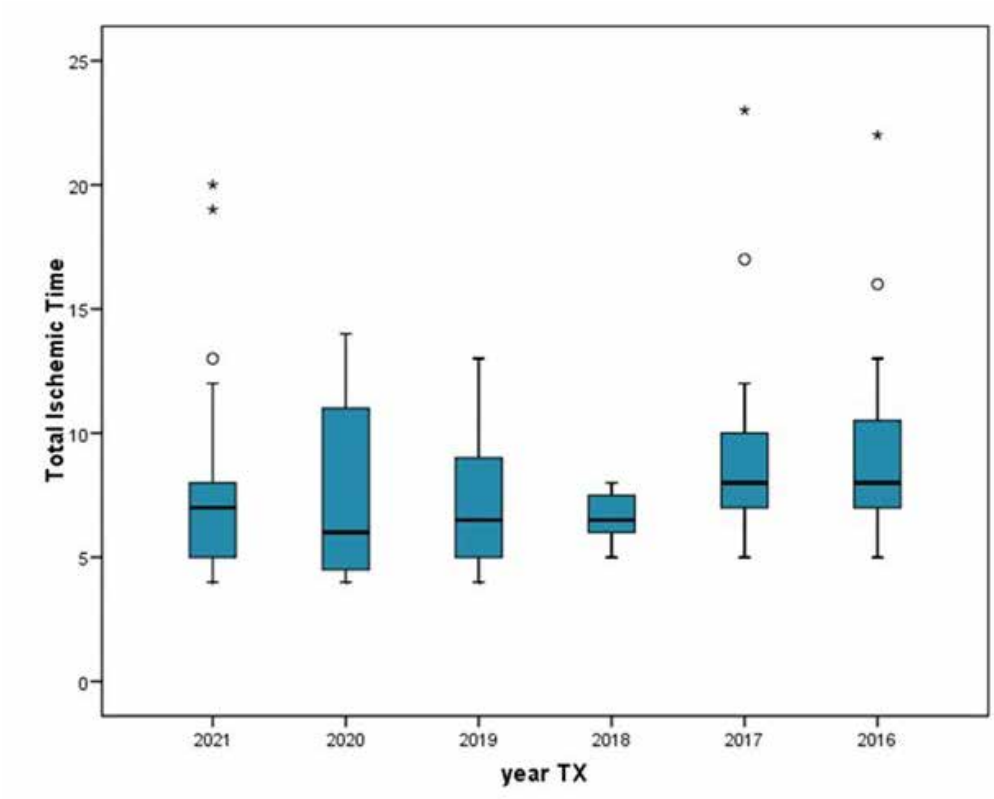

Fig 2: Total ischemic time (TIT) per year

transplants from deceased donors following brain death[6-10]. This rate goes, as expected, much higher to around 50% for donation following cardiac death[1], while it is less than 5% in the case of live donation[3]. Ischemia time is undoubtedly one of the many factors that play a role in increasing the risk of developing DGF. Given the unique set up of the kidney transplant program in Kuwait, that helps in achieving below average ischemia times compared to many other programs, and the younger donors on average, one would anticipate a lower rate of DGF. Despite this, the overall rate of DGF in our center is 33%. However, there was a clear correlation between the downward trend in DGF rate over the year and the decreasing median TIT. The low DGF rate seen in 2017 compared to 2016 and 2018 can be potentially explained by the large number of missing files in this year (6 out of the 8 for the whole study period). In a recent single center study from Finland on 896 consecutive deceased donor kidney recipients, they demonstrated a significant drop in the incidence of DGF from 31% to 24% after decreasing cold ischemia time from a mean of over 20 hours to under 16 hours[6]. In our study, even within the less than 10 hours of ischemia time, which is considered a relatively short ischemia time for deceased donors[11], there was more than a 3-fold increase in the risk of DGF between those with less than 6 hours of ischemia time and recipients with 6-8 or 8-10 hours (P<0.05).

The effect of the recipient and donor genders on the incidence of DGF has been demonstrated in various studies[12], and the same was found in our study. Male recipients and female donors were both independent risk factors for developing DGF. However, it has to be noted that the number of female donors in the study was low at 31 donors (17%), and some larger single center studies have failed to found a statistically significant difference[6,9,10]. In terms of the donor type, most of our donors are considered to be SCD at 88%. Despite being twice as likely for ECD to have DGF compared to ECD in our study, this did not reach statistical significance, unlike what the literature suggest. This is likely to be due to our small number of ECD.

Recipients' spent days on the waiting list before transplant was another independent risk factor for DGF (P=0.012). Recipients who had DGF spent an average of 8 more months on the list than those without DGF. This is probably synonymous to what other studies measure as the duration on dialysis, which is also found to significantly increase the risk of DGF[9].

Since DGF is a multi-factorial event, with at least 15 factors found in multiple studies to be implicated in its risk[12], many explanations can be found to justify the rate of DGF in our study, despite the short average ischemia time. One of the areas with many potential modifiable factors is the donor care. For example, one landmark study in 2015 found that by applying mild targeted hypothermia to brain-dead donors while in the ICU, compared to normothermia, can result in reduction of DGF incidence from 39% to 28%[13]. With the lack of a standardised donor care in Kuwait, despite all the efforts of the organ procurement team, this can potentially be a big area of improvement for the future.

An obvious limitation of this study is due to its retrospective nature. The limited number of studied factors compared to the suggested ones in the literature is due to the unavailability of many such factors in medical records for a significant number of the patients. Another one is the grouping together of both cold ischemia time and warm ischemia time (the time from the start of venous anastomosis until the time of kidney reperfusion) and hence we called it the total ischemia time.

CONCLUSION

Despite being able to achieve a very short total ischemia time, the DGF rate was not as low as anticipated, owing probably to the effect of other factors. However, this study demonstrates that even within the generally considered short ischemia times, to achieve shorter than 6 hours can potentially reduce DGF significantly.

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Case Report

Management of first branchial cleft anomalies in children and its outcome

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ABSTRACT

First branchial cleft anomalies represent a rare congenital entity with aberrant development of the first branchial cleft that usually present during childhood. Rarity and diverse clinical presentations often lead to misdiagnosis and delay in treatment. A diagnostic workup requires computed tomography or magnetic resonance imaging to define the exact location of the lesion. Surgical excision is the definitive treatment. Prognosis is often favourable with meticulous identification and preservation of facial nerve intraoperatively with parotidectomy. Herein, we report a series of three cases of first branchial cleft anomalies in pediatric patients with the aim to shed light on the management and its comparative outcomes in accordance to the different surgical and medical approaches adopted in this rare entity.

KEY WORDS: congenital anomaly, facial nerve, parotid gland

INTRODUCTION

Cervicoaural or collaural fistula was first described by Sir James Paget in 1878, which is a form of first branchial cleft anomalies. It accounts for less than 8% of all branchial cleft anomalies with higher female preponderance[1]. A brief review of embryology is of paramount importance in understanding the pathogenesis of first branchial cleft anomalies. It is also essential to apply the knowledge during surgery, particularly the relationship between the anomaly and the facial nerve. During the fourth week of human embryological development, six pairs of branchial arches appear, which are separated by five branchial clefts externally (ectoderm) and five pharyngeal pouches internally (endoderm). These branchial arches are mesodermal in origin and disappear by the seventh week. Many anomalies of the head and neck region have been attributed to the aberrant development of these structures. First branchial cleft anomalies are a result of incomplete closure of the cleft or incomplete division of the contents of the tube[2]. The parotid gland on the other hand appears at the sixth week of development with the migration of the muscle and facial nerve between sixth to eighth week. Due to the embryological development, these anomalies are closely related to the parotid gland and have variable relations to the facial nerve, hence the fistula tract may pass above, between, or below the branches of the facial nerve, postulating difficulties during surgical intervention[2,3]. Although first branchial cleft anomalies are exceedingly rare, it is imperative to discuss the optimal surgical approach to obtain the best outcome.

CASE REPORTS

Case 1

A 4-year-old girl was referred for recurrent left neck abscess. She had two previous episodes at 2 and 3 years old, which was treated with incision and drainage. On examination, there was no facial nerve palsy with the presence of a painless well-healed scar at the left infra-auricular region (Fig. 1A). External ears and otoscopic examination were normal bilaterally with no sinus opening seen. Magnetic resonance imaging

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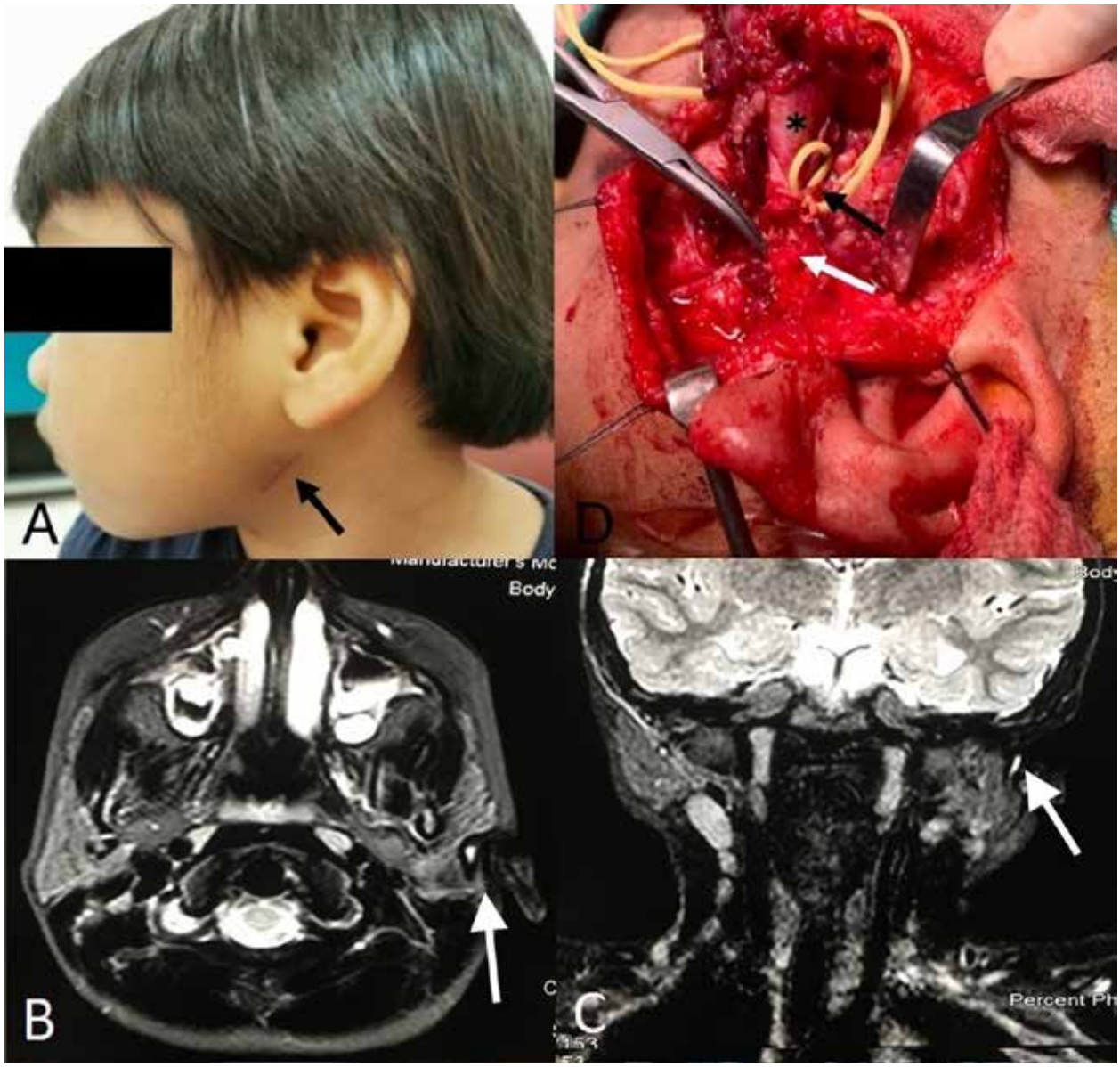

Fig 1, Case 1: A: Clinical photograph demonstrated a well healed scar at the left infra auricular region (arrow); **B,C**: T2 weighted MRI of neck - axial (B) and coronal (C) view demonstrated fistulous communication (arrow) between the left external auditory canal and cutaneous opening at the left infra auricular region; **D**: intraoperative picture showed fistula tract (*) located medial to facial nerve (black arrow) at the left parotid gland and it terminated before the skin of the cartilaginous part of the left external auditory canal (white arrow).

(MRI) of neck demonstrated fistulous communication between the cartilaginous part of left external auditory canal and the scar at the left infra-auricular previous incision site. The tract measured approximately 5cm in length and ran through the superficial lobe of the left parotid gland (Fig. 1B&C). An excision of the tract was done and completed by superficial parotidectomy. Intraoperatively, due to scarring and fibrotic changes, identification of facial nerve was extremely difficult. Therefore, facial nerve was traced via retrograde manner from the buccal branch with facial nerve monitoring. The fistula tract ran medial and deep to the facial nerve at the left parotid gland and terminated at the skin of the cartilaginous part of the left external auditory canal (Fig. 1D). The fistula was excised completely together with the superficial lobe of parotid gland, preserving the facial nerve. The child recovered well with no facial nerve and showed no recurrence at 3rd month follow up.

Case 2

A 2-year 1-month-old girl presented with recurrent right neck swelling associated with fever for two days. Prior to this, she had three episodes of hospitalization

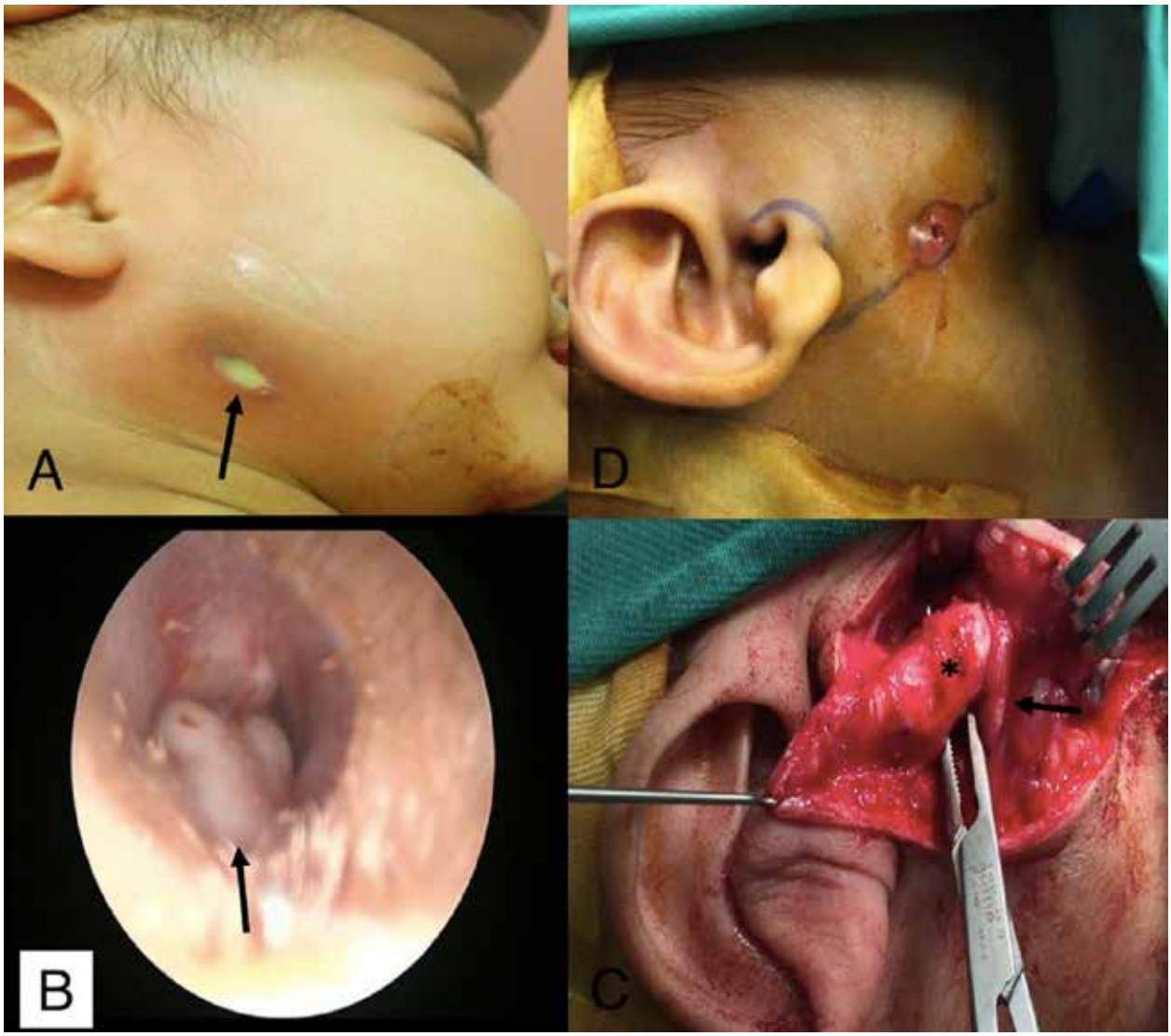

Fig 2, Case 2: A: Clinical photograph showed an erythematous cutaneous opening with purulent discharge (arrow) at the right Pochet's triangle; **B**: Endoscopic examination demonstrated pearl-like cystic swelling (arrow) arising from floor of the right external auditory canal; **C**: Intraoperatively fistula tract (asterix*) seated medial to the facial nerve (arrow); **D**: Incision line for first branchial cleft lesion.

for right-sided neck abscess, which required incision and drainage. On examination, there was an erythematous sinus opening with purulent discharge over the right submandibular swelling (Fig. 2A). Surrounding skin appeared to be warm and tender on palpation. Otoscopic examination of the right ear revealed a whitish cystic swelling arising from the floor of external auditory canal (EAC) (Fig. 2B). MRI with gadolinium contrast showed a vertical fistula tract passing through the right parotid gland extending from the floor of right EAC to right submandibular region measuring 2 cm in length. There were cystic dilatations at both ends of the tract. She underwent examination under anaesthesia and the fistula tract was found to be medial to the facial nerve, extending from the floor of right EAC to right angle of mandible (Fig. 2C). Besides, there was coincidental finding of canal cholesteatoma where keratin debris was seen at posterior and inferior walls of the EAC eroding into hypotympanum. The tympanic membrane was intact. The whole fistula tract was excised together with the sinus opening following the skin incision shown (Fig. 2D). Histopathological examination of the fistula tract was consistent with branchial cleft anomaly. The child was discharged well without facial asymmetry. However, two months post operation, the child developed recurrence with intermittent foul-smelling discharge from the right ear and anterior neck, which persisted for a duration of two years, which likely represented residual tract. Patient refused further

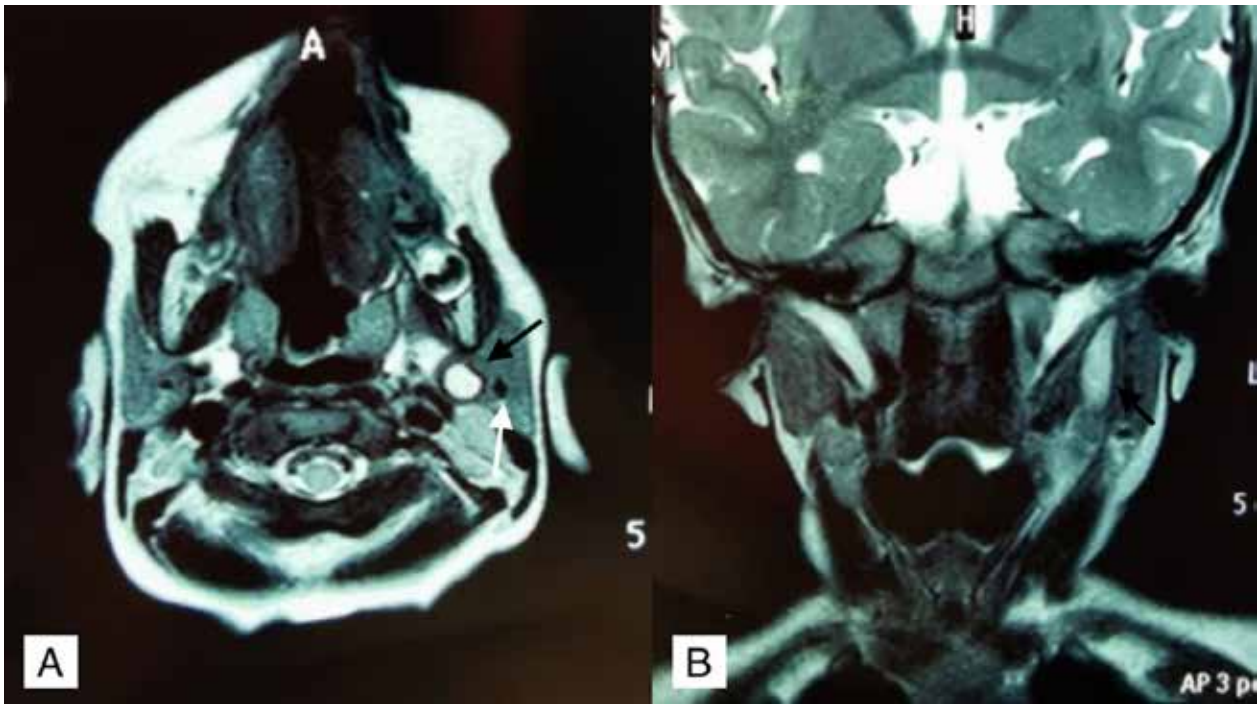

Fig 3, Case 3: T2 Weighted MRI neck (A) axial view (B) coronal view demonstrated fistula tract (black arrow) seated at the deep lobe of parotid gland medial to the retromandibular vein (white arrow).

surgical intervention and subsequently defaulted follow up.

Case 3

A one-year 11-month-old boy presented with recurrent purulent foul-smelling discharge from the left ear and left anterior neck since 3 months of age, despite multiple courses of antibiotics. Examination showed a small sinus opening at left level II region of the neck. It was not tender on palpation with minimal pus discharge on milking. Otoscopic examination revealed purulent discharge at the floor of the left EAC. MRI showed a fistula tract measuring 5.5 cm extending from left EAC to the left neck sinus opening at the level of hyoid bone. The fistula traversed within the left parotid gland, and passed antero-inferiorly in between left submandibular gland and sternocleidomastoid muscle, in keeping with first branchial cleft anomalies (Fig. 3). The parents were counselled for excision of the lesion but they were not keen, with the concern of facial nerve injury. Therefore, a conservative chemical cauterization approach was adopted, in which 10% silver nitrate was instilled into the left neck sinus opening and the floor of EAC. There was temporary resolution of symptoms, but it recurred two months later with purulent discharge from both openings at the EAC and anterior neck.

DISCUSSION

First branchial cleft anomalies are rare entities with extreme clinical heterogeneity. To date, there are several classifications available for the first branchial cleft anomalies based on the morphology, histology and clinical appearance. Back in year 1971, Arnot proposed the first classification for the first branchial cleft anomalies, wherein there are divided into type 1 and type II based on morphology. Type 1 lesions appear in the parotid region and usually present during early or middle adult life. Type II lesions, on the contrary, are seen at the anterior cervical triangle with a tract extending to the EAC, and often present during infancy or early childhood[4]. Work advocated two distinct anomalies of the first branchial cleft histologically: type I (ectodermal) and type II (ectodermal and mesodermal). Work classified type I anomalies lie parallel to the duplicated membranous EAC, wherein they possess skin with association of only first branchial cleft. Type II anomalies are the duplication of the membranous EAC and pinna, consist of skin and adnexal structures with association of not only first cleft, but also first arch and likely second arch. Classically, type I defects are situated inferior, medial and posterior to the pinna whereas type II defects are generally located within the parotid gland in which they pass upwards and run medial or lateral to the facial nerve or rarely they may split

Table 1: Summary of cases

Case number	1	2	3
Age of presentation	2 years	2 years and 1 month	1 year and 11 months
Clinical presentation	Recurrent neck abscess	Recurrent neck abscess	Ear discharge Neck abscess
Site	Left	Right	Left
Location of cutaneous opening	Parotid	Submandibular	Floor of cartilaginous part of external ear canal Level II neck
Work classification (Histology)	Type II	Type II	Undetermined
Arnot classification	Type I	Type II	Type II
Relation to facial nerve	Medial	Medial	Medial
Management	Surgery; Excision with parotidectomy	Surgery; Excision without parotidectomy	Conservative; Chemical cauterisation
Recurrence	No	Yes	Yes

the main trunk[5]. Olsen and colleagues proposed a simpler classification on 1980, in which first branchial cleft anomalies are grouped into isolated cyst, sinus and fistula in view of the management of each of the condition differs otherwise[6].

All three classifications, however, provide little clinical significance and relevance, as first branchial cleft anomalies are a heterogenous group of defects that may depict clinically in different ways. Hence, McMurran *et al* suggested for a classification based on the relation of first branchial cleft anomalies with the facial nerve, as it can provide an insight for surgical planning, and hence be of more clinical worthy[7].

In our case series as shown in Table 1, the mean age of presentation is 2-years-old with left side predominance, similar to the study conducted by Triglia *et al*. The clinical presentations of first branchial cleft anomalies differ in accordance with the anatomical sites involved, ranging from ear to head and neck features. Auricular, parotid and cervical symptoms constitute 24%, 35% and 41% of the clinical presentation respectively[8]. Patients may present with a combination of symptoms consisting of ear, head and neck features as in cases 2 and 3 (Table 1). Fistula openings into the floor of EAC are not always present upon clinical examination like in case 1. The variety of presentations and its rarity often make diagnosis difficult, and hence lead to delay in treatment.

Radiological modalities are deemed invaluable in aiding the diagnosis of first branchial cleft anomalies. High resolution computed tomography of temporal bone can show the relationship of the lesion to the EAC and middle ear, whereby MRI is superior in delineating the extent of the soft tissue lesion. However, both modalities could not fully ascertain the anatomical relation of the fistula tract to the facial nerve[8,9]. Nevertheless, MRI is preferable in most of the cases as it does not put the child at risk for ionizing radiation.

Management and surgical planning need to be tailored in accordance to each case in view of the anatomical variety of first branchial anomalies. The mainstay of definitive treatment is surgical resection. However, it could be challenging owing to the fact that the intimate relationship of the facial nerve with the fistula[9]. Identification and preservation of facial nerve intraoperatively is often the main focus of the surgical treatment. Therefore, proper pre-operative planning with meticulous intraoperative delineation of the relationship between the fistula tract and the facial nerve is crucial in order to minimize the risk of facial nerve injury and recurrence[3,8-10]. D'Souza *et al* reported that facial nerve palsy constitutes 22% of the overall complications if facial nerve was identified as compared to 41% if facial nerve was not identified intraoperatively[11]. In addition, previous incision and drainage that leads to scarring of the operative site often make definite surgical excision more difficult, as occurred in case 1[9,12]. Of note, facial nerve in the pediatric population is often smaller in size and lies more superficial. The landmarks used to identify facial nerve in adults may not be applicable in this context[13]. It was reported that the first branchial cleft fistula often situated medial to facial nerve as compared to sinus tract with high preponderance in younger children[3,11].

Olivas and Sherman advocated that Work type 2 lesions should be approached via a parotidectomy incision, as it often involves the parotid gland and the fistula may be seated lateral, medial or in between the branches of facial nerve. Work type 1 lesions can be excised via retro-auricular incision without parotidectomy, as it tends to be postero-superior to the facial nerve branches[12]. On the other hand, Solares *et al* proposed that superficial parotidectomy should be performed in all cases to expose the facial nerve and its branches adequately to ensure a complete excision[3]. In clinical practice, the surgical approach is often based on the surgeon's preference and justification.

In case 1, superficial parotidectomy was performed together with excision of fistula, as it was seated medial to the facial nerve. With this approach, facial

nerve can be identified and preserved fully. Given the high rate of recurrence with incomplete excision, identification of the entire fistula tract during surgery is of paramount importance. Excision of first branchial cleft anomalies with superficial parotidectomy gives a better exposure of the facial nerve and fistula, and thus ensures complete resection and avoids facial nerve injury. With appropriate facial nerve identification and complete excision of the tract intraoperatively, this patient exhibited good post-operative outcome with no recurrence at four months follow up.

In case 2, excision of the first branchial cleft lesion was performed by an experienced otologist without superficial parotidectomy based on the surgeon's preference. Upon pre-operative planning, fistula tract was thought to be running superficial to the facial nerve; however intraoperative findings revealed that the tract was seated medial to the facial nerve. The patient developed recurrence two months after operation. This may be due to incomplete excision of the fistula as a result of inadequate exposure of the surgical field without parotidectomy. Incomplete excision often leads to residual and recurrence. Some experienced surgeon may advocate this technique as it generates a smaller scar, however risk of facial nerve injury and recurrence is higher due to incomplete excision as in this case[2].

Prior to the surgery, the family members must be informed regarding risk of facial nerve injury in view of the close relation of first branchial cleft anomalies with facial nerve[9]. Although surgical excision is the mainstay of treatment, case 3 adopted a non-surgical approach in fear of facial nerve injury, as this could lead to psychological and aesthetic impact to the child. Chemical cauterization with silver nitrates was reported in the successful treatment of third and fourth branchial apparatus anomalies[14]. However, there is no report in the treatment for first branchial cleft anomalies. We adopted this approach with the similar concept to obliterate the cutaneous opening, thus hoping to reduce the risk of infection. However, the outcome was unfavorable in this case, as the child reported persistent infection post-chemical cauterization.

The outcome of all the 3 cases reported (Table 1) varies with different treatment approaches. For the definitive treatment of first branchial cleft anomalies, we advocate routine superficial parotidectomy to facilitate complete excision of the fistula. This would also enable accurate identification and preservation of facial nerve, aided by intraoperative facial nerve monitoring. This approach ensures a good surgical field exposure, thus reduce the risk of facial nerve injury and recurrence.

CONCLUSION

First branchial cleft anomalies, though uncommon, are essential to be recognized. Its rarity with diverse presentations frequently lead to misdiagnosis and late definitive treatment. Hence, it is imperative for healthcare providers to have a high index of suspicion in children who present with similar ear or neck symptoms towards this entity. Definitive treatment of this anomaly requires complete surgical excision. Avoiding injury to the facial nerve with adequate surgical exposure is of utmost importance upon surgical excision with parotidectomy. Facial nerve monitoring is particularly crucial in the pediatric population in view of the superficially located facial nerve. We believe this will subsequently reduce postoperative facial nerve palsy.

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Author contributions: Chow Xiao Hong was involved in concept, designs, materials, data collection, literature search and writing the manuscript. Shifa Zulkifli was involved in concept, design, supervision, materials, data collection and critical reviews. Lum Sai Guan was involved in concept, design, supervision, and critical reviews.

Conflicts of interest: None

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Case Report

COVID-19 disease is no longer alone: A case of severe COVID-19 pneumonia with pulmonary embolism and deep vein thrombosis

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ABSTRACT

Almost eight million people were affected by the novel coronavirus (COVID-19) disease outbreak until now. The understanding of the disease has not fully emerged, but recent studies showed that thromboembolic events are frequently seen in this unique patient group as a contributor to mortality.

A 65-year-old female was admitted to the emergency department (ED) with shortness of breath and fever for three days. Physical examination was notable with tachypnea and right lower extremity edema. The bedside ultrasound evaluation showed right-sided non-compressible common femoral vein with thrombus, and her laboratory was remarkable with a high D-dimer value (39.4 μg/dl). Finally, the patient was sent to the radiology unit for pulmonary computed tomography angiography, revealing filling defects at the pulmonary arteries and parenchymal findings that are consistent with COVID-19 pneumonia and pulmonary embolism (PE).

Here, we presented a case of venous thromboembolism without any risk factor but COVID-19 pneumonia. To the best of our knowledge, this is one of the first cases reported in the literature diagnosed as COVID-19 pneumonia simultaneously with PE and deep vein thrombosis in the ED. Eventually, physicians should be vigilant about the occult pathologies associated with the novel coronavirus infection.

KEY WORDS: case reports, coronavirus infections, deep vein thrombosis, emergency medicine, pulmonary embolism

INTRODUCTION

The COVID-19 infection induced by the novel coronavirus (SARS-CoV-2), which emerged in China at the end of 2019, has been accepted as a global outbreak by the World Health Organization. Almost eight million people were directly affected by the outbreak according to the data of Johns Hopkins University Coronavirus Resource Centre, and nearly 6% of them died until now[1]. Unfortunately, the mortality rate is two times more (up to 15%) in some European countries such as Italy, France, Spain and England, where the epidemic spread rapidly. In emergency departments (ED), the most common complaints of patients are fever, cough, severe fatigue and shortness of breath. The most alarming reasons for hospitalization are severe interstitial pneumonia and acute respiratory distress syndrome. According to recently published case series and retrospective studies, thromboembolic events are frequently observed in COVID-19 patients, especially in critical care units and even individuals taking prophylactic anticoagulation[2,3]. Here, we illustrated a case of COVID-19 infection diagnosed with concomitant deep vein thrombosis and pulmonary embolism during the emergency evaluation.

CASE REPORT

A 65-year-old female was admitted to the ED with shortness of breath, fatigue and fever for three days. Although the first two days were uneventful with a mild cough and fever, she had to come to ED because of worsening shortness of breath and exertional

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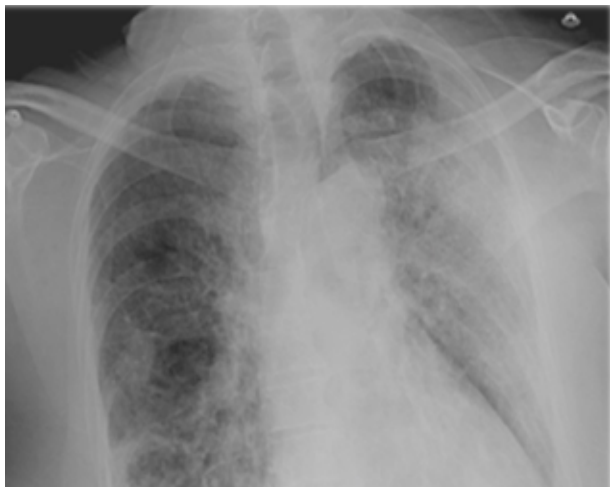

Fig 1: Chest X-ray of the patient showed bilateral ground-glass opacities and infiltrations

dyspnea. Her medical history is unremarkable, but carbamazepine (400 mg b.i.d) use for epilepsy. Admission Glasgow coma scale was 15 and vitals were a temperature of 37.6 ºC, a pulse of 102 per minute, a respiratory rate of 30 per minute, oxygen saturation of 84% in room air, and blood pressure of 123/81 mmHg. On physical examination, there was tachypnea with bilateral rale at lower zones and also right lower extremity edema with palpable pulses. Subsequently, chest X-ray was obtained, and a bedside ultrasound examination was performed. Bilateral ground-glass opacities (Fig 1) were observed that suggested viral pneumonia on chest X-ray. Then, the bedside three-point compression ultrasound evaluation showed right-sided non-compressible common femoral vein with thrombus material, diagnosed as deep vein thrombosis (DVT). After

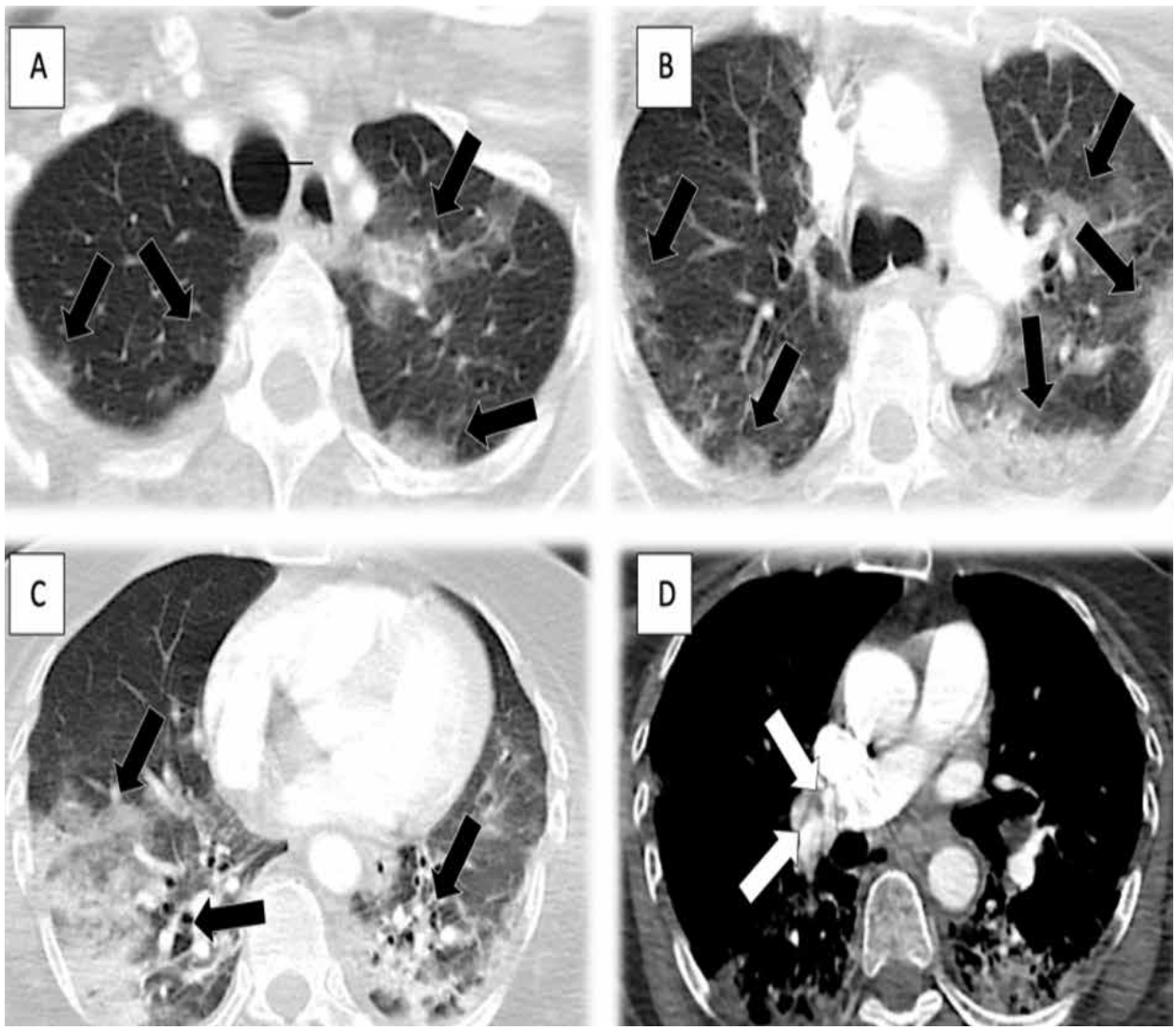

Fig 2: Parenchymal views of chest CT shows ground-glass opacities (black arrows) at all zones of both lungs, especially peripheric regions and infiltrations dominantly at basal regions (A, B, C). Pulmonary CT angiography view shows filling defects (white arrows) at the right common pulmonary artery and segmental branches (D).

that, sinus tachycardia with T-wave inversions in leads d_3–avf was seen on electrocardiography (ECG). Her laboratory analysis was notable for D-dimer of 39.4 (μgFEU/dl), leucocytosis of $13.8x10^3/\mu L$, lymphocyte count of $1.7x10^3/\mu L$, hemoglobin count of 8.6 g/dl, C-reactive protein of 206 mg/L, LDH of 495 units/L, pH of 7.479, PCO_2 of 37.8 mmHg, PO_2 of 48.3 mmHg, SO_2 of 83%, BE of 4.3 mmol/L and lactate 1.7 mmol/L with normal renal and liver function tests. After isotonic fluid infusion and low molecular weight heparin injection, the patients sent to the radiology unit for pulmonary computed tomography angiography (PCTA), revealed with filling defects at the pulmonary arteries and parenchymal findings that are consistent with COVID 19 pneumonia and pulmonary embolism (PE; Fig 2). The patient was finally admitted to a private COVID-19 clinic with the diagnosis of COVID-19 pneumonia, DVT and PE. The day after the admission, the diagnosis was confirmed with a real-time reverse transcription-polymerase chain reaction of naso-oropharyngeal swab.

DISCUSSION

Venousthromboembolism (VTE), most commonly DVT or PE, is one of the most common types of acute cardiovascular syndrome that caused so much death globally[4]. Additionally, it was agreed that acute infections are potentially risky conditions for VTE. Due to the recent global outbreak caused by COVID-19, thromboembolic events have increased. Sociolegal circumstances that cause immobility and the infection-induced procoagulant state are the major determinants of these results. For instance, recent studies showed PE incidence in ICU patients with COVID-19 pneumonia is much more than expected[5]. In the retrospective studies of Klok *et al* and Grillet *et al*, VTE was reported as 31% and 23% of ICU patients with COVID-19 that were taking a standard dose of prophylactic anticoagulant[3,6]. Therefore, some of the current reports suggested at least twice the usual prophylactic dose of 40 mg daily low molecular weight heparin to dose of 80- 100 mg daily in patients with severe pneumonia or acute respiratory distress syndrome[7]. Also, some studies showed mortality benefit from routine anticoagulant use for patients in critical condition[8].

In the diagnosis of COVID-19 pneumonia, non-contrasted high-resolution computed tomography is recommended and widely used in emergency settings[9]. Nevertheless, there is no supportive suggestion for a routine using contrasted ones so far because of the high risk for contrast-induced nephropathy. Thus in many reports, progressive worsening of respiratory symptoms and the presence of shock are assumed as indications of PCTA for selected patients[3]. In the report of Casey *et al*, it is declared that hemoptysis is an infrequent symptom of individuals with COVID-19 pneumonia[10]. So in some reports, it was assumed as a strong predictor of PE and an indication of PCTA[10,11]. Besides, three-point venous compression ultrasonography of lower extremity and point of care cardiopulmonary ultrasound would help identify DVT and PE to start a more appropriate dose of anticoagulation.

In our case, we detected DVT by point of care ultrasound and hints of PE on ECG before confirmation of PE by PCTA. Eventually, point of care ultrasound and ECG are valuable tools in selecting the right patients for PCTA. The patient's D-dimer result was very high (39.4 μg/dl), and future studies are necessary to find out whether a higher cut-off value could be accurately ruling in or out PE for this unique patient group.

CONCLUSION

In conclusion, emergency physicians should be vigilant about clues of thromboembolic complications of the novel corona virus disease, and the use of PCTA should be encouraged for patients with suspicion of severe COVID-19 pneumonia and PE. Furthermore, the decision should be made according to the presence of hemoptysis, sonographic findings, ECG findings, clinical severity, contraindications, and higher D-dimer results.

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Informed consent: An informed consent document was signed by the patient and attached to the statements. The principles outlined in the Declaration of Helsinki have been followed.

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Case Report

Pneumocystis jirovecii pneumonia with diffuse alveolar hemorrhage in a patient with rheumatoid arthritis receiving infliximab

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ABSTRACT

Pneumocystis jirovecii pneumonia (PCP) is an opportunistic pulmonary infection in immunosuppressed hosts such as human immunodeficiency virus-positive or organ transplant patients. An increasing number of PCP cases have been reported among patients with rheumatoid arthritis (RA) treated with disease-modifying anti-rheumatic drugs. While PCP with diffuse alveolar hemorrhage (DAH) has been mostly documented in human immunodeficiency virus-positive patients, it has been rarely reported in patients with RA. Herein, we report a case of PCP with DAH in a female patient with RA who was treated with infliximab. We confirmed PCP and DAH by bronchoalveolar lavage, and the patient was successfully treated with trimethoprim-sulfamethoxazole. PCP should be considered in the differential diagnosis of DAH in RA patients receiving infliximab.

KEY WORDS: diffuse alveolar hemorrhage, disease-modifying anti-rheumatic drugs, *Pneumocystis jirovecii* pneumonia, rheumatoid arthritis

INTRODUCTION

Pneumocystis jirovecii pneumonia (PCP), which was initially discovered in human immunodeficiency virus (HIV-positive) patients in the 1980s, is an opportunistic pulmonary infection caused by *Pneumocystis jirovecii* in immunosuppressed patients[1]. PCP cases were also reported to increase in rheumatoid arthritis (RA) patients who were treated with disease-modifying anti-rheumatic drugs, including biologic agents, and resulted in high mortality rates[2]. However, it is difficult to diagnose PCP, because often, the condition has not only non-specific symptoms such as cough and fever, but also non-specific findings on radiographic examination[1,3].

Diffuse alveolar hemorrhage (DAH) is a distinct syndrome of pulmonary hemorrhage due to disruption of the alveolar-capillary basement membrane[4]. In general, pulmonary infections are rarely associated with DAH, and infectious etiologies such as infection with cytomegalovirus, adenovirus, and *Mycoplasma* and *Legionella* species; influenza; invasive aspergillosis; leptospirosis; and malaria have been reported[5]. While PCP-associated DAH has been mostly documented in HIV-positive patients[6], it has been rarely reported in patients with RA.

Herein, we report a case of PCP complicated by DAH in an RA patient receiving infliximab, who was stabilized with antibiotics.

CASE REPORT

A 75-year-old woman was admitted to our hospital with a 2-week history of general weakness. She was diagnosed with RA 10 years ago, and disease remission was maintained with infliximab treatment for 2.5 years (200 mg intravenously per 2 months), methotrexate (10 mg per week), and acetaminophen (650 mg per day). She also had a history of osteoporosis and hypertension. For the former, she received denosumab (60 mg subcutaneous injection per 6 months), calcium carbonate (1250 mg per day), and cholecalciferol (1000

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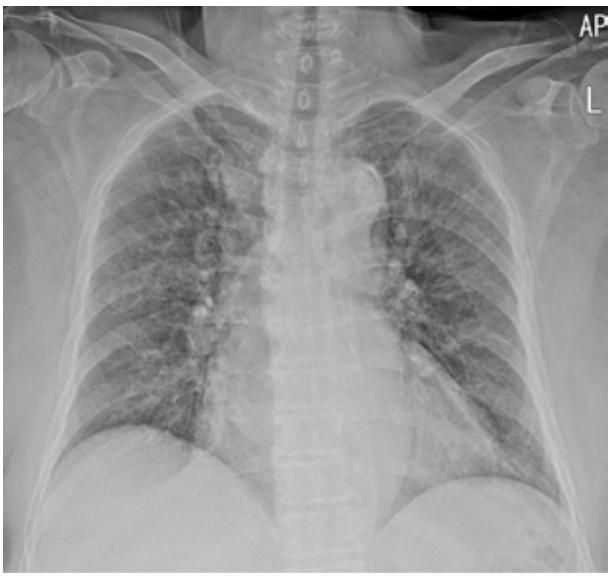

Fig 1: Chest X-ray obtained at admission. Diffuse mildly increased interstitial opacities in both lungs.

international unit per day), and for the latter, she received amlodipine 5 mg daily and losartan 50 mg daily. The patient denied any smoking history and was a social drinker.

On admission, her blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation on room air were 135/85 mmHg, 93 beats/min, 38.1°C, 20 breaths/min and 91%, respectively. She complained of mild respiratory symptoms such as dry cough and sore throat; however, sputum production was scanty. Physical examination revealed clear lung sounds and no pharyngeal injection. The patient was awake and alert, and the rest of her examinations, including cardiac and abdominal examinations, were normal. Initial laboratory tests showed a mildly elevated white blood cell count (10,740/mm^3; polysegmented neutrophils: 59.7%, lymphocytes, 30.3%), but a normal hemoglobin level (12.4 g/dL) and platelet count (362,000/mm^3). The results of the coagulation profile, liver function and serum creatinine tests were within the normal range; however, erythrocyte sedimentation rate (73 mm/h) and C-reactive protein level (3.71 mg/dL) were elevated. An arterial blood gas test on room air showed a pH, partial pressure of carbon dioxide, partial pressure of oxygen, and oxygen saturation of 7.440, 36.2 mmHg, 58.1 mmHg, and 92%, respectively. A chest X-ray showed diffuse mildly increased interstitial opacities in both lungs (Fig 1), while chest computed tomography (CT) showed multiple ill-defined ground-glass opacities in both lungs (Fig 2). Blood culture and tests for *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Mycobacterium tuberculosis*, and influenza were negative. Initially, the patient was started on ceftriaxone (2000 mg per day intravenously) and azithromycin (500 mg per day intravenously) for community-acquired pneumonia. Of the RA medications, methotrexate and infliximab were discontinued. Despite using the above antibiotics for three days, clinical symptoms such as fever, dyspnea and elevated C-reactive protein level did not improve.

On day 4 of admission, fiberoptic bronchoscopy was performed, and it revealed airway erythema in the left and right bronchial trees. Bronchoalveolar

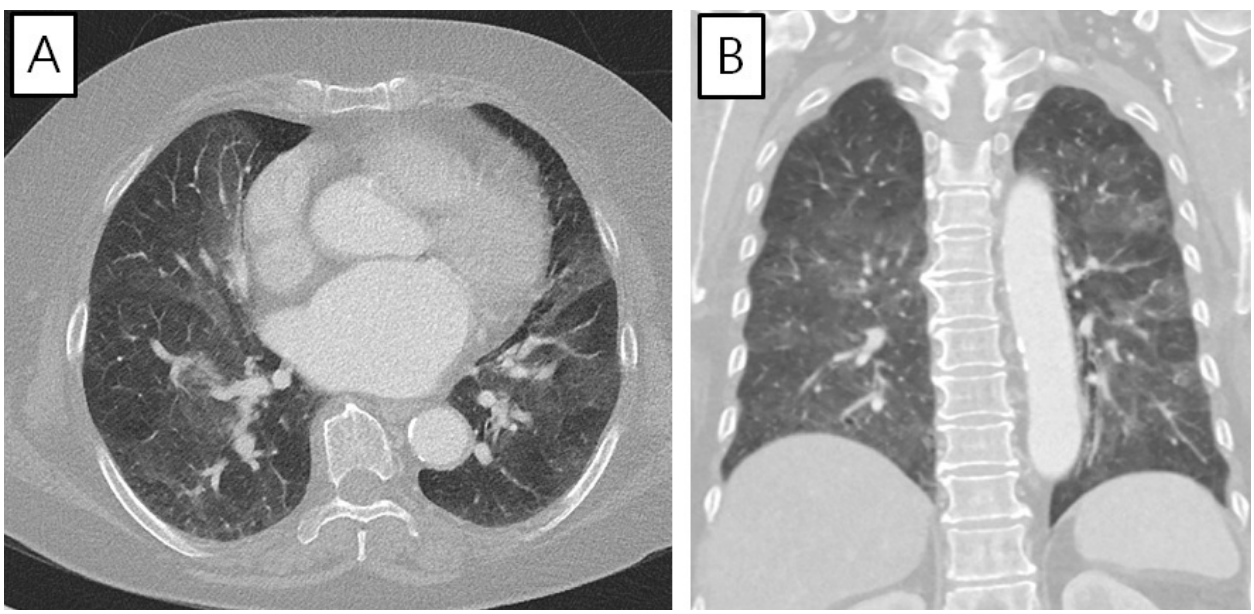

Fig 2: Computed tomography of the chest showing multiple ill-defined ground-glass opacities in both lungs. (A: axial plane, B: coronal plane)

Fig 3: Examination of serially collected bronchoalveolar lavage fluid samples revealed progressively bloody returns, suggesting alveolar hemorrhage.

lavage (BAL) performed in the lower left lobe showed progressive bloody returns consistent with DAH (Fig 3). Examination of the BAL fluid revealed 190 cells/mm^3 of white blood cells and 17,000 cells/mm^3 of red blood cells. Hemosiderin-laden macrophages were found in the BAL fluid (Fig 4). BAL cultures and galactomannan test and the molecular diagnostic test for tuberculosis were negative, while polymerase chain reaction for *Pneumocystis jirovecii*-specific DNA was positive. The results of additional autoimmune workup, including tests for antinuclear antibody, cytoplasmic and perinuclear antineutrophilic cytoplasmic autoantibodies, and glomerular basement membrane antibody, were negative. Based on the clinical, bronchoscopic and laboratory findings, a diagnosis of PCP complicated by DAH was established.

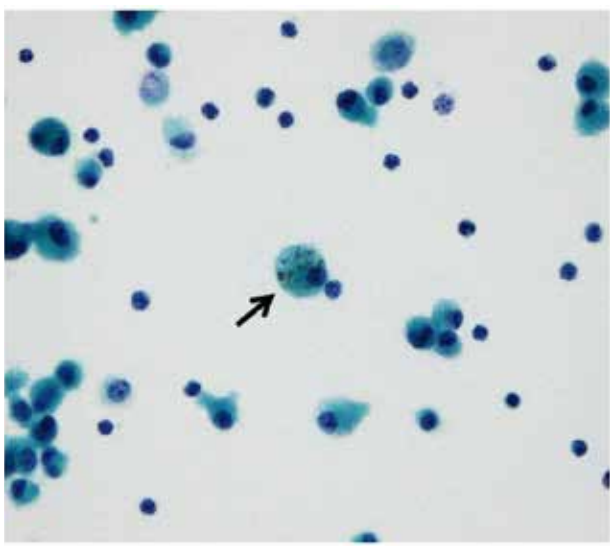

Fig 4: Hemosiderin-laden macrophages seen on bronchoalveolar lavage smears (Papanicolaou staining, ×400).

Therefore, treatment with trimethoprim-sulfamethoxazole (TMP-SMX) (15 mg TMP/kg/day intravenously divided q 6 h) was started. Methylprednisolone (8 mg per day) was administered due to inflammatory exacerbation of RA accompanied by PCP. Her symptoms and laboratory data gradually improved with a 3-week course of TMP-SMX treatment. At follow-up 2 weeks after discharge, she was free of symptoms, and methotrexate and infliximab were restarted.

DISCUSSION

Over the past decades, the management of RA has changed markedly through the early use of methotrexate and introduction of biological disease-modifying anti-rheumatic drugs. With the increased use of such anti-rheumatic drugs, RA patients are at increased risk of PCP[2]. However, DAH related to PCP has been rarely reported in patients with RA; it has been described mostly in HIV-positive patients[6]. To our knowledge, this is the first report of PCP complicated by DAH in an RA patient receiving infliximab.

The incidence of PCP in RA patients treated with tumor necrosis factor inhibitors (TNFis) varies among countries, with the rate being 0.4% in Japan[7], 0.02% in the United Kingdom[2], and 0.01% in the United States[8]. The possible explanations for the difference include a possibly more severe influence of TNFis on host defenses among Asian patients, owing to ethnic differences and a higher prevalence of *Pneumocystis jirovecii* colonization in Japanese patients. Meanwhile, there were several pieces of evidence suggesting that TNF plays a critical role in host defenses against a *Pneumocystis* infection. First, *Pneumocystis murina* has been shown to directly enhance the secretion of TNF from murine alveolar macrophages by activation of Toll-like receptors. Second, *Pneumocystis*-induced TNF stimulated the production of reactive nitrogen substances, which are important mediators for killing microorganisms. Finally, adenoviral gene transfer of the mouse IgG/p55 TNF receptor in immunocompetent mice delayed the clearance of *Pneumocystis jirovecii* after intratracheal inoculation[9].

DAH is a distinct syndrome of pulmonary hemorrhage that could complicate many clinical conditions and might be life-threatening, requiring prompt treatment[10]. It may have various

manifestations such as acute or subacute cough, hemoptysis, diffuse radiographic pulmonary infiltrates and hypoxemic respiratory distress. Hemoptysis, the major sign of DAH, may develop suddenly or over a period of days to weeks. However, as in the case of our patient, this sign is initially absent in up to 30% of patients, in whom establishing a diagnosis could be difficult. Therefore, a high degree of suspicion is necessary for the early recognition and diagnosis of DAH[5].

The diagnosis of DAH required bronchoscopy with BAL, revealing progressively bloody returns, and additionally hemosiderin-laden macrophages could be found in the BAL. BAL cultures also need to be evaluated for potential infectious causes[11]. Routine laboratory studies and serologic analyses for connective tissue diseases and systemic vasculitis are essential as part of the initial workup in patients diagnosed with DAH. In rare cases, a surgical biopsy might be necessary, if the history and laboratory examinations are not adequate to establish a diagnosis of DAH[12]. In our case, DAH was diagnosed based on both progressively increased red coloration and hemosiderin-laden macrophages in BAL, along with extensive ill-defined ground-glass opacities in both lungs on chest CT. Chest radiography is usually performed to further support the diagnosis of DAH. Radiological findings of DAH might include areas of widespread ground-glass opacities or consolidation in the acute phase. In the subacute phase, chest CT might show fine, diffuse, nodular densities, and in the later stage, there might be evidence of interlobular septal thickening due to intralymphatic accumulation of hemosiderin[13]. However, early-stage DAH is difficult to diagnose because chest X-ray and CT findings are non-specific and required differentiation from other lung diseases.

The etiology of DAH could be categorized into infectious and non-infectious causes. Usually, pulmonary infections are rarely reported in association with DAH; however, they should be considered in the diagnostic evaluation, due to the obvious therapeutic implications[10]. In immunocompromised patients, the main causes of DAH are infection with cytomegalovirus, adenovirus, and *Mycoplasma*, *Legionella*, and *Strongyloides* species; and invasive aspergillosis. On the other hand, in immunocompetent patients, the infectious diseases that frequently cause DAH are influenza A (H1N1), dengue, leptospirosis, malaria and *Staphylococcus aureus* infection[5]. Very few reports have described an association between PCP and DAH[14], and that too only in HIV-positive patients[6,15]. In our patient, DAH was related to PCP, suggesting that PCP might be considered as one of the possible causes of DAH in RA patients.

Treatment of DAH involves supportive respiratory care and control of any underlying systemic disease. In patients with pulmonary capillaritis, a combination of systemic glucocorticoids and immunosuppressive therapy should be considered. For patients with infection-related DAH, treating the underlying infection is essential[4]. In our case, as soon as positivity of *Pneumocystis jirovecii*-specific DNA was confirmed, TMP-SMX was administered. With a 3-week course of TMP-SMX treatment, her symptoms and laboratory data improved without any complications.

CONCLUSION

PCP complicated by DAH is rare in RA patients receiving immunosuppressive drugs, but could be lethal. Both PCP and DAH might be difficult to diagnose in the early stage, because the symptoms and radiologic findings of both are initially non-specific and require differentiation from those of other lung diseases. Therefore, when an RA patient with respiratory symptoms does not respond to the initial treatment, we suggest early bronchoscopic examination with BAL, as this will enable the diagnosis of DAH as well as associated infections.

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Author contributions: Seongmin Kang collected the data and wrote the original draft; Seung Won Choi and Doo-Ho Lim supervised, wrote, reviewed and edited the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest: None

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Case Report

Nasolacrimal duct lymphoma mimicking sinonasal tumour: Rare but possible

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ABSTRACT

Malignant lymphoma of the nasolacrimal duct is an unusual site for extra-nodal lymphoma. It is usually associated with systematic lymphoproliferative disorder, whilst primary manifestation is exceedingly rare.

A 61-year-old male presented with progressive left nasal obstruction, epiphora and medial canthal swelling for six months. Nasal endoscopy showed irregular mass over the left lateral wall of the nose. Histopathological examination revealed diffuse large B-cell lymphoma (DLBCL) of the nasolacrimal duct. Positron emission tomography-computed tomography scan revealed Stage IIe tumor and bone marrow aspiration and trephine showed no evidence of marrow infiltration. He completed seven cycles of chemotherapy.

Primary non-Hodgkin lymphoma of the nasolacrimal duct is extremely rare, and it can present atypically. Although DLBCL is an aggressive tumour, current treatment regime is proven to improve overall survival outcome. Thus, a nasal mass requires thorough investigation and a wide differential diagnosis should be considered.

KEY WORDS: extra-nodal, lymphoma, nasolacrimal duct

INTRODUCTION

Tumours of the nasolacrimal drainage system are rare. More than half of the tumours are malignant and 90% originated from the epithelium[1]. The non-epithelial tumours, such as malignant lymphoma, accounts for only 2 to 8% of all nasolacrimal drainage system tumours. It is often manifested as secondary to systemic lymphoproliferative malignancy, and primary involvement is exceedingly rare[2].

Patients often presented with epiphora and medial canthal swelling. Hence, it may simulate recurrent dacryocystitis during initial presentation[2]. We encountered a case of extensive primary diffuse large B-cell lymphoma (DLBCL) of the nasolacrimal duct with atypical presentation of nasal obstruction.

CASE REPORT

A 61-year-old male, a chronic smoker, presented with left medial canthal swelling, epiphora and persistent left nasal obstruction for six months. There was no epistaxis, purulent nasal discharge or facial pain. He had no B symptoms either. On clinical examination, there was a firm and painless swelling over the left nasofacial angle. Anterior rhinoscopy revealed a diffuse irregular mass on the lateral wall of the nose occupying the left nasal cavity (Fig 1). Multiple cervical nodes were palpable at left side of the neck, level Ib and III.

The fine needle aspiration of the neck nodes was suggestive of granulamatous inflammation. Investigations for tuberculosis were negative. Computed tomography scan of paranasal sinuses, as in Fig 2 and 3, showed an enhancing mass measuring 5.6 x 3.1 x 4.0 cm occupying the left nasal cavity, causing obliteration of the left inferior, middle and left osteomeatal complex with erosions of medial wall of left maxilla, nasolacrimal canal and inferior turbinate. There were enlarged enhancing cervical lymph nodes at level Ib, IIa, IIb, III and IV. The largest node was at level IIa measuring 1.6cm x 2.2cm. The left level IIb

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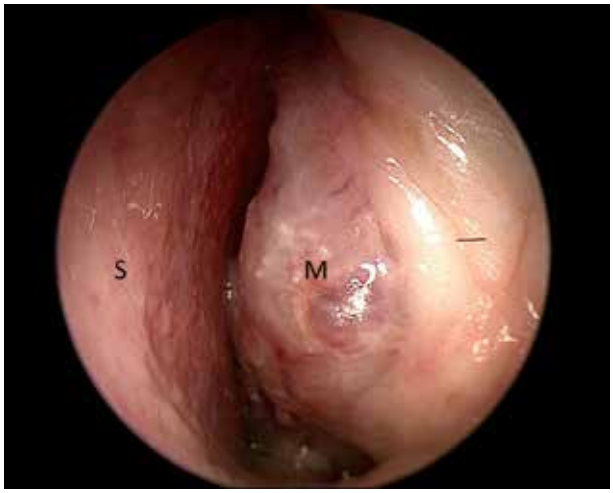

Fig 1: Endoscopic view of left nose. S: nasal septum; M: nasal mass arising from the lateral nasal wall.

lymph node had necrotic center within measuring 1.1 x 1.7cm. Computed tomography scan findings were indicative of sinonasal tumour.

This patient underwent endoscopic sinus surgery and medial maxillectomy. Intraoperatively, there was an irregular friable mass involving left inferior turbinate, nasolacrimal duct and middle turbinate. Left maxillary sinus mucosa was normal. Histopathology revealed a diffuse infiltration by malignant lymphoid cells interspersed with some small lymphocytes with area of tumour necrosis. The malignant cells are large in size, exhibiting pleomorphic round to oval vesicular nuclei, and some show presence of prominent nucleoli. Mitotic figures and apoptotic bodies are easily seen. Immunohistochemistry studies show the malignant cells are positive for CD20, MUM-1 and BCL-2. Ki67 proliferative index is ~70%. These findings were suggestive of diffuse large B-cell lymphoma, activated B-cell subtype.

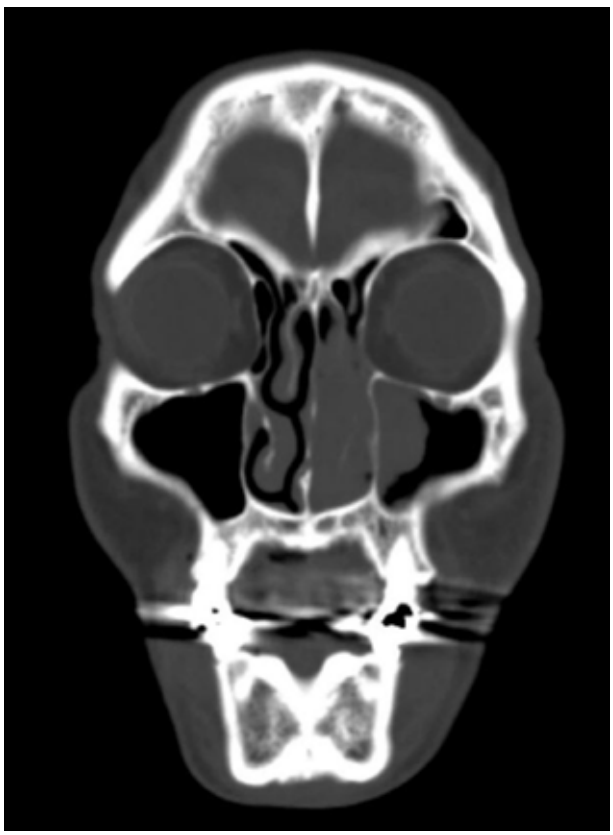

Fig 2: Coronal view of the CT para nasal sinuses showed a homogenous mass occupying the left nasal cavity, eroding the medial wall of left maxilla and inferior turbinate.

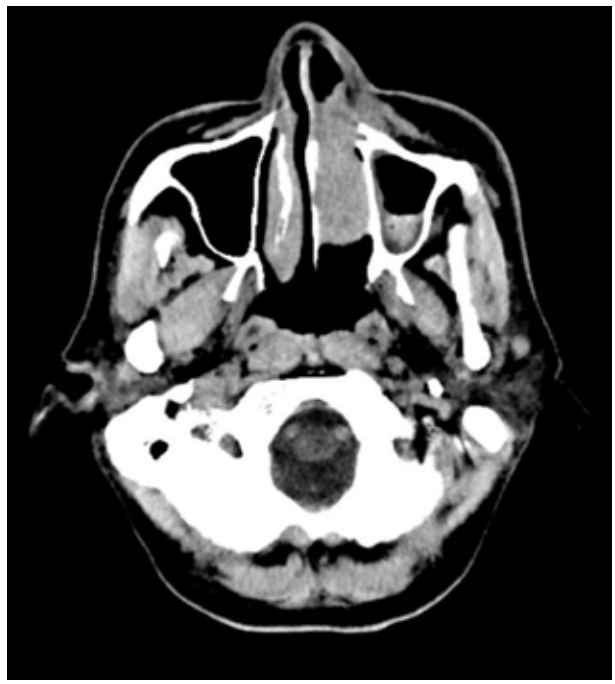

Fig 3: Axial view of CT para nasal sinuses showed mass in left nasal cavity causing bulging of the left nasal bone and the overlying skin. The left nasolacrimal duct is obliterated.

Initial positron emission tomography-computed tomography (PET-CT) scan showed hypermetabolic activity involving the left nasal cavity and enlarged cervical and supraclavicular nodes which were consistent with Stage IIe (Fig 4A). Bone marrow aspiration and trephine confirmed no evidence of lymphoma infiltration. The repeat PET-CT scan following surgery and rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine sulfate and prednisolone (R-CHOP) chemotherapy regime showed good chemoresponse (Fig 4B). At follow up six months post-surgery, there was no evidence of tumour recurrence on endoscopic examination (Fig 5).

DISCUSSION

Malignant lymphoma of the nasolacrimal system is extremely rare, with approximately less than 90 cases reported in the literature over the last 60 years.

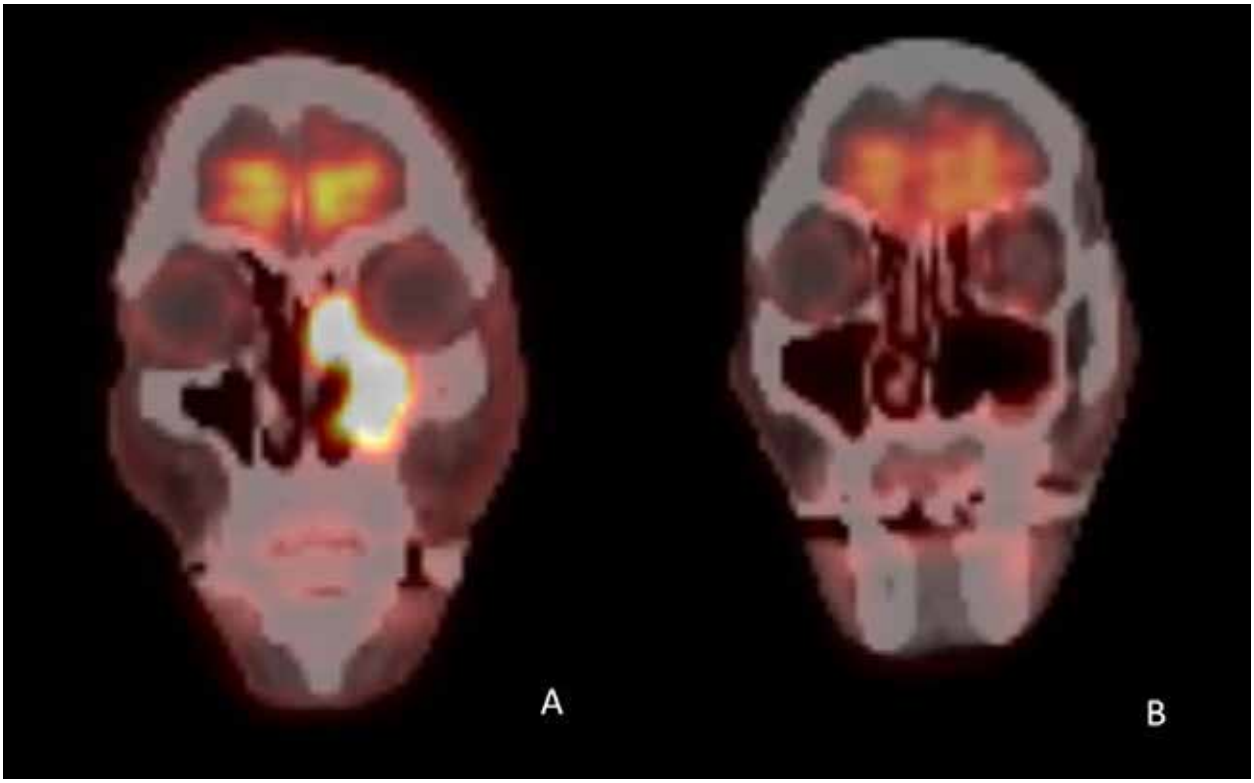

Fig 4: A, axial view of the PET-CT scan prior to surgery; **B**, axial view of the PET-CT scan post endoscopic medial maxillectomy and forth cycle of chemotherapy. There is a significant reduction in size and metabolic activity of the mass in the left nasal cavity.

Primary lymphoma of the nasolacrimal apparatus is even rarer and has been mainly reported in Europe, United States and Japan. Kajita *et al* concluded that malignant lymphoma of nasolacrimal duct is uncommon in Asian population[3]. Our case is the third documented primary nasolacrimal duct lymphoma in Malaysia[4,5]. However, Krishna *et al* claimed that there is no predilection for ethnicity or gender[2]. It predominantly affects the elderly, with median age of diagnosis at 69 years old[6].

Almost 90% of patients presented with epiphora, followed by lacrimal sac region swelling (79%) and dacryocystitis (21%)[6]. The initial presentations are frequently misdiagnosed as recurrent dacryocytitis in many reports and hence, may lead to delay in correct diagnosis. Nasal obstruction, such as in our case, was hardly ever seen in primary nasolacrimal duct tumour. In a review by Gao *et al*, only one case has nasal obstruction out of 25 patients with primary nasolacrimal duct lymphoma[7]. Nasal obstruction is more suggestive of sinonasal tumour, and it is the key differentiating symptom from nasolacrimal duct lymphoma[1].

According to a review by the European Organization for Research and Treatment of Cancer study, diffuse large B-cell lymphoma (DLBCL) is the most common primary nasolacrimal sac lymphoma, as well as mucosa associated lymphoid tissue lymphoma (MALT), both 33%. These are followed by transitional MALT (20%) and unclassified B-cell lymphoma (13%)[6]. DLBCL is observed to be over-represented in nasolacrimal sac as it only comprises up to 13% of all ocular adnexal malignancy[6]. It is an aggressive tumour with poor prognosis. The 5-year overall survival rate is between

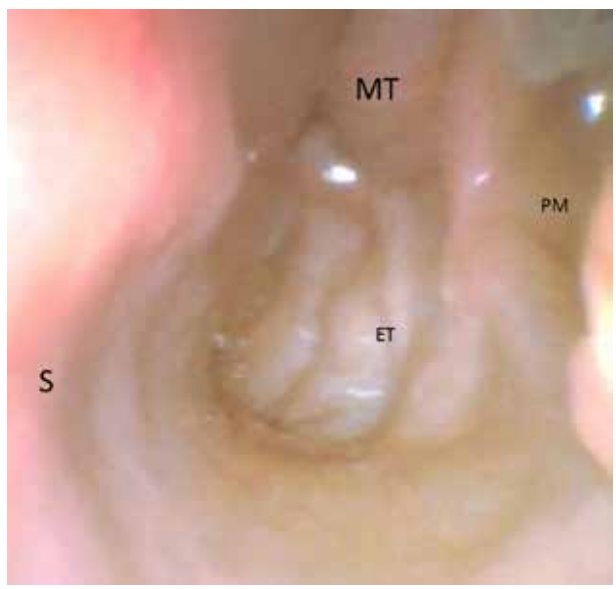

Fig 5: Endoscopic view of right nose at six months post-surgery. S: nasal septum; M: middle turbinate; ET: eustachian tube; PW: posterior wall of the right maxillary sinus.

20% to 65%[8]. Concordant bone marrow involvement and International Prognostic Index (IPI) score are the key determinant factors of the overall survival rate[9]. In this case, the treatment outcome is favorable as there was no concordant bone marrow involvement and the IPI score risk is low (age more than 60 years and more than one extra-nodal site).

The management of primary nasolacrimal duct lymphoma is not well established due to limited sample size[2]. Rasmussen *et al* recommended a combination of rituzimab and systemic chemotherapy (R-CHOP regime) in treating DLBCL of nasolacrimal duct, which is similar to the management in this case. The R-CHOP is able to improve overall survival rate up to 60% at 5 years[9]. A combination of surgery, irradiation and chemotherapy was suggested by several authors[2,6,10]. Radiotherapy alone was associated with poor outcome[9]. A multidisciplinary approach including ophthalmologist and haematologist is crucial in managing the patients. Despite completed primary treatment, regular follow is important, as recurrence can occur[2].

CONCLUSION

Primary diffuse large B-cell lymphoma of the nasolacrimal duct is a rare entity. Clinical history can be non-specific and masquerade neoplasm. An accurate diagnosis is vital to guide appropriate management and predict survival outcome.

ACKNOWLEDGMENT

Author's contribution: Khairil Afif Mahmud searched the literature and drafted the manuscript; Salina Husain searched literature, and drafted, reviewed and approved the manuscript; Aneeza Khairiyah Wan Hamizan reviewed and approved the manuscript.

Conflict of interest: None

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Case Report

Rare case of prolapse of trigonal tissue of urinary bladder causing recurrent urinary retention

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Kuwait Medical Journal 2023; 55 (1): 77 - 80

ABSTRACT

Prolapsed avulsed urinary bladder causing recurrent urinary retention is rarely reported. We present a case of a 60-year-old female, para 10, with a history of controlled blood hypertension who presented to our clinic with a history of lower urinary tract symptoms of about 15-years duration. Diagnostic cystoscopy had been done for her three times and she was on treatment for chronic cystitis. Two years back, she had a complaint of recurrent urinary retention, and she was on foley's catheter. Diagnostic cystoscopy revealed signs of bladder neck inflammation and mucosal eruptions that floated like wave forms around the internal urinary meatus. The tissue was mostly found hidden on the posterior wall of the neck of the bladder.

KEY WORDS: cystoscopy, metaplastic, retention, urinary bladder

INTRODUCTION

Incomplete bladder emptying, also known as urinary retention, is a condition where the urinary bladder does not get completely emptied after an act of micturition[1]. The cause of this condition is multiple, and several interventions might be performed to accomplish complete bladder emptying. These interventions include urethral catheterisation, which can be done in a hospital setting or by the individual as a self-catheterisation procedure[2]. Patients can have a catheter permanently placed in the bladder (chronic catheterisation) or the catheter may intermittently be passed to drain urine (intermittent catheterisation).

Sometimes, it is impossible to pass a urethral catheter to drain the bladder; such cases may require the passage of a catheter via the supra-pubic route[3]. In all cases where urinary catheterisation is required, investigations to determine the cause of the obstruction to urine flow is required[4]. The index case presented with recurrent urinary retention, which could be relieved by urethral catheterisation. However, our finding of an unusual cause of the urinary obstruction, not documented in the literature, prompted this case report.

CASE REPORT

A 60-year-old female, para 10, with a history of controlled blood hypertension, presented to our clinic with a history of lower urinary tract symptoms of about 15 years duration. She had visited many clinics without resolution of her problem. Diagnostic cystoscopy had been done for her three times and was on treatment for chronic cystitis at the time of her visit. Two years prior to presentation, she complained of recurrent urinary retention and had a Foley catheter inserted. Cystoscopy was done and findings were normal. A working diagnosis of neurogenic bladder was made. However, urodynamic study was not done, and patient was placed on solifenacin 10mg per day without improvement.

Patient had no previous history of trauma, urolithiasis, radiation exposure, surgical procedures, cystocele, rectocele or utero-vaginal prolapse. Patient was eventually diagnosed (following the frustration of not finding the cause of her intermittent urinary retention) as a psychogenic case.

On physical examination, we found a well looking female in no painful distress. Her vital signs were normal, as were her chest and abdominal

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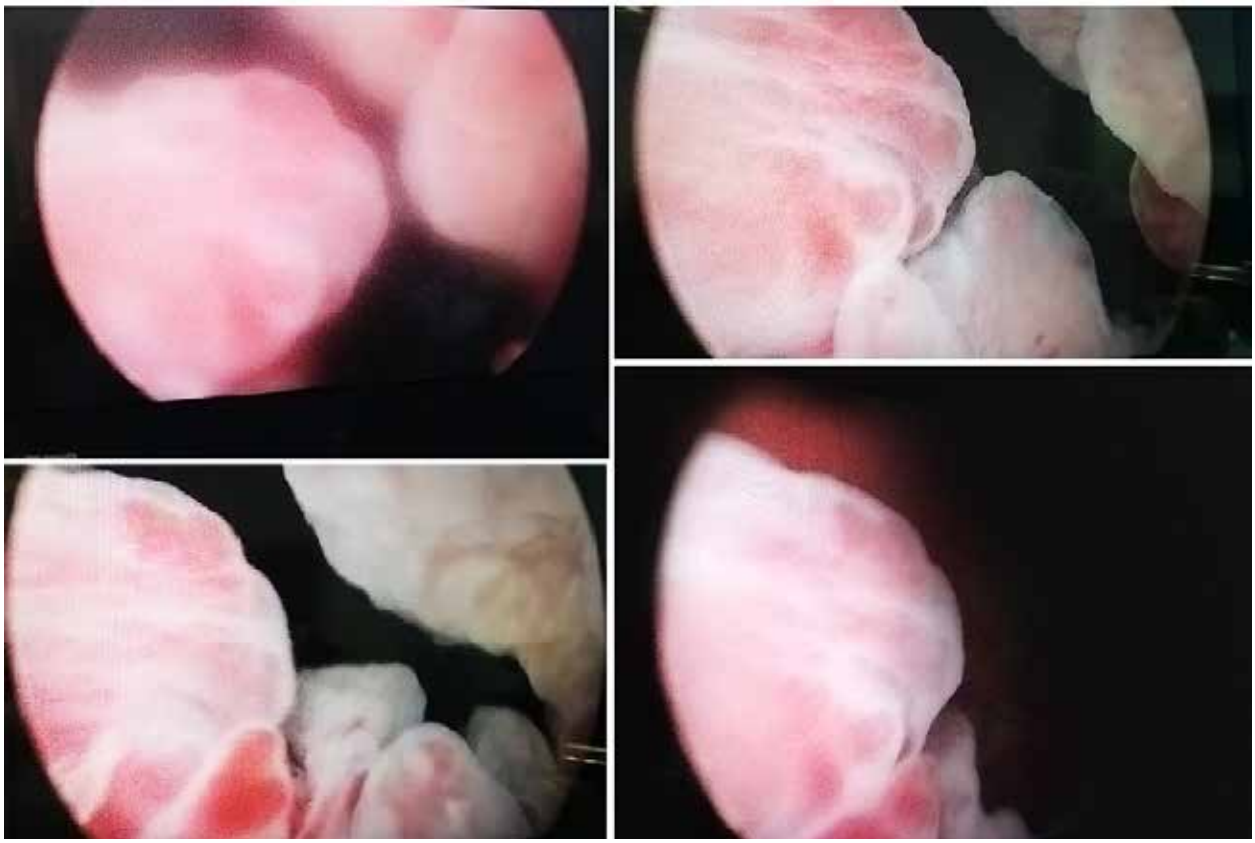

Fig 1: Cystoscopy view of inflamed, avulsed and prolapsing bladder epithelium

examinations. She had a Foley's urethral catheter connected to a urine bag containing clear amber coloured urine. Abdominal ultrasound scan was essentially normal, except for a mildly thickened bladder wall. Diagnostic cystoscopy revealed signs of bladder neck inflammation and mucosal eruptions that floated like wave forms around the internal urinary meatus. The tissue was mostly found hidden on the posterior wall of the neck of the bladder (Fig. 1).

Upon examination with a flexible cystoscopy, we found that the trigonal tissue worked like a valve causing urinary retention after removal of the cystoscope. Excision biopsy was done, and the tissue was sent for histopathology. The patients' post-operative hospital course was smooth, and she was discharged after two days to the outpatient. The histopathology report for the bladder wall and bladder neck tissue biopsy was reported as chronic non-specific cystitis with squamous non-keratinized metaplasia (Fig. 2). Subsequently, she had no further episodes of urinary retention and was discharged from the outpatient clinic after two visits. It is expected that she will visit the hospital for routine cystoscopy to follow the resolution of the bladder neck lesion.

DISCUSSION

The ability of the detrusor muscles of the urinary bladder to relax during bladder filling and contract upon a person's desire to micturate is a major requirement for normal urinary continence[5]. This physiologic process however requires a responsive and patent bladder outlet for the voiding of urine to take place. Whenever the bladder outlet gets obstructed by either congenital or acquired causes, progressive urinary retention sets in. Retained urine may get infected and reflux into the upper urinary tracts, resulting in a myriad of urinary system pathologies[6].

Multiparous females may develop pelvic floor complications associated with increased intra-abdominal pressure. Descent of the pelvic floor can result in varying degrees of compression or kinking of the urethra leading to urinary retention and later overflow or stress incontinence. Urinary stasis in such persons provides a good medium for recurrent urinary tract infection, which may result in cystitis presenting symptomatically as lower urinary tract symptoms[7].

Even though the urinary tract infection may respond to initial antibiotic treatment with short lived improvement in urinary symptoms, recurrence is inevitable if the underlying cause of outflow obstruction is left untreated[8]. The cause of outflow

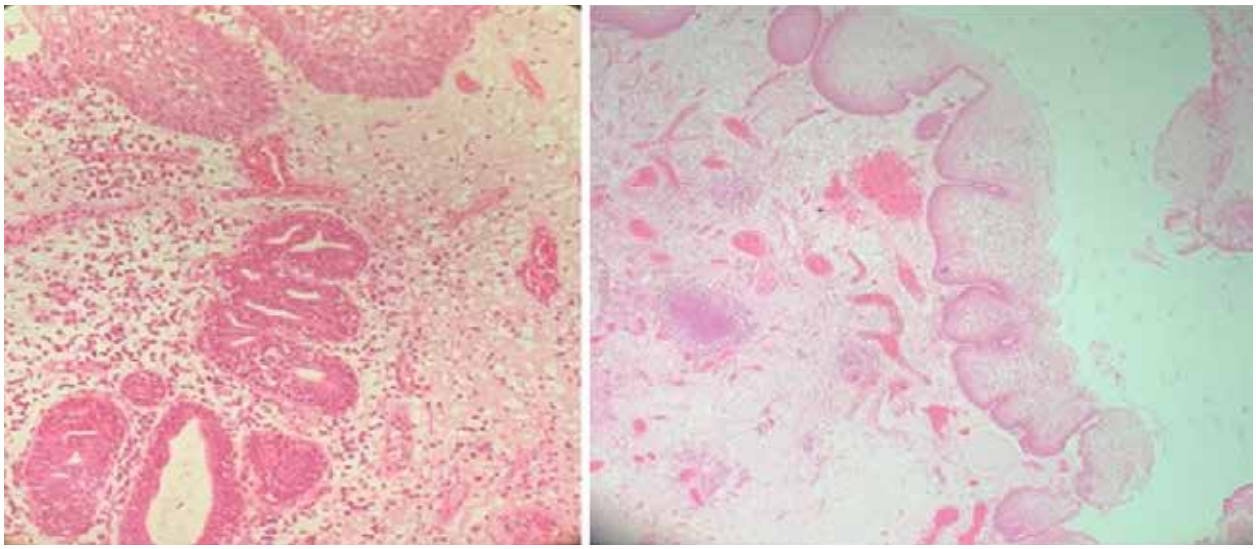

Fig 2: Fig. 2a and 2b. Histology of bladder epithelium showing chronic non-specific cystitis with squamous non-keratinized metaplasia.

obstruction may in certain cases be obvious; however, it may pose a significant diagnostic challenge to the clinician, as was the case with our index patient.

A known response to chronic urinary retention is straining during micturition. Unrelieved, bladder wall changes set in, manifesting as thickening of the bladder wall with mucosal changes which progress from cellules to trabeculation, sacculation and eventually, diverticula formation. In the presence of urinary infection, the bladder wall will also develop inflammatory changes, affecting mostly the bladder epithelium[9].

Our patient experienced all these changes; in addition, she had repeated urethral catheterization which inflicted further traumatic damage to an already infected and inflamed bladder mucosa. Cystoscopy should normally identify any inflammatory processes taking place within the bladder, as well as other causes of outflow obstruction like a neoplastic growth or urinary calculi. However, initial cystoscopy in our patient did not reveal the real cause of her recurrent urinary obstruction. Flexible cystoscopy eventually revealed the cause of her obstruction and provided the opportunity for a resection of the culprit valvular lesions. The histology report of the biopsied specimen returned as metaplastic changes, consistent with chronic trauma. Irregularity of the bladder wall around the bladder neck is more likely due to the bladder wall changes associated with the chronic urinary obstruction.

Bladder epithelial avulsion and prolapse is reported in the literature as a complication of pelvic injuries associated with the bladder neck[10], per se they have not been identified however as a primary cause of recurrent urinary obstruction. It was therefore not high on the suspicion list of possible causes of our patient's recurrent obstruction. The use of flexible cystoscopy and operator diligence made the diagnosis possible. Once the cystoscope was removed, the avulsed bladder epithelium prolapsed into the internal urinary meatus causing a valve-like obstruction and resulting in urinary retention. Resection of the redundant tissue resulted in the treatment of the patient.

This case report therefore highlights the importance of diligence in the cystoscopy evaluation of patients with chronic recurrent urinary obstruction when there is no other obvious abnormality. Our patient was seen at the outpatient clinic, where she confirmed that the symptoms had completely resolved. She was however advised to report back to the clinic for follow-up cystoscopy after six months.

CONCLUSION

Bladder outlet obstruction may result from congenital and acquired causes. Obstruction can clinically present as acute, chronic or recurrent urinary retention. In the presence of infection, chronic cystitis and ascending upper urinary infection due to reflux may supervene. Chronic catheterisation may result in epithelial inflammation, avulsion and prolapse of the bladder wall epithelium, which may present as difficult to diagnose and treat complication. Diligence during cystoscopy and resection of the redundant bladder epithelium is curative. Finally, this patient will be followed for at least one year to understand the effectiveness of the treatment.

ACKNOWLEDGMENT

Edet Eman Ikpi and Muhannd F Alanazi have contributed towards the study.

Authors contribution: Mohammed J Alenzi designed the study; acquired and interpreted the data related to the case and drafted the article. Edet Eman Ikpi and Muhannd F Alanazi contributed to concepts and design of the study and discussed and interpretation of the case. Edet Eman Ikpi was involved in acquisition of data related to the case. All other authors were involved in critically revising the manuscript; approved the final version of manuscript to be published and agreed to be accountable for all aspects of the work.

Conflict of interest: None

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2023; 55 (1): 81 - 83

COVID-19 vaccination in people with multiple sclerosis, real-life experience

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BACKGROUND

Vaccination against the severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) virus is recommended in multiple sclerosis (MS) to reduce the risk of complications from Coronavirus disease 2019 (COVID-19) infection. These vaccines were not investigated in people with MS (PWMS).

OBJECTIVE

This study aimed to report the short-term safety of the COVID-19 vaccines among PWMS.

METHODS

Pfizer-BioNTech mRNA (BNT162b2) vaccine and Oxford-Astra Zenecaa chimpanzee adenovirus-vectored (ChAdOx1 nCoV-19) vaccine have been approved to be used in Kuwait since December 2021. PWMS registered in Kuwait national registry were contacted by phone, WhatsApp, or through face-to-face interviews and were invited to complete our questionnaire. Demographic, clinical data, symptoms following the vaccine, worsening of pre-existing MS symptoms, and occurrence of relapse were recorded.

RESULTS

Of the 820 PWMS, 647 completed the questionnaire. Between January 2021 and 31 August 2021, 383 (59.28%) PWMS received at least one dose of the approved vaccinations versus 63.4% of the general population on the same date. Their mean age was 36.82 + 8.80, and most of them, 247 (64.3%), were females. A total of 356 vaccinated cohorts (92.6%) were treated with disease-modifying therapies. Adverse events were reported by 261 (68.15%) subjects. One case of COVID-19 infection was encountered after the first dose of the BNT162b2 vaccine. Twenty-one (5.48%) cases reported worsening of pre-existing MS symptoms after the vaccine. Five patients (1.31%) reported relapse after the COVID-19 vaccine. The most common adverse events of the COVID-19 vaccine were pain at the injection site, fatigue, low-grade fever, and body ache; and resolved within one week. There was no significant association between use of disease modifying therapy (DMT) and COVID-19 vaccine adverse events.

CONCLUSION

BNT162b2 and ChAdOx1 nCoV-19 are safe for PWMS. No increased risk of relapse activity or worsening of pre-existing MS symptoms.

Symptomatic Giant Primary Nonparasitic Splenic Cyst Treated with Laparoscopic Decapsulation: A Case Report and Literature Review

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Am J Case Rep. 2020 Nov 19;21:e927893. doi: 10.12659/AJCR.927893.

BACKGROUND
Primary nonparasitic splenic cysts (PNSC) are unusual epithelial fluid lesions of the spleen. They are considered congenital cysts and are often discovered incidentally in young people. Larger cysts can be symptomatic and are traditionally managed with splenectomy. This report is of a woman with a large symptomatic PNSC that was managed surgically by laparoscopic decapsulation.

CASE REPORT
A 22-year-old Lebanese woman presented with left upper-quadrant pain, left pleuritic pain, food intolerance, and significant weight loss. Investigations showed a 20×17×15 cm cystic lesion in the spleen. Secondary causes were ruled out and tumor marker and hydatid serology were unremarkable. Laparoscopic decapsulation of the cyst with spleen preservation was performed with no perioperative complications. The patient's 3-year follow-up visit revealed no clinical or radiological recurrence.

CONCLUSIONS
True congenital splenic cysts are rare clinical findings. Generally, they do not have malignant potential. The development of minimally invasive techniques has shifted the trend toward splenic salvaging procedures. Literature review revealed an acceptable recurrence rate with near-total rather than partial unroofing. Laparoscopic decapsulation can be a safe and adequate therapeutic option in selected cases.

COVID-19 pandemic and its effect on resident physicians' mental well-being: A cross-sectional study in Kuwait

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Cureus 15(1): e33606. DOI 10.7759/cureus.33606

OBJECTIVE
Concerns about COVID-19's long-term consequences on the mental health of frontline health professionals are mounting as the entire world strives anew to contain it. The primary objective of this research is to describe the impact of working during the COVID-19 pandemic on resident physicians' mental health.

SUBJECT AND METHODS
A cross-sectional online survey using the Google Forms platform was conducted from May 1 to May 30, 2021, on 311 residents currently enrolled in a residency program at the Kuwait Institutional of Medical Specialization (KIMS). Socio-demographic details of each resident physician were collected and the scores related to depression, anxiety, and stress were measured using the previously validated depression anxiety stress scale-21 (DASS-21).

RESULTS
Higher stress and depression scores were seen in those who were devoid of the option to work with COVID-19 patients, who reported that working during the pandemic affected their study schedule, and who lost off-service training time. Further, the anxiety scores were significantly higher in females.

CONCLUSION
The impact of the ongoing pandemic on residents' mental health is grave, necessitating psychological treatment and support. The study discovered various factors linked to depression, anxiety, and stress. As a result, these aspects must be regarded to protect the doctors' mental health.

Coronavirus Infection in Neonates: Neurodevelopmental Outcomes at 18 Months of Age

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BACKGROUND
Although most neonates with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection experience only mild disease, its impact on neurodevelopmental outcomes is unknown. This study aimed to assess the 18-month neurodevelopmental outcomes of infants who had SARS-CoV-2 infection as neonates.

METHODS
The authors conducted a prospective cohort study of neonates diagnosed with SARS-CoV-2 infection from June 2020 to December 2020 through nasopharyngeal coronavirus disease 2019 (COVID-19). A total of 58 neonates were identified from the Kuwait National COVID-19 Registry and enrolled. Historical controls were selected from the neonatal follow-up registry and matched in a 2 : 1 ratio based on sex and gestational age. When the subjects were 18 months of age, their neurodevelopmental outcomes were assessed by two trained assessors using the Bayley Scales of Infant and Toddler Development-3rd Edition (BSID-III).

RESULTS
Forty children diagnosed with SARS-CoV-2 infection were included in the final analysis. The median age at infection was 18 days (range: 10-26 days). Eighteen (45%) patients were asymptomatic, 15 (37.5%) had a sepsis-like presentation, 5 (12.5%) exhibited respiratory distress, and 2 (5%) had a multisystem inflammatory syndrome in children (MIS-C)-like presentation. At the 18 months follow-up, only one child showed a severe developmental delay and one child had a language delay. BSID-III outcomes did not differ significantly between the SARS-CoV-2-infected and control groups.

CONCLUSIONS
There was no difference in neurodevelopmental outcomes at 18 months in children infected with SARS-CoV-2 compared with controls, although longer neurodevelopmental follow-up studies are required.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2023; 55 (1): 84 - 91

1329th International Conference on **Sports Nutrition and Supplements**
Mar 01, 2023
United Arab Emirates, Dubai
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/UAE/2/ICSNS/

1287th International Conference on **Medical & Health Science**
Mar 01, 2023
Ireland, Dublin
Email: info@researchfora.com
Event Website: http: //researchfora.com/Conference2023/Ireland/1/ICMHS/

1479th International Conference on **Medical and Health Sciences**
Mar 02, 2023
Germany, Berlin
Email: info@iserd.co
Event Website: http: //iserd.co/Conference2023/Germany/2/ICMHS/

1330th International Conference on **Sports Nutrition and Supplements**
Mar 03, 2023
Germany, Munich
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/Germany/1/ICSNS/

2nd Emirates **Allergy & Clinical Immunology** Conference
Mar 03, 2023
United Arab Emirates, Dubai City, Dubai
Email: allergy@pemsevents.com
Event Website: https: //www.eacic uae.com/

Webinar on **Healthcare Innovation and Technology**
Mar 04, 2023
United Arab Emirates, Dubai
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/6152/WHIT/

1473rd International Conference on Recent Advances in **Medical and Health Sciences**
Mar 07, 2023
United Kingdom, London
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2023/UK/4/ICRAMHS/

1509th International Conference on Recent Advances in **Medical Science**
Mar 08, 2023
Australia, Brisbane
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/Australia/3/ICRAMS/

Internal Medicine Review 2023 - Virtual Conference
Mar 08-11, 2023
Kuwait, Virtual Conference
Organizer: Farwaniya Hospital Internal Medicine
Event website:www.imr2023.com

1472nd International Conference on **Medical and Biosciences**
Mar 09, 2023
Netherlands, Amsterdam
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/Netherlands/1/ICMBS/

25th **OBGYN** Conference - Recent Updates and Future Prospects
Mar 09-11, 2023
Kuwait, Waldorf Astoria Hotel
Organizer: Jaber Al Ahmad Hospital
Event Website: www.25obgynkw.com

International Conference on **Virology**
Mar 10, 2023
United Arab Emirates, Abu Dhabi
Email: papers.itrgroup@gmail.com
Event Website: http: //itrgroup.net/Conference/791/ICV/

The 6th Kuwait **Neurology** Conference
Mar 10-11, 2023
Kuwait, St. Regis (Sheraton)
Event website:www.kuwaitneurology.com

International Virtual Conference on **Covid 19** and its Effect
Mar 11, 2023
United Arab Emirates, Dubai
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/1050/IVCCE/

1475th International Conference on **Medical and Biosciences**
Mar 14, 2023
Saudi Arabia, Jeddah
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/SaudiArabia/2/ICMBS/

International Conference on Recent Advances in **Medical Science**
Mar 15, 2023
United States, Massachusetts
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/US/22/ICRAMS/

1381st International Conference on **Food Microbiology and Food Safety**
Mar 16, 2023
United States, New York
Email: info@theires.org
Event Website: http: //theires.org/Conference2023/USA/6/ICFMFS/

International Conference on **Healthcare and Clinical Gerontology**
Mar 16, 2023
Swaziland, Geneva
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/22426/ICHCG/

1340th International Conference on **Sports Nutrition and Supplements**
Mar 18, 2023
United Kingdom, Manchester
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/UK/1/ICSNS/

International **Surgery and Surgeons** Meet
Mar 18, 2023
Philippines, Manila
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/5238/ISSM/

International Conference on **Medical, Medicine and Health Sciences**
Mar 19, 2023
United Kingdom, George Town
Email: contact.iierd@gmail.com
Event Website: http: //iierd.com/Conference/2454/ICMMH/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Mar 20, 2023
South Korea, Seoul
Email: info.gsrd@gmail.com
Event Website: http: //gsrd.co/Conference/11998/ICMPH/

1470th International Conference on **Science, Health and Medicine**
Mar 21, 2023
Czech Republic, Prague
Email: info@iser.co
Event Website: http: //iser.co/Conference2023/CzechRepublic/1/ICSHM/

International Conference on **Nursing Science and Healthcare**
Mar 21, 2023
France, Paris
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/344/ICNSH/

Webinar on **Diabetes and Metabolism**
Mar 24, 2023
United States, New York
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/4786/WDM/

European **Pathology** Congress
Mar 24, 2023
United States, New York
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/4736/EPC/

1387th International Conference on **Food Microbiology and Food Safety**
Mar 25, 2023
South Africa, Johannesburg
Email: info@theires.org
Event Website: http: //theires.org/Conference2023/SouthAfrica/1/ICFMFS/

International Conference on **Sports Nutrition and Supplements**
Mar 26, 2023
Slovakia, Bratislava
Email: info.wrfase@gmail.com
Event Website: http: //wrfase.org/Conference/9689/ICSNS/

International Virtual Conference on **Covid 19 and its Effect**
Mar 26, 2023
United Arab Emirates, Abu Dhabi
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/1002/IVCCE/

1304th International Conference on **Medical & Health Science**
Mar 28, 2023
Kuwait, Kuwait City
Email: info@researchfora.com
Event Website: http: //researchfora.com/Conference2023/Kuwait/1/ICMHS/

1505th International Conference on Recent Advances in **Medical and Health Sciences**
Mar 28, 2023
Kuwait, Kuwait City
Email: info@academicsworld.org
Event Website: https: //academicsworld.org/Conference2023/Kuwait/2/ICRAMHS/

International Virtual Conference on **Medical Biological and Pharmaceutical Science**
Mar 29, 2023
United Kingdom, London
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/986/IVCMBPS/

International Video Conference on **Healthcare**
Mar 31, 2023
Japan, Kyoto
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/979/IVCH/

International Conference on **Medical, Medicine and Health Sciences**
Mar 31, 2023
United States, Boston
Email: contact.iierd@gmail.com
Event Website: http: //iierd.com/Conference/2438/ICMMH/

1488th International Conference on Recent Advances in **Medical and Health Sciences**
Apr 01, 2023
Ireland, Dublin
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2023/Ireland/1/ICRAMHS/

International Conference on **Healthcare and Clinical Gerontology**
Apr 02, 2023
United Arab Emirates, Dubai
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/22257/ICHCG/

European **Pathology** Congress
Apr 03, 2023
Malaysia, Kuala Lumpur
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/3847/EPC/

International Conference on **Medical and Health Sciences**
Apr 04, 2023
United Kingdom, London
Email: papers.scienceplus@gmail.com
Event Website: http: //scienceplus.us/Conference/24594/ICMHS/

International Research Conference on Covid 19 and its Impact on **Mental Health**
Apr 04, 2023
United States, New York
Email: info.researchconferences@gmail.com
Event Website: http: //researchconferences.in/Conference/3320/IRCCIMH/

International Conference on **Medical and Health Sciences**
Apr 07, 2023
New Zealand, Wellington
Email: papers.academicsconference@gmail.com
Event Website: http: //academicsconference.com/Conference/29924/ICMHS/

Webinar on **Diabetes and Metabolism**
Apr 08, 2023
Indonesia, Bali
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/3349/WDM/

International Conference on **Oncolytic Virus Therapeutics**
Apr 11, 2023
United Arab Emirates, Dubai
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/725/ICOVT/

1555th International Conference on Recent Advances in **Medical and Health Sciences**
Apr 12, 2023
Egypt, Cairo
Email: info@academicsworld.org
Event Website: https: //academicsworld.org/Conference2023/Egypt/5/ICRAMHS/

1506th International Conference on **Medical, Biological and Pharmaceutical Sciences**
Apr 13, 2023
Saudi Arabia, Dammam
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/SaudiArabia/2/ICMBPS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Apr 14, 2023
Saudi Arabia, Medina
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/26246/ICRAMMHS/

International Conference on **Healthcare and Clinical Gerontology**
Apr 15, 2023
Swaziland, Bern
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/22101/ICHCG/

International Conference on **Cardiology and Diabetes**
Apr 16, 2023
France, Paris
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/430/ICCD/

1498th International Conference on **Medical and Biosciences**
Apr 17, 2023
United States, Denver
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/USA/6/ICMBS/

1487th International Conference on **Science, Health and Medicine**
Apr 19, 2023
Italy, Florence
Email: info@iser.co
Event Website: http: //iser.co/Conference2023/Italy/6/ICSHM/

Webinar on **Antibiotics and Antimicrobial Resistance**
Apr 20, 2023
United Arab Emirates, Dubai
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/2580/WAAR/

Asian **Pulmonology** Summit
Apr 20, 2023
United *Arab Emirates*, Dubai
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/2515/APS/

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Apr 24, 2023
Italy, Rome
Email: papers.issrd@gmail.com
Event Website: http: //issrd.org/Conference/18831/ICMPB/

International Conference on **Dentistry**
Apr 24, 2023
United States, New York
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/2393/ICD/

International Conference on **Medical and Biological Engineering**
Apr 29, 2023
India, Agra, Uttar Pradesh
Email: papers.techno@gmail.com
Event Website: http: //technoconferences.com/Conference/10283/ICMBE/

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Apr 30, 2023
Canada, Ottawa
Email: papers.issrd@gmail.com
Event Website: http: //issrd.org/Conference/18804/ICMPB/

Webinar on **Diabetes and Metabolism**
Apr 30, 2023
Thailand, Bangkok
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/2154/WDM/

1410th International Conference on **Food Microbiology and Food Safety**
May 01, 2023
United Arab Emirates, Dubai
Email: info@theires.org
Event Website: http: //theires.org/Conference2023/UAE/4/ICFMFS/

European **Surgery and Surgeons** Meeting
May 01, 2023
Singapore, Singapore
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/5618/ESSM/

World Conference on **Pharma Industry and Medical Devices**
May 03, 2023
United Arab Emirates, Dubai
Email: info.ifearpworld@gmail.com
Event Website: http: //ifearp.org/Conference/8984/WCPIMD/

Webinar on **Dental** Care
May 03, 2023
Malaysia, Kuala Lumpur
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/5502/WDC/

Webinar on **Diabetes and Metabolism**
May 04, 2023
United Arab Emirates, Dubai
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/5395/WDM/

European **Pathology** Congress
May 04, 2023
United Arab Emirates, Dubai
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/5345/EPC/

Global Summit on **Breast Cancer & Blood Cancer**
May 04, 2023
United Arab Emirates, Dubai
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/5271/GSBCBC/

International Conference on **Medical, Pharmaceutical and Health Sciences**
May 05, 2023
Japan, Tokyo
Email: info.gsrd@gmail.com
Event Website: http: //gsrd.co/Conference/11590/ICMPH/

1370th International Conference on **Sports Nutrition and Supplements**
May 07, 2023
United Kingdom, Edinburgh
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/UK/4/ICSNS/

1513th International Conference on Recent Advances in **Medical and Health Sciences**
May 09, 2023
Netherlands, Amsterdam
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2023/Netherlands/1/ICRAMHS/

World **Disability & Rehabilitation** Conference
May 10, 2023
India, Puducherry
Email: papers.asar@gmail.com
Event Website: http: //asar.org.in/Conference/40897/WDRC/

International Conference on Advances in **Health and Medical Science**
May 13, 2023
United Arab Emirates, Dubai
Email: info.saard.org@gmail.com
Event Website: http: //saard.org/Conference/2234/ICAHMS/

Global Summit on **Breast Cancer & Blood Cancer**
May 14, 2023
Malaysia, Kuala Lumpur
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/4381/GSBCBC/

International Conference on **Medical and Health Sciences**
May 17, 2023
United States, Boston
Email: papers.academicsconference@gmail.com
Event Website: http: //academicsconference.com/Conference/29602/ICMHS/

International Conference on **Virology**
May 18, 2023
Japan, Kyoto
Email: papers.itrgroup@gmail.com
Event Website: http: //itrgroup.net/Conference/886/ICV/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
May 19, 2023
Ireland, Dublin
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/25998/ICRAMMHS/

International Research Conference on **Covid 19** and its Impact on Mental Health
May 20, 2023
United Arab Emirates, Dubai
Email: info.researchconferences@gmail.com
Event Website: http: //researchconferences.in/Conference/3374/IRCCIMH/

International Conference on **Dentistry**
May 20, 2023
United Arab Emirates, Dubai
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/3914/ICD/

International **Vaccine R&D** Congress
May 20, 2023
United Arab Emirates, Dubai
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/3840/IVRDC/

International Conference on **Virology**
May 22, 2023
United Arab Emirates, Dubai
Email: papers.itrgroup@gmail.com
Event Website: http: //itrgroup.net/Conference/891/ICV/

1531st International Conference on **Medical, Biological and Pharmaceutical Sciences**
May 24, 2023
Australia, Sydney
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/Australia/3/ICMBPS/

Webinar on **Clinical & Medical Case Reports**
May 24, 2023
United States, New York
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/3618/WCMCR/

1523rd International Conference on **Medical and Biosciences**
May 25, 2023
South Africa, Johannesburg
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/SouthAfrica/2/ICMBS/

International Virtual Conference on **Covid 19** and its Effect
May 27, 2023
United Kingdom, London
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/786/IVCCE/

1511th International Conference on **Science, Health and Medicine**
May 28, 2023
Kuwait, Kuwait City
Email: info@iser.co
Event Website: http: //iser.co/Conference2023/Kuwait/1/ICSHM/

Webinar on **Diet & Nutrition**
May 28, 2023
Korea (*South*), Seoul
Email: info@meetingfora.com
Event Website: http: //meetingfora.com/Conference/3270/WDN/

International Conference on **Obesity and Chronic Diseases**
May 31, 2023
Germany, Berlin
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/444/ICOCD/

National Conference on **Medical and Health Sciences**
May 31, 2023
India, Mysore, Karnataka
Email: papers.nrf@gmail.com
Event Website: http: //nationalconference.org.in/Conference/10802/NCMHS/

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Jun 01, 2023
United States, New York
Email: papers.issrd@gmail.com
Event Website: http: //issrd.org/Conference/18696/ICMPB/

1564th International Conference on Recent Advances in **Medical Science**
Jun 01, 2023
United Arab Emirates, Dubai
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/UAE/5/ICRAMS/

International Conference on **Virology**
Jun 04, 2023
Japan, Tokyo
Email: papers.itrgroup@gmail.com
Event Website: http: //itrgroup.net/Conference/901/ICV/

International Conference on **Medical, Medicine and Health Sciences**
Jun 05, 2023
Egypt, Cairo
Email: contact.iierd@gmail.com
Event Website: http: //iierd.com/Conference/2658/ICMMH/

International Conference on **Medical Ethics and Professionalism**
Jun 10, 2023
Japan, Fukuoka
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/21486/ICMEP/

International Conference on **Cell and Tissue Science**
Jun 10, 2023
France, Marseille
Email: info@conferencefora.org
Event Website: http: //conferencefora.org/Conference/43331/ICCTS/

World **Disability & Rehabilitation** Conference
Jun 11, 2023
Malaysia, George Town
Email: papers.asar@gmail.com
Event Website: http: //asar.org.in/Conference/38129/WDRC/

International Conference on **Obesity and Chronic Diseases**
Jun 11, 2023
France, Paris
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/492/ICOCD/

1392nd International Conference on **Pharma and Food**
Jun 13, 2023
Saudi Arabia, Medina
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/Belgium/1/ICPAF/

International Conference on Recent Advances in **Medical Science**
Jun 15, 2023
United States, Massachusetts
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/US/52/ICRAMS/

International Conference on **Medical and Health Sciences**
Jun 16, 2023
Australia, Sydney
Email: papers.academicsconference@gmail.com
Event Website: http: //academicsconference.com/Conference/29350/ICMHS/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Jun 17, 2023
Swaziland, Bern
Email: info.gsrd@gmail.com
Event Website: http: //gsrd.co/Conference/11218/ICMPH/

International Conference on **Medical and Biological Engineering**
Jun 20, 2023
United States, Edinburg
Email: papers.techno@gmail.com
Event Website: http: //technoconferences.com/Conference/9896/ICMBE/

1546th International Conference on **Medical and Biosciences**
Jul 01, 2023
United Arab Emirates, Dubai
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/UAE/5/ICMBS/

1558th International Conference on **Medical and Health Sciences**
Jul 02, 2023
United Arab Emirates, Abu Dhabi
Email: info@iserd.co
Event Website: http: //iserd.co/Conference2023/UAE/3/ICMHS/

International Conference on **Medical, Medicine and Health Sciences**
Jul 02, 2023
New Zealand, Wellington
Email: contact.iierd@gmail.com
Event Website: http: //iierd.com/Conference/2430/ICMMH/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jul 03, 2023
United States, Houston
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/25702/ICRAMMHS/

1451st International Conference on **Food Microbiology and Food Safety**
Jul 07, 2023
United Kingdom, Edinburgh
Email: info@theires.org
Event Website: http: //theires.org/Conference2023/UK/5/ICFMFS/

International Conference on **Healthcare and Clinical Gerontology**
Jul 08, 2023
Australia, Adelaide
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/24012/ICHCG/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Jul 09, 2023
Qatar, Doha
Email: info.gsrd@gmail.com
Event Website: http: //gsrd.co/Conference/11014/ICMPH/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jul 13, 2023
United Arab Emirates, Dubai
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/25630/ICRAMMHS/

International Conference on Recent Advances in **Medical Science**
Jul 14, 2023
United States, San Francisco
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/US/61/ICRAMS/

1578th International Conferences on **Medical and Health Science**
Jul 15, 2023
Saudi Arabia, Mecca
Email: info@theires.org
Event Website: http: //theires.org/Conference2023/SaudiArabia/5/ICMHS/

International Conference on **Medical and Health Sciences**
Jul 21, 2023
France, Paris
Email: papers.academicsconference@gmail.com
Event Website: http: //academicsconference.com/Conference/33994/ICMHS/

International Conference on **Cardiology and Diabetes**
Jul 22, 2023
United States, Washington, D.C
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/517/ICCD/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jul 23, 2023
Spain, Barcelona
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/25558/ICRAMMHS/

International Conference on **Cardiology and Diabetes**
Jul 23, 2023
Germany, Berlin
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/509/ICCD/

WHO-Facts Sheet

1. Blindness and vision impairment
2. Epilepsy
3. Human T-lymphotropic virus type 1
4. Nursing and midwifery
5. Rift valley fever

Compiled and edited by
Vineetha E Mammen

Kuwait Medical Journal 2023; 55 (1): 92 - 103

1. Blindness and vision impairment

KEY FACTS

- Vision impairment poses an enormous global financial burden with the annual global costs of productivity losses associated with vision impairment estimated to be US$ 411 billion.
- The leading causes of vision impairment and blindness are uncorrected refractive errors and cataracts.
- The majority of people with vision impairment and blindness are over the age of 50 years; however, vision loss can affect people of all ages.
- Globally, at least 2.2 billion people have a near or distance vision impairment. In at least 1 billion – or almost half – of these cases, vision impairment could have been prevented or has yet to be addressed.

Definitions

The International Classification of Diseases 11 (2018) classifies vision impairment into two groups, distance and near presenting vision impairment.

Distance vision impairment:

- Mild – visual acuity worse than 6/12 to 6/18
- Moderate – visual acuity worse than 6/18 to 6/60
- Severe – visual acuity worse than 6/60 to 3/60
- Blindness – visual acuity worse than 3/60

Near vision impairment:

- Near visual acuity worse than N6 or M.08 at 40cm.

A person's experience of vision impairment varies depending upon many different factors. This includes for example, the availability of prevention and treatment interventions, access to vision rehabilitation (including assistive products such as spectacles or white canes), and whether the person experiences problems with inaccessible buildings, transport and information.

Prevalence

Globally, at least 2.2 billion people have a near or distance vision impairment. In at least 1 billion – or almost half – of these cases, vision impairment could have been prevented or has yet to be addressed.

This 1 billion people includes those with moderate or severe distance vision impairment or blindness due to unaddressed refractive error (88.4 million), cataract (94 million), age-related macular degeneration (8 million), glaucoma (7.7 million), diabetic retinopathy (3.9 million) (1), as well as near vision impairment caused by unaddressed presbyopia (826 million) (2).

In terms of regional differences, the prevalence of distance vision impairment in low- and middle-income regions is estimated to be four times higher than in high-income regions (1). With regards to near vision, rates of unaddressed near vision impairment are estimated to be greater than 80% in western, eastern and central sub-Saharan Africa, while comparative rates in high-income regions of North America, Australasia, Western Europe, and of Asia-Pacific are reported to be lower than 10% (2).

Population growth and ageing are expected to increase the risk that more people acquire vision impairment.

Causes

Globally, the leading causes of vision impairment are:

- age-related macular degeneration
- cataract
- diabetic retinopathy
- glaucoma
- uncorrected refractive errors

There is substantial variation in the causes between and within countries according to the availability of eye care services, their affordability, and the eye care

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literacy of the population. For example, the proportion of vision impairment attributable to cataract is higher in low- and middle-income countries than high-income countries. In high income countries, diseases such as glaucoma and age-related macular degeneration are more common.

Among children, the causes of vision impairment vary considerably across countries. For example, in low-income countries congenital cataract is a leading cause, whereas in middle-income countries it is more likely to be retinopathy of prematurity.

As in adult populations, uncorrected refractive error remains a leading cause of vision impairment in all countries amongst children.

Impact of vision impairment

Personal impact

Young children with early onset severe vision impairment can experience delayed motor, language, emotional, social and cognitive development, with lifelong consequences. School-age children with vision impairment can also experience lower levels of educational achievement.

Vision impairment severely impacts quality of life among adult populations. Adults with vision impairment often have lower rates of workforce participation and productivity and higher rates of depression and anxiety.

In the case of older adults, vision impairment can contribute to social isolation, difficulty walking, a higher risk of falls and fractures, and a greater likelihood of early entry into nursing or care homes.

Economic impact

Vision impairment poses an enormous global financial burden with an estimate annual global productivity loss of about US$ 411 billion purchasing power parity (3). this figure far outweighs the estimated cost gap of addressing the unmet need of vision impairment (estimated at about US$ 25 billion).

Strategies to address eye conditions to avoid vision impairment

While a large number of eye diseases can be prevented (such as infections, trauma, unsafe traditional medicines, perinatal diseases, nutrition-related diseases, unsafe use or self-administration of topical treatment), this is not possible for all.

Each eye condition requires a different, timely response. There are effective interventions covering promotion, prevention, treatment and rehabilitation which address the needs associated with eye conditions and vision impairment; some are among the most cost-effective and feasible of all health care interventions to implement. For example, uncorrected refractive error can be corrected with spectacles or surgery while cataract surgery can restore vision.

Treatment is also available for many eye conditions that do not typically cause vision impairment, such as dry eye, conjunctivitis and blepharitis, but generate discomfort and pain. Treatment of these conditions is directed at alleviating the symptoms and preventing the evolution towards more severe diseases.

Vision rehabilitation is very effective in improving functioning for people with an irreversible vision impairment that can be caused by eye conditions such as diabetic retinopathy, glaucoma, consequences of trauma, and age-related macular degeneration.

WHO response

WHO's work is guided by the recommendations of the WHO World report on vision (2019) and the resolution on «integrated, people-centred eye care, including preventable blindness and vision impairment» that was adopted at Seventy-third World Health Assembly in 2020. The key proposal of the report and resolution is to make integrated people-centred eye care (IPEC) the care model of choice and to ensure its widespread implementation. It is expected that by shaping the global agenda on vision, the report and resolution will assist Member States and their partners in their efforts to reduce the burden of eye conditions and vision impairment and achieve the Sustainable Development Goals (SDGs), particularly SDG target 3.8 on universal health coverage.

Some of WHO's key areas of work and activities in the prevention of blindness include:

1. Working with Member States and other partners in the field to monitor the global targets for 2030 on integrated people-centred eye care.
2. Observing and promoting World Sight Day as an annual advocacy event.
3. Supporting the integration of eye care in health systems through the implementation of a series of technical tools:
    - eye care in health sytems – Guide for action providing practical, step-by-step support to Member States in the planning and implementation of the recommendations of the World report on vision.
    - package of Eye Care Interventions (PECI): a tool for planning and budgeting for eye care at each level of the health system.
    - Eye Care Competency Framework (ECCF): a planning tool for eye care human resources based on competencies; and
    - mobile health toolkit for myopia to increase awareness and health literacy of modifiable

risk factors, potential irreversible consequences of myopia and the importance of spectacle compliance and regular eye examinations.

4. The development and implementation tools to support countries to assess the provision of eye care services such as:
   - Eye care services assessment tool
   - Tool for Assessment of Diabetes and Diabetic Retinopathy Services
   - Tool for the Assessment of Glaucoma Services
   - Tool for the Assessment of Refractive Services
   - Tool for the Assessment of Rehabilitation Services and Systems

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2. Epilepsy

KEY FACTS

- Epilepsy is a chronic noncommunicable disease of the brain that affects people of all ages.
- Around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally.
- Nearly 80% of people with epilepsy live in low- and middle-income countries.
- It is estimated that up to 70% of people living with epilepsy could live seizure-free if properly diagnosed and treated.
- The risk of premature death in people with epilepsy is up to three times higher than for the general population.
- Three quarters of people with epilepsy living in low-income countries do not get the treatment they need.
- In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination.

Overview

Epilepsy is a chronic noncommunicable disease of the brain that affects around 50 million people worldwide. It is characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function.

Seizure episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Seizures can vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions. Seizures can also vary in frequency, from less than one per year to several per day.

One seizure does not signify epilepsy (up to 10% of people worldwide have one seizure during their lifetime). Epilepsy is defined as having two or more unprovoked seizures. Epilepsy is one of the world's oldest recognized conditions, with written records dating back to 4000 BCE. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. This stigma continues in many countries today and can impact on the quality of life for people with the disease and their families.

Signs and symptoms

Characteristics of seizures vary and depend on where in the brain the disturbance first starts, and how far it spreads. Temporary symptoms occur, such as loss of awareness or consciousness, and disturbances of movement, sensation (including vision, hearing and taste), mood, or other cognitive functions.

People with epilepsy tend to have more physical problems (such as fractures and bruising from injuries related to seizures), as well as higher rates of psychological conditions, including anxiety and depression. Similarly, the risk of premature death in people with epilepsy is up to three times higher than in the general population, with the highest rates of premature mortality found in low- and middle-income countries and in rural areas.

A great proportion of the causes of death related to epilepsy, especially in low- and middle-income countries, are potentially preventable, such as falls, drowning, burns and prolonged seizures.

Rates of disease

Epilepsy accounts for a significant proportion of the world's disease burden, affecting around 50 million people worldwide. The estimated proportion of the general population with active epilepsy (i.e. continuing seizures or with the need for treatment) at a given time is between 4 and 10 per 1000 people.

Globally, an estimated 5 million people are diagnosed with epilepsy each year. In high-income countries, there are estimated to be 49 per 100 000 people diagnosed with epilepsy each year. In low- and middle-income countries, this figure can be as high as 139 per 100 000. This is likely due to the increased risk of endemic conditions such as malaria or neurocysticercosis; the higher incidence of road traffic injuries; birth-related injuries; and variations in medical infrastructure, the availability of preventive health programmes and accessible care. Close to 80% of people with epilepsy live in low- and middle-income countries.

Causes

Epilepsy is not contagious. Although many underlying disease mechanisms can lead to epilepsy, the cause of the disease is still unknown in about 50% of cases globally. The causes of epilepsy are divided into the following categories: structural, genetic, infectious, metabolic, immune and unknown. Examples include:

- brain damage from prenatal or perinatal causes (e.g. a loss of oxygen or trauma during birth, low birth weight);
- congenital abnormalities or genetic conditions with associated brain malformations;
- a severe head injury;
- a stroke that restricts the amount of oxygen to the brain;
- an infection of the brain such as meningitis, encephalitis or neurocysticercosis,
- certain genetic syndromes; and
- a brain tumour.

Treatment

Seizures can be controlled. Up to 70% of people living with epilepsy could become seizure free with appropriate use of antiseizure medicines. Discontinuing antiseizure medicine can be considered after 2 years without seizures and should take into account relevant clinical, social and personal factors. A documented etiology of the seizure and an abnormal electroencephalography (EEG) pattern are the two most consistent predictors of seizure recurrence.

- In low-income countries, about three quarters of people with epilepsy may not receive the treatment they need. This is called the "treatment gap".
- In many low- and middle-income countries, there is low availability of antiseizure medicines. A recent study found the average availability of generic antiseizure medicines in the public sector of low- and middle-income countries to be less than 50%. This may act as a barrier to accessing treatment.
- It is possible to diagnose and treat most people with epilepsy at the primary health-care level without the use of sophisticated equipment.
- WHO pilot projects have indicated that training primary health-care providers to diagnose and treat epilepsy can effectively reduce the epilepsy treatment gap.
- Surgery might be beneficial to patients who respond poorly to drug treatments.

Prevention

An estimated 25% of epilepsy cases are potentially preventable.

- Preventing head injury, for example by reducing falls, traffic accidents and sports injuries, is the most effective way to prevent post-traumatic epilepsy.
- Adequate perinatal care can reduce new cases of epilepsy caused by birth injury.
- The use of drugs and other methods to lower the body temperature of a feverish child can reduce the chance of febrile seizures.
- The prevention of epilepsy associated with stroke is focused on cardiovascular risk factor reduction, e.g. measures to prevent or control high blood pressure, diabetes and obesity, and the avoidance of tobacco and excessive alcohol use.
- Central nervous system infections are common causes of epilepsy in tropical areas, where many low- and middle-income countries are concentrated. Elimination of parasites in these environments and education on how to avoid infections can be effective ways to reduce epilepsy worldwide, for example those cases due to neurocysticercosis.

Social and economic impacts

Epilepsy accounts for more than 0.5% of the global burden of disease, a time-based measure that combines years of life lost due to premature mortality and time lived in less than full health. Epilepsy has significant economic implications in terms of health-care needs, premature death and lost work productivity.

Out-of-pocket costs and productivity losses can create substantial burdens on households. An economic study from India estimated that public financing for both first- and second-line therapy and other medical costs alleviates the financial burden from epilepsy and is cost-effective.

The stigma and discrimination that surround epilepsy worldwide are often more difficult to overcome than the seizures themselves. People living with epilepsy and their families can be targets of prejudice. Pervasive myths that epilepsy is incurable, or contagious, or a result of morally bad behaviour

can keep people isolated and discourage them from seeking treatment.

Human rights

People with epilepsy can experience reduced access to educational opportunities, a withholding of the opportunity to obtain a driving license, barriers to enter particular occupations, and reduced access to health and life insurance. In many countries legislation reflects centuries of misunderstanding about epilepsy, for example, laws which permit the annulment of a marriage on the grounds of epilepsy and laws that deny people with seizures access to restaurants, theatres, recreational centres and other public buildings.

Legislation based on internationally accepted human rights standards can prevent discrimination and rights violations, improve access to health-care services, and raise the quality of life for people with epilepsy.

WHO response

The 75th WHA adopted the Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031, which recognizes the shared preventive, pharmacological and psychosocial approaches between epilepsy and other neurological disorders that can serve as valuable entry points for accelerating and strengthening services and support for these conditions.

Recently, WHO published an epilepsy technical brief, which outlines actions for policy makers and healthcare planners to reduce the burden of epilepsy in countries through finding and prioritizing the most effective solutions in a wide range of societal sectors.

WHO, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) led the Global Campaign Against Epilepsy to bring the disease out of the shadows to provide better information and raise awareness about epilepsy and to strengthen public and private efforts to improve care and reduce the disease's impact.

These efforts have contributed to the prioritization of epilepsy in many countries and projects have been carried out to reduce the treatment gap and morbidity of people with epilepsy, to train and educate health professionals, to dispel stigma, to identify potential prevention strategies, and to develop models integrating epilepsy care into local health systems. Combining several innovative strategies, these projects have shown that there are simple, cost-effective ways to treat epilepsy in low-resource settings. The WHO Programme on reducing the epilepsy treatment gap and the mental health Gap Action Programme (mhGAP) achieved these goals in Ghana, Mozambique, Myanmar and Viet Nam, where 6.5 million more people have access to treatment for epilepsy should they need it.

3. Human T-lymphotropic virus type 1

KEY FACTS

- The human T-lymphotropic virus type 1 is also known by the acronym HTLV-1, or as human T-cell leukaemia virus type 1.
- The virus can cause a type of cancer called adult T-cell leukaemia/lymphoma (ATL).
- HTLV-1 is transmitted primarily through infected bodily fluids including blood, breast milk and semen.
- Risk factors include unprotected sex, injecting drug use and transplantation of tissue, blood and blood products.
- An estimated 5–10 million people globally are infected with HTLV-1, although that number is probably higher due to a lack of reliable data.

Overview

The human T-lymphotropic virus type 1 (HTLV-1) was the first oncogenic human retrovirus to be discovered. It was first studied in 1977. The virus can cause adult T-cell leukaemia/lymphoma (ATL) and progressive nervous system condition known as HTLV-1-associated myelopathy or tropical spastic paraparesis (HAM/TSP).

The current best estimates for the total number of people living with HTLV-1 infection range from 5 million to 10 million. The scarcity of reliable data indicates that is likely an underestimation of actual global numbers.

Transmission

HTLV-1 is understood to be transmitted primarily through direct contact via cell-containing bodily fluids including blood, breast milk and semen. Transmission via direct contact is also considered feasible, although the virus usually exists in the intra-cellular form.

Mothers can pass the virus to children through breastfeeding, and there is limited evidence of transmission before or during birth. The estimated mother to child transmission rate has ranged from 3.9% to 27%.

HTLV-1 has been detected in cervical secretions and semen. The elevated presence of the virus has been reported among the sexual partners of people with HTLV-1 infection, which supports evidence of sexual transmission. A history of unprotected sex, earlier age at first sex and a higher number of partners increase the risk of transmission.

Several studies have reported transmission rates of up to 63% from transfusions of blood from a donor with HTLV-1. One study reported transmission rate of 87% from tissue transplants from positive donors.

Injecting drug use is also a risk factor for HTLV-1 infection.

Screening and diagnosis

Following current practices, screening tests for HTLV-1 should be followed by confirmatory tests for the diagnosis of HTLV-1. Most screening tests use immunoassays, which rely on detecting anti-HTLV-1 antibodies. Commonly used confirmatory tests detect antibody responses to specific HTLV-1 antigens. Test types include the western blot, radioimmunoprecipitation assay (RIA) and line immunoassay; however, the western blot test has been found to give unreliable results. Several studies have proposed transitioning from using western blot for confirmation in routine testing to using line immunoassay or NAT.

Testing can be made more complicated due to the length of time between contracting the virus and the seroconversion required for the virus to appear on tests. This period has been reported to be as long as 65 days. Delayed seroconversion lasting several years has also been reported. Infants born to seropositive mothers have been reported to seroconvert within 1–3 years of age.

Symptoms

Most people with HTLV-1 infection are asymptomatic and do not develop conditions that can be causally linked to the infection. However, several serious diseases are thought to be caused by or strongly associated with the virus. These diseases each show specific symptoms that may point to the presence of HTLV-1.

For example, the lifetime risk of developing adult T-cell leukaemia/lymphoma (ATL) among people with an HTLV-1 infection is about 5% (although this may be conservative due to unreported cases). ATL presents as four clinical subtypes: acute, lymphomatous, chronic and smouldering, with the more aggressive subtypes (acute and lymphomatous) representing the majority of cases. Clinical presentation depends on the subtype. People may present with lymphadenopathy, hepatosplenomegaly, hypercalcaemia through involvement of the skin, lung, bones and other organs.

Another disease is HTLV-1-associated myelopathy or tropical spastic paraparesis (HAM/TSP). This is a chronic inflammatory disease of the central nervous system, characterized by progressive spastic weakness of the lower limbs, lower back pain and bowel and bladder dysfunction. Clinical findings can include muscle weakness, hyperreflexia and clonus in the lower limbs, along with extensor plantar responsive and a spastic gait. Estimates of the lifetime risk of HAM/TSP among people with HTLV-1 infection have ranged from 0.18% to 1.8%.

Other diseases connected to HTLV-1 infection include HTLV-1-associated uveitis (HAU), infective dermatitis, bronchiectasis, bronchitis and bronchiolitis, seborrheic dermatitis, Sjögren's syndrome, rheumatoid arthritis, fibromyalgia and ulcerative colitis. There is little evidence that HTLV-1 infections cause other forms of cancer.

Prevention

Few observational studies have investigated specific preventions for HTLV-1. There are no reports related to preventing sexual transmission nor to prevention among people who inject drugs. Currently studied strategies include:

- Cessation of breast feeding: Based on observational studies of mother-to-child transmission, it was determined that shortening the duration of breastfeeding or even eliminating it altogether could enable women with HTLV-1 to limit the extent of exposure to their infants.
- Breast milk freeze thaw method: The freeze-thaw method effectively eliminates the cells in breast milk that are infected with HTLV-1 and hence the source of transmission.
- Antibody screening amongst blood donors: Mandatory HTLV-1 antibody screening of all blood donations has been implemented in 23 countries.
- Leukoreduction: Because HTLV-1 is almost always cell associated, leukoreduction may be as effective as blood donation screening in preventing transmission.

There is currently no vaccine for HTLV-1, although development of a vaccine is considered feasible. However, animal models may not be suitable to study vaccine effects in HTLV-1. No candidate HTLV-1 vaccine has proceeded to a clinical trial with an efficacy endpoint so far.

Treatment

No treatment is currently recommended for people with asymptomatic HTLV-1 infection. Treatment should instead focus on the symptoms of associated diseases, namely ATL and HAM/TSP, and screening for comorbidities and coinfection.

Currently, no single biological marker or clinical feature accurately predicts the development of or quantifies the risk of diseases associated with HTLV-1, although the levels of HTLV-1 proviral load has been suggested as a possible indicator. Improvements in risk prediction would assist in clinical management.

WHO Response

In collaboration with Member States and partners, WHO works to develop guidance on HTLV-1 surveillance methods, including methods to determine prevalence and methods for monitoring interventions. This includes rapid assessment methods and burden of disease estimates. Specific guidance is also needed for low-resource settings on testing approaches and strategies for HTLV-1 detection that are appropriate to the setting and the purpose.

Further testing and analysis will determine whether there is a level of proviral load below which transmission risk is negligible, as well as specific data to better define the risk of mother-to-child HTLV-1 transmission and the effectiveness of prevention strategies.

4. Nursing and midwifery

KEY FACTS

- Approximately 27 million men and women make up the global nursing and midwifery workforce. This accounts for nearly 50% of the global health workforce.
- There is a global shortage of health workers, in particular nurses and midwives, who represent more than 50% of the current shortage in health workers.
- The largest needs-based shortages of nurses and midwives are in South East Asia and Africa.
- For all countries to reach Sustainable Development Goal 3 on health and well-being, WHO estimates that the world will need an additional 9 million nurses and midwives by the year 2030.
- Nurses play a critical role in health promotion, disease prevention and delivering primary and community care. They provide care in emergency settings and will be key to the achievement of universal health coverage.
- Achieving health for all will depend on there being sufficient numbers of well-trained and educated, regulated and well supported nurses and midwives, who receive pay and recognition commensurate with the services and quality of care that they provide.
- Investing in nurses and midwives is good value for money. The report of the UN High Level Commission on Health Employment and Economic Growth concluded that investments in education and job creation in the health and social sectors result in a triple return of improved health outcomes, global health security, and inclusive economic growth.
- Globally, 70% of the health and social workforce are women compared to 41% in all employment sectors. Nursing and midwifery occupations represent a significant share of the female workforce.

Nurses and midwives are central to Primary Health Care and are often the first and sometimes the only health professional that people see and the quality of their initial assessment, care and treatment is vital. They are also part of their local community – sharing its culture, strengths and vulnerabilities – and can shape and deliver effective interventions to meet the needs of patients, families and communities.

Source: The State of the World's Nursing 2020 Report ; The State of the World's Midwifery 2021 Report

WHO work

WHO's work relating to nursing and midwifery is currently directed by World Health Assembly resolution WHA74.15 (2021) which calls on WHO Member States and WHO to strengthen nursing and midwifery through the Global Strategic Directions for Nursing and Midwifery (SDNM) 2025–2021. The SDNM is an interrelated set of policy priorities that can help countries to ensure that midwives and nurses optimally contribute to achieving universal health coverage (UHC) and other population health goals .

The SDNM comprises four policy focus areas: education, jobs, leadership, and service delivery Each area has a "strategic direction" articulating a goal for the five-year period, and includes between two and four policy priorities If enacted and sustained, these policy priorities can support advancement along the four strategic directions: 1) educating enough midwives and nurses with competencies to meet population health needs; 2) creating jobs, managing migration, and recruiting and retaining midwives and nurses where they are most needed; 3) strengthening nursing and midwifery leadership throughout health and academic systems; and 4) ensuring midwives and nurses are supported, respected, protected, motivated and equipped to safely and optimally contribute in their service delivery settings.

WHO engages ministries of health, the Government Chief Nurses and Midwives (GCNMOs) and other relevant stakeholders to enable effective planning, coordination and management of nursing and midwifery programmes in countries. The Global Forum for the Government Chief Nurses and Midwives, established in 2004, is organized by WHO and meets every two years. It is a Forum for senior nursing and midwifery officials to develop and inform areas of shared interest. WHO also engages with academic institutions specialised in nursing and midwifery. Forty-seven academic centres are designated as Collaborating Centres for Nursing and Midwifery with

WHO. The academic centres are affiliated to the Global Network of WHO Collaborating Centres for Nursing and Midwifery.

WHO has established a Nursing and Midwifery Global Community of Practice (NMGCoP). This is a virtual network created to provide a forum for nurses and midwives around the world to collaborate and network with each other, with WHO and with other key stakeholders (e.g WHO collaborating centres for nursing and midwifery, WHO Academy, Nursing and Midwifery Associations and Institutions.) The network will provide discussion forums, a live lecture programme, opportunities to develop and share policies, WHO documents and tools, and facilitated innovation workshops, masterclasses and webinars.

The Nursing and Midwifery Global Community of Practice is free to join and available to nurses and midwives everywhere. From May 2022 it will be possible to access the virtual community via a smartphone, by downloading the Nursing and Midwifery Global Community of Practice App Nurses Beyond the Bedside_WHO_CSW66 Side Eventavailable for Android and IOS system via the APP store.

A 2017 Report on the history of nursing and midwifery in the World Health Organization 1948–2017, demonstrates how WHO, since its inception, has given this workforce a voice, and highlights the critical role nurses and midwives play in improving health outcomes across the world.

5. Rift valley fever

KEY FACTS

- Rift Valley fever (RVF) is a viral zoonosis that primarily affects animals but can also infect humans.
- The majority of human infections result from contact with the blood or organs of infected animals.
- Human infections have also resulted from the bites of infected mosquitoes.
- To date, no human-to-human transmission of RVF virus has been documented.
- The incubation period (the interval from infection to onset of symptoms) for RVF varies from 2 to 6 days.
- Outbreaks of RVF in animals can be prevented by a sustained programme of animal vaccination.

Rift Valley fever (RVF) is a viral zoonosis that primarily affects animals but also has the capacity to infect humans. Infection can cause severe disease in both animals and humans. The disease also results in significant economic losses due to death and abortion among RVF-infected livestock.

RVF virus is a member of the *Phlebovirus* genus. The virus was first identified in 1931 during an investigation into an epidemic among sheep on a farm in the Rift Valley of Kenya.

Since then, outbreaks have been reported in sub-Saharan Africa. In 1977 an explosive outbreak was reported in Egypt, the RVF virus was introduced to Egypt via infected livestock trade along the Nile irrigation system. In 1997–98, a major outbreak occurred in Kenya, Somalia and Tanzania following El Niño event and extensive flooding. Following infected livestock trade from the horn of Africa, RVF spread in September 2000 to Saudi Arabia and Yemen, marking the first reported occurrence of the disease outside the African continent and raising concerns that it could extend to other parts of Asia and Europe.

Transmission in humans

The majority of human infections result from direct or indirect contact with the blood or organs of infected animals. The virus can be transmitted to humans through the handling of animal tissue during slaughtering or butchering, assisting with animal births, conducting veterinary procedures, or from the disposal of carcasses or fetuses. Certain occupational groups such as herders, farmers, slaughterhouse workers, and veterinarians are therefore at higher risk of infection.

The virus infects humans through inoculation, for example via a wound from an infected knife or through contact with broken skin, or through inhalation of aerosols produced during the slaughter of infected animals.

There is some evidence that humans may become infected with RVF by ingesting the unpasteurized or uncooked milk of infected animals.

- Human infections have also resulted from the bites of infected mosquitoes, most commonly the *Aedes* and *Culex* mosquitoes and the transmission of RVF virus by hematophagous (blood-feeding) flies is also possible.
- To date, no human-to-human transmission of RVF has been documented, and no transmission of RVF to health care workers has been reported when standard infection control precautions have been put in place.
- There has been no evidence of outbreaks of RVF in urban areas.

Clinical features in humans

Mild form of RVF in humans

The following are clinical features of the mild form of RVF in humans:

- The incubation period (the interval from infection to onset of symptoms) for RVF varies from 2 to 6 days.

- Those infected either experience no detectable symptoms or develop a mild form of the disease characterized by a feverish syndrome with sudden onset of flu-like fever, muscle pain, joint pain and headache. Some patients develop neck stiffness, sensitivity to light, loss of appetite and vomiting; in these patients the disease, in its early stages, may be mistaken for meningitis.
- The symptoms of RVF usually last from 4 to 7 days, after which time the immune response becomes detectable with the appearance of antibodies and the virus disappears from the blood.

Severe form of RVF in humans

While most human cases are relatively mild, a small percentage of patients develop a much more severe form of the disease. This usually appears as 1 or more of 3 distinct syndromes: ocular (eye) disease (0.5–2% of patients), meningoencephalitis (less than 1% of patients) or haemorrhagic fever (less than 1% of patients).

The following are clinical features of the severe form of RVF in humans:

- **Ocular form:** In this form of the disease, the usual symptoms associated with the mild form of the disease are accompanied by retinal lesions. The onset of the lesions in the eyes is usually 1 to 3 weeks after appearance of the first symptoms. Patients usually report blurred or decreased vision. The disease may resolve itself with no lasting effects within 10 to 12 weeks. However, when the lesions occur in the macula, %50 of patients will experience a permanent loss of vision. Death in patients with only the ocular form of the disease is uncommon.
- **Meningoencephalitis form:** The onset of the meningoencephalitis form of the disease usually occurs 1 to 4 weeks after the first symptoms of RVF appear. Clinical features include intense headache, loss of memory, hallucinations, confusion, disorientation, vertigo, convulsions, lethargy and coma. Neurological complications can appear later (after more than 60 days). The death rate in patients who experience only this form of the disease is low, although residual neurological deficit, which may be severe, is common.
- **Haemorrhagic fever form:** The symptoms of this form of the disease appear 4–2 days after the onset of illness, and begin with evidence of severe liver impairment, such as jaundice. Subsequently signs of haemorrhage then appear such as vomiting blood, passing blood in the faeces, a purpuric rash or ecchymoses (caused by bleeding in the skin), bleeding from the nose or gums, menorrhagia and bleeding from venepuncture sites. The case-fatality ratio for patients developing the haemorrhagic form of the disease is high at approximately 50%. Death usually occurs 3 to 6 days after the onset of symptoms. The virus may be detectable in the blood for up to 10 days, in patients with the hemorrhagic icterus form of RVF.

The total case fatality rate has varied widely between different epidemics but, overall, has been less than 1% in those documented. Most fatalities occur in patients who develop the haemorrhagic icterus form.

Outbreaks that have occurred since 2000:

Severe form of RVF in humans

2016, Republic of Niger: As of 11 October 2016, Ministry of Health reported 105 suspected cases including 28 deaths of RVF in humans in Tahoua region.

2012 Republic of Mauritania: The Ministry of Health in Mauritania declared an outbreak of RVF on 4 October 2012. From 16 September 2012 (the date of onset of the index case) to 13 November 2012, a total of 36 cases, including 18 deaths were reported from 6 regions.

2010, Republic of South Africa: From February to July 2010, the Government of South Africa reported 237 confirmed cases of RVF in humans, including 26 deaths from 9 provinces.

2009–2008, Madagascar: From December 2008 to May 2009, the Ministry of Health, Madagascar reported 236 suspected cases including 7 deaths.

2008, Madagascar: The Ministry of Health, Madagascar reported an outbreak of RVF on 17 April 2008. From January to June 2008, a total of 476 suspected cases of RVF including 19 deaths were reported from 4 provinces.

2007, Sudan: The Federal Ministry of Health, Sudan, reported an outbreak of RVF on 28 October 2008. A total of 738 cases, including 230 deaths, were reported in Sudan between November 2007 and January 2008.

2006, Kenya, Somalia and Tanzania: From 30 November 2006 to 12 March 2007, a total of 684 cases including 234 deaths from RVF was reported in Kenya. From 19 December 2006 to 20 February 2007, a total of 114 cases including 51 deaths was reported in Somalia. From 13 January to 3rd May 2007, a total of 264 cases including 109 deaths was reported in Tanzania.

2003, Egypt: In 2003 there were 148 cases including 27 deaths of RVF reported by the Ministry of Health of Egypt.

2000, Saudi Arabia and Yemen: There were 516 cases with 87 deaths of RVF reported by the Ministry of Health of Saudi Arabia. In 2000, the Ministry of Public Health in Yemen reported 1087 suspected cases, including 121 deaths.

Diagnosis

Because the symptoms of Rift Valley fever are varied and non-specific, clinical diagnosis is often difficult, especially early in the course of the disease. Rift Valley fever is difficult to distinguish from other viral haemorrhagic fevers as well as many other diseases that cause fever, including malaria, shigellosis, typhoid fever, and yellow fever.

Definitive diagnosis requires testing that is available only in reference laboratories. Laboratory specimens may be hazardous and must be handled with extreme care. Rift Valley fever virus infections can only be diagnosed definitively in the laboratory using the following tests:

- reverse transcriptase polymerase chain reaction (RT-PCR) assay
- IgG and IgM antibody enzyme-linked immunosorbent assay (ELISA)
- virus isolation by cell culture.

Treatment and vaccines

As most human cases of RVF are relatively mild and of short duration, no specific treatment is required for these patients. For the more severe cases, the predominant treatment is general supportive therapy.

An inactivated vaccine has been developed for human use. However, this vaccine is not licensed and is not commercially available. It has been used experimentally to protect veterinary and laboratory personnel at high risk of exposure to RVF. Other candidate vaccines are under investigation.

RVF virus in host animals

RVF is able to infect many species of animals causing severe disease in domesticated animals including cattle, sheep, camels and goats. Sheep and goats appear to be more susceptible than cattle or camels.

Age has also been shown to be a significant factor in the animal's susceptibility to the severe form of the disease: over 90% of lambs infected with RVF die, whereas mortality among adult sheep can be as low as 10%.

The rate of abortion among pregnant infected ewes is almost 100%. An outbreak of RVF in animals frequently manifests itself as a wave of unexplained abortions among livestock and may signal the start of an epidemic.

Ecology and mosquito vectors

Several different species of mosquito are able to act as vectors for transmission of the RVF virus. The dominant vector species varies between different regions and different species can play different roles in sustaining the transmission of the virus.

Among animals, the RVF virus is spread primarily by the bite of infected mosquitoes, mainly the *Aedes* species, which can acquire the virus from feeding on infected animals. The female mosquito is also capable of transmitting the virus directly to her offspring via eggs leading to new generations of infected mosquitoes hatching from eggs.

However, when analysing RVF major outbreaks, 2 ecologically distinct situations should be considered. At primary foci areas, RVF virus persists through transmission between vectors and hosts and maintains through vertical transmission in *Aedes* mosquitoes. During major outbreak in primary foci, the disease can spread to secondary foci through livestock movement or passive mosquitoes dispersal and amplifies in naïve ruminants via local competent mosquitoes like *Culex*, *Mansonia* and *Anopheles* that act as mechanical vectors. Irrigation schemes, where populations of mosquitoes are abundant during long periods of the year, are highly favourable places for secondary disease transmission.

Prevention and control

Controlling RVF in animals

Outbreaks of RVF in animals can be prevented by a sustained programme of animal vaccination. Both modified live attenuated virus and inactivated virus vaccines have been developed for veterinary use. Only 1 dose of the live vaccine is required to provide long-term immunity but this vaccine may result in spontaneous abortion if given to pregnant animals. The inactivated virus vaccine does not have this side effect, but multiple doses are required in order to provide protection which may prove problematic in endemic areas.

Animal immunization must be implemented prior to an outbreak if an epizootic is to be prevented. Once an outbreak has occurred animal vaccination should NOT be implemented because there is a high risk of intensifying the outbreak. During mass animal vaccination campaigns, animal health workers may, inadvertently, transmit the virus through the use of multi-dose vials and the re-use of needles and syringes. If some of the animals in the herd are already infected and viraemic (although not yet displaying obvious signs of illness), the virus will be transmitted among the herd, and the outbreak will be amplified.

Restricting or banning the movement of livestock may be effective in slowing the expansion of the virus from infected to uninfected areas.

As outbreaks of RVF in animals precede human cases, the establishment of an active animal health surveillance system to detect new cases is essential in providing early warning for veterinary and human public health authorities.

Public health education and risk reduction

During an outbreak of RVF, close contact with animals, particularly with their body fluids, either directly or via aerosols, has been identified as the most significant risk factor for RVF virus infection. Raising awareness of the risk factors of RVF infection as well as the protective measures individuals can take to prevent mosquito bites is the only way to reduce human infection and deaths.

Public health messages for risk reduction should focus on:

- reducing the risk of animal-to-human transmission as a result of unsafe animal husbandry and slaughtering practices. Practicing hand hygiene, wearing gloves and other appropriate individual protective equipment when handling sick animals or their tissues or when slaughtering animals.
- reducing the risk of animal-to-human transmission arising from the unsafe consumption of fresh blood, raw milk or animal tissue. In the epizootic regions, all animal products (blood, meat, and milk) should be thoroughly cooked before eating.
- the importance of personal and community protection against mosquito bites through the use of impregnated mosquito nets, personal insect repellent if available, light coloured clothing (long-sleeved shirts and trousers) and by avoiding outdoor activity at peak biting times of the vector species.
- Guide on safe food for travellers

Infection control in health care settings

Although no human-to-human transmission of RVF has been demonstrated, there is still a theoretical risk of transmission of the virus from infected patients to healthcare workers through contact with infected blood or tissues. Healthcare workers caring for patients with suspected or confirmed RVF should implement Standard Precautions when handling specimens from patients.

Standard Precautions define the work practices that are required to ensure a basic level of infection control. Standard Precautions are recommended in the care and treatment of all patients regardless of their perceived or confirmed infectious status. They cover the handling of blood (including dried blood), all other body fluids, secretions and excretions (excluding sweat), regardless of whether they contain visible blood, and contact with non-intact skin and mucous membranes.

Standard precautions in health care

As noted above, laboratory workers are also at risk. Samples taken from suspected human and animal cases of RVF for diagnosis should be handled by trained staff and processed in suitably equipped laboratories.

Vector control

Other ways in which to control the spread of RVF involve control of the vector and protection against their bites.

Larviciding measures at mosquito breeding sites are the most effective form of vector control if breeding sites can be clearly identified and are limited in size and extent. During periods of flooding, however, the number and extent of breeding sites is usually too high for larviciding measures to be feasible.

RVF forecasting and climatic models

Forecasting can predict climatic conditions that are frequently associated with an increased risk of outbreaks, and may improve disease control. In Africa, Saudi Arabia and Yemen RVF outbreaks are closely associated with periods of above-average rainfall. The response of vegetation to increased levels of rainfall can be easily measured and monitored by Remote Sensing Satellite Imagery. In addition RVF outbreaks in East Africa are closely associated with the heavy rainfall that occurs during the warm phase of the El Niño–Southern Oscillation (ENSO) phenomenon.

These findings have enabled the successful development of forecasting models and early warning systems for RVF using satellite images and weather/climate forecasting data. Early warning systems, such as these, could be used to trigger detection of animal cases at an early stage of an outbreak, enabling authorities to implement measures to avert impending epidemics.

Within the framework of the new International Health Regulations (2005), the forecasting and early detection of RVF outbreaks, together with a comprehensive assessment of the risk of diffusion to new areas, are essential to enabling the implementation of effective and timely control measures.

WHO response

For the 2016, Niger outbreak, WHO sent a multisectoral national rapid response team, including members from the Ministry of Health, veterinary services and Centre de Recherche Médicale et Sanitaire (CERMES). The unit was deployed for field investigation on 31 August 2016.

In Niger, the WHO Country Office provides technical and financial support for surveillance, outbreak investigation, technical guidelines regarding case definition, case management, shipment of samples, and risk communication.

The Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and WHO are coordinating on animal and human health and providing additional support to Niger for the outbreak response.

WHO is working with partners in the Global Outbreak Alert and Response Network (GOARN) to coordinate international support for the response. The International Federation of Red Cross and Red Crescent Societies (IFRC) and UNICEF are supporting outbreak response.