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Review Article

Studies on osteoporosis in Saudi Arabia

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ABSTRACT

Background: Osteoporosis is a major health problem both worldwide and in Saudi Arabia. It is distinguished by decreased bone mass with modification in microarchitecture leading to bone fragility and enhanced risk of fracture. Osteoporosis risk factors include age, gender, genetic history and menopause. Furthermore, various diseases affect the prevalence of osteoporosis such as diabetes mellitus, hyperparathyroidism and vitamin D deficiency. Multiple studies have addressed different aspects of osteoporosis within Saudi Arabia.

Objective: The purpose of this review is to highlight and summarize studies investigating the degree, the effects and factors affecting osteoporosis in Saudi Arabia and exposes their recommendations.

Discussion & conclusion: Several studies have exposed the prevalence of osteoporosis in the Saudi population. Other studies discussed risk factors, introduced methods of measurement, examined genetic influence and studied different types of treatment on an animal model. Within Saudi Arabia, osteoporosis detection and measurements started in 1993 and continues to date. It was found to be more common in females than in males. Low sun exposure, vitamin D deficiency and low physical activity are some factors, among others, that are suggested to contribute to the high prevalence of the disease in Saudi Arabia. Additional research is required, and prevention and management of osteoporosis studies are essential.

KEY WORDS: bone mineral density, dual-energy X-ray absorptiometry, osteopenia, osteoporosis, Saudi population

INTRODUCTION

Osteoporosis is a silent disease, which goes undetected and is considered a serious public health disease. Osteoporosis provokes painful fractures, causing diminished mobility and reduced quality of life; these fractures are frequently developed among elderly. There are some common sites where osteoporotic fractures take place such as hip, pelvis, forearm, spine and ankle[1]. Due to its prevalence worldwide, osteoporosis has attracted a lot of attention in the last two decades[2].

According to the International Osteoporosis Foundation, osteoporosis targeted about 75 million patients in USA, Europe and Japan causing more than 8.9 million fractures annually[3], and around 200 million women will be affected by osteoporosis[4]. In Saudi Arabia, studies in 2012 reported the incidence of osteoporosis as 30.7% and 34% in men and women above 50 years[5]. It was calculated that the cost of managing one patient with osteoporotic fractures equaled to SR 48,712 (US$ 12,989.90)[6]. With 7528 fractures in a population of 1,300,336 people who are 55 years or older, it was estimated that the cost to the health system will be approximately SR 564.75 million ($ 150.60 million)[7].

METHODS

Literature search on PubMed and Google scholar for published literature using keywords osteopenia, osteoporosis, dual-energy X-ray absorptiometry (DXA), bone mineral density (BMD) and quantitative sonography (QUS) in Saudi Arabia was conducted. Attention was directed to evaluate the prevalence of osteoporosis among the Saudi Arabian population in the last few decades. Studies evaluated included the studies discussing risk factors, methods of

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measurement, genetic effects and the effect of treatments in animal models[2,8-10]. Studies that investigated the effect of education were not included in this review. The review summarizes the previously mentioned studies and their recommendations. Studies have been classified and tabulated in to four sub-sections (Tables 1-4), which included osteoporosis detection and measurements, the effect of various diseases on bone mineral density, genetic influence on the prevalence of osteoporosis and finally, animal studies in Saudi Arabia.

LITERATURE REVIEW

Methods of measurement of bone strength

BMD was defined by the World Health Organization as a typical tool in the estimation of bone strength in medical practice[11], and is measured at different skeletal sites using DXA. Bone material features are the key element for bone strength, with osteoporotic bones having abnormal bone matrix[12]. Although bone strength depends on bone mass, bone geometry and composition, larger bones are stronger than smaller ones even with the same BMD. This is due to the difference in bone diameter; as it grows radially, the strength of bone is enhanced by the radius of the participated bone elevated to the fourth power[12].

Although DXA is the gold standard for the measurement of osteoporosis, some vital factors couldn't be observed by DXA which include intrinsic properties of bony tissue, cortical thickness and trabecular bone morphology. Other methods can be used for evaluating bone strength and stiffness[13], which include QUS; a technique suggested to provide information regarding bone structure. QUS offers stiffness index through measurements of broadband ultrasound attenuation and speed of sound values in the calcaneus region[14]. The advantages of this technique include being portable, simple, inexpensive and non-invasive with no ionizing radiation, but the significant low correlation between BMD of the lumbar spine and QUS of the heel, with QUS detecting significantly less osteoporosis than DXA scan[15] and the moderate positive correlation between QUS T-score and DXA T-score[15] limited the use of QUS as a replacement technique for BMD measurements despite the high reliability of QUS and precision[16].

Various other techniques used to evaluate the quantity of minerals present in bone include mineral and calcium percent determination, gravimetric determination of ash weight, conventional radiography, single photon and x-ray absorptiometry, quantitative computed tomography and quantitative magnetic resonance[17,18].

Osteoporosis detection and measurement studies in Saudi population

There are 16 documented studies that investigated the presence of osteopenia and osteoporosis in the Saudi population (Table 1) arranged chronologically, not including studies that investigated secondary osteoporosis in the Saudi population. Table 1 documented the city/area in which the study was conducted, the technique used, sample size and sex, percentage of osteoporosis and osteopenia and any other findings. Techniques incorporated in the above studies varied from the use of calcaneal and femur X-ray radiography (1 study) and Gammadensit x-ray bone mineralometer (1 study) to the use of QUS (3 studies) and DXA (11 studies).

Calcaneal X-ray radiography as a tool to examine the presence or absence of osteoporosis was unable to detect bone loss of less than 30%, and positioning in radiography was found to alter the results[19]. In Saudi females, Ghannam *et al* described one peak spine BMD to occur at 31-40 years and the presence of two peaks for femur, the first peak BMD in femur occurring at 10 to 20 years and second occurring between 41 to 50 years. In addition to that, mean BMD measured in post-menopausal females were less than BMD in peak bone mass females[10]. BMD in healthy Saudi females aged 12-71 years (n=321) were found to be lower than their USA counterparts; these results were justified partially by the high number of pregnancies accompanied by longer lactation duration. Other findings include vitamin D deficiency and calcidiol, 25-hydroxycholecalciferol levels and several BMD measurements negatively correlated with parathyroid hormone (PTH) levels[10].

Using QUS, the occurrence of osteopenia and osteoporosis in the calcaneus region were reported to be 24.2% and 11.9% respectively in peak bone age women (mean age: 29 years)[20]. When using the same technique, the percentage of osteopenia was higher and osteoporosis was lower (33% and 3% respectively) in young (mean age: 21.35 years, age range: 20-29 years) university Saudi females. The differences between the two studies might be attributed to demographic and educational differences, with the sample in the later study being younger and university educated[21].

In young Saudi females, the occurrence of osteopenia equaled to 37.4% in the lumbar spine, 34% in the femur, with 5% osteoporosis in the lumbar spine with DXA. A positive correlation between BMD and weight was noted[22]. High consumption of soft drinks, low exercise, insufficient intake of dairy products and milk, and inadequate calcium and vitamin D supplementation were found in young females with osteopenia or osteoporosis[23].

Table 1: Osteoporosis/osteopenia detection and measurements studies on Saudi population

S. no	Reference	Location	Study population	Type of measurements	Prevalence of osteoporosis/	Prevalence of osteopenia	Other findings
1	Sadat-Ali *et al*, 1993 [19]	Dammam city (Eastern region),	110 post-menopausal (PM) females (45-80 years)	Calcaneal and femur X-ray radiography. Using Aggarwell classification	PM 76%, Control 4%		
2	Sadat-Ali *et al*, 1996 [8]	Al-Khobar city (Eastern region)	150 Saudi PM females (44-71 years), 150 peak bone mass (PBM) age females (24-33 years)	Gammadensit x-ray bone mineralometer			Mean BMD 0.440 g/cm2 PM group, 0.660 g/cm2 PBM females. Rural Saudi females had higher BMD compared with urban living females. Lower BMD in female bearing 10 children.
3	Ghannam *et al*, 1999 [10]	Riyadh city (central region)	321 Saudi females aged 12-71 years	DXA	0% to 7% (in ≥30 years)	18% to 41% (in ≥30 years)	Peak spine BMD at 31-40 years. Two peaks for femur BMD 10-20 years and 41-50 years. vitamin D deficiency. Negative correlation between parathyroid hormone and BMD and V. D BMD values negatively correlated with number of pregnancies and the total duration of lactation
4	El-Desouki, 2003 [2]	Riyadh city (central region)	830 PM Saudi women (50-80 years)	DXA	In lumbar spine total 39.5% (in age group 50-59 years 24.3%; in age group 60-69 years 62%; in age group 70-80 years 73.84%)	In lumbar spine total 30.6% (in age group 50-59 years 33.4%; in age group 60-69 years 27%; in age group 70-80 years 21.5%)	
5	Sadat-Ali *et al* 2004 [29]	Al-Khobar city (Eastern region)	256 postmenopausal women attending orthopedic clinics at a University Hospital	DXA	Lumbar spine 46.7%, hip 44.1%	Lumbar spine 30.5%, hip 31.6%	Increased risk of fracture was 74.2% in the lumbar spine and 59% in the hip
6	Addar *et al*, 2005 [26]	Riyadh city (Central region)	935 postmenopausal females (mean age 48.1 years)	DXA			Osteoporosis was associated with either early or late onset of menopause
7	Ardawi *et al* 2005 [24]	Jeddah city (Western region)	1980 randomly selected Saudis aged 20-79 years (915 males and 1065 females)	DXA	Saudis (50-79 years): lumbar spine (38.3-47.7% manufacturer, 30.5-49.6% Saudi reference) and total hip (6.3-7.8% manufacturer,1.2-4.7% Saudi reference)		In males, the annual % reduction in BMD was 0.3-0.8% (lumbar spine), 0.2-1.4% (Ward's triangle), 0.2-0.4% (femoral trochanter), and 0.2-0.7% (femoral neck). In females, annual %reduction in BMD was 0.8-0.9% (lumbar spine), 0.7-0.9% (Ward's triangle) and 0.3-0.7% (femoral neck).
8	Sadat-Ali M & Al-Elq AH, 2006 [27]	Al-Khobar city (Eastern region)	115 Saudi male (50-76 years) at a University hospital	DXA	Lumbar spine 37.4%, hip 24.3%	Lumbar 33.9%, Hip 64%	In Saudi males: spinal osteoporosis was more common than hip osteoporosis
9	El-Desouki & Sulimani, 2007 [30]	Riyadh city (Central region)	429 healthy Saudi men from the community	DXA	Lumbar spine 21.4% femoral neck 11.4% In ≥50 years (spine 23.5%, hip 17%) In ≤50 years (spine19.2%, hip 4.9%)	Lumbar spine 35.7%, femoral neck 38% In ≥50 years (spine 35%, hip 41.5%) In ≤50 years (spine36.5%, hip 34%)	In Saudi males, spinal osteoporosis was more common than hip osteoporosis

S. no	Reference	Location	Study population	Type of measurements	Prevalence of osteoporosis/	Prevalence of osteopenia	Other findings
10	Al-Habdan *et al*, 2009 [20]	Dammam, Al-Khobar, Thoqba, Al-Hofuf, Qatif, Saihat and Al-Hassa (Eastern region)	3269 peak bone age (PBA) women (mean age 29 years) and 3131 postmenopausal age (PMA)	QUS	23% in the PMA group, 11.9% in PBA group	30.3% in PMA group, 24.2% in the PBA group	In the PMA group, urban women were more osteopenic than rural or industrial women. Education, number of children, and place of living influence the risk for osteopenia and osteoporosis
11	Hammad, 2013 [21]	Riyadh city (Central region)	101 young female (20-24.9 years) with no previous history of fracture or known bone disease nor any treatment affecting bone status	QUS	3%	33%	
12	Oommen and AlZahrani, 2014 [28]	Arar city (Northern area)	100 females, 40-75 years	DXA	18%	40%	82% had vitamin D deficiency, 21% had sunlight exposure, 5% had Vitamin D and Calcium rich diet and 7% exercised
13	Hammad 2015 [22]	Riyadh city (Central region)	101 young female (20-24.9 years) with no previous history of fracture or known bone disease nor any treatment affecting bone status	DXA	Lumbar spine 5%	Lumbar spine 37.4%, hip 34% (both sites 22.7%)	Strong association between BMD values with weight
14	Yousef 2017 [25]	Jeddah city (Western region)	200 PM females (50-82 years)	DXA			BMD had a positive correlation with BMI and a negative correlation with age. positive correlation between age and waist/hip ratio. Most of participants suffering from deficiency of vitamin D and hyperparathyroidism manifested itself as negative correlation between PTH and Vitamin D.
15	Sadat-Ali *et al*, 2017 [31]	Al-Khobar city (Eastern region)	Retrospective study, hospital based 371 Saudi male (50–97 years) referred for DXA	DXA	Lumbar spine 59.8% (of the above percentage: 57.5% with cardiac disease, 65.3% with diabetes, 58.9% with osteoarthritis and 55.1% with respiratory system diseases). hip 32.3%	Lumbar spine 30.5%, hip 47.8%	From 222 (59.83%) patients who were diagnosed to have osteoporosis only 108 (48.64%) were on appropriate treatment for osteoporosis.
16	Hammad and Benajiba. 2017 [23]	Riyadh city (Central region)	101 young female (20-24.9 years) with no previous history of fracture or known bone disease nor any treatment affecting bone status	QUS	3%	33%	Participants with osteopenia/osteoporosis had low BMD and strong correlation with high consumption of soft drinks, low exercise, insufficient intake of dairy products and milk, inadequate calcium and vitamin D supplementation.

BMD: bone mineral density; PM: post-menopausal; PBM: peak bone mass; DXA: dual-energy X-ray absorptiometry; QUS: quantitative sonography

Table 2: Detection and measurements of secondary osteoporosis/ osteopenia in the Saudi population

S. no	Reference	Location	Primary disease	Study population	Type of measurements	Prevalence of osteoporosis	Prevalence of osteopenia	Other findings
1	Huraib *et al*, 1993 [33]	Riyadh city (Central region)	Haemodialysis	Multicenter study, 209 haemodialysis patients mean duration on dialysis was 3.5±1.5 years. mean age 39.4±14 (18-70 years), 128 males and 81 females	Dual–photon absorptiometry			65% low bone mineral density, 92% hyperparathyroidism changes, 66% pure hyperparathyroidism, 60% with variable degrees of AL intoxication
2	Al-Maatouq *et al*, 2004 [9]	Riyadh city (Central region)	Type-2 diabetes mellitus (T2D)	104 T2D PM Saudi female (mean age= 63 years) and 101 non-diabetic PM Saudi female (mean age = 60 years)	DXA	T2D group (Lumbar spine 46.8%, hip 19.8%) Control group (Lumber spine 22.2% & hip 12.1%)	T2D (Lumbar spine 43.68%, hip 44.7%) Control group (Lumber 46.5% spine Hip 49.5%)	A reduction in BMD in T2D compared to non-diabetic group
3	Al-Elq & Sadat-Ali 2006 [35]	Al-Khobar city (Eastern region)	T2D	154 Saudi male (57 T2D male (mean age= 59.76 years), 34 patients (mean age= 60.90 years) with impaired fasting glucose and 63 normal glucose level patients (mean age= 62.53 years))	DXA	Lumbar spine 40.7% hip 27.9%	Lumbar spine 35% hip 53.2%	No significant differences between the three groups in BMD, T-score and Z-score
4	Malabu and Founda, 2007 [32]	Riyadh city (Central region)	Primary hyperparathyroidism	N= 46, Female=35, Male=11,	DXA			83% of patients had osteopenia/osteoporosis. 45.7% complained of Bone pains, 15.2% had renal stones, 6.5% polyuria, 4.3% had depression and constipation.
5	Sadat-Ali *et al*, 2008 [34]	Al-Khobar city (Eastern region)	Adolescent idiopathic scoliosis (AIS)	32 girls with AIS (mean age of 18.42±5.71, 14-26 years) and their siblings (N=27, (mean age of 17.65±4.5; 14-25years)	DXA	AIS lumbar spine & hip 62.5%	AIS lumbar spine & hip 28.1%	Girls with normal spine had significant higher BMI and BMD than AIS siblings. The degree of Cobb angle affecting the severity of disease
6	Sadat-Ali *et al*, 2008 [42]	Al-Khobar city (Eastern region)	Sickle cell anemia	103 patients (45M & 58F)	DXA	35% (15M+21F)	30% (13M+18F)	A reduction in testosterone and estradiol in osteoporotic SCD female and lower estradiol in SCD osteoporotic/ osteogenic males
7	Sadat-Ali *et al*, 2009 [37]	Al-Khobar city (Eastern region)	Glucocorticoid therapy	Retrospective study, 165 patients prescribed ≥7.5 mg of Prednisolone/day, ≥6 months (26 patients had DXA, 21F, 5M)	DXA	50%, N=13(10F &3M)	50%, N=13 (11F &2 2M)	Calcium and Vitamin D were prescribed to the majority of patients but none had antiresorptive/anabolic therapy
8	AlAmri and Sadat-Ali, 2009 [44]	Al-Khobar city (Eastern region)	Chemotherapy treated cancer patient	N=71 patients, mean age= 49.29 years, age range 29-67 years	DXA	Spine 25.8% & hip 22.6%	Spine 33.87% & hip 29%	Osteopenia and osteoporosis found in 65.6% patients ≤50 years, compared to 56.4% patients ≥51 years old. Normal BMD in patients with 48.68 ± 27.35 months earlier last chemotherapy cycle compared to more osteoporosis in patients who received last chemotherapy for less than 2 years.

S. no	Reference	Location	Primary disease	Study population	Type of measurements	Prevalence of osteoporosis	Prevalence of osteopenia	Other findings
9	Al-Turki 2009 [43]	Al-Khobar city (Eastern region)	Pregnancy in sickle cell anemia	N=38 (20 parous, mean age= 27.55±4.9 years and 18 nulliparous, mean age= 26.33±2.1 years)	DXA	65% in parous SCD, 27.7% in nulliparous SCD	20% in parous SCD, 38.9% in nulliparous SCD	Osteoporosis in both groups were higher at lumbar spine compared to the hip region (P= 0.001). BMD was lower in parous women when compared to the nulliparous women.
10	Sadat-Ali *et al*, 2011 [40]	Al-Khobar city (Eastern region)	Vitamin D deficiency in sickle cell anemia	Sickle cell group (86M, 100F) Control group (100M, 100F)	DXA	Sickle cell female (spine 78% & hip 74%). Sickle cell male (spine 72% & hip 71%). Controls female (spine 26% &hip 22%). Controls male (spine 13% & hip 12%).	Sickle cell female (spine 15% & hip 17%). Sickle cell male (spine 12% & hip 15%). Control female (spine 12% & hip 11%). Control male (spine 10% & hip 9%).	Patients with SCD had significantly elevated serum alkaline phosphatase and PTH levels in the presence of low vitamin D status
11	Sadat-Ali *et al*, 2011 [38]	Al-Khobar city (Eastern region)	Vitamin D deficiency	400 Saudi men and women	DXA	Normal 25OHD (>30 pg/mL) 8.8%, insufficiency of 25OHD (21-29 pg/mL) 33.67%, deficiency of 25OHD (<20 pg/mL) 67.31%	Normal 25OHD (>30 pg/mL) 24.4%, insufficiency of 25OHD (21-29 pg/mL) 50%, deficiency of 25OHD (<20 pg/mL) 32.69%	Positive relationship between vitamin D serum level and BMD, low BMD in subjects with Vitamin D deficiency and significant negative correlations between BMD and parathyroid hormone.
12	Ardawi *et al*, 2012 [39]	Jeddah city (Western region)	Vitamin D deficiency	834M (20–74 years)	DXA			Deficiency (25(OH)D<50 nmol/L) and insufficiency (≥50–75 nmol/L) were present in 87.8% and 9.7%, positive correlation between and serum 25(OH) D levels
13	Khoshhal *et al*, 2015 [36]	Al-Madinah Al-Monawarah (Western region)	Type 1 diabetes (T1D)	36 T1D children & 39 control	QUS		In T1D (13.9% with Z-score ≤-1). Controls (0% with Z-score ≤-1).	Significantly lower levels of osteocalcin and procollagen N-terminal peptide and significantly higher serum levels of bone resorption markers were found in the diabetic group.
14	Alhamad and Nadama, 2015 [45]	Riyadh city (Central region)	Interstitial lung disease (ILD)	196 newly diagnosed ILD patients	DXA	Spine 33%, hip 13%, distal radius 20% (55% one side involvement, 21% had two sites involvement, 24% had three sites involvement).	Spine 41%, Hip 40%, Distal radius 32%(39% had one site involvement, 17% had two sites, 44% had three sites involvement)	The need for screening and aggressive treatment with various anti-bone resorptive therapies for patients with ILD
15	Al-Omran *et al*, 2016 [46]	Al-Khobar city (Eastern region)	Antipsychotic drugs	120M & 25F (mean age 40.75 ±7.16, age range 26-56years) Mean duration of antipsychotic medication = 8.45±5.4years)	DXA	Spine 44% hip 14.2%	Spine 45.7% hip 59.42%	Attributed to hyperprolactemia induced by antipsychotic medication, other factors such as levels of Vitamin D were not controlled

T2D: Type-2 diabetes mellitus; ILD: interstitial lung disease; DXA: dual-energy X-ray absorptiometry; QUS: quantitative sonography

In Saudi females aged 20-79 years, the annual percentage reduction in BMD was 0.8-0.9% in the lumbar spine, 0.7-0.9% in the Ward's triangle and 0.3-0.7% in the femoral neck[24]. In addition to that, the presence of lower BMD in urban living females compared to rural Saudi females were reported[8]. BMD values were found to correlate positively with body mass index[25] and negatively with number of pregnancies and total duration of lactation[8,10]. Osteoporosis was associated with either early or late onset of menopause, possibly due to genetic factors, as Saudi women had similar age of menopause to Arabic ladies but lower than western countries[26].

In postmenopausal women, an increase in osteoporosis was found to occur with age[2]; in subjects below 60 years, 33.4% had osteopenia and 24.3% had osteoporosis, with the incidence of osteopenia and osteoporosis being increased (27% osteopenic and 62% osteoporotic) in ladies between 60-69 years old. In ladies of older age (70-79 years), 21.5% had osteopenia and 73.8% had osteoporosis[2]. In other areas within Saudi Arabia, osteoporosis/osteopenia percentage varied from 24.3% to 64% in Al-Khobar city (Eastern region)[27] and 18% to 40% in Arar city (northern area)[28]. The risk of fracture was calculated as 74.2% in the lumbar spine and 59% in the hip in postmenopausal women[29].

In Saudi males, the annual percentage reduction in BMD was 0.3-0.8% in the lumbar spine, 0.2-1.4% in Ward's triangle, 0.2-0.4% in the femoral trochanter, and 0.2-0.7% in the femoral neck[24]. Spinal osteoporosis was found to exist in 21.4-37.4% of the population studied compared to 11.4-24.3% with hip osteoporosis[27,30]. A positive correlation was found between osteoporosis/osteopenia and age in the Saudi male population[30]. In a hospital based retrospective study on 371 Saudi males (age range: 50-97 years) referred for DXA, percentage of osteoporosis in the lumbar spine and hip area equaled to 59.8% and 32.3% respectively. Of the 222 (59.83%) patients who were diagnosed to have osteoporosis, only 108 (48.64%) were on appropriate treatment for osteoporosis[31].

Effect of various diseases on bone mineral density in Saudi Arabian population

Secondary osteoporosis occurs as a result of some diseases, or from hormonal or drug inducing changes in bones. Table 2 summarizes the studies conducted in Saudi Arabia to investigate changes in BMD secondary to these diseases. There are 15 documented studies that reported the presence of secondary osteopenia and osteoporosis in the Saudi population arranged chronologically. The table documented the city/area at which the study was conducted, the main disease, sample size and sex, technique used, percentage of osteoporosis and osteopenia found and any other findings. Efforts are required to formulate policies to diagnose and treat osteoporosis secondary to these diseases.

Bone pain was reported by 45.7% of patients with primary hyperparathyroidism, attributed to skeletal and renal manifestation of the primary hyperparathyroidism[32], whereas low BMD was found in hemodialytic patients with 66% of patients suffering from pure hyperparathyroidism and 92% of patients from hyperparathyroidism changes[33]. In adolescent idiopathic scoliosis, lower body mass index and BMD were found in subjects with scoliosis compared to their siblings, and the degree of Cobb angle was found to affect the severity of disease[34].

A reduction in BMD was found among post-menopausal Saudi women with type-2 diabetes mellitus (T2D) compared to non-diabetic group. The reduction was attributed to the presence of T2D as both groups had similar life style factors[9]. In contrast to the previous study, T2D male patients demonstrated no differences in BMD, T-score and Z-score compared to both patients with impaired fasting glucose and normal glucose level patients[35]. The relationship between type 1 diabetes (T1D) and bone quality in Saudi children investigated using QUS, biochemical bone markers and bone alkaline phosphatase activity revealed the presence of significant high serum levels of bone resorption markers and the presence of Z-score below -1 in 13.9% of the T1D children compared to none in the non-diabetic children. These findings indicate that children with T1D may have low bone formation with high bone resorption markers leading to an increase in both osteoporosis and bone fracture susceptibility in the future[36].

In a retrospective study investigating glucocorticoid-induced osteoporosis (n=26), 47.6% females and 50% males were osteoporotic and 52.4% females and 40% males had osteopenia. Calcium and vitamin D were prescribed to the majority of patients but none had antiresorptive/anabolic therapy. It was recommended that proper investigation and treatment are required for the management of glucocorticoid-induced osteoporosis[37].

Vitamin D deficiency had a positive relationship with low BMD and PTH. The studies attributed low BMD and vitamin D deficiency to lifestyle, age, obesity and low exposure to sun light and suggested the importance of evaluating hypovitaminosis during the management of low bone mass[38-40].

The risk of osteoporosis and osteopenia in Saudi patients with sickle cell disease (SCD) was reported as a reduction in BMD values[41] associated with lower vitamin D and higher alkaline phosphatase

Table 3: Genetic influence on the prevalence of osteoporosis/osteopenia in Saudi Population

Reference	Location	Aim	Study population	Type of measurements	Other findings
Abdu-Allah *et al*, 2015 [47]	Al-Madinah Al-Monawarah (Western region)	Association of serum amyloid a gene polymorphism (rs12218) m with lipid profile	Osteoporosis/ osteopenic females (N=138), mean age= 22.15±1.89 years and control group N=128, mean age= 21.76±2.01 years	QUS	A significant association between rs12218 with plasma total cholesterol, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), triglyceride (TG), T-score and Z-score in osteoporotic/ osteopenic Saudi females
Al Neghery *et al*, 2018 [48]	Riyadh city (Central region)	Effect of estrogen receptor alpha gene (ERα) on osteoprosis	40 females with osteoporosis and 41 healthy controls (age range 35 to 75 years)	DXA	No relation between single-nucleotide polymorphisms (SNP) in Estrogen receptor alpha gene (ERα) and osteoporosis. Significant low estrogen levels and waist-hip ratio in osteoporotic group compared to non-osteoporotic group respectively (mean±SD E2: 46.6±30.7 vs. 68.7±47.1 pg/ mL), group (0.8±0.1 vs. 0.9±0.0)

DXA: dual-energy X-ray absorptiometry; QUS: quantitative sonography

and PTH values[38]. Possible causes for the reduction in vitamin D were suggested to include malabsorption, insufficient vitamin D consumption, reduction in activity related to repeated crisis and lower sun exposure[38]. A reduction in testosterone and estradiol in osteoporotic females with SCD and estradiol in SCD osteoporotic/osteogenic males convey the important role that sex steroids hormone plays in the development of secondary osteoporosis[42]. When the influence of pregnancy on bone mass was investigated in 38 sickle cell anemic Saudi females, a significant increase in osteoporosis within the parous group (n=13/20) compared to nulliparous group (n=5/18) was found. The presence of no significant difference in calcium level, phosphorus level, hemoglobin electrophoresis and parathyroid hormone found between the two groups suggested that pregnancy was the possible cause of osteoporosis, though no comparison with non-sickle cell controls were made[43].

In another context, time of the last chemotherapy cycle was found to impact bone mass, with normal BMD found in patients who got their last chemotherapy cycle 48.68±27.35 months earlier as opposed to more osteoporosis in patients who received chemotherapy within less than 2 years. Surprisingly, osteopenia and osteoporosis were found to be more common (65.6%) in patients with an age of ≤50 years, compared to 56.4% in patients of ≥51 years[44].

The need for screening and treatment with various anti-bone resorptive therapies for patients with interstitial lung disease was suggested based on the low bone mass observed in 196 newly diagnosed subjects with interstitial lung disease. In addition to that, the diagnosis of usual interstitial pneumonia was more frequently observed in patients with osteoporosis than in those without osteoporosis[45].

Negative effects on bone mass were found in patients taking antipsychotic drugs. Although the significant reduction in bone mass compared to controls were attributed to hyperprolactemia induced by antipsychotic medication, other factors such as levels of vitamin D were not controlled[46].

Genetic influence on the prevalence of osteoporosis in Saudi Arabian population

Table 3 summarizes the studies conducted to examine genetic influence on the prevalence of osteoporosis in Saudi Arabian population arranged chronologically. There are two documented studies; more studies are required to examine the genetic influence on bone density within the Saudi population[47,48].

The first study examined the association of serum amyloid A, a group of proteins secreted in the blood more than 1,000-fold during any inflammatory process, with lipid profile and osteoporosis in Saudi female population[47]. The presence of an association between serum amyloid A1 gene polymorphism (rs12218) with plasma total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, T-score and Z-score in osteoporotic/ osteopenic Saudi females was found[47].

The second study looked at the effect of estrogen receptor alpha gene on osteoporosis. Estrogen, similar to many sex hormones, was found to play an essential role in the management of bone density and distribution and bone maintenance, with estrogen receptors playing a major role in controlling estrogen effects on the bone. Although estrogen receptor alpha gene was assumed to be the dominant receptor controlling estrogen effects on the bone and so stirring the etiology of osteoporosis, the study by Al Neghery *et al* found no correlation between single-

Table 4: Animal studies on osteoporotic treatment in Saudi Arabia

	Reference	Location	Aim	Study population	Type of measurements	Other findings
1	Hosny *et al* 2013 [49]	Jeddah city (Western region)	Alendronate sodium (ALS) enteric-coated nanoliposomes (NLS) to increase bioavailability and overcome esophageal ulcer	rabbits		70 to 150 nm Spherical NLS resisted the release of ALS in acidic environments and 12-fold enhanced the bioavailability compared with the marketed tablets
2	Elshal *et al*, 2013 [50]	Jeddah city (Western region)	Effect of Lepidium Sativum (LS) and Alendronate (ALD) in glucocorticoid-induced osteoporosis rats	Wistar rats	Histopathological examination	Enhanced serum calcium, bone architecture, percentage of trabecular area or bone marrow area, bone-specific alkaline phosphatase and decreased tartrate-resistant acid phosphatase in LS and LS+ALD groups compared to that of animals treated with ALD alone.
3	Ardawi *et al*, 2016 [51]	Jeddah city (Western region)	The effect of Lycopene on the loss of bone mass, microarchitecture and strength in a postmenopausal osteoporosis model	264 Wistar rats	Micro computed tomography	Lycopene suppressed bone turnover manifested as changes in serum osteocalcin (s-OC), serum N-terminal propeptide of type 1 collagen (s-PINP), serum cross-linked carboxyterminal telopeptides (s-CTX-1), and urinary deoxypyridinoline (u-DPD). Improvement in OVX-induced loss of bone mass, bone strength, and microarchitectural deterioration
4	Sadat –Ali *et al* 2019 [52]	Dammam city (Eastern region)	The effect of mesenchymal stem cells, osteoblast and exosomes on bone formation in ovariectomized model	40 female Sprague Dawley rats	High-resolution peripheral quantitative computed tomography	Osteoblast-treated animals showed significant differences in all parameters compared to control. Osteoblasts had positive significant new-bone formation compared to mesenchymal stem cells and exosomes

nucleotide polymorphisms in estrogen receptor alpha gene and osteoporosis (measured by DXA) in Saudi women[48].

Animal studies in Saudi Arabia

Table 4 summarizes pharmacological studies conducted on animals in Saudi Arabia arranged chronologically. There are four documented studies included enhancing the bioavailability of enteric-coated alendronate sodium nanoliposomes in rabbits[49] and examining the synergistic antiosteoporotic effect of *Lepidium Sativum* and bisphosphonates alendronate in Wistar rats[50]. In induced osteoporotic rats by ovariectomy, lycopene (a carotenoid hydrocarbon found in tomatoes among other vegetables) was found to restore bone strength and microarchitecture, decrease osteoclast differentiation and increased osteoblast function[51], whereas osteoblast stem-cell therapy demonstrated positive bone formation both in distal femur and spine in ovariectomized Wistar rats[52].

DISCUSSION

Osteoporosis is considered a serious public health disease. It provokes painful fractures causing diminished mobility, reduced quality of life and morbidity. In recent decades, special attention has been directed to evaluate the prevalence of osteoporosis among the Saudi Arabian population. Studies discussed several risk factors, methods of measurement and impact of early intervention programs in the way to control the problem. In the Saudi Arabian population, many factors seem to increase the prevalence of osteoporosis including low sun exposure, vitamin D deficiency and low physical activity, with osteoporosis being more common in females than in males. Although the Saudi Osteoporosis Society recommended that all women above 60 years of age should be scanned[53], others recommended that 55 years of age is perfect for screening for low bone mass among the Saudi population, when compared to western countries, where the ideal age is ≥65 years[5]. The Ministry of Health national plan for osteoporosis prevention and management in the kingdom of Saudi Arabia 2018 guidelines did not discuss the screening program for osteoporosis nor the age recommendation to undertake a test for measuring BMD[54]. The Ministry of Health 2018 guidelines contained 11 recommendations which included the importance of increasing the awareness about osteoporosis, education and health programs, developing evidence-based local treatment guidelines, periodic (every two

years) updates to guidelines, developing local fracture risk assessment tool in addition to regulation of post-fracture care to control secondary fractures[54].

CONCLUSION

Further studies are needed not only for diagnosis and treatment purposes, but as well as on topics related to prevention, education, management and the use of herbal medicine for prevention and treatment. A local fracture risk assessment tool or other programs to evaluate the 10-year probability of bone fracture risk by integrating clinical risk factors and bone mineral density are required.

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Original Article

Comparison of the prognostic value of neutrophil to lymphocyte ratios at different time points in patients with ST segment elevation myocardial infarction by five-year follow-up

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ABSTRACT

Objective: Previous studies have shown that the neutrophil to lymphocyte ratio (NLR), an indicator of systemic inflammation, is associated with mortality in patients with ST-segment elevation myocardial infarction (STEMI). The association between the timing of NLR measurements and short- and long-term outcomes is not clear.
Design: Prospective study
Setting: Tertiary university hospital
Subjects: One hundred and ten consecutive patients with STEMI who were treated with primary percutaneous coronary intervention (PCI) were enrolled prospectively in the study in a tertiary hospital over 9 months.
Interventions: NLRs at admission and 4, 24 and 48 hours after admission were compared to determine outcomes in patients with STEMI who were treated with primary PCI.
Main Outcome measure: In this study with 5-year follow-up, we aimed to determine the appropriate timing of NLR to predict 30-day and 5-year mortality in patients with STEMI undergoing primary PCI.
Results: Remarkably, in our study, NLR at 48 hours after admission was more accurate for predicting major adverse cardiac events (MACE) within 30 days, as well as 5-year mortality. Nevertheless, we found that NLR, when time was not taken into consideration, was also associated with mortality at 30-day and 5-year follow-up and MACE at 30-day follow-up.
Conclusion: Our findings indicate that NLR at 48 hours after admission or before discharge is more accurate for predicting clinical outcomes in patients with STEMI.

KEY WORDS: mortality, myocardial infarction, neutrophil to lymphocyte ratio, outcomes

INTRODUCTION

Inflammatory processes that are the initial cause in the progression of atherosclerosis also have an important role in the development of myocardial infarction (MI), which is caused by destabilization and rupture of plaques[1]. An elevated leukocyte count, an important indicator of inflammation, has been shown to be associated with worse clinical outcomes in patients with acute coronary syndromes[2,3] and acute ST-segment elevation myocardial infarction (STEMI)[4-6]. Previous studies have shown an increase in neutrophil and monocyte counts in patients with MI[7-9]. Lymphocytopenia, as well as high neutrophil counts, was found to be associated with worse clinical outcomes in patients with acute STEMI[10-13].

The distribution of leukocyte subtypes plays an important role in modulating the inflammatory response. Hence, the neutrophil to lymphocyte ratio (NLR) can also be an indicator of systemic

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inflammation[14]. Moreover, NLR has recently emerged as a better indicator of an inflammatory state in clinical studies[15]. The NLR is calculated by dividing the neutrophil count to the lymphocyte count[16]. The usefulness of the NLR in predicting short- and long-term mortality in patients with STEMI was demonstrated in previously published studies[10,11,16-20].

In this respect, the majority of studies assess laboratory data obtained at admission because of their retrospective design. Hence, the optimal timing of NLR measurements for the prediction of short-and long-term outcomes is not clear. In this prospective study with a five-year follow-up, we aimed to determine the optimal timing of NLR to predict clinical outcomes in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

SUBJECTS AND METHODS

Study population

This is a prospective, observational study evaluating the prognostic value of NLR at different time points in patients with STEMI. The study protocol was approved by the Eskişehir Osmangazi University ethical committee. After the approval, a total of 147 consecutive STEMI patients treated with primary PCI in a tertiary hospital over 9 months were enrolled in the study. The exclusion criteria were severe valvular heart disease, previous history of coronary artery disease (CAD), active infection, systemic inflammatory disease, chronic liver and kidney disease, malignancy, cardiogenic shock on admission and absence of TIMI 3 flow after PCI. Thus, 24 patients with previous history of CAD, two patients with active infection, one patient with transaminase levels more than three times the normal limit, three patients with creatinine levels above 1.5 mg/dl, eight patients with cardiogenic shock on admission and four patients without TIMI 3 flow were excluded from the study. Finally, a total of 105 patients with STEMI who were treated with primary PCI were included in the analysis. STEMI was defined as ST segment elevation of >0.1 mV in at least two consecutive ECG leads with typical angina lasting more than 20 minutes. STEMI was defined based on the criteria formulated by "A consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction"[21]. Briefly, an increase in troponin I of more than 1 ng/ml with a new ST elevation measured from the J point in two contiguous leads with at least 0.2 mV in leads V1, V2 and V3 or at least 0.1 mV in the remaining leads during the first 24 hours after the onset of symptoms was designated as diagnostic criteria.

Demographic characteristics of the patients and risk factors such as diabetes mellitus, hypertension, hyperlipidaemia, smoking and family history of CAD were recorded. Those who had been treated with antihypertensive drugs or had a baseline blood pressure level above 140/90 mmHg were diagnosed with hypertension. Those who were previously diagnosed with diabetes mellitus with or without antidiabetic drug treatment and those with fasting blood glucose ≥126 mg/dL or blood glucose ≥200 mg/dL at any time were considered as diabetic patients.

All patients were treated on the basis of established guidelines[22]. All patients received chewable aspirin 300 mg and a loading dose of clopidogrel 600 mg on admission and intravenous standard heparin 70 U/kg before the procedure. Coronary angiography was performed on each patient, and all patients underwent PCI. Stent implantation was performed on the culprit lesion in each patient.

Percutaneous coronary intervention procedure

All primary PCI procedures were performed with the Judkins technique by experienced interventional cardiologists through a femoral approach with a 6 Fr catheter. Coronary arteries were imaged at right and left oblique positions with cranial and caudal angles by contrast medium injection. In all patients, primary PCI was performed only on the culprit vessel. In appropriate cases, direct stenting was performed first; otherwise, balloon dilatation was applied prior to stent implantation.

Laboratory analysis

Serum sodium, potassium, blood urea nitrogen and creatinine determinations were carried out at admission, and a full blood count was performed at admission and at 4, 24 and 48 hours after admission on all patients. Complete blood counts were performed by using a Beckman Coulter device, and biochemical parameters were measured with a Cobas 6000 device. A complete blood count includes measures of haemoglobin, haematocrit, white blood cells (WBC), neutrophil percentage, absolute neutrophil count, lymphocyte percentage, absolute lymphocyte count and platelet count. The NLR is calculated by dividing the neutrophil count by the lymphocyte count, both obtained from the same blood sample.

Follow-up

Follow-up visits were planned at 30 days and 60 months after discharge. Major adverse cardiac events (MACE) including death, re-infarction, stent thrombosis and cerebrovascular events within 30 days were determined as the primary end points. All-cause mortality at the five-year follow-up visit was determined as a secondary end point. Patients were evaluated by phone contact with the patient or family only if clinical visits were not possible.

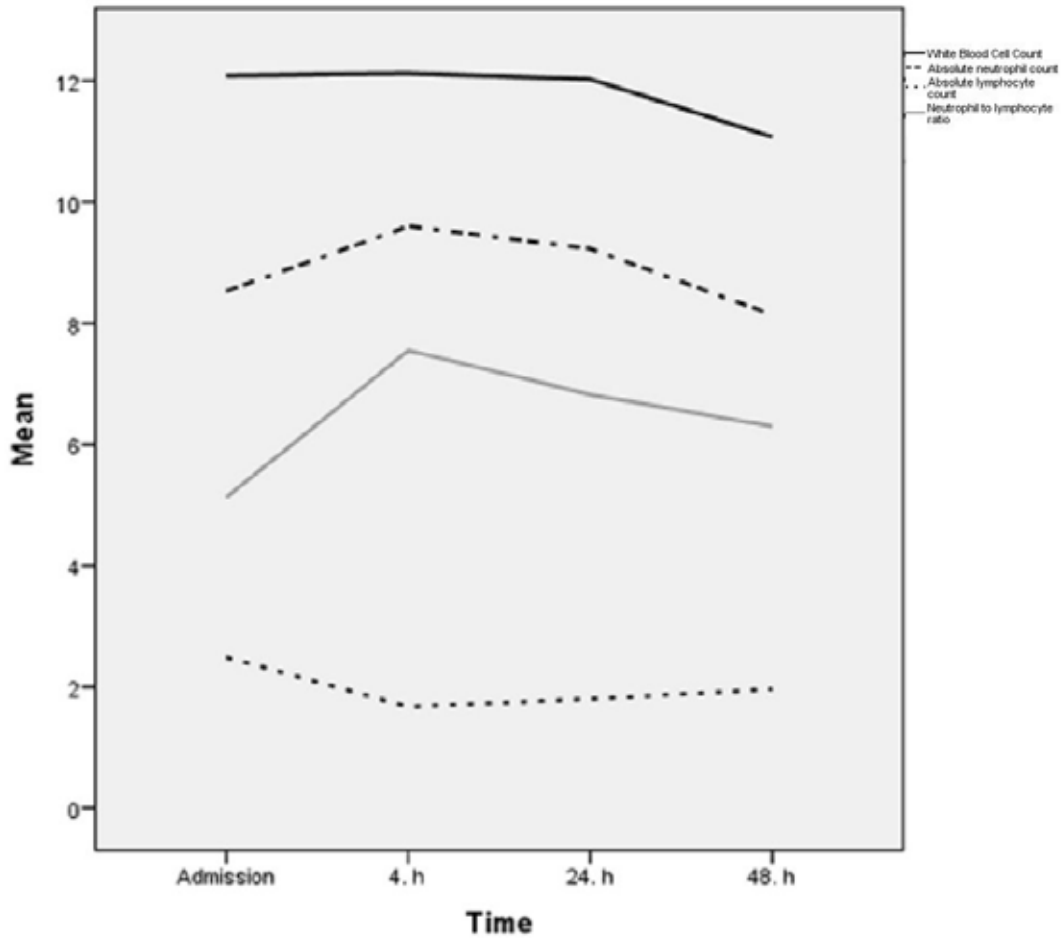

Fig 1: Changes in white blood cells, neutrophils, lymphocytes and NLR over time.

Statistical analysis

Statistical analyses were performed using the IBM statistics 21.0 MedCalc 11.0 software package. Patient characteristics are presented as the mean ± standard deviation or median (interquartile range) for continuous variables when appropriate and as percentages for discrete variables. The variables were tested for a normal distribution by the Shapiro-Wilk normality test. Differences in categorical variables were analysed by Pearson's chi-square test or Fisher's exact test. An independent-sample *t*-test was used for the analysis of normally distributed variables and a Mann-Whitney U-test was used for the analysis of non-normally distributed variables.

Via MedCalc11.0, complete sensitivity/specificity reports were created with receiver operating characteristic (ROC) curves and the area under the curve (AUC) and cut-off points of the parameters measured. We used the method of Deong *et al*[23] to calculate the standard error of the AUC and of the difference between AUCs. The diagnostic performance of the tests to discriminate endpoints were revealed by backward stepwise logistic regression analysis and also by comparing AUCs. A two-tailed $P < 0.05$ was considered to indicate statistical significance.

RESULTS

A total of 105 patients [81% male (n: 85), mean age: 58.36±13.01] with STEMI who were treated with stent implantation were included in the analysis. MI was revealed as follows: 35 (33.3%) anterior MI, 13 (12.4%) anteroseptal MI, 32 (30.5%) inferior MI, 23 (21.9%) inferior and right ventricular MI and two (1.9%) lateral MI. The culprit coronary artery was detected as the left main coronary artery in one (1%), left anterior descending artery in 50 (47.6%), circumflex artery in 12 (11.4%) and the right coronary artery in 42 (40%) patients.

The total WBC count was elevated at admission and decreased after the 24-hour plateau. The neutrophil count reached its maximum value four hours after admission and decreased until the 48th hour. Conversely, lymphocytes followed an inverse curve to that of neutrophils, reaching their lowest value four

Table 1: Patients' laboratory findings

Laboratory findings	30-day survival (n=92)	30-day mortality (n=13)	*P*	5-year survival (n=80)	5-year mortality (n=25)	*P*
Na	137.61±0.29	136.92±1.05	0.434	137.75±2.71	136.8±3.54	0.159
K	4.22±0.47	4.57±0.24	0.188	4.21±0.49	4.41±0.71	0.100
Creatinine	0.94±0.3	1.30±0.23	0.161	0.93±0.21	1.18±0.75	0.571
Hgb	14.53±1.78	12.99±1.63	0.006	14.76±1.69	13.01±1.63	<0.001
Hct	42.06±5.33	38.16±5.3	0.025	42.66±5.15	38.14±5.06	<0.001
WBC at 0 hour	10.80 (8.76-14.0)	13.5 (10.15-18.40)	0.049	10.95 (8.78-14.0)	13.1 (9.45-17.2)	0.129
WBC at 4th hour	10.85 (8.98-13.88)	15.0 (11.5-19.6)	0.001	10.85 (8.98-13.73)	13.1 (10.33-17.47)	0.022
WBC 24th hour	10.29 (8.47-12.56)	15.8 (12.77-22.60)	<0.001	10.24 (8.42-12.33)	13.10 (11.31-19.27)	<0.001
WBC 48th hour	9.15 (7.33-11.25)	22.20 (14.3-25.50)	<0.001	8.94 (7.22-11.08)	14.2 (9.75-22.35)	<0.001
Abs. Neutrophils at 0 hour	7.21 (5.52-9.76)	10.20 (7.7-15.7)	0.01	7.02 (5.13-9.35)	8.4 (7.15-14.99)	0.006
Abs. Neutrophils at 4th hour	8.42 (6.61-10.95)	13.2 (10.15-16.5)	<0.001	8.37 (6.61-10.8)	11.3 (8.26-14.8)	0.01
Abs. Neutrophils at 24th hour	7.57 (5.8-9.5)	12.0 (10.9-19.0)	<0.001	7.26 (5.79-9.5)	11.3 (8.18-17.13)	<0.001
Abs. Neutrophils at 48th hour	5.83 (4.8-7.85)	19.8 (12.55-22.60)	<0.001	5.7 (4.8-7.25)	12.5 (6.38-20.1)	<0.001
Abs. Lymphocytes at 0 hour	2.09 (1.48-3.46)	1.60 (1.11-2.84)	0.291	2.2 (1.54-3.86)	1.6 (0.93-2.84)	0.032
Abs. Lymphocytes at 4th hour	1.60 (1.29-2.10)	1.09 (0.71-1.55)	0.005	1.6 (1.29-2.09)	1.3 (0.74-1.95)	0.035
Abs. Lymphocytes at 24th hour	1.89 (1.34-2.20)	0.94 (0.74-1.22)	<0.001	1.87 (1.33-2.28)	1.3 (0.88-1.97)	0.003
Abs. Lymphocytes at 48th hour	2.07 (1.60-2.58)	0.84 (0.61-1.14)	<0.001	2.03 (1.67-2.56)	1.14 (0.77-2.24)	0.001
NLR at 0 hour	3.19 (1.66-6.45)	7.79 (2.97-10.09)	0.033	2.98 (1.63-5.88)	6.96 (3.01-10.09)	0.002
NLR at 4th hour	5.40 (3.76-8.21)	10.27 (7.38-23.80)	<0.001	5.30 (3.67-8.21)	8.10 (5.47-16.32)	0.003
NLR at 24th hour	4.20 (2.73-6.61)	17.32 (8.82-21.36)	<0.001	3.99 (2.67-6.51)	8.97 (5.02-18.74)	<0.001
NLR at 48th hour	2.87 (2.20-4.39)	20.40 (15.83-29.33)	<0.001	2.85 (2.26-4.11)	12.31 (4.64-21.97)	<0.001

Na: sodium; K: potassium; Hgb: haemoglobin; Hct: haematocrit; WBC: white blood cell; NLR: neutrophil lymphocyte ratio

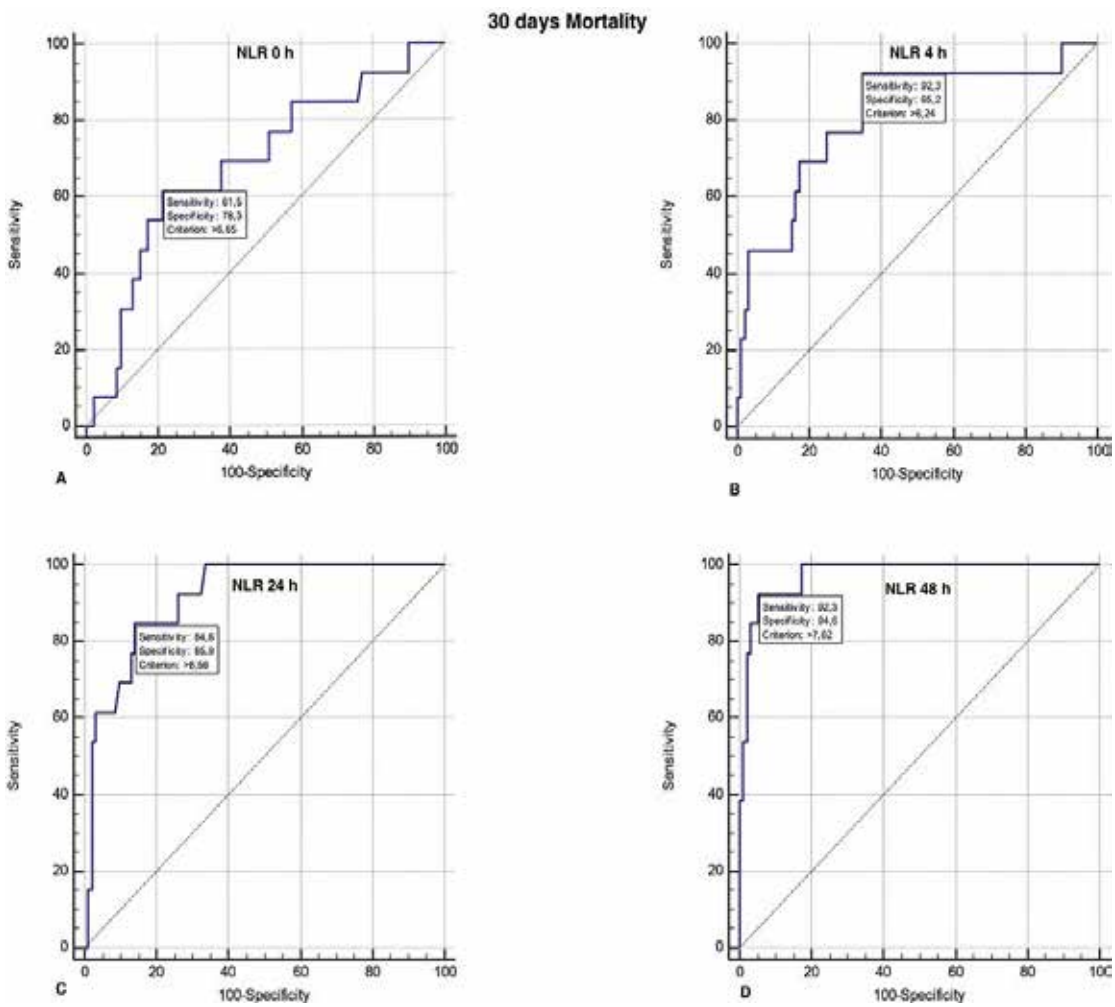

Fig 2: The receiver operating characteristic curve for NLR at different times was identified as an effective cut-off point for 30-day mortality.

hours after admission. As expected, the NLR peak was at four hours, and a parallel trajectory was observed with simultaneous changes in neutrophils and lymphocytes (Figure 1).

In the 30-day follow-up, mortality occurred in 13 (12.4%), stent thrombosis and re-infarction in four (3.8%) and cerebrovascular events in two (1.9%), thus MACE occurred in 19 (18.1%) of the population. Of the 105 patients, mortality occurred in 25 (23.8%) patients of the total population at five-year follow-up. It was established that MACE was associated with a decrease in haemoglobin, haematocrit and an increase in the absolute neutrophil count at 0, 4, 24 and 48 hours and also increased in WBC at 4, 24 and 48 hours. Not only a higher neutrophil count but also a lower lymphocyte count was associated with MACE at the 30-day follow-up. Thus, higher NLR was significantly associated with MACE in patients with STEMI undergoing primary PCI. No statistical significance was found when sodium, potassium, creatinine, platelets, absolute lymphocyte count, WBC at admission and NLR at admission were assayed for MACE prediction. Death from any cause after 30 days (median: 24 months; range: 7.0-42.75) was selected as an outcome. Similar to previous findings about MACE, follow-up results regarding mortality were summarized in Table 1.

MACE was significantly associated with an increase in NLR at 4, 24 and 48 hours (P <0.001). MACE was higher at the 30-day follow-up in patients with four-hour NLR >6.05 (84.2% sensitivity and 64% specificity), 24-hour NLR >4.8 (84.2% sensitivity and 62.8% specificity), and 48-hour NLR >5 (78.9% sensitivity and 81.4% specificity). Moreover, it was revealed that a higher NLR is significantly related to mortality in patients with STEMI within 30 days and five years of

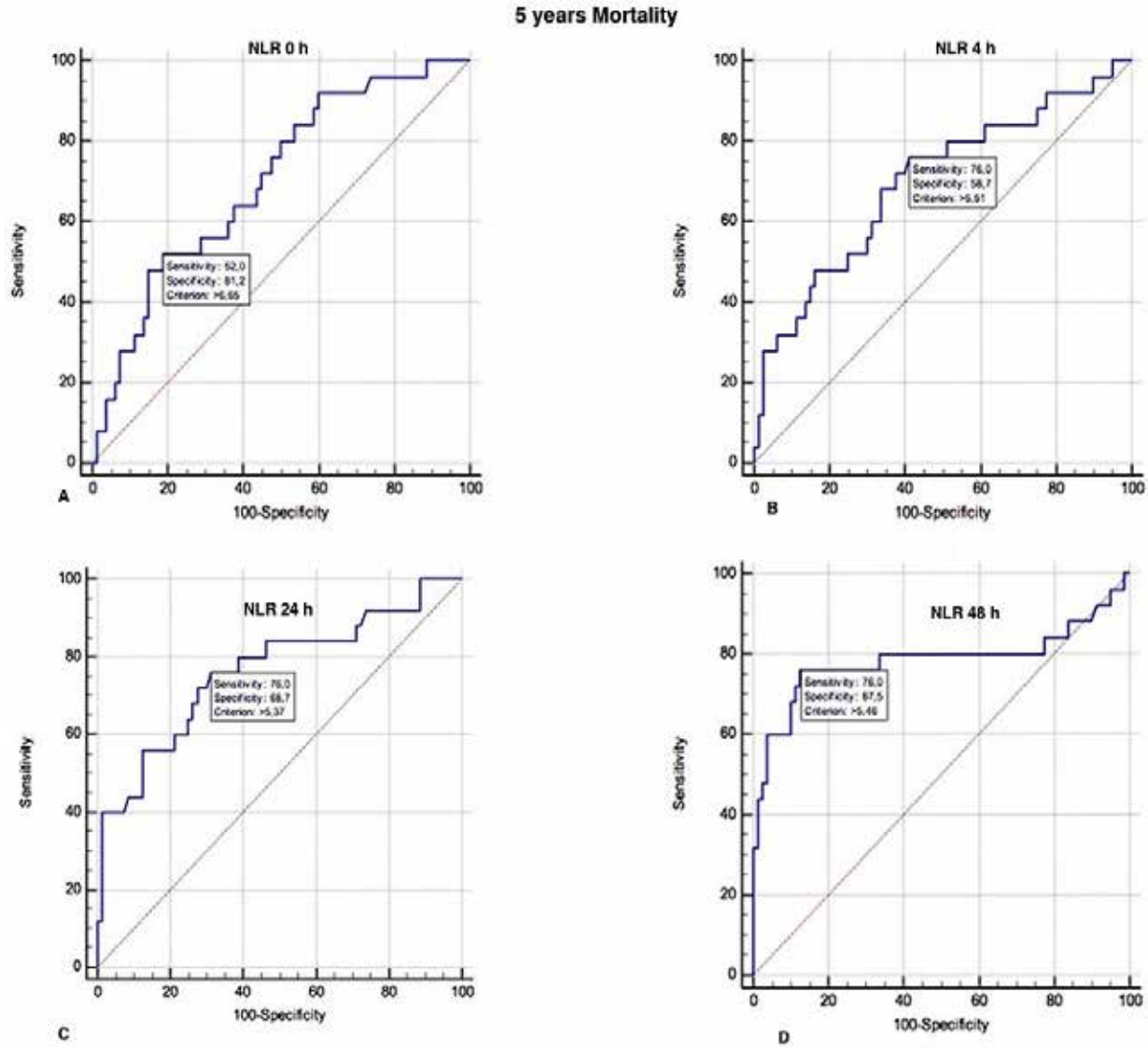

Fig 3: The receiver operating characteristic curve for NLR at different times was identified as an effective cut-off point for five-year mortality.

Table 2: Backward-stepwise logistic regression analysis to evaluate test performance

Step 1-4	30-day MACE				30-day mortality				60-month cumulative			
	Odd's Ratio	95% C.I.		*P*	Odd's Ratio	95% C.I.		*P*	Odd's Ratio	95% C.I.		*P*
		Lower	Upper			Lower	Upper			Lower	Upper	
Step 1												
NLR at 0 hour	0.794	0.623	1.013	0.063	0.619	0.385	0.995	0.048	1.082	0.946	1.236	0.249
NLR at 4th hour	1.079	0.896	1.299	0.422	1.185	0.858	1.637	0.304	0.911	0.772	1.076	0.273
NLR at 24th hour	0.841	0.693	1.020	0.078	0.790	0.605	1.030	0.082	0.978	0.819	1.168	0.802
NLR at 48th hour	1.495	1.156	1.935	<0.001	1.961	1.298	2.963	0.001	1.338	1.067	1.679	0.012
Step 4												
NLR at 48th hour	1.236	1.124	1.359	<0.001	1.385	1.197	1.602	<0.001	1.250	1.127	1.388	<0.001

MACE: major adverse cardiac events; NLR: neutrophil lymphocyte ratio

discharge. Likewise, NLR cut-off values to determine mortality at the 30-day and five-year follow-up are shown by ROC curves in Figures 2 and 3.

Backward stepwise logistic regression analyses were carried out to assess the diagnostic performance of NLR measurements in determining outcomes (Table 2). Herein, NLR at the 48th hour was found significantly more convenient according to stepwise model. Therefore, the ROC curves were compared to determine the differences between AUCs (Table 3). When compared with NLR at 0, 4 and 24 hours, NLR at the 48th hour was significantly more powerful for predicting MACE and mortality at the 30-day follow-up. Although AUCs of NLR at the 48th hour were greater than NLR at 0, 4 and 24 hours, there was no statistical significance for indicating five-year mortality (Figure 4).

DISCUSSION

In our study, NLRs at admission and 4, 24, 48 hours after admission were compared to determine outcomes in patients with STEMI who were treated with primary PCI. Remarkably, in our study, NLR at 48 hours after admission was more useful and accurate to predict MACE within 30 days, as well as mortality within five years. Nevertheless, we found that NLR, when time was not taken into consideration, was also associated with mortality at the 30-day and five-year follow-up and MACE at the 30-day follow-up. There are many studies in the literature that are concerned with the prognosis of acute coronary syndrome and NLR. No study has examined the time at which the measured NLR is more closely related to the prognosis. Demonstrating that the NLR level at the 48th hour is more closely related to prognosis constitutes the unique aspect of our study.

Due to inflammation of the coronary arteries in the acute phase of STEMI, leucocytosis develops in proportion to the size of the necrosis. The magnitude of elevation in the leukocyte count is associated with mortality after STEMI, and leukocyte subtypes regulate the inflammatory response[17,18]. In particular, neutrophils are the first type of leukocytes seen in damaged myocardial tissue. A large amount of

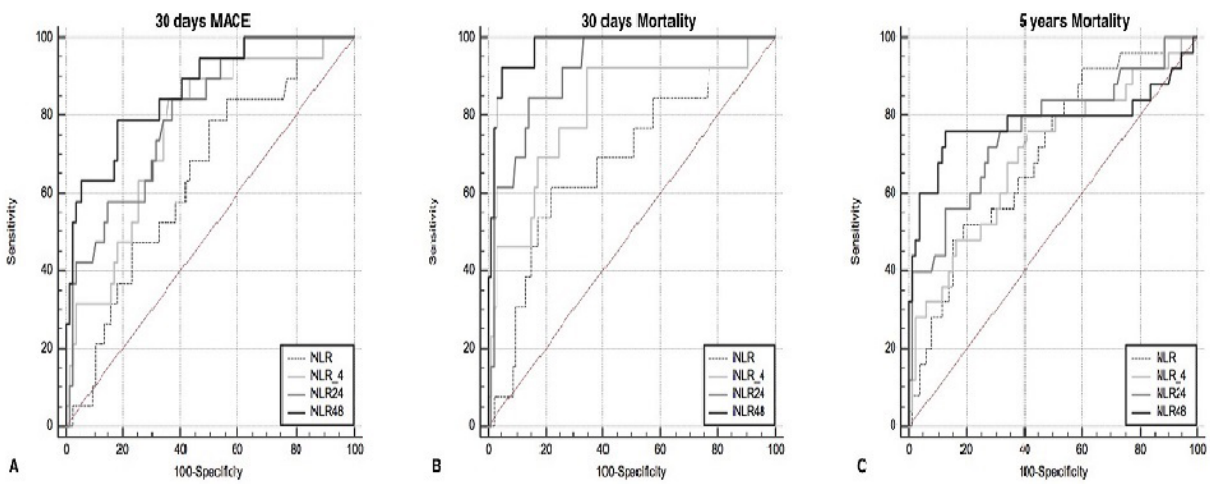

Fig 4: Comparison of the receiver operating characteristic curves for NLR at different times for clinical outcomes

Table 3: Comparison of the area under the curves for NLR at different times for clinical outcomes

Steps	30-day MACE			30-day mortality			5-year mortality		
	AUC	95% C.I.		AUC	95% C.I.		AUC	95% C.I.	
		Lower	Upper		Lower	Upper		Lower	Upper
NLR at 0 hour	0.639	0.540	0.731	0.684	0.586	0.771	0.703	0.606	0.788
NLR at 4th hour	0.757	0.663	0.835	0.812	0.724	0.882	0.697	0.600	0.783
NLR at 24th hour	0.799	0.710	0.871	0.914	0.843	0.960	0.763	0.670	0.841
NLR at 48th hour	0.865*	0.785	0.924	0.974#	0.923	0.995	0.784Ø	0.693	0.858

MACE: major adverse cardiac events; NLR: neutrophil lymphocyte ratio
* NLR at 48th hour vs NLR at 0 hour: *P* <0.001; NLR at 48th hour vs NLR at 4th hour: *P*=0.081; NLR at 48th hour vs NLR at 24th hour: *P*=0.034
# NLR at 48th hour vs NLR at 0 hour: *P* <0.001; NLR at 48th hour vs NLR at 4th hour: *P*=0.025; NLR at 48th hour vs NLR at 24th hour: *P*=0.0452
Ø NLR at 48th hour vs NLR at 0 hour: *P*=0.379; NLR at 48th hour vs NLR at 4th hour: *P*=0.238; NLR at 48th hour vs NLR at 24th hour: *P*=0.562

inflammatory mediators are secreted from activated neutrophils. These mediators have microcirculatory effects and regulate the inflammatory response to the damaged myocardial tissue[17]. Previous studies have shown that there is an independent relationship between increased neutrophil count and infarct size, mechanical complications and mortality in patients with acute MI[20,24]. Furthermore, lymphocytopenia, as well as high neutrophil counts, was found to be associated with worse clinical outcomes in patients with acute STEMI[10-13]. The balance between the leukocyte subtypes modulates the inflammatory response. Based on this, NLR is thought to be a better indicator of systemic inflammation, and studies have been carried out on that[14,15]. Studies have shown that NLR is superior to leukocyte count and its subtypes in predicting mortality in patients with CAD[15,25]. Likewise, Nunez *et al*[19] clearly demonstrated that NLR has superior discriminative ability to total WBC while predicting mortality in patients with STEMI. This ratio combines independent markers of inflammation that point to clinical outcomes in opposite directions. We revealed that the NLR peak was higher than those of other markers; therefore, NLR is thought to be the better indicator of an inflammatory state in STEMI. We decided to evaluate NLR 48 hours after admission because it was shown previously that NLR has a plateau trajectory at 48-96 hours after STEMI[19].

In patients with cardiovascular disease, NLR has been shown to be associated with adverse cardiac events. Hartaigh *et al*[26] found that NLR was an independent predictor of cardiovascular mortality at the end of a median 7.8-year follow-up in their study of 3316 patients undergoing coronary angiography. Akpek *et al*[18] demonstrated that pre-procedural NLR is an independent predictor of no reflow in patients with STEMI. In their study, MACEs were significantly higher in patients with no reflow, and there was a significant and positive correlation between high-sensitivity C-reactive protein and the NLR[18]. There is also a positive correlation between NLR and MACEs[27]. Moreover, Duffy *et al* showed that elevated pre-procedural NLR was associated with an increased risk of long-term mortality in patients undergoing PCI[28]. Admission NLR is an independent predictor of in-hospital and six-month mortality in patients with acute coronary syndromes[29]. Nunez *et al*[19] found that increased NLR was associated with increased long-term mortality in patients with STEMI in their 4.2-year follow-up study. Also, it has been shown that NLR is a strong independent predictor of long-term mortality in STEMI patients treated with early revascularization[17]. Recently, Oncel *et al*[30] showed the association between NLR and adverse outcomes in STEMI patients, independent of the GRACE risk score. In a meta-analysis, it was found that the NLR is a predictor of all-cause mortality and cardiovascular events in patients undergoing angiography or cardiac revascularization[31]. We analysed MACE and mortality within 30 days and five years in patients with STEMI. Similarly, higher NLRs were found to predict worse short-term and long-term clinical outcomes in patients with STEMI undergoing primary PCI.

In addition to the current risk scores, interest has recently been directed to the development of an inexpensive marker which is simple to obtain for predicting the prognosis. Electrocardiographic and biochemical parameters are the most studied admission parameters to define the prognosis of patients with STEMI. In this respect, NLR has been evaluated in various studies and has emerged as a new risk assessment tool for patients with STEMI prior to revascularization[18,19,29,32,33]. Previously, NLR has been evaluated at admission or prior to revascularization because the vast majority of studies in this context were retrospective[33-37]. Hereby, we prospectively assessed the timing of NLR measures, and unlike previous studies, in our work it was shown that NLR at 48 hours after admission is a better predictor of prognosis in STEMI patients who were treated with primary PCI.

Study limitations

In our study, we did not evaluate in-hospital MACE and mortality because we excluded early complications and patients with cardiogenic shock to obtain blood counts until 48 hours from each patient. Also, we did not take into consideration five-year MACE because of the study design. A well-designed (prospective, randomized, and multi-centre) study with larger study populations is needed to evaluate this reasonable marker in order to confirm our findings.

CONCLUSION

It can be concluded from our findings that the NLR is a marker which predicts short- and long-term outcomes in STEMI patients treated with primary PCI. To the best of our knowledge, this is the first study that identifies the prognostic importance of the timing of NLR measures to predict clinical outcomes. It is logical to postulate that NLR at 48 hours after admission or before discharge is more accurate for predicting clinical outcomes in patients with STEMI.

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Author contribution: Gurbet Ozge Mert: study design, data collection, literature review and wrote manuscript; Muhammet Dural: critical review; Kadir Ugur Mert: study design and supervision, data collection, analysis and interpretation, and wrote manuscript; Muzaffer Bilgin: data analysis and interpretation, and literature review; Bulent Gorenek: study design, supervision and critical review.

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Original Article

Evaluation on predictive values of risk scores in non-variceal upper gastrointestinal bleeding

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ABSTRACT

Objective: To determine which is the best score in predicting re-bleeding and mortality for patients with acute non-variceal upper gastrointestinal bleeding (NVUGIB) among seven scores (Forrest, full Rockall score (RS), admission Rockall, Glasgow-blatchford score (GBS), Cedars-Sinai medical center predictive index (CMCPI), T score, AIMS65 score (AIMS65), Progetto nazionale emorragia digestive (PNED)).
Design: Prospective study
Setting: Pyongyang medical University Hospital, Gastroenterology Department from 1/2015 to 4/2019
Subjects: This study included 404 adult patients with NVUGIB
Interventions: Fluid resuscitation, blood transfusion, pharmacologic therapy proton pump inhibitor (intravenous or oral), endoscopic hemostasis and surgery were considered according to national guidelines for management of upper gastrointestinal bleeding
Main outcome measures: Main clinical outcomes were re-bleeding and 30-day mortality. Predictive ability of all scores were estimated using area under the receiver operating curve (AUROC).
Results: The largest AUROC (0.846) was obtained from the Forrest score, followed by T score (AUROC: 0.818), full RS (AUROC: 0.813), CMCPI (AUROC: 0.799) and GBS (AUROC: 0.794) when predicting re-bleeding. Admission RS (AUROC: 0.716) and AIMS65 (AUROC: 0.691) were less predictive than other scores. Regarding mortality, PNED (AUROC: 0.955) score had the highest predictive ability followed by full RS (Rockall score) (AUROC: 0.919), admission RS (AUROC: 0.917), AIMS65 (AUROC: 0.899), CMCPI (AUROC: 0.872) GBS (AUROC: 0.854), T score (AUROC: 0.851). Forrest score (AUROC: 0.590) had the worst performance at predicting death.
Conclusion: Forrest score is the best at predicting re-bleeding and PNED score predicts mortality for patients with NVUGIB with high accuracy.

KEY WORDS: mortality, non-variceal upper gastrointestinal bleeding, re-bleeding, risk score

INTRODUCTION

Nonvariceal upper gastrointestinal bleeding (NVUGIB) is a common gastrointestinal emergency with an annual incidence of 50 to 150 per 100,000 adults. Mortality from upper gastrointestinal bleeding (UGIB) is around 10% and may reach 35% in aged patients with comorbidities[1]. Although 80% of UGIB stop spontaneously, the remaining patients re-bleed or continue bleeding. Re-bleeding or continuous bleeding is an independent risk of mortality[2].

Therefore, early identification of patients at high risk of re-bleeding or death is an essential part in the management of NVUGIB helping clinicians guide appropriate treatment. Identifying patients who are at low risk of poor outcome is also important to reduce hospital stay and medical resources.

To date, several clinical scores have been developed to predict re-bleeding, mortality, clinical intervention and urgent endoscopy for patients with NVUGIB. Recent international recommendations regarding management of NVUGIB encourage gastroenterologists to perform these scoring systems for risk stratification. These scores vary from simple classification (Forrest score) to complex model based

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on clinical, laboratory parameters and endoscopic finding[3-9]. Among them, Rockall and Glasgow-Blachford score (GBS) have been more externally validated than other scores[4,5]. Different studies indicated that Rockall score is useful in prediction of mortality risk[10,11]. In addition, some studies have suggested GBS could be used to identify patients who need outpatient care[12,13].

Besides Cedars-Sinai medical center index (CMCPI), T score, AIMS65 and Progetto nazionale emorragia digestive (PNED) have also been described and these scores require further evaluation[6-9]. Marmo R *et al* developed Italian PNED score and they concluded it was superior to Rockall score in predicting mortality[9]. Some studies reported AIMS65 had better accuracy than GBS in predicting in-patient mortality and the need for emergency intervention[14,15]. It was also suggested that T score is helpful for the prediction of high-risk patients who need a very early therapeutic endoscopy[16]. The power of pre-endoscopy scores (GBS, AIMS65, T score, admission Rockall) is to eliminate endoscopist's labor on weekend, since these scores only use clinical, haemodynamic and easily available laboratory variables to calculate.

Though many studies have compared risk scores in their ability to predict various outcomes, it remains controversial which score has the best predictive value[17-20]. It is probably due to variety in demography, difference in medical care level and study design.

We compared seven scoring systems (Forrest score, full Rockall score, admission Rockall score, GBS, CMCPI, T score, AIMS65 score and PNED score) to determine which is the best score in predicting re-bleeding and mortality for patients with acute NVUGIB in our tertiary care center.

SUBJECTS AND METHODS

Study population

This prospective study included all adult patients with UGIB admitted to Pyongyang medical University Hospital, Gastroenterology Department from 1/2015 to 4/2019. UGIB was defined as 'confirmed' if patients with suspected UGIB met the following criteria[21]:

- Combination of reported signs of melena and/or hematemesis with
  - ✓ Anemia (Hb <13.0g/dl for men or <12.0g/dl for women), or
  - ✓ Hemodynamic instability (a state requiring pharmacologic or mechanical support to maintain a normal blood pressure or adequate cardiac output), or
  - ✓ Discrepant increased urea
- Confirmed bleeding during endoscopy or manifest old/fresh blood

Inclusion criteria

Patients diagnosed with NVUGIB (peptic ulcer, erosive gastritis and duodenitis, malignancy of upper gastrointestinal tract, esophagitis, esophageal ulcer, Mallory-Weiss syndrome, vascular abnormalities)

Exclusion criteria

Cirrhotic patients with variceal bleeding.

In all patients, demographic data (age, sex), co-morbidities (liver disease, chronic kidney disease, cardiovascular disease, cerebral disease, diabetes, pulmonary disease, malignancy of other tract), previous history of peptic ulcer, UGIB and use of medication (non-steroid anti-inflammatory drug, oral anti-coagulants, corticosteroids, acetylsalicylic acid, clopidogrel) were collected by taking history.

Vital signs were measured through physical examination and shock index was calculated to assess the haemodynamic status. Shock was defined as the presence of a decrease in systolic blood pressure to <90 mmHg, tachycardia >100 beats/minute, and a decreased central venous pressure or jugular venous pressure.

Complete blood count, liver function, serum creatinine, albumin, urea and international normalized ratio were recorded serially during hospitalization. All the patients underwent upper endoscopy, ultrasound and chest X-ray. Our study was approved by the Ministry of Public Health and Pyongyang Medical College Ethic Review Committee.

Treatment

All patients were treated according to national guidelines for management of UGIB. The first step is the assessment of the hemodynamic status and fluid resuscitation. Proton pump inhibitor (PPI) intravenous continuous infusion was performed before endoscopy. After endoscopy, PPI (omeprazole, 80 mg bolus, followed by 8 mg/h continuous infusion for 72 hours) was given intravenously in high-risk patients (active bleeding, visible vessel, adherent clot) whereas oral PPI (omeprazole, 80 mg, twice daily) was done for low risk lesions (esophagitis, gastritis, duodenitis, clean-based or dark-spot ulcers, and Mallory-Weiss tears)

Endoscopic hemostasis was considered in high risk of re-bleeding patients with peptic ulcer (active bleeding, visible vessel, adherent clot). Surgery was performed in patients who had failed endoscopic treatment or had continuous bleeding despite vigorous resuscitation. Patients with malignancy or perforation also underwent surgical treatment. Blood transfusions were indicated when the hemoglobin value is <7 g/dL.

Performance of all scoring systems, definition of clinical outcomes.

Endoscopic evaluation of bleeding lesions was defined according to Forrest score[3]

- ✓ Active arterial bleeding (Forrest Ia-score of 5), oozing with or without visible vessel (Forrest Ib-score of 4);
- ✓ Non-bleeding visible vessel (Forrest IIa-score of 3),
- ✓ Adherent clot (Forrest IIb-score of 2), and flat spot(Forrest IIc-score of 1)
- ✓ Clean ulcer base (Forrest III-score of 0)

The scores for the full Rockall, admission Rockall, GBS, CMCPI, T score, AIMS65 and PNED were calculated in each patient based on their clinical and laboratory data[4-9].

Clinical outcomes were re-bleeding and mortality.

Rebleeding was defined as following[21]:

- recurrent haematemesis of fresh blood (>200 ml), active bleeding or fresh blood found during endoscopy, or
- two of the following
- ✓ Hb drop >20 g/L within 24 hours
- ✓ Hb increase <10 g/L after adequate blood transfusion
- ✓ Systolic RR <90 mm Hg or pulse rate >110 /min after initial stabilization

Mortality was in-hospital or 30-day death of follow up.

Statistical analysis

Statistical analysis was performed with Statistical Package for Social Sciences version 20.0 for windows (SPSS Inc.; Chicago, IL, USA). We calculated the area under the receiving operating characteristics curve (AUROC) for all scores to compare ability in prediction of re-bleeding and mortality. The performance of the scores was assessed by calculation of Youden index, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

RESULTS

Patient characteristics and baseline scores

Four hundred and four patients with NVUGIB were enrolled in our study. The mean age of the studied population was 50.7 years (range: 17-84) and 72.5% of the patients were male. Their clinical, laboratory data and interventions are shown in Table 1. In our study, 46 patients (11.4%) had re-bleeding and 37 patients (9.2%) died. Fourteen patients died from uncontrolled bleeding, whereas 23 deaths had non-bleeding causes (exacerbation of co-morbidities).

Table 2 shows endoscopic findings of study population. Peptic ulcer disease was the most frequent cause of NVUGIB representing 61.4% of all cases, followed by gastroduodenal erosions (18.3%). All patients were classified according to the Forrest score as follows; four (1%) FIa patients, 22 (5.4%) FIb, 22 (5.4%) FIIa, 118(29.3%) FIIb, 38 (9.4%) FIIc and 200 (49.5%) F III. The mean ± SD (range) of full Rockall score, admission Rockall score, GBS, CMCPI, T score, AIMS65 score and PNED score were 3.1±2.1 (0-10), 1.4±1.6 (0-7), 7.5±4.5 (0-20), 2.2±1.9 (0-8), 8.5±2.0 (4-12), 0.6±0.9 (0-4) and 1.7±2.2 (0-12) respectively.

Table 1: Clinical characteristics of patients (n=404)

Parameter	Value
Age (years), X±SD	50.7±14.5
Sex (male) , n(%)	293(72.5)
Melena, n(%)	173(42.8%)
Use of medication, n (%)	94(23.3%)
Previous history of peptic ulcer or UGIB, n (%)	106(26.2%)
Co-morbidities, n (%)	
Liver disease	55(13.6%)
Cardiovascular disease (myocardial infarction, cardiomyopathy, hypertension etc)	37(9.2%)
Chronic kidney disease	4(0.1%)
Diabetes	18(4.5%)
Cerebral disease	6(1.5%)
Pulmonary disease	9(2.2%)
Malignancy of other tract	9(2.2%)
Shock at admission, n (%)	44(10.9%)
Hb (<70g/L), n(%)	166(41.1%)
INR >1.5, n (%)	19(4.7%)
Albumin <3g/dL, n (%)	83(20.5%)
Serum creatinine(μmol/L), X±SD	127.2±81.5
BUN (mmol/L), X±SD	19.3±11.7
Patients with 1 or more blood transfusions, n (%)	191(47.3%)
Endoscopic intervention, n(%)	83(20.5%)
Surgery, n(%)	20(5%)
Length of hospital stay(d), X±SD	7.0±4.1

UGIB: upper gastrointestinal bleeding; Hb: haemoglobin; INR: international normalized ratio; BUN: blood urea nitrogen

Comparison of score's ability to predict clinical outcomes

Re-bleeding

We excluded PNED score to compare predictive value for re-bleeding, since re-bleeding is included as a variable to calculate it. In other words, Forrest score, full Rockall score, admission Rockall score, GBS, CMCPI, T score and AIMS65 score were evaluated in prediction of re-bleeding.

Table 2: Endoscopic findings of study population (n=404)

Findings	n(%)
Peptic ulcer disease (including anastomotic gastric ulcer)	248(61.4)
Gastroduodenal erosions	74(18.3)
Malignancy of upper GI tract	43(10.7)
Mallory-Weiss tear syndrome	15(3.7)
Esophagitis, esophageal ulcer	10(2.5)
Vascular malformation	5(1.2)
Lesions not identified	9(2.2)

Table 3: Comparison of the area under the curve of re-bleeding for evaluated scoring systems

Scoring system	AUROC	S.E.	95% CI	AUROC difference	P-value
Forrest score	0.846	0.030	0.788-0.905	-	-
Full Rockall score	0.813	0.028	0.758-0.867	0.033	0.421
Admission Rockall score	0.716	0.039	0.640-0.793	0.130	0.008
GBS	0.794	0.031	0.733-0.856	0.052	0.229
CMCPI	0.799	0.035	0.730-0.868	0.047	0.308
T score	0.818	0.028	0.762-0.874	0.028	0.495
AIMS65 score	0.691	0.046	0.600-0.781	0.155	0.005

AUROC: area under the receiver operating curve; GBS: Glasgow-Blachford score; CMCPI: Cedars-Sinai medical center index

Forrest score had the largest area under the curve in prediction of re-bleeding (AUROC: 0.846). A pair-wise comparison between Forrest score and four scores (full Rockall score, GBS, CMCPI and T score) did not show significant difference (P >0.05, Table 3, Figure 1). However, Forrest score was better than admission Rockall score (0.716, P=0.008) and AIMS65 score (0.691, P=0.005).

After comparison of the AUROC, we assessed Youden index, sensitivity, specificity, PPV and NPV for all scores. The Forrest score showed the best performance in the prediction of re-bleeding having the highest Youden index (0.58), sensitivity (93.5%), PPV (25.6%) and NPV (98.7%), but CMCPI had the highest specificity (69.4%, Table 4).

Mortality

For prediction of mortality, PNED score had the highest predictive ability (AUROC: 0.955), but it was comparable to full Rockall score (AUROC: 0.919, P=0.163) and admission Rockall score (AUROC: 0.917, P=0.180) (Table 5, Figure 2). PNED score was superior to Forrest score (AUROC: 0.590, P <0.001), GBS (AUROC: 0.854, P=0.004), CMCPI (AUROC: 0.872, P=0.011), T score (AUROC: 0.851, P=0.001) and AIMS65 (AUROC: 0.899, P=0.048).

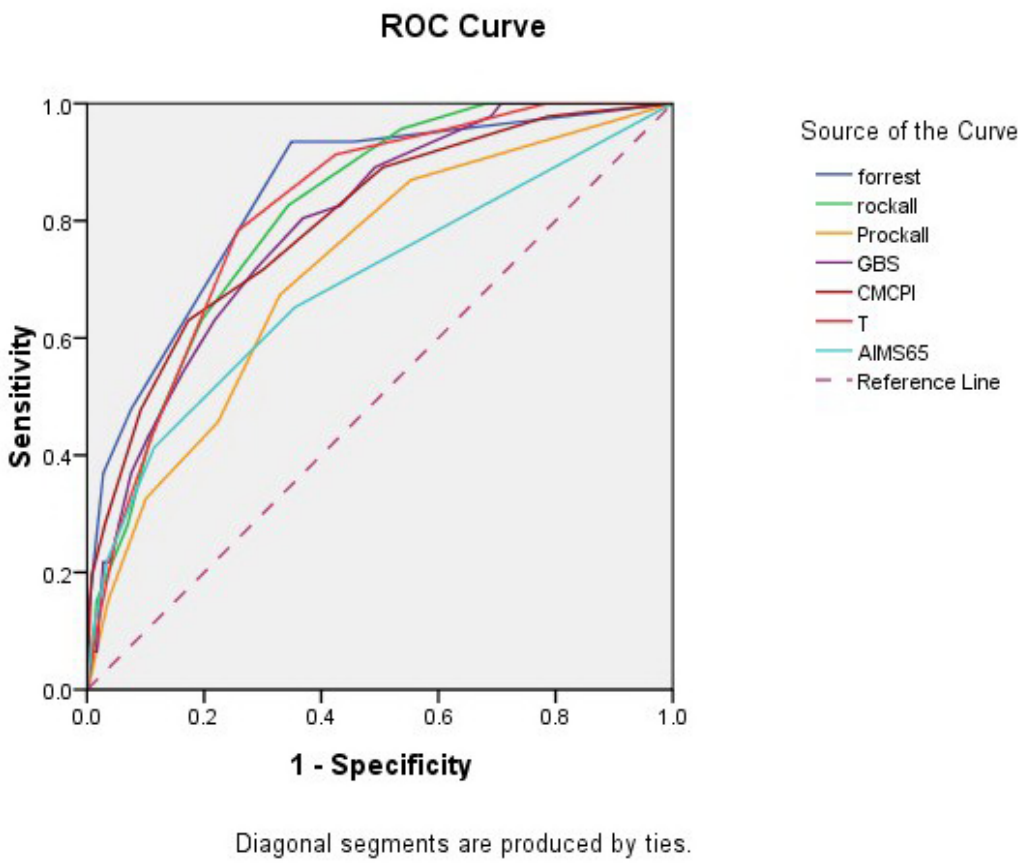

Figure 1: Receiver operating curves of different scores in prediction of re-bleeding.

Table 4: Performance of scoring systems in the prediction of re-bleeding

Scoring system	Cut off	Youden index	Sensitivity	Specificity	PPV	NPV
Forrest score	≥2	0.58	93.5	65.1	25.6	98.7
Full Rockall score	≥4	0.48	82.6	65.6	23.6	96.7
Admission Rockall score	≥1	0.32	87.0	55.7	16.8	96.4
GBS	≥7	0.40	89.1	50.8	18.9	97.3
CMCPI	≥2	0.39	89.1	69.4	18.5	97.3
T score	≤8	0.58	91.3	57.5	21.6	98.7
AIMS65 score	≥1	0.30	65.2	64.5	19.1	93.5

PPV: positive predictive value; NPV: negative predictive value; GBS: Glasgow-Blachford score; CMCPI: Cedars-Sinai medical center index

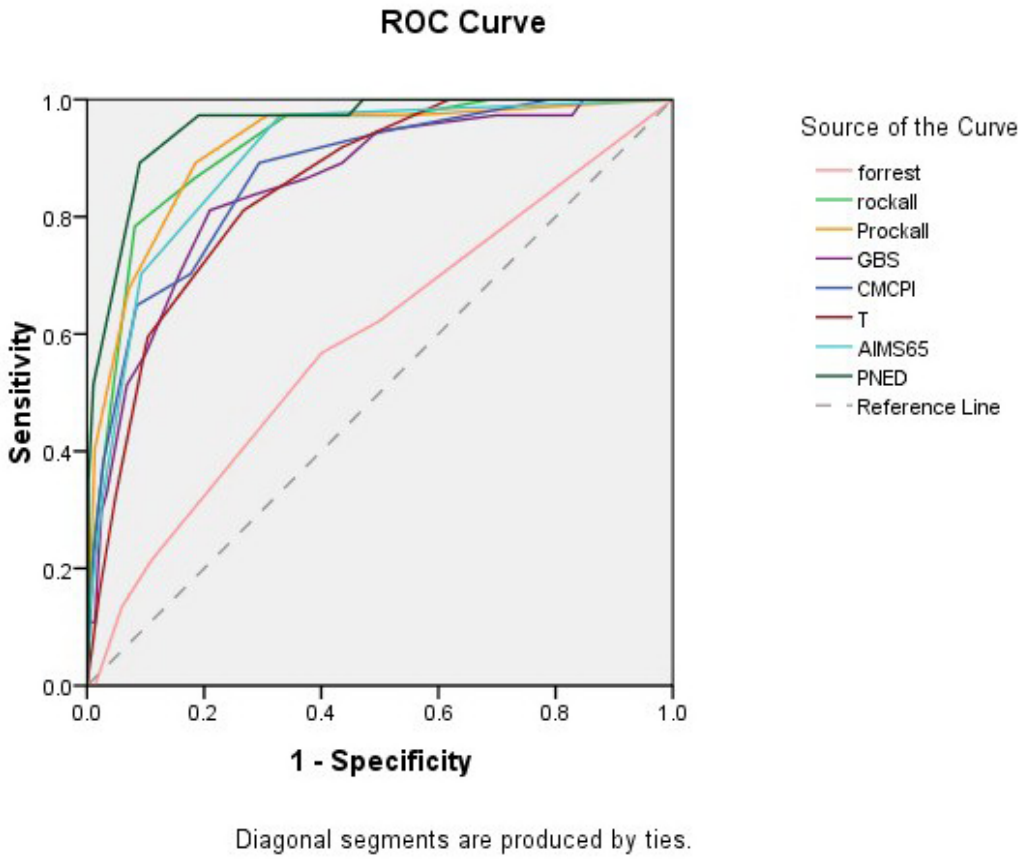

Figure 2: Receiver operating curves of different scores in prediction of mortality.

Table 5: Comparison of the area under the curve of mortality for evaluated scoring systems

Scoring system	AUROC	S.E.	95% CI	AUROC difference	*P*-value
PNED score	0.955	0.015	0.927-0.984	-	-
Forrest score	0.590	0.051	0.490-0.691	0.365	<0.001
Full Rockall score	0.919	0.021	0.877-0.961	0.036	0.163
Admission Rockall score	0.917	0.024	0.870-0.965	0.038	0.180
GBS	0.854	0.032	0.790-0.917	0.101	0.004
CMCPI	0.872	0.029	0.815-0.930	0.083	0.011
T score	0.851	0.028	0.796-0.906	0.104	0.001
AIMS65 score	0.899	0.024	0.852-0.945	0.056	0.048

AUROC: area under the receiver operating curve; CI: confidence interval; PNED: Progetto nazionale emorragia digestive; GBS: Glasgow-Blachford score; CMCPI: Cedars-Sinai medical center index

Table 6: Performance of scoring systems in the prediction of mortality

Scoring system	Cut off	Youden index	Sensitivity	Specificity	PPV	NPV
PNED score	≥3	0.78	97.3	80.9	34.0	99.7
Forrest score	≥2	0.13	56.8	59.9	11.9	92.8
Full Rockall score	≥4	0.67	97.3	69.2	24.2	99.6
Admission Rockall score	≥2	0.63	97.3	65.9	22.4	99.6
GBS	≥7	0.45	94.6	50.4	16.1	98.9
CMCPI	≤2	0.44	89.2	70.6	15.8	98.9
T score	≥8	0.48	91.3	57.5	17.5	98.6
AIMS65 score	≥1	0.64	97.3	67.0	22.9	99.6

PPV: positive predictive value; NPV: negative predictive value; PNED: Progetto nazionale emorragia digestive; GBS: Glasgow-Blachford score; CMCPI: Cedars-Sinai medical center index

Table 6 shows Youden index, sensitivity, specificity, PPV and NPV for all scores in prediction of mortality. The sensitivity of full Rockall score, admission Rockall score, AIMS65 score and PNED score was 97.3%, but PNED score had the highest Youden index (0.78), specificity (80.9%), PPV (34.0%) and NPV (99.7%).

DISCUSSION

Early risk stratification is significantly important to improve patient's management and promote cost-effective use of resources. Re-bleeding is the only independent predictor of mortality[22,23]. Identification of patients at high risk of re-bleeding is helpful to achieve adequate hemostatic purpose. It is also important to identify patients with low risk of re-bleeding. In a previous study, low-risk of re-bleeding enabled patients to have early discharge[24]. Oral PPI is recommended instead of endoscopic hemostasis and intravenous PPI therapy in patients with low-risk of re-bleeding.

In this single-center prospective study, we compared several scoring systems' ability to predict re-bleeding for patients with NVUGIB. Interestingly, Forrest score had the largest AUROC, although it was formed four decades ago. We concluded that this simple score was a significant assessment tool of re-bleeding in NVUGIB. It implies type of bleeding lesion is more closely associated with the presence of re-bleeding rather than age, shock, and co-morbidity.

Guglielmi A *et al* reported that liver cirrhosis, recent surgery, systolic blood pressure below 100 mmHg, hematemesis, Forrest score, ulcer size and site were significantly predictive variables for the recurrence of hemorrhage[25]. Among these, Forrest score was the most important. We also found that admission Rockall score and AIMS65 score had poor performance at predicting re-bleeding.

Finally, we evaluated different scoring systems for prediction of mortality. PNED score had the highest predictive value followed by full Rockall score and admission Rockall score. An Italian prospective study from a cohort of 1360 patients compared PNED score with Rockall score[9]. The researchers reported that PNED score was superior to Rockall score for prediction of 30-day mortality. In another multi-center prospective study, PNED score and AIMS65 had similar ability at predicting 30-day mortality (AUROC: 0.77)[20]. PNED score was better at predicting mortality than the admission Rockall score (0.72; *P*=0.05), full Rockall score (0.72; *P*=0.05), and Glasgow Blatchford score (0.64; *P* <0.001).

Similar to the literature mentioned above, we found that the PNED score is the best for predicting mortality among the seven scores, as it has the highest area under the curve. A weak point of Rockall score is that it does not include hemoglobin value. Low hemoglobin at admission is closely associated with poor outcome[26]. In contrast with Rockall score, GBS includes hemoglobin, but endoscopic findings and age are not included in the calculation. Though AIMS65 is a validated simple prognostic score, it includes liver-specific parameters (albumin, international normalized ratio).

Levin *et al* reported that re-bleeding is the only predictor of 3-day mortality in multivariate analysis[23]. PNED score is superior to others because it includes hemoglobin value, and it evaluates patient's general condition and presence of co-morbidity using American Society of Anesthesiology classification. Moreover, re-bleeding is used as a parameter in PNED scoring system unlike other scoring systems.

The limitation of this score is that it is necessary to re-calculate after re-bleeding. Thus, PNED score is difficult to use at admission, since re-bleeding usually occurs within three days after initial presentation. Rockall score seems to be more suitable for predicting mortality at admission.

One important difference in our study is the significant difference between PNED and AIMS65 scores, which is in contrast with other literature[20]. This is probably due to exclusion of variceal bleeding patients, and AIMS65 is a well-established prognostic model in cirrhotic patients with variceal bleeding[27,28]. In addition, we observed 30-day as well as in-hospital mortality. In fact, AIMS65 score accurately predicts in-hospital mortality[14,15].

In this study, cut off for admission Rockall, full Rockall, PNED and AIMS65 are 2, 4, 3, and 1, which are lower than those reported in a previous study[20]. It is due to differences in inclusion criteria, etiology of UGIB and patient's demography. We also considered cut off associated with sensitivity to be more important than specificity. Forrest score has the worst performance prediction of mortality and it suggests mortality is not closely associated with endoscopic findings. It suggests serious co-morbidities increase the risk of mortality rather than bleeding itself.

There are some limitations to this study. First, it was performed in a single institution. Secondly, the calculation of mortality only referred to the time of hospital admission and 30-day follow-up. Further follow-up of the patients for 60 days and one year is required.

CONCLUSION

Forrest score is the best at predicting re-bleeding and PNED score as it predicts mortality for patients with NVUGIB with high accuracy.

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Original Article

Electromechanical delay and 4-chamber longitudinal strain in patients with obstructive sleep apnea

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ABSTRACT

Objectives: The aim of this study was to evaluate atrial electromechanical delay (AEMD), apical 4-chamber longitudinal strain (4C-LS) and echocardiographic changes in patients with obstructive sleep apnea (OSA).
Design: Prospective cross-sectional study
Setting: Secondary care hospital
Subjects: Forty-six patients (32 male, 14 female) who were diagnosed as mild-to-severe OSA (apnea hypopnea index ≥5 events/h) and control group consisted of 35 healthy subjects (18 male, 17 female)
Intervention: Polysomnography, blood samples and transthoracic echocardiograhy (TTE) were evaluated
Main outcome measures: TTE was used to evaluate echocardiographic changes, AEMD and 4C-LS
Results: Left ventricle end-diastolic and end-systolic diameter, interventricular septum and posterior wall thickness were significantly higher; left ventricular ejection fraction and Ea/Aa mitral ratio were lower; right ventricle basal, mid and vertical diameters, Emax, Amax, and Ea tricuspid, tricuspid regurgitan velocity, systolic pulmonary artery pressure, and systolic motion tricuspid were significantly higher in the OSA group. Tricuspid annular plane systolic excursion (TAPSE) was significantly lower and AEMD lateral/tricuspid, lateral/mitral and septal were significantly higher in the OSA group. Mid anterolateral, apicolateral, apex, apical septal strains and 4C-LS were decreased significantly in the OSA group
Conclusion: Right-left ventricular systolic-diastolic functions were impaired in patients with OSA. In these patients, apical 4C-LS was lower and AEMD was prolonged.

KEY WORDS: atrial electromechanical delay, longitudinal strain, obstructive sleep apnea

INTRODUCTION

Obstructive sleep apnea (OSA) is a serious, life-threatening and common chronic disease affecting particularly middle-aged men in the populations[1,2]. OSA is characterized by repetitive surcease episodes of breathing while sleeping, by the reason of complete or partial airway obstruction[1,2]. Hypoxia and hypercapnia caused by OSA increases the arousal of the patient throughout the night[3]. These arousals associated with hypoxia and hypercapnia stimulate the sympathetic nervous system, increase catecholamine release and myocardial oxygen consumption[3]. Increased myocardial oxygen consumption causes cardiac ischemia, myocardial infarction, hypertrophy, hypertension, increase in left ventricle wall tension, congestive heart failure, arrhythmias such as atrial fibrillation and stroke[3,4]. Cardiovascular complications are the most common complications of OSA. Echocardiography is the gold standard noninvasive imaging method for evaluating myocardial functions of these type of patients and assessing the effects of OSA on heart[5].

Atrial electromechanical delay (AEMD) is the time interval between the beginning of P wave on surface electrocardiography and beginning of the late diastolic wave on Tissue Doppler Imaging (TDI)[6]. The

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structural changes of atrial tissue cause delay between the electrical stimulation and mechanical contraction[6]. Atrial tissue changes can cause prolongation of P wave on surface electrocardiogram[7]. Prolongation of P wave can be seen in patients undergoing coronary artery bypass surgery, patients with hypertrophic cardiomyopathy, right atrial dilatation, atrial septal defect hypertension and chronic obstructive pulmonary disease due to affected atrial tissue[7].

Two-dimensional speckle tracking echocardiography is a strain measurement method to obtain the size of regional myocardial deformations[8,9]. Myocardial deformations can be obtained by this easily applied method in the longitudinal, circumferential and radial pointing[8,9].

The aim of this study was to evaluate AEMD, apical 4-chamber longitudinal strain (4C-LS) and echocardiographic changes in patients with OSA. We especially focused on AEMD, longitudinal strain and diastolic-systolic functions of right-left heart in these patients.

SUBJECTS AND METHODS

Study population

This prospective study was conducted with the approval of the Caucasian University Medical Faculty ethics committee between April and August 2018. The patient group consisted of 46 patients (32 male, 14 female) who were referred to the Sleep Disorders Center of Caucasian University Hospital and were diagnosed as mild-to-severe OSA (apnea hypopnea index (AHI) ≥5 events/h) on polysomnographic evaluation. The control group consisted of 35 healthy subjects (18 male, 17 female) who were found not to have OSA (AHI <5 events/h) on polysomnographic evaluation.

The exclusion criteria were as follows: chronic obstructive pulmonary disease on pulmonary function tests, patients with valvular and structural heart disease, wall-motion abnormality, coronary artery disease, acute coronary syndrome, heart failure, atrioventricular conduction abnormalities, previous history of atrial fibrillation, ejection fraction <50%, use of drugs that affect atrioventricular conduction system, uncontrolled hypertension, pulmonary embolism, pneumonia, insulin dependent diabetes mellitus, history of cerebrovascular disease, history of continuous positive airway pressure, renal impairment, hypo-hyperthyroidism, anemia, electrolyte disorders, acid-base disorders, malignancy, patients using two or more oral antidiabetic drugs, systemic inflammatory response syndrome, poor echocardiographic view.

The following parameters of all patients were evaluated: age, gender, body mass index, comorbidity, blood glucose, electrolytes, liver function tests, renal function tests, complete blood count, transthoracic echocardiography and polysomnography. All patients were informed about the study. An informed and signed consent was obtained for all procedures.

Blood samples

All blood samples were drawn from the vein in the forearm and collected into 2 mL Lavender (EDTA) top tube and 5 mL Yellow top tube were analyzed with Pentra DF Nexus, Horiba Medical, Japan with Automated Cell Counter Methodology and Cobas C 501, Roche. The complete blood samples were stabilized optimally when run within four hours of collection, stable for 24 hours at room temperature, and stable for 36 hours at 2-8 °C. The biochemical blood samples were stabilized optimally when run within two hours of collection, stable for 24 hours at +4° C.

Polysomnography

Overnight polysomnography was performed in all patients using conventional and analysis according to the American Academy of Sleep Medicine[10]. All patients spent one entire night in the sleep laboratory with the aim of capturing a typical night's sleep. The wakefulness, sleep stages, respiration, cardiopulmonary functions and body movements of patients were evaluated. Electroencephalography, electro-oculography and chin muscle electromyography channels were used to monitor sleep stages. Airflow and respiratory effort channels were used to assess sleep-disordered breathing. Arterial oxygen saturation was measured with finger pulse oximetry channel. Movement changes of the chest and abdomen during breathing were recorded by using respiratory inductive plethysmography. Limb electromyogram channels were placed on the legs (tibialis anterior muscle) and evaluated periodical limb movements. An oronasal flow cannula attached to pneumotachograph and apneas-hypopneas. Apneas were defined as the cut-off of airflow for more than ≥10 s. Hypopnea were defined as peak signal excursion drop by ≥30% of pre-event baseline using nasal pressure, duration of the ≥30% drop in signal excursion is ≥10 seconds and ≥3% oxygen desaturation from pre-event baseline and/or the event is associated with an arousal[11]. The AHI was obtained by dividing the total number of apneas and hypopneas during the entire sleeping time. OSA classification was made according to American Academy of Sleep Medicine: mild OSA was defined as AHI of 5-15, moderate OSA was defined as AHI of 15-30 and severe OSA was defined AHI of more than 30[10].

Echocardiography

Transthoracic echocardiography (Epiq 7; Philips) was evaluated by a practitioner in a standard protocol in all patients. A 2.5 MHz probe was used for the Doppler measurements and 2.5-3.5 MHz probe for tissue Doppler measurements. Patients were monitored using electrocardiographic leads and were placed in the left lateral decubitus position. Echocardiographic images were obtained from the parasternal views (long axis, short axis), the apical four-chamber view and the subcostal view. Echocardiographic measurements were performed at the end of expiration according to the recommendations of the American Society of Echocardiography/European Association of Echocardiography[12]. 1) diameters of right ventricle (RV) measured in apical view; 2) left ventricle (LV) diameter and wall thickness were measured in the parasternal view; 3) left atrial diameter measured in the parasternal view; 4) aortic root diameters, measured at the sinus of Valsalva; 5) LV ejection fraction measured in apical 4-chamber view by modified Simpson method; 6) RV and LV functions were evaluated as follows: a) maximal peak velocity of early diastolic flow (Emax), maximal peak velocity of atrial contraction (Amax), and ratio of these (Emax/Amax), measured over the mitral and tricuspid valves; b) TDI measured in the mitral and tricuspid lateral annulus at early diastole (Ea), atrium systole (Aa) and ratio of these (Ea/Aa); c) the ratio of Emax/Ea; 7) aortic, tricuspid, mitral and pulmonary valvular evaluation; 8) tricuspid regurgitant velocity (TRV) recorded by continuous wave Doppler.

AEMD was calculated from colored-TDI recordings. AEMD was determined as the time interval between the beginning of echocardiographic P wave to the initial of late diastolic wave in TDI recordings. AEMD was measured from lateral/tricuspid, lateral/mitral and septal anulus from apical 4-chamber views.

The echocardiographic examinations and standard 2D measurements for strain were acquired according to American Society of Echocardiography recommendations[12]. The images were digitally stored and measurements were performed by the same practitioner. Images were obtained at a frame rate of 50 to 70 per second, and digital loops were saved onto optical disc for off-line analysis. The cardiac cycle with the best image quality and without any artefacts was selected for reporting results. Two and three-chambers images were not used due to intense artefacts. Apical 4-chamber longitudinal strain images were obtained. The practitioner identified three points on each view (two borders of the mitral annulus and the apex). Speckles were tracked frame by-frame throughout the LV wall during the cardiac cycle and basal, mid, and apical regions of interest were created.

Table 1: Clinical characteristics of the study population

Clinical Profile	OSA (n=46) Mean±SD / n (%)	Controls (n=35) Mean±SD / n (%)	*P*-value
Age	49.3±10.5	48.3±5.1	NS
Gender			
Male	32 (69.6%)	18 (51.4%)	NS
Female	14 (30.4%)	17 (48.6%)	NS
BMI (kg/m^2)	35.67±5.77	28.41±4.1	<0.001
Comorbidities			
Hypertension	28 (60.9%)	3 (8.6%)	<0.001
Diabetes Mellitus	-	1 (2.9%)	NS
Hyperlipidemia	6 (13%)	1 (2.9%)	NS

OSA: obstructive sleep apnea; continuous variables are expressed as mean ± standard deviation; NS: non-significant; BMI: body mass index.

Statistical analysis

All statistical calculations were performed with SPSS 23.0 (SPSS for Windows, Chicago, IL, SA). All continuous variables were expressed as mean±standard deviation; categoric variables were defined as percentages (%). The categorical parameters were compared with Chi Square test and Fischer's exact test. The normal distribution was determined by histogram and Kolmogorov-Smirnov test. Mean values of continuous variables were compared between the groups using Mann-Whitney U test. All tests were applied as two tailed; the statistical significance level was P <0.05.

RESULTS

Baseline clinical characteristics of the study population are presented in Table 1. Body mass index

Table 2: Biochemical parameters of the study population

Biochemical parameters	OSA (Mean±SD)	Controls (Mean±SD)	*P*-value
Glucose	108.1±15.5	98.5±11.8	0.007
Urea	35.6±9.2	30±7.4	0.001
Creatinine	0.87±0.16	0.72±0.19	0.001
Uric acid	6.22±1.3	4.89±1.57	<0.001
HDL	42.6±8.2	48.9±12.6	0.048
Triglyceride	176±61	170.6±80.7	NS
C-reactive protein	0.59±0.87	0.37±0.33	NS
Albumin	4.31±0.33	4.59±0.24	<0.001
AST	24.5±8.2	20.1±8.6	0.018
ALT	33.6±15.2	21.6±14.3	<0.001
LDH	188±36.6	198.9±40.1	NS
Calcium	9.5±0.3	9±0.4	NS
Sodium	140.7±3.2	140.5±1.9	NS
Potassium	4.49±0.35	4.42±0.34	NS
ALP	82.4±24.8	100.5±13.4	NS
Total Bilirubin	0.43±0.21	0.46±0.24	NS
Protein	7.07±1.68	7.34±0.45	NS

OSA: obstructive sleep apnea; continuous variables are expressed as mean ± standard deviation; NS: non-significant; HDL: high density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase.

Table 3: Complete blood counts of the study population

Biochemical parameters	OSA (Mean±SD)	Controls (Mean±SD)	*P*-value
Hemoglobin (mg/dL)	15.9±1.44	15.02±1.26	0.011
Hematocrit	48.05±4.4	45.15±3.5	0.002
WBC	7.86±1.87	7.38±2.18	NS
MPV	8.44±0.58	8.91±0.79	0.006
Platelet count	262.4±58.8	259.4±57	NS
Lymphocyte count	2.36±0.73	2.34±0.63	NS
Lymphocyte percent	31.03±8.95	32.47±7.12	NS
PLR	122±47.32	118.83±41.94	NS
Neutrophil count	4.61±1.36	4.26±1.7	NS
Neutrophil percent	58.91±7.81	56.82±8.13	NS
NLR	2.17±1.08	1.91±0.85	NS
Eosinophil count	0.26±0.15	0.21±0.29	0.002
Eosinophil percent	3.16±1.42	2.77±2.99	0.009
RDW	15.4±1.98	15.12±1.23	NS
PCT	0.22±0.06	0.23±0.04	NS

OSA: obstructive sleep apnea; continuous variables are expressed as mean ± standard deviation; NS: non-significant; WBC: white blood cell; MPV: mean platelet volume; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; RDW: red blood cell distribution width; PCT: plateletcrit

and number of patients with hypertension were higher in the OSA group (P <0.001).

Biochemical blood parameters of the study population are presented in Table 2. Glucose levels, urea, creatinine, uric acid, aspartate transaminase and alanine aminotransferase were higher significantly in the OSA group.

Complete blood counts of the study population are presented in Table 3. Hemoglobin, hematocrit, eosinophil count and percentage were significantly higher in the OSA group.

Conventional and tissue Doppler echocardiographic parameters of left heart and septum for two groups are shown in Table 4. LV end-diastolic diameter, end-systolic diameter, interventricular septum and posterior wall thickness were significantly higher in the OSA group (P <0.05). LV ejection fraction and Ea/Aa mitral ratio were lower in the OSA group.

Conventional and tissue Doppler echocardiographic parameters of right heart for two groups are shown in Table 5. Right ventricle basal, mid

Table 4: Echocardiographic findings of the left heart and septum in both groups

Left heart and septum	OSA (Mean±SD)	Controls (Mean±SD)	*P*-value
Left heart			
Dimensions			
Left atrium (parasternal long axis)			
Diameter (mm)	38±0.38	35.2±3.1	0.007
Left ventricle (parasternal long axis)			
End-diastolic diameter (mm)	49.4±0.42	46.2±3.9	0.004
End-systolic diameter (mm)	31±0.36	26.6±0.31	<0.001
Left ventricle wall thickness			
Interventricular septum (mm)	11.8±1.4	10.7±1.3	<0.001
Posterior wall (mm)	10.5±1.4	9.6±1.2	0.003
Ventricular function			
Systolic function			
LV ejection fraction (%)	58.27±5.54	61.73±3.31	0.008
Diastolic function			
Emax mitral (cm/s)	74.59±16.57	70.18±13.62	NS
Amax mitral (cm/s)	75.96±12.33	70.43±19.13	NS
Emax/Amax mitral	1.01±0.27	1.33±1.94	NS
Ea (tissue doppler lateral mitral) (cm/s)	10.93±3.48	11.25±3.06	NS
Aa (tissue doppler lateral mitral) (cm/s)	12.34±3.28	11.38±2.46	NS
Ea/Aa mitral	0.65±0.24	0.78±0.29	<0.001
Emax/Aa	0.97±0.45	1.05±0.42	NS
Emax/Ea	7.32±2.13	6.69±2.48	NS
Mitral E wave decelaration time (ms)	153.9±21.6	145.1±24.7	NS
Aortic root diameter (cm)	3.52±0.25	3.41±0.33	NS
Septum			
Ea (tissue doppler septal) (cm/s)	7.41±1.63	7.7±2.7	NS
Aa (tissue doppler septal) (cm/s)	11±2.12	10.77±2.6	NS
Ea/Aa septal	0.71±0.27	0.76±0.35	NS
Emax/Ea	1.08±0.54	1.01±0.71	NS
Systolic motion mitral	9.91±3.11	8.99±1.98	NS
Systolic motion septal	8.42±1.47	7.78±1.35	NS
Heart rate, beats/min	76.6±8.8	73.6±10.1	NS

OSA: obstructive sleep apnea; continuous variables are expressed as mean ± standard deviation; NS: non-significant; LV: left ventricle.

Table 5: Echocardiographic findings of the right heart in both groups

Right heart	OSA (Mean±SD)	Controls (Mean±SD)	*P*-value
Right Heart			
Dimensions			
Right ventricle (mm)			
Basal			
Mid	35.8±4.5	32.4±4	0.001
Vertical	23.7±3.4	21.6±4.4	0.007
TAPSE (mm)	58.1±5.9	54.2±4.6	0.002
Ventricular function	23.3±0.27	27.6±2.8	<0.001
Diastolic function			
Emax tricuspid (cm/s)			
Amax tricuspid (cm/s)	57.39±11.09	52.59±8.11	0.009
Emax/Amax tricuspid	55.87±14.97	47.32±8.71	0.007
Ea (tissue doppler tricuspid) (cm/s)	1.11±0.39	1.14±0.23	NS
Aa (tissue doppler tricuspid) (cm/s)	10.35±2.55	9.38±2.52	0.048
Ea/Aa tricuspid	13.75±3.52	13.84±3.1	NS
Emax/Ea	0.82±0.34	0.72±0.29	NS
Assessment of pulmonary hypertension	5.8±1.51	5.91±1.49	NS
TRV (m/s)	2.412±0.429	2.217±0.306	0.030
Systolic pulmonary arterial pressure (mmHg)	24.1±8.3	20.1±5.5	0.034

COPD: chronic obstructive pulmonary disease; continuous variables are expressed as mean ± standard deviation; NS: non-significant; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitant velocity

and vertical diameters, Emax, Amax and Ea tricuspid, TRV, systolic pulmonary artery pressure and systolic motion tricuspid were significantly higher in the OSA group. Tricuspid annular plane systolic excursion (TAPSE) was significantly lower in the OSA group compared to healthy subjects (*P* <0.001).

Colored-TDI measurements of AEMD and two-dimensional speckle tracking echocardiography measurements of apical 4C-LS for two groups are presented in Table 6**.** AEMD lateral/tricuspid, lateral/mitral and septal were significantly higher in the OSA group (*P* <0.001). Mid anterolateral, apicolateral, apex, apical septal strains and 4C-LS were decreased significantly in the OSA group (*P* <0.001).

Polysomnography findings of OSA patients according to classifications are presented in Table 7. AHI and hypopnea significantly differed between three groups (*P* <0.001).

Table 6. Atrial conduction times and apical 4-chamber longitudinal strains are both groups

Atrial conduction times and strains	OSA (Mean±SD)	Controls (Mean±SD)	*P*-value
Atrial electromechanical delay			
Lateral/tricuspid (msec)	26.4±9	16.9±8.9	<0.001
Lateral/mitral (msec)	62.7±12	38.6±14.6	<0.001
Septal (msec)	41.5±8.8	22.4±10.1	<0.001
Longitudinal strain			
Basal Anterolateral	-20±3.3	-20.9±3.3	NS
Mid Anterolateral	-17.3±3.6	-20.1±3	<0.001
Apicolateral	-18.8±3.3	-21.8±2.3	<0.001
Apex	-21.7±3.3	-25.5±2.5	<0.001
Apical Septal	-24.7±4.2	-28.8±4.1	<0.001
Mid Inferoseptal	-14.7±4.9	-16.4±4.2	NS
Basal Inferoseptal	-15.2±2.4	-15±2.5	NS
4C-LS	-18.69±2.16	-21.07±1.93	<0.001

OSA: obstructive sleep apnea; continuous variables are expressed as mean ± standard deviation; NS: non-significant; 4C-LS: 4-chamber longitudinal strain

DISCUSSION

OSA is a well-known disease with numerous systemic complications, which can cause cardiovascular diseases in multifold phases and pathological pathways[13]. In OSA patients, apnea-hypopnea periods revealed by partial and complete airway obstruction cause sleep fragmentations[14-16]. In patients with OSA, hypoxia and hypercapnia-induced sustained sympathetic nervous system activation, low-grade chronic inflammation, oxidative stress and vascular inflammation are the main mechanisms that explain cardiac diseases[2,17]. In this study, cardiac changes caused by OSA were evaluated by echocardiography.

Our results suggest that LV end-diastolic and end-systolic diameters, interventricular septum and posterior wall thickness were significantly higher in patients with OSA. LV ejection fraction and Ea/Aa mitral ratio known as early diastole/atrium systole were lower in these patients. There was an increase in both LV hypertrophy and LV diameters in patients with OSA. The increase in LV end-diastolic diameter was associated with lower ejection fraction. Ea/Aa, which is the indicator of diastolic function, was lower in patients with OSA. Hypoxia and hypercapnia periods

Table 7: Polysomnographic findings of the OSA group according to classification

Polysomnographic findings	OSA Classification			*P*-value		
	Mild OSA (n=8) Mean±SD / n (%)	Moderate OSA (n=6) Mean±SD / n (%)	Severe OSA (n=32) Mean±SD / n (%)	Mild vs. Moderate	Mild vs. Severe	Moderate vs. Severe
Sleep latency (minute)	27.75±14.51	49.67±21.75	18.38±18.39	0.037	NS	0.002
Sleep efficiency (%)	78.3±9.66	73.47±17.57	81.83±13.97	NS	NS	NS
AHI	9.6±2.77	23.33±3.25	52.13±21.81	0.002	<0.001	<0.001
Obstructive apnea	0.93±0.46	2.53±3.08	11.34±15.13	NS	0.004	0.045
Central apnea	0.43±0.46	0.5±0.63	2.42±2.89	NS	0.010	0.016
Mix apnea	0±0	0±0	2.13±5.45	NS	0.026	NS
Mean oxygen saturation	88.08±3.44	88.1±4.13	89.22±4.23	NS	NS	NS
Minimum oxygen saturation	70.25±12.41	73.67±14.46	71.25±12.07	NS	NS	NS
Hypoapnea	7.98±1.88	20.3±0.78	36.18±12.93	0.002	<0.001	<0.001

OSA: obstructive sleep apnea; continuous variables are expressed as mean ± standard deviation; NS: non-significant; AHI: apnea/hypopnea index

may influence the proportion in myocardial oxygen requirement and supplement[17]. Myocardial ischemia, oxidative stress and activation of sympathetic nervous system increase left ventricular afterload and decrease in left ventricular preload[17,18]. OSA may impair LV function and additively LV hypertrophy is associated with elevated blood pressure levels during sleep[18].

In this study, right ventricle basal, mid and vertical diameters, Emax, Amax and Ea tricuspid, tricuspid regurgitant velocity, and systolic pulmonary artery pressure were significantly higher in patients with OSA. TAPSE was significantly lower in the OSA group. The diameters and TAPSE were used to evaluate RV systolic functions. Increased basal diameter and decreased TAPSE were indicative of RV systolic dysfunction. Although Emax/Amax, which is a diastolic function indicator, insignificantly decreased in patients with OSA. A larger scale working group is needed. Increased TRV and systolic pulmonary artery pressure showed increased pulmonary artery pressure. In OSA patients, pulmonary vasoconstriction secondary to hypoxia period may contribute to pulmonary hypertension, and this hypertension leads to right ventricular dysfunction and hypertrophy[19,20]. TAPSE is a measurement for RV function and it gives information about RV ejection fraction[21].

In the present study, we found that lateral/tricuspid, lateral/mitral and septal AEMD were significantly higher in patients with OSA. The prolongation of AEMD was an expected result for patients with OSA. AEMD is known as the time interval between the intervals between the atrial depolarization and the beginning of atrial mechanical contraction[22]. Prolonged AEMD is predisposed to atrial fibrillation[22]. In OSA patients, repetitive forced inspiration against an obstructed airway may cause a negative intrathoracic pressure that may lead to elevated cardiac afterload, increased atrial dimension, wall tension and resulting atrial remodeling[14]. Autonomic nervous system irregularity with elevated-depressed heart rates triggered by hypoxemia, hypercapnia and acidosis may stimulate electrical changes in atrium[14]. Structural remodeling of the heart with increased left atrial dilatation and increased fibrosis of tissue caused by intrathoracic pressure shift is another mechanism for prolonged AEMD[23,24]. The nightlong renin-angiotensin system fluctuations and increased aldosterone in OSA patients also may precipitate resistant hypertension and atrial fibrillation[25,26]. As in similar study samples, AEMD prolongs significantly in patients with mild-to-severe OSA[27,28].

The basal longitudinal strain measurements such as mid anterolateral, apicolateral, apex, apical septal and 4C-LS we used to evaluate left ventricular myocardial function were significantly low in patients with OSA compared to healthy subjects. Ventricular strain and strain rates, which are deformation indicator of myocardium, are used for to measure ventricular dysfunction[29]. The LV consists of three non-homogenous fiber layers. Reverse positioning of subendocardial and subepicardial layer fibers is important for redistribution of the strain in the heart. Heterogenous deterioration of basal, middle and apical ventricular segments provide coordinated ventricular contraction. This LV contraction, which shows strain of the heart, can be impaired after decreased arterial oxygen saturation and increased negative intrathoracic pressure[30,31]. Nocturnal pulse oximetry, which is a method for monitoring the arterial blood oxygen saturation, can demonstrate significant changes in patients with OSA due to recurrent apnea periods[32]. Hypoxia with apnea episodes may lead to decreased myocardial oxygenation, decreased LV contraction and decreased strain. Longitudinal strain reduction is expected in patients with OSA and there are studies supporting this result[5,8,33].

The small number of patients and the presence of longitudinal strain images in only 4-chamber due to artefacts are the main limitations of the study. The patients were enrolled from only one sleep center, hence limiting the variegation of the patients.

CONCLUSION

This study revealed that OSA is a disease that can impair the left-right ventricular systolic-diastolic functions of the heart and it may cause structural changes in the heart. Moreover, OSA may cause prolongation of atrial conduction times and it may decrease the contraction forces of the heart.

This prospective clinical study is important because of the combined evaluation right-left ventricular functions, AEMD and longitudinal strain.

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Original Article

Single tertiary center experience from Turkey regarding the experience for cardiac implantable electrical devices

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ABSTRACT

Objective: To present our experience of cardiac implantable electrical devices (CIED) implantation and complications in a tertiary referral centre and to compare these data with literature
Design: Retrospective observational study
Setting: Izmir Katip Çelebi Universty, Ataturk Research and Education Hospital, Turkey
Subjects: One thousand two hundred and nine de-novo CIED patients and 50 patients who underwent revision and battery exchange procedures
Intervention: Hospital records were scanned.
Main outcome measures: Compared to most other studies in literature, the population of this study was younger. The complication rate of cardiac resynchronization therapy (CRT) implantation was low, but the actual cause of six of the 10 mortalities could not be determined.
Results: 38.6% (n=486) of patients had a cardiac pacemaker (CPM), 53.6% (n=675) an implantable cardioverter-defibrillators (ICD), and 7.8% (n=98) had CRT-D. The mean age of patients was 63.9±14.8 years and 66.8% (n=842) were male. The main indication for ICDs was primary prevention in 715 (56.8%) patients. The main indications for CPM implantation were as follows: 234 (18.6%) complete atrioventricular block and 83 (6.6%) sick sinus syndrome. The mean left ventricular ejection fraction value was 39.5%±16.5 before CIED implantation and 40.1%±%16.1 after CIED implantation. Device infection was determined at 2.1% (n=27); pocket infection at 1.7% (21), pneumothorax at 0.6% (n=7) and tamponade at 30.3% (n=3). The rate of pocket hematoma was 3.4% (n=42). Mortality occurred in 10 patients. Subclavian thrombus developed in three patients, shock in 773 and lead dysfunction in 70 patients.
Conclusion: In contrast to general knowledge, no gender difference was determined in terms of complication rates, which were also lower than literature rates, despite operation complexity. Therefore, these data present different knowledge from the data available in literature.

KEY WORDS: cardiac implantable electrical devices, complication, implantable cardioverter defibrillator, pacemaker

INTRODUCTION

Under appropriate indications, cardiac pacemakers (CPM), implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT), under the collective term of cardiac implantable electrical devices (CIED), have been applied in increasing numbers due to low associated risks and favorable outcomes. With increasing ageing populations worldwide, there has been a parallel increase in the prevalence of CIEDs[1]. As a result of the rapidly expanding number of patients and developments in technology, ~1 million transvenous CIEDs are now implanted annually worldwide[2].

Since CPM was first introduced in 1958, CIEDs have undergone great technological advances[3]. Nevertheless, despite the increasing complexity and the development of numerous features, the issues of CIEDs have remained similar. Indications for CIED are chronotropic incompetence or prevention of malignant arryhthmia, and complications may be acute, related to implantation, or long-term, related to the pulse generator or lead[4].

The aim of this study was to present the experience of CIED implantation and associated problems during follow-up in a tertiary health centre in Turkey.

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SUBJECTS AND METHODS

Patient selection

A retrospective review was made of patients who underwent CIED implantation between January 2007 and June 2018. The cases in the study cohort were predominantly those implanted with a first cardiac device, and cases of revision and battery exchange procedures were a minority. All patient data were retrieved from the hospital medical report system archive.

For each patient, a record was made of gender, age at pacemaker implantation, indication, type and working mode of CIED, complication rates with associated causes, treatment and results, pocket hematomas, comorbid coronary arterial disease (CAD), arterial hypertension (HT), diabetes mellitus (DM), and left vetricular ejection fraction (LVEF) values before and after CIED implantation. CAD was defined as a history of coronary stent, coronary arterial by-pass grafting, non-critical CAD (<50% lesion on coronary angiography), and no CAD was defined as normal coronary artery on coronary angiography. Comorbid HT and DM were defined as regulated blood pressure or blood glucose, respectively, with the use of at least one drug.

Anticoagulant therapies were classified as warfarin, rivaroxaban, apixaban, dabigatran or edoxaban, and anti-aggregant therapies as acetylsalicylic acid, clopidogrel, ticagrelor, prasugrel and acetylsalicylic acid combination therapies.

Data were recorded with regard to application of therapy on ICD-enabled devices and the details of which arrhythmias (ventricular tachycardia (VT), ventricular fibrillation (VF), supraventricular tachycardia (SVT), atrial fibrillation (AF)) were treated before any shock therapy, and a separate record was made of appropriate (VT-VF) or inappropriate shocking (SVT-AF).

The LVEF values before CIED were accepted as persistent LVEF rate for at least three months, and LVEF of patients with a minimum value of one year after the procedure was accepted as the value after the CIED. Patients with no LVEF record at one year after the procedure were excluded from the study.

Data were also collected related to pocket hematomas, lead dysfunctions, pocket or lead infections, upgrade (CPM to ICD, CPM or ICD to CRT-D), revision (lead or pocket problems) or extraction procedures of CIEDs.

Approval for the study was granted by the Local Ethics Committee with decision date 26-09-2019 and number 400. All procedures were performed following patient verbal and/or written informed consent.

Statistical analysis

Data obtained in the study were analysed statistically using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were stated as mean ± standard deviation, median and range. Categorical variables were stated as number (n) and percentage (%). A value of P <0.05 was considered statistically significant.

RESULTS

The study sample comprised 1209 patients with first application of CIED and 50 patients who underwent revision and battery exchange procedures.

In the total study population, 38.6% (n=486) of patients had a CPM, 53.6% (n=675) had an ICD, and 7.8% (n=98) had a biventricular ICD (CRT-D) (Table 1). In the distribution of these CIEDs, 15.1% (n=190) of patients had dual chamber CPM (DDD-CPM),

Table 1: General data and comorbid diseases of patients

Variable	CIED without defibrillation function	CIED with defibrillation function		Total	*P*-value
	CPMs	ICDs	CRT-Ds		
Number of patients	486	675	98	1259	
Mean age (years)	58.9±12.1	71.1±15.1	60.0±10.4	63.9 ± 14.8	<0.001
Gender (Male/Female)	234/252	540/135	68/30	842/417	<0.001
HT	396	306	77	779	0.07
DM	115	87	19	221	0.94
CAD					<0.001
Normal coronary	123	64	29	216	
Non-critical CAD	102	75	26	203	
Operated CABG	136	33	16	185	
Inoperable multiple vessel-serious CAD	198	61	18	277	

CIED: cardiac implantable electronic device; CPM: cardiac pacemaker; ICD: implantable cardioverter defibrillator; CRT: cardiac resynchronization therapy; HT: arterial hypertension; DM: diabetes mellitus, CAD: coronary arterial disease; CABG: coronary arterial by-pass grafting

10.2% (n=129) had single chamber CPM (VVI-CPM), 13.3% (n=167) had single chamber with atrial sense (VDD-CPM), 53.3% (n=462) had single ventricular chamber ICD (VVI-ICD), 16.6% (n=209) had dual chamber ICD (DDD-ICD), and 0.3% (n=4) of patients had single chamber ICD with atrial sense (VDD-ICD). The mean number of leads for each patient was 1.47±0.63 (Table 2).

The mean age of the whole cohort was 63.9±14.8 years, and male gender was dominant at 66.8% (n=842). The mean age was 58.9±12.1 years in the CPM group, 71.1±15.1 years in the ICD group and 60.0±10.4 years in the CRT group. The mean age was determined to be similar in the CPM and CRT groups, and a statistically significant difference was determined in the ICD group (P <0.001) (Table 1).

Table 2: Mode of CIEDs

CIED	Number, percentage
VVI-CPM	n:129; 10.2
DDD-CPM	n:190; 15.1
VDD-CPM	n:167; 13.3
VVI-ICD	n:462; 53.3
DDD-ICD	n:209: 16.6
VDD-ICD	n:4; 0.3
CRT-ICD	n:98; 7.8

CIED: cardiac implantable electronic device; CPM: cardiac pacemaker; ICD: implantable cardioverter defibrillator

Of the patients with ICD implantation, 56.8% (n=715) had an indication for primary prevention of malignant arrhythmia and 4.0% (n=50) had an indication for secondary prevention after a documented malignant arrhythmia.

The CPM implantation indications were as follows: 18.6% (n=234) complete atrioventricular (AV) block, 6.6% (n=83) sick sinus syndrome (SSS), 3.6% (n=46) symptomatic sinus bradycardia, 3.3% (n=41) Mobitz type 2 AV block, 1.4% (n=17) junctional rhythm, 0.8% (n:10) symptomatic atrial fibrillation with slow ventricular response, 0.4% (n=5) cardio-inhibitory syncope, 0.3% (n=4) symptomatic carotid sinus hypersensitivity, and 0.3% (n=4) Mobitz type 1 AV block (Table 3). Of this CPM group, complete AV block persisted in two patients after percutaneous coronary intervention, in two patients after electrophysiology, and in two patients after myocardial infarction.

In these indications, there were some intersecting sets. In the CRT-D group, implantation indication was left ventricular bundle block + LVEF≤ 35 + symptomatic sinus bradycardia in two patients and complete AV block with indication for primary prevention in five patients. Due to coronary sinus stenosis, four patients underwent coronary sinus balloon dilation.

Table 3: CIED procedure indications

Variable	Number	Percentage
Complete AV block	234	18.6
ICD primary prevention	715	56.8
Sick sinus syndrome	83	6.6
ICD secondary prevention	50	4.0
Symptomatic sinus bradycardia	46	3.6
Mobitz type 2 AV block	41	3.3
CIED revision	32	2.5
ERI/EOL. CIED Replacement	18	1.4
Junctional rhythm	17	1.4
Symptomatic atrial fibrillation with slow ventricular response	10	0.8
Cardio-inhibitory syncope	5	0.4
Mobitz type 1 AV block	4	0.3
Carotid sinus hypersensitivity	4	0.3
Total	1259	100.0

AV: atrioventrıcular; ICD: implantable cardioverter defibrillator; EOL: end of life; ERI: elective replacement indication; CIED: cardiac implantable electronic devices

In the whole CIED group, 2.5% (n=32) of patients underwent a pacemaker revision procedure and 1.4% (n=18) of patients underwent CIED battery exchange due to replacement indication (Table 3).

The mean LVEF value before CIED implantation was 39.5±16.5%, and mean LVEF value at one year after CIED implantation was 40.1±16.1% for all groups. There was no statistical difference. For the ICD and CRT-D patients, who had a CIED implantation for primary prevention, the mean LVEF value was 28.07±9.73% before CIED implantation, and the mean LVEF increased to 29.22±10.09% after CIED implantation (P<0.001). There was a statistically significant difference regarding LVEF increase for these groups, but not at a level to indicate changing the ICD implantation.

Arterial hypertension was the most frequent comorbid disease at 61.9% (n=779), DM was detected at the rate of 17.6% (n=221), and CAD at 59.2% (n=745). The clinical distribution of CAD was as follows: non-critical CAD 16.1% (n=203), coronary arterial by-pass grafting history 14.7% (n=185), coronary stent implantation 22% (n=277), and inoperable multiple vessel, serious CAD history 6.4% (n=80). In 17.2% (n=216) of patients, the coronary artery was observed to be normal on coronary angiography. No statistically significant difference was determined between all the groups (CPMs, ICDs, CRT-Ds) in respect of DM comorbidity, but for CAD and HT, there were statistically low rates in the CPM group (P=0.94 for DM, P <0.001 for CAD, P=0.07 for HT) (Table 1).

In respect of complications, local infections, such as device infections needing extraction of all the leads, the generator and antibiotic therapy were seen in 2.1% (n=27) of the patients. Pocket infection requiring

hospitalization with treatment of IV or oral antibiotherapy only was determined in 1.7% (n=21) of patients, pneumothorax in 0.6% (n=7) and pericardial/cardiac tamponade in 0.3% (n=3). No statistically significant difference was determined between the groups in respect of pneumothorax and pericardial/cardiac tamponade complications (CPMs, ICDs, CRT-Ds) (*P*=0.75 for pneumothorax, *P*=0.32 for tamponade). Both local and device infections were determined at statistically significantly lower rates in the CRT-D group (*P*=0.001 for local infections, *P*=0.001 for device infections) (Table 4).

Battery pocket hematoma was detected in 3.4% (n=42) of patients, 32 of which were treated with the application of a heavy object such as a sandbag on the battery pocket, and 10 were treated with percutaneous draining of the hematoma from the pocket with a syringe. No statistically significant difference was determined between the groups (CPMs, ICDs, CRT-Ds) in respect of the rate of pocket hematomas (*P*=0.44).

Mortality developed in 10 patients during the hospitalisation period after CIED implantation. The reason for mortality could not be detected in six cases, in all of which the general condition deteriorated after the procedure and death occurred in intensive care follow-up. In the other three mortality cases, three occured due to pneumosepsis and one due to pericardial/cardiac tamponade.

Table 4: CIED complications

Variable	CIED without defibrillation function	CIED with defibrillation function		*P*-value
	CPMs	ICDs	CRT-Ds	
Device infections	20	6	1	0.001
Local/Pocket infection	16	5	0	0.001
Pneumothorax	3	3	1	0.75
Tamponade	2	1	1	0.32
Pocket hematoma	14	27	1	0.44
Subclavian thrombus	1	2	0	-
Lead dysfunction	43	18	9	<0.001

CIED: cardiac implantable electronic device; CPM: cardiac pacemaker; ICD: implantable cardioverter defibrillator; CRT: cardiac resynchronization therapy

During the follow-up period after CIED implantation, three patients developed subclavian thrombus. All three cases developed unilateral upper extremity edema. One patient was VVI-ICD and thrombus was detected in the first week. One of these was DDD-ICD and thrombus was detected in the fourth week, and the other was VVI-CPM and thrombus was detected in the second month. The first case with thrombus detected in the first week was treated with low-dose alteplase infusion (25 mg for 25 hours), and the other two were administered anticoagulants of coumadin-warfarin with 2-3 INR value.

During the follow-up period of CIED implantation, some ICD patients received therapeutic shock; 4.5% (n=35) of patients received appropriate shocks for ventricular tachycardia and 0.8% (n=6) for ventricular fibrillation. Inappropriate shocks were received by 2.5% (n=19) of patients for supraventricular tachycardia, by 1.8% (n=14) for atrial fibrillation, and by 0.2% (n=2) for external noise (Table 5).

Table 5: Shock record/status of defibrillator CIEDs during the follow-up period

Shock status	Number	Percentage
None	697	55.3
Appropriate shocks for VT	35	2.8
Appropriate shocks for VF	6	0.5
Inappropriate shocks for SVT	19	1.5
Inappropriate shocks for AF	14	1.1
Inappropriate shocks for any external noises*	2	0.2
Total	1259	100.0

VT: ventricular tachycardia; VF: venticular fibrillation; SVT: supra-ventricular tachycardia; AF: atrial fibrillation, * External noise: an oversensed wave due to external electromagnetic energy, far-field R-waves or electrical activity of the musculoskeletal system noise which is secondary to lead or battery dysfunction .

No ICD shocks were reported by 90.2% (n=697) of patients during follow-up. In the total CIEDs, lead dysfunction was determined during the follow-up period in 5.6% (n=70) of patients, because of symptoms such as inappropriate shocks, CPM dysfunction or muscle stimulation due to pacing (Table 4,5). Lead revision was applied to 32 cases, and in the other 38 cases, the problem was resolved with re-programming of the CIED. Statistically significant differences were determined between the CPM and ICD/CRT-D groups in respect of lead dysfunction (*P* <0.001) and the difference was greater in the CPM group (n=531 vs. 657).

Two patients underwent left ventricular assist device implantation, and three patients underwent cardiac transplantation during the follow-up period.

DISCUSSION

Following the first successful cardiac electro-stimulation, the development of modern CIEDs started in the early 19th century[5]. In 1869, rhythm control could be performed via external electrical energy application to the precordium of a patient with tachycardia. This was possibly the first report of external cardioversion[6].

Over the years, temporary pacing in humans became successful[7]. In 1952, Madsen *et al* described a precordial plate and oesophageal electrode which could pace the heart for emergent cases[8]. In 1958, Furman *et al* described an externally powered transvenous bipolar catheter[9].

With advancements in techology, Larsson *et al* presented the first epicardial leads and self-contained pacemaker[10].

After all these steps in CIED technologies, current modern cardiology can manage to treat symptomatic bradycardia, prevent sudden cardiac death, and reduce heart failure symptoms with the use of CPMs, ICDs, and CRT-Ds.

The increasing aging population has led to increasing numbers of CIEDs used in modern cardiology over recent decades[11].

According to the data of this study, our hospital has a year-on-year increasing number of CIED implantations, revisions and battery replacements. These numbers are expected to increase further due to changes in the healthcare reimbursement procedures, and that more patients from all over the Aegean region in Turkey are being referred to our hospital.

In this study, a retrospective examination was made of 1259 patients with cardiac device (CPM, ICD and CRT-D) implantation, revision or replacement applied between January 2007 and June 2018. The aim of the study was to present the experiences of our CIED procedures, patient features and complication rates/results. Male gender was seen to be predominant overall (66.8%, n:841), which was consistent with the findings of other studies[12-14]. However, there were more females in the ICD group with 252 female to 234 male patients. This could be partly related to the overall increase in referral rates of female patients from other hospitals to avoid the known higher complication rates[15] and concern for higher hospital costs. The gender distribution of the other groups was compatible with the male predominance of the total patient population (539 male to 132 female in CPM group, 68 male to 30 female in CRT-D group). The overall mean age of the patients was 63.9±14.8 years, which was younger than ages reported in other studies. In those previous studies, ~ 80% of CIEDs were implanted in patients aged >70 years, with a mean age of 74 years[14,15]. The younger mean age could be explained by the overall younger population age, and due to limited medical resources, perhaps only the younger patients have access to such therapy. The overall mean age of the current study is similiar to the 63±14 years reported in a study of pocket hematomas in Turkey by Demir *et al*[16]. The mean age of patients in the CPM and CRT groups was determined to be statistically similar, but in the ICD group an older mean age was identified (CPM: 58.9±12.1 years; ICD: 71.1±15.1 years; CRT: 60.0±10.4 years; $P<0.01$).

Of the total patients in the current study, 38.6% (n=486) had a CPM, 53.6% (n=675) had an ICD, and 7.8% (n=98) had a CRT-D. The mean age was 71.1±15.1 years in the ICD group, 61.6±10.2 years in the CRT-D group, and 58.9±12.9 years in the CRT-D group. As CAD and low LVEF are known to increase with aging, it is to be expected that the ICD group would be older than the CPM group and the CRT-D group would be younger than the ICD group, as life expectancy is longer for young patients and younger patients were more frequently selected for CRT-D implantation.

The most frequent comorbid disease in the current cohort was found to be HT (61.9%, n: 77), which was similiar to the rate of 72.8% reported by Demir *et al*[16].

In the current study, indications for CPM implantation were as follows: 18.6% (n=234) complete AV block, 6.6% (n=83) SSS, 3.6% (n=46) symptomatic sinus bradycardia, 3.3% (n=41) Mobitz type 2 AV block, 1.4% (n=17) junctional rhythm, 0.8% (n=10) symptomatic atrial fibrillation with slow ventricular response, 0.4% (n=5) cardio-inhibitory syncope, 0.3% (n=4) symptomatic carotid sinus hypersensitivity, and 0.3% (n=4) Mobitz type 1 AV block. This distribution was similiar to the rates reported by Proclemer *et al*, of 45% AV conduction disturbances, and 25% SSS[14]. In the current study, atrioventricular synchrony mode (DDD-CPM 15.1%, n=190, and VDD-CPM 13.3%, n=167) was preferred more frequently than asynchronous mode (VVI-CPM 10.2%, n=129), which was consistent with the findings of Coma *et al*[17], but unlike those in the study by Proclemer *et al*[14] and Aktoz *et al*[12]. In those two studies, there was a higher rate of VVI mode than DDD mode.

In the ICD group, primary prevention indication was more frequent than secondary prevention indication (56.8%, n=715 vs. 4.0%, n=50), and 14 patients underwent ICD implantation for hypertrophic cardiomyopathy. One patient in the ICD group had Brugada syndrome, one had arrhythmogenic right ventricular dysplasia, and one had permanent low LVEF after Takotsubo syndrome. These data were compatible with those of the study by Proclemer *et al*[18], where more frequent primary prevention rates were also determined. There could also be an association with the aim of clinicians to protect the societally more active young population from sudden cardiac events. In the current study, there was a higher rate of VVI-ICD than DDD-ICD

(53.3%, n=462 vs. 16.6%, n=209) as VVI-ICD is preferred in our centre for primary prevention of malignant arrhythmias, and this finding was compatible with the Israeli ICD Registry result[19]. In the Israeli ICD Registry, there was reported to be no difference between VVI-ICD and DDD-ICD in reducing mortality rates or heart failure episodes and inappropriate shock application.

The total infection rate in the current study was 3.8%, including device infections (2.1%, n=27) and local infections (1.7%, n=21). This rate is higher than the data of previous studies. According to literature, the risk of CIED infection is 0.5% after new implantation, and ~1–5 % after replacement or revision[20,21]. The hematoma rate was 3.4% (n=42), pneumothorax 0.6% (n=7) and pericardial/cardiac tamponade 0.3% (n=3). No significant difference was determined between the genders in respect of all the complications (device infection p=0.98; local infection p=0.98; hematoma p=0.28; pneumothorax p=0.17; tamponade p=0.47). According to literature, females are at higher risk of developing pneumothorax and tamponade[15]. No statistically significant difference was determined between all the groups (CPMs, ICDs, CRT-Ds) in respect of pocket hematomas, pneumothorax and pericardial/ cardiac tamponade (p=0.44 for hematomas, p=0.75 for pneumothorax, p=0.32 for tamponade). Both local and device infections had statistically significantly lower rates in the CRT-D group (p=0.001 for local infections, p=0.001 for device infections). This differences originated between CPM via CRT-D (p=0.075). It has been reported in literature that larger and more rigid defibrillator leads constitute an increased risk for complications[22]. In this context, the current study data are controversial as lower complication rates were determined in the CRT-D group, but this can be attributed to more experienced operators performing CRT-D implantation in our center.

Hematoma was detected in 3.4% (n=42) of patients, with no statistically significant difference determined between all the groups (CPMs, ICDs, CRT-Ds) in respect of pocket hematomas (*P*=0.24). Although this finding is similiar to the rate reported by Demir *et al*[16], larger series such as in the study by Sridhar *et al*[23] with 1677 hematomas, have shown that the complexity of CIED is associated with more frequent hematomas (CRT>DDD>VVI)

On the defibrillator CIEDs, a total of 41 (5.3%) patients received appropriate shock (35 patients for VT and 6 patients for VF) and 35 (4.5%) received inappropriate shock (19 patients for SVT, 14 patients for AF and two patients for external noise or T wave oversensing). Wide ranges have been reported in literature, with a meta-analysis stating inappropriate shocks in 10% - 24% of patients and appropriate ICD therapies in 17-64% of patients[24]. The rates in the current study were low in comparison to previously reported values. This can be associated with shocks not felt by the patient or it could be related to patient follow-up continuing at a different center.

Lead dysfunction was determined in 5.6% (n=70) of patients in the current study through the detection of inappropriate shocks, pacing dysfunction or diaphragmatic stimulation of cardiac pacemaker. Lead revision was required in 32 cases, and in the other 38 patients the problem was resolved by re-programming. There is a reporting bias about lead dysfunction, with a range of 0.28% to 1.14% reported in one study[25] and up to 40% in another[26]. Statistically significant differences were determined between the CPM and ICD/CRT-D groups in respect of lead dysfunction (*P*<0.001) and the difference was greater in the CPM group (n=531 vs. 657).

A previous study in Japan reported that only 0.3% of patients (one patient in 330 transvenous permanent cases) suffered upper extremity thrombosis due to pacemaker implantation[26]. In the current study, three patients were determined with subclavian thrombus after CIED (one VVI-ICD, one DDD-ICD, one VVI-CPM). Of these cases, two were treated with anticoagulation and one with low dose fibrinolytic therapy.

Mortality following CIED implantation is rare and has been reported at rates of 0.08-1.1%[27]. When mortality occurs, it is frequently due to cardiac or major vascular perforation or massive hemopneumothorax. In the current study, mortality occurred in 10 (0.79%) patients after CIED implantation; three because of pneumosepsis, one because of pericardial/cardiac tamponade, and in the other six patients, the exact cause of mortalitiy could not be determined, although with a deteroration in the general condition after the procedure, there could have been an association with pulmonary embolization.

Limitations of the study are mostly related to the retrospective nature of the study and that the data were collected from a single center database. Therefore, the findings do not reflect the experience of other pacing centres.

CONCLUSION

This is a single center experience for overall CIED implantations. Some of the complications rates in this study are lower compared to published data, which can be attributed to the fact that complex

CIED implantations are performed by more experienced operators in our centre. The mortality rate was within the published range. In contrast to the current general knowledge, no difference was determined between the genders in respect of complication rates and our center had a younger population than that reported in most studies.

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Author contributions: Emre Ozdemir did data design and collection, and manuscript writing; Mert Pehlivan Altin did data collection; Sadik Volkan Emren did statistical analysis; Cem Nazli and Mehmet Tokac reviewed the manuscript.

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Original Article

Evaluation of facilities for diagnostic imaging at the primary health care centres in Al-Madinah, Saudi Arabia

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ABSTRACT

Objectives: To evaluate the availability of radiological services in primary health care centres (PHCCs) and the abilities of general practitioners (GP) and family physician (FP) to interpret the radiological investigations and the referral of the radiological images to radiologists

Design: Descriptive quantitative cross-sectional study

Setting: The study was conducted on 44 randomly selected PHCCs in Al-Madinah, Saudi Arabia

Subjects: One hundred and four participants were included in this study; GPs and FPs, residents, specialists and consultants.

Interventions: A self-administered questionnaire was used.

Main outcome measure: To investigate the availabilities of radiological facilities in the PHCCs in Al-Madinah

Results: This study included 44 PHCCs in Al Madinah of which 20 (45.5%) have radiological services, while 24 (54.5%) did not. Among the 20 PHCCs that had radiological services, 11 (55%) had working equipment while radiology service equipment was not working in 9 (45%). The most common reason for radiographs referral was to consult a radiologist to help in making a final diagnosis.

Conclusions: A higher percentage of PHCCs in Al Madinah did not have radiological services. Meanwhile, a high percent of available radiological services was not working yet. Providing radiology services in PHCCs increase the efficiency of the work in PHCCs, thus reducing patients' waiting times.

KEY WORDS: family physician, general practitioners, radiological services, ultrasound, x-ray

INTRODUCTION

Primary health care centers (PHCC) are considered the foremost level of contact with patients through the general practitioners (GPs) and family medicine physicians (FPs)[1], who provide comprehensive, continuous, coordinated and accessible care for patients, and deal with all populations of different age, sex and diseases[2].

GPs and FPs require the availability of imaging services within the PHCC to manage patients appropriately, without the demand to hospital services and to streamline the referral to secondary care[3]. Imaging services enable GPs and FPs to investigate the patients more fully before their referral. This will result in more specified referral[4]. Overall, the involvement of imaging modalities in PHCCs will increase efficiency of primary care services and save time and cost[1].

Appropriate PHCC service needs excellent communication between GPs/ FPs and radiologists to use all imaging modalities in PHCCs effectively[1]. This will help in patient management and can help to identify false-negative or false-positive cases[2].

Objectives

To evaluate the availability of radiological services in the PHCCs, the needs of GPs and FPs and their ability to interpret the available radiological investigations, and the reasons for referral of the radiological images to radiologists in Al-Madinah, Saudi Arabia.

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MATERIALS AND METHODS

This cross-sectional study was conducted on 44 randomly selected PHCCs in Al-Madinah, Saudi Arabia. One hundred and four participants including GPs, FPs, residents, specialists and consultants were included in this study.

Study tools

The tool used in this study was developed by researchers after extensive review of the relevant and current literature. A self-administered questionnaire was used. It is composed of four parts of 11 questions, targeting the research objectives.

1. **To investigate the availabilities of radiological facilities in the PHCCs in Al-Madinah** through three questions:
   a. Are there any imaging (radiology) services in the PHCCs?
   b. What are the types of available radiology services?
   c. Are the currently available radiology devices working?
2. **To explore the importance of radiological investigations in helping FPs for the diagnosis of certain diseases in PHCCs** through five questions:
   a. What was the extent of your need as a GP/ FP for the presence of radiology service in the PHCC to facilitate the diagnosis of certain diseases?
   b. Could the radiographic findings of cases change or affect the patients' diagnosis or their management plan?
   c. Does the provision of radiology services in PHCCs decrease the referral of cases to tertiary centers?
   d. Would the availability of radiology services increase the efficacy of your work?
   e. In your opinion, what is the most important type of radiology services that can be useful for you in diagnosing and developing a management plan for patients?
3. **To know if FPs can interpret radiological images by themselves or if they need to refer to a radiologist** through two questions:
   a. Did you read the radiograph issued by the PHCCs by yourself?
   b. If you need to communicate with radiologists, how did you contact them?
4. **To know the reasons for referral of the radiological images to a radiologist** through one question:
   a. What are the reasons behind sending the radiographs to be read by the radiologist?

Administrative and ethical consideration

This prospective research was conducted after approval of the institutional board of ethics numbered 071-1439. The assurance of anonymity of participants was provided by asking the participants not to put their names on the questionnaire and all information remained confidential. Participants were reassured that participation in this study was voluntary and withdrawal from the study can be done at any time if they wish. Confidentiality and privacy were maintained by data coding to eliminate identifying data with personal information. Researchers provided the participants with the questionnaire involving covering page that included the ethical considerations, the purpose of the study and the right to accept or refuse to participate. The researchers published the link of electronic questionnaires in each healthcare centre for the period June to August 2018.

Data analysis

Data were gathered and analyzed using IBM SPSS software (release 25), SPSS Inc., for Windows (Microsoft), United States of America). Statistical methods included descriptive analysis, such as number and percentage, and frequencies. Microsoft word and Excel have been used to generate graphs and tables.

RESULTS

This study included 44 PHCC's in Al Madinah. The availabilities of radiological facilities showed that 20 (45.5%) of the total PHCC's had radiological services, while 24 (54.5%) did not.

Among the 20 PHCCs that had radiological services, 10 (50%) had both x-rays and ultrasound, while 9 (45%) had only x-rays and one center (5%) had only ultrasound. Out of the 20 PHCCs that have available radiological services, 11 (55%) PHCCs had working equipment while radiology service equipment was not working in 9 (45%) PHCCs.

Overall, 104 participants were enrolled in this study and they were split into two groups; Group 1 included the participants who work in PHCCs with available radiological services (n=56) while Group 2 included the participants who work in PHCCs with no available radiological services (n=48). Nine of the participants (8.7%) were FP consultants (six in centers with radiological services and three in centers with no radiological services), 32 (30.8%) were FP specialists (20 in centers with radiological services and 12 in centers with no radiological services), 18 (17.3%) were FP residents (12 in centers with radiological services and six in centers with no radiological services) and 45 (43.3%) were GPs (18 in centers with radiological

services and 27 in centers with no radiological services).

In Group 1, 45 (80.4%) were usually using x-rays in diagnosis of different cases, six (10.7%) were usually using ultrasound, and the remaining five participants were usually using both the x-ray and ultrasound in their diagnoses. In Group 2, 31 (64.6%) of them believed that both x-rays and ultrasound were considered the most important types of radiological services that can be useful for them in diagnosing and developing the management plan that's suitable for the patients, while 17 (35.4%) believed that x-ray alone was the most important.

In Group 1, 21 (37.5%) participants referred that they were strongly in need of the presence of radiological services in PHCCs to facilitate the diagnoses for certain diseases, while 31 (55.4%) referred that they found themselves sometimes in need for the presence of radiological services and four (7.1%) were rarely in need for the service. Fifty-two (92.9%) of the participants admitted that the presence of radiology services in PHCCs can decrease the number of referred cases to tertiary centers, while four (7.1%) showed that it will not change the number of referred cases (Table 1).

Table 1: Distribution of participants' responses to explore the importance of radiological investigations in helping them for the diagnosis of certain diseases in PHCCs

Variables	Group 1 n (%)	Group 2 n (%)
What is the extent of your need as a GP/ FP for the presence of radiology service in the PHCCs to facilitate the diagnosis of certain diseases?		
Strongly	21/56 (37.5)	23/48 (47.9)
Sometimes	31/56 (55.4)	25/48 (52.1)
Rarely	4/56 (7.1)	0/48 (0)
Does providing radiology services in PHCCs can decrease the referral of cases to tertiary centers?		
Yes	52/56 (92.9)	47/48 (97.9)
No	4/56 (7.1)	1/48 (2.1)
Would the availability of radiology services increase the efficiency of your work in PHCCs?		
Yes	54/56 (96.4)	47/48 (97.9)
No	2/56 (3.6)	1/48 (2.1)
Could the radiographic findings of a case change or affect the patients' diagnosis or their management plan?		
Yes	56/56 (100)	47/48 (97.9)
No	0/56 (0)	1/48 (2.1)

Group 1: Practitioners who work in PHCCs with available radiological services (n=56)
Group 2: Practitioners who work in PHCCs with no radiological services (n=48)

Table 2: Distribution of participants regarding to the reasons for referral of the radiological images to a radiologist

Variables	Responses	N
Variables Reasons to send the radiographs to be read by the radiologist	Consult a radiologist to help in making a final decision for the diagnosis	26
	Consult the radiologist to confirm the final diagnosis established by the GPs/FPs.	14
	Consult the radiologist in severe cases.	15
	Follow a certain protocols or work routine.	8
	Avoid Medical-legal Issues	3
	Total	66

Fifty-four (96.4%) of the sample agreed that the availability of radiology services increased the efficiency of their work in health centres, while two (3.6%) did not agree. All 56 participants (100%) agreed that the radiographic findings could change or affect the patients' diagnosis or their management plan (Table 1).

In Group 2, 23 (47.9%) participants referred that they were strongly in need of the presence of radiological services in PHCCs to facilitate the diagnoses for certain diseases, while 25 (52.1%) participants found themselves sometimes in need for the presence of radiological services (Table 1).

Forty-seven (97.9%) of the participants thought that the availability of radiology services increases the efficiency of their work and it can decrease the number of referred cases to tertiary centers , and the radiological findings of cases can affect the patients' diagnosis or their management plan (Table 1).

This study revealed that among practitioners of Group 1 (n=56) who work in PHCCs with available radiological services, 18 (32.1%) of the practitioners read the radiograph by themselves and sometimes they sent the radiographs to radiologists in (n=36, 64.3%), while two (3.6%) always sent the radiographs to be read by radiologists. This study found that 42 (75%) of the practitioners communicate with a radiologist only by referral, while eight (14.3%) didn't have a way for communication and six (10.7%) communicated by phone.

The current study discussed the reasons behind sending the radiographs for reading by radiologists among practitioners who work in PHCCs with available radiological services (n=56). The responses were as follows: 26 participants consulted a radiologist to help make the final decision for the diagnosis; 15 consulted the radiologist in severe cases; 14 consulted the radiologist to confirm the final diagnosis established by the GP/FP; eight followed a certain protocol or work routine and three avoided medical-legal issues (Table 2).

The most common combinations of choices were "to consult a radiologist to help in making a final

Table 3: Combinations of responses of participants regarding to the reasons for referral of the radiological images to a radiologist

Response of Participants	Response 1	Response 2	Response 3	Response 4	Response 5
Response 1	26	5	2	1	1
Response 2	5	14	1	2	-
Response 3	2	1	15	-	1
Response 4	1	2	-	8	-
Response 5	1	-	1	-	3

Response 1: "Consult a radiologist to help in making a final decision for the diagnosis"
Response 2: " Consult the radiologist to confirm the final diagnosis established by the GPs/FPs "
Response 3: "Consult the radiologist in severe cases"
Response 4: "Follow a certain protocols or work routine"
Response 5: "Avoid medical-legal issues"

decision for the diagnosis" and "to consult the radiologist in severe cases" in five responses and both "to consult a radiologist to help and to confirm making a final decision for the diagnosis" in two responses, also the combination of both "to consult the radiologist in severe cases" and "to follow certain protocols or work routine" in two cases (Table 3).

DISCUSSION

The PHCCs have a key role in providing basic healthcare services and in reducing the pressure on higher healthcare centers[5,6]. The use of imaging modalities such as ultrasound and x-ray in PHCCs can save time and help to diagnose several diseases without the need for patient referral to a higher center[2].

The Kingdom of Saudi Arabia is seeking to encourage the evolution of a comprehensive PHC strategy and restructure its existing health care system to ameliorate the caliber of services offered to its citizens[7,8]. Although the establishment of primary care services in Saudi Arabia has improved in recent years, as evidenced by the number of staff present in most PHCCs, studies point to several organizational obstacles, including shortage of resources[8,9].

This matched with the results of the current study that found 24 (54.5%) of the 44 PHCCs in AL-Madinah did not have radiological services while 20 (45.5%) PHCCs did. X-ray and ultrasound were the diagnostic imaging equipment available in these PHCCs. Meanwhile the radiological services of 9 (45%) out of the 20 centers were not working. These findings are similar to the results of the previous study conducted in Jeddah by Mumenah & Al-Raddadi *et al* that aimed to determine the difficulties faced by FPs, and they found that 21.3% of FPs reported unavailability of x-ray equipment and 38.2% reported unavailability of ultrasound equipment[8]. It also matched the results of the study by Al-Khaldi *et al* that aimed to assess the current situation and the current practice of the programs in family medicine in KSA and draw a roadmap to achieve Saudi vision 2030. They found that 65% of PHCCs had no x-ray services[10], and results of study by Alsaad *et al* found that there was a substantial deficiency in x-ray machines, which was available in only 53.84% of their sampled centers, and only 38.46% of those available equipment were working[11].

Regarding the needs of GPs/FPs for radiological services in PHCCs, this study showed that the participants in both groups were either strongly in need or sometimes in need of the presence of radiological services. The results of this study also showed that most of the participants agreed that providing radiology services in PHCCs can reduce the number of referred patients, and the availability of radiology services increase the efficiency of their work in health centres. All the participants agreed that the radiographic findings of a case could change or affect the patients' diagnosis or their management plan. Most of the participants thought that the most important types of radiology services that would be useful for them in diagnosis were x-rays and ultrasound. These matched the results of studies that found that there is growing evidence that PHCCs with strong primary care facilities contribute to efficiency and quality in healthcare[12,13].

Since the diagnostic radiology service form an integral part of the evaluation and management of acute and chronic illnesses, offering radiology service in the family medicine practice reduces access issues and decreases the time to diagnosis and treatment[14]. Moreover, a lack of clinical suspicion, limited exposure, and referral of patients to nonspecialized centers can delay the management of cases, which in turn can increase morbidity and mortality[15,16].

The importance of imaging for the management of the patient in the primary care setting was emphasised by the Royal College of General Practitioners and the Royal College of Radiologists in 1993 and re-emphasised in 2004[1]. Among practitioners who work

in PHCCs with available radiological services (Group 1), this study revealed that 18/56 (32.1%) of the sample read the radiograph by themselves and 36/56 (64.3%) sent the radiographs to radiologists. This study also found that 75% of the practitioners communicate with a radiologist only by referral. These findings were supported by the results in a cross-sectional study that was conducted by Al-Yami *et al*. The authors concluded their findings as the physicians in many PHCCs need practice in reading normal X-ray films to avoid unnecessary referral of patients to specialized medical centres[16].

Sometimes GPs and FPs in PHCC refer patients directly to imaging departments for image-guided procedures. So, good collaboration between them and radiologists is needed and challenging at the same time. It serves both clinical disciplines and their patients; GP/FP currently aiming to refine its targets and strategy and radiology where a multiplicity collaboration has been key to the future of the discipline[1]**.** Referrals from primary to secondary care reflect this key role of GPs/FPs. The results of this study have shown that the most common reasons among the sampled practitioners to send the radiographs to be read by the radiologist were; "Consult a radiologist to help in making a final decision for the diagnosis", "Consult the radiologist in severe cases" and "Consult the radiologist to confirm the final diagnosis established by the family doctor", respectively.

The results of this study were supported by the findings in a cross-sectional study by Tandjung *et al* in Swiss primary care. They found that the most frequent referral recipients were radiologists (21.14%) and the most frequent aim of referrals was advice concerning diagnosis or therapy (46.3%)[17]. Grieve *et al*, in their study, mentioned that for these imaging examinations to be used effectively, the GPs/FPs should communicate formally with the radiologist outlining the clinical history and potential diagnosis for the radiologist to justify the investigation of choice[18].

CONCLUSION

This study revealed that a higher percentage of the PHCCs in Al Madinah did not have radiological services. Meanwhile, a high percent of available radiological services were not working yet. The most common available imaging equipment were x-rays and ultrasound. Providing radiology services in PHCCs increased the efficiency of the work in PHCCs and can reduce the referring of patients. Radiological findings of cases could affect the patients' diagnosis and their management plan.

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Original Article

The management of mucinous appendiceal lesions: Case series and review of the literature

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ABSTRACT

Objective: The management strategy of mucinous appendiceal tumors in the context of our clinical experiences was discussed.
Design: Retrospective study
Settings: Department of General Surgery and Surgical Oncology, Gaziosmanpaşa University Hospital, Turkey
Subjects: Our registries were reviewed to retrieve cases of mucinous appendiceal tumors treated in our hospital between March 2010 and November 2018.
Interventions: None
Main outcome measure: The role of minimally invasive surgery in the management of appendiceal mucinous lesions.
Results: Eleven cases, six males and five females, with a median age of 65.3 years were included. Laparoscopic appendectomy was performed in seven cases of low grade appendiceal mucinous neoplasm (LAMN), all of which did not require further surgery, except for one patient whose definitive histopathological result showed LAMN with the entrapment of the base of the appendix and a recurrent mass in the 5th month postoperatively requesting further surgery (laparoscopic right hemicolectomy). One case of LAMN with entanglement of the base of the appendix necessitated a partial typhlectomy (partial cecectomy), and three cases of large mucocele with high malignancy suspicion were treated with laparoscopic right hemicolectomy the definitive; pathologic reports showed LAMN in two cases and mucinous adenocarcinoma in one.
Conclusion: In elderly patients, right lower quadrant pain should be attentively approached and one should keep in mind mucocele lesions of the appendix. Careful history-taking, physical examination and necessary radiological imaging will help the diagnosis preoperatively. Mucinous appendiceal lesions should be rather managed under elective circumstances where the need of frozen section examination may be required. Laparoscopic approach is appropriate in experienced hands.

KEY WORDS: appendix, cystadenoma, laparoscopy, mucocele

INTRODUCTION

The word mucocele denotes a clinical condition which is characterized by the dilation and the accumulation of the mucoid fluid within the lumen[1]. This non-specific term, even though it seems to describe a benign condition, can be potentially malignant. Appendiceal mucocele (AM) is a very rare disease that is encountered in 0.2-0.7% of the pathological examination of appendiceal specimens[2-4]. Preoperative and even postoperative diagnosis can be bothersome. Since the disease is rare, the reports of patients' management are usually in the form of case reports or case series with limited number of subjects. AM is generally symptom-free and incidentally diagnosed by radiological studies, occasionally by means of endoscopic examinations, and sometimes are diagnosed intraoperatively; the most common symptom is right lower abdominal pain[5,6]. Right lower abdominal mass, bleeding, obstruction, acute abdomen due to mucocele perforation are the other

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Table 1: Patients demographics, diagnostic properties and management

Patient's ID	Age	Sex	Follow up (month)	Preoperative diagnostic tool	Preoperative diagnosis	Postoperative diagnosis	WBC (4,3 - 10,3) 10^{+3}/µml	Surgery type	Appendix diameter (mm)
#1	50	M	14	CT	AM	LAMN	9.36	LA	25
#2	80	F	94	CT	AM	LAMN	7.66	LA	30
#3	56	F	47	CT	AM	LAMN	4.99	LPC	30
#4	40	F	19	CT	AM	LAMN	6.6	LA,then LRH	30
#5	43	F	53	USG: +CT:-	AM	LAMN	9.86	LA	28
#6	62	M	95	CT	AM	LAMN	5.86	LA	25
#7	65	M	53	CT	AM	LAMN	7.08	LA	30
#8	64	M	13	CT	Appendeceal mucinous malignancy	Mucinous adenocarcinoma	9.92	LRH	50
#9	84	F	11	CT	Appendeceal mucinous malignancy	LAMN	9.24	LRH	50
#10	90	M	81	CT	Appendeceal mucinous malignancy	LAMN	7.64	LRH	46
#11	84	M	7	CT	AM	LAMN	7.86	LA	32

LA: laparoscopic appendectomy, LRH: laparoscopic right hemicolectomy, LPC: laparoscopic partial cecectomy; LAMN: low grade appendiceal mucinous neoplasm; AM: appendiceal mucocele; CT: computed tomography; USG: ultrasound

rare but possible symptoms[5-8]. In addition to careful history-taking and thorough physical examination, biochemical tests may show elevated levels of CEA and Ca19-9[9,10]. Computed tomography (CT) of the abdomen and the pelvis has an important contribution to the diagnosis. The major complication of AM surgery is the unfortunate conversion of a benign disease to a potentially "difficult to handle" malignant disease "pseudomyxoma peritonei" due to the perforation of the AM during surgery. The rarity of the disease and the ambiguous histopathological interpretation make it difficult to attribute an approved universal approach. The requirements for prompt management are the standardization of classification system including the nomenclature, the appropriate diagnostic approach and the systematization of the treatment strategies. Therefore, the importance of mucocele should be stressed in resident as well as postgraduate education. Here, we would like to present our cases of AM lesions within the context of new nomenclature and emphasize the role of minimally invasive surgery for the treatment of these lesions.

SUBJECTS AND METHODS

The study was designed retrospectively, and the Ethical Committee approval was obtained from Gaziosmanpasa University registered under the number 18-KAEK-154. All methods were performed in accordance with the relevant guidelines and regulations of the institution. All patients provided written informed consent and basic demographic information was collected. The data was retrieved from electronic database of our University hospital patients' files using both International Classification of Diseases codes (K35, K36, K37 and K38) and the words "appendectomy, acute appendicitis, mucocele", between 01/03/2010 and 01/11/2018. Then, only the data about patients with confirmed histopathological diagnosis of mucocele was recruited for further analysis. The electronic database of pathological reports for appendectomy and radiological database for abdominal CT reports were both examined to catch the cases that were possibly overlooked by above mentioned ICD-10 code search. The demographic findings, clinical presentation, management and treatment of patients and the follow-up were recorded. The standard treatment of acute appendicitis in our center is laparoscopic appendectomy, which was performed either by a senior surgeon or a surgical resident supervised by a senior surgeon. All patients' treatment and follow up were conducted in our center. After discharge, the patients were followed weekly for one month, and thereafter every six months, mainly by routine visits, if not by phone calls.

RESULTS

Out of 892 patients who underwent appendectomy in our institution, eleven cases of AM were retrieved from medical records. More than half of the patients were male (54.5%) and the mean age at presentation was 65.3 years (±17.3). The incidence rate was 1.2% in appendectomy specimens. The demographic features, preoperative findings, pathological results and management were all shown in Table 1. The main complaint of all patients was right lower quadrant abdominal pain. In addition to the abdominal pain, mass findings and sensation of fullness in the right lower quadrant were also noticed in six patients (54.5%).

The preoperative diagnoses were appropriately made in eight patients. In the remaining three patients with relatively large mucocele who were preoperatively diagnosed as potentially malignant, one subject was postoperatively diagnosed as mucinous malignant tumor and the rest two subjects as low grade appendiceal mucinous neoplasm (LAMN). Abdominal CT was performed in all patients with a diagnostic yield of 90.9%. Colonoscopy was performed in four patients and findings were documented as mucus discharge from appendiceal orifice in one patient and incidentally found polyps in four patients. Out of eleven patients, twelve laparoscopic interventions were performed, where one patient had a recurrent mass five months after initial surgery and was reoperated laparoscopically. No incidence of perforation or spillage was encountered in any of the cases.

The histopathological examination showed LAMN in ten cases and one case of mucinous adenocarcinoma. The mean appendeceal diameter was 34.2 mm (± S: 8.7).

The management and follow-up of all patients were done in our university hospital. The mean follow-up period was 44.3 months (±34.0) with no morbidity or mortality recorded so far.

DISCUSSION

The term mucocele simply means dilatation and accumulation of mucin in the appendiceal tubular cavity; most of the time it can be of benign causes, but in more extreme cases it represents a neoplastic process. The management of this rare disease is still under debate, not just due to the difficulty in diagnosis, but also its clinical behavior and lack of common and well-defined algorithm in histopathological identification. Review of the literature showed papers in the order of few case reports or case series. Subjects with AM mostly show up with atypical clinical presentation, with indistinct abdominal pain mimicking acute appendicitis. In the present study, all patients complained of atypical right lower quadrant abdominal pain with sensation of fullness in the right lower quadrant, while some pointed out that these lesions tend to show female preponderance; in our study, there was tendency of the disease to affect male gender. The mean age at diagnosis in the literature ranges from 62 to 66 years; in this study, it is reported to be 65.3 years, all the patients were treated successfully by means of minimal invasive surgery with no mortality records.

In 2012, the Peritoneal Surface Oncology Group International and eighth edition of American Joint Committee on Cancer (AJCC) brought up new nomenclature and histologic staging concerning the appendiceal mucinous neoplasia which can significantly affect patient management[11]. The eighth edition of AJCC Staging Manual now uses a 3-tiered approach (low-grade tumors are classified as grade G1, but high-grade tumors are classified as grade G2 or grade G3) which corresponds to the descriptive terminology of well-differentiated, moderately, and poorly differentiated in parallel with the alphanumeric grades (G1, G2, G3, respectively)[12].

The term "low-grade appendiceal mucinous neoplasm" was replaced for cystadenoma in this consensus. A new definition, "high-grade appendiceal mucinous neoplasm" (HAMN), was proposed for lesions without infiltrative invasion but with high-grade cytologic atypia. LAMN is further subdivided into LAMN T1, T2, T3, T4 with T4a and T4b substages.

The AM lesions can be benign, such as simple and hyperplastic mucoceles, and correspond to 5 to 25% of the cases with acellular mucus[13]. It can also be of neoplastic origin, such as LAMN and HAMN, which are neoplasia with dysplastic epithelium similar to colon adenomatous polyps corresponding to 63 to 84% of the cases[14]. Finally, the mucinous adenocarcinoma conventionally known as mucinous cystadenocarcinoma, was described as the presence of infiltrative and destructive stromal invasion into the wall of the appendix and represents 11 to 20% of the cases. The extreme presentation of AM is pseudomyxoma peritonei (PMP).

PMP, described previously by Werth in 1884[15], is a rare condition characterized by mucinous accumulation in the peritoneal surfaces accompanied by implants. In almost all cases (94%), it originates from a perforated mucinous tumor of the appendix[16,17].

Some LAMN may breakthrough to PMP via peritoneal spread. The apparition of mucin or neoplastic cells exterior to the lumen, in places like the appendiceal submucosa, wall or periappendiceal tissue, is associated with PMP[18,19]. Lesions of such kind are labeled as HAMN, whereas lesions confined to the lumen are defined as LAMN. Approximately only 2% of LAMNs progress to PMP, whereas it goes up to 20 to 23% in case of mucinous adenocarcinomas[20]. The five-year survival of non-complicated mucinous adenocarcinoma of the appendix is reported to be 32-58%. However, this survival rate is just the half in case of high-grade PMP, which is thought to be 23%[11,21-24].

The most common presentation of mucocele is abdominal pain followed by mass in the right lower quadrant; the female predominance[21] is mentioned in many articles with a peak incidence at the 6th decade[20,21]. Other than clinical suspicion, radiological imaging is considered to be mandatory. While ultrasonography may show a cystic mass with internal echogenicity and an "onion skin sign" which may be

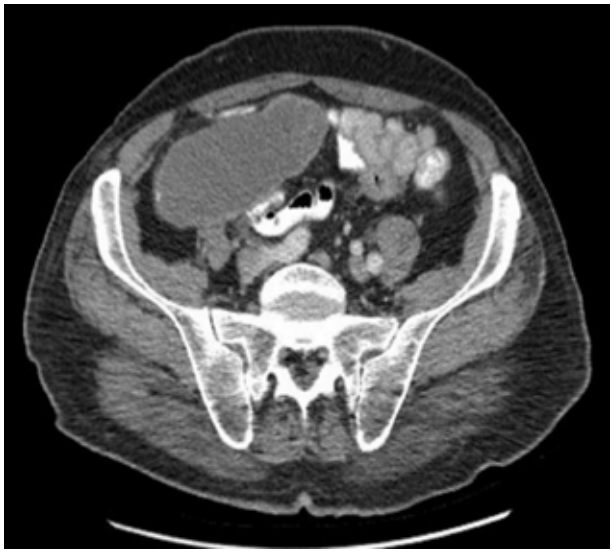

Fig 1 : CT scan demonstrating a cystic mass in the right lower quadrant (patient #8).

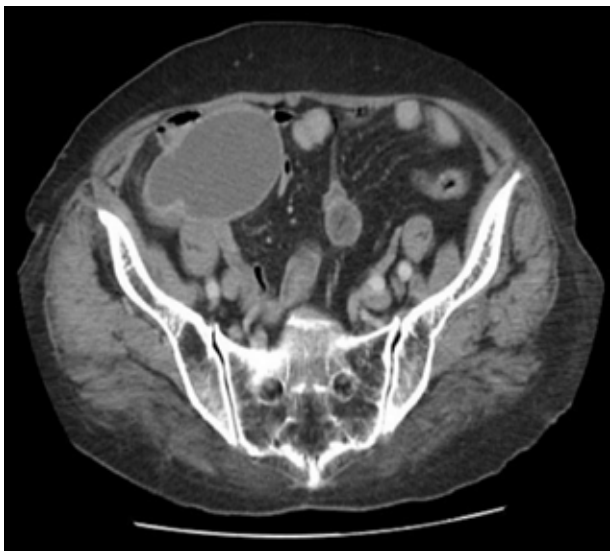

Fig 2: CT scan showing a large cystic mass originating from the appendix (patient #9).

considered to be pathognomonic due to cystic layering or even an acoustic shadowing due to mural calcifications[25], the CT demonstrates well-circumscribed spherical or tubular mass contiguous with the base of the caecum (Figure 1, 2). Magnetic resonance imaging may sometimes be necessary for differential diagnosis of ovarian masses. Other studies that can support the diagnosis and follow-up are colonoscopy, which may show the mucin oozing from appendiceal orifice (Figure 3). It is worthy to note that in our case series, all patients were afebrile and white blood count were within normal range. This may help the clinician in addition to careful history taking and physical examination to differentiate between acute appendicitis and AM.

According to Lien *et al*[26], an ultrasonographic report of an appendiceal diameter greater than 15 mm may correspond to AM with a sensitivity of 83% and a specificity of 92%. Another large American analysis of 2101 cases of mucinous adenocarcinoma showed that tumor size is likely to be greater than four cm with moderate to well differentiated histopathological behavior and nodal metastasis in only 20% of the cases[22]. In this series, all detected mucinous appendiceal lesions were larger than 20 mm (mean: 34.2 mm) and these lesions were detected in 90.9% by means of abdominal CT. So, any cystic lesion of the appendix larger than 20 mm detected via any radiologic tool should be suspected of AM. However,

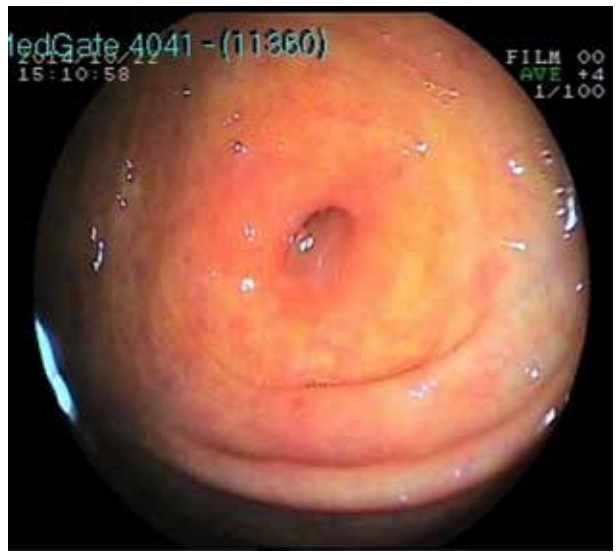

Fig 3: Protrusion of the appendecial osstium resembling a Volcano crater view with mucin secretion during colonoscopy (patient #7).

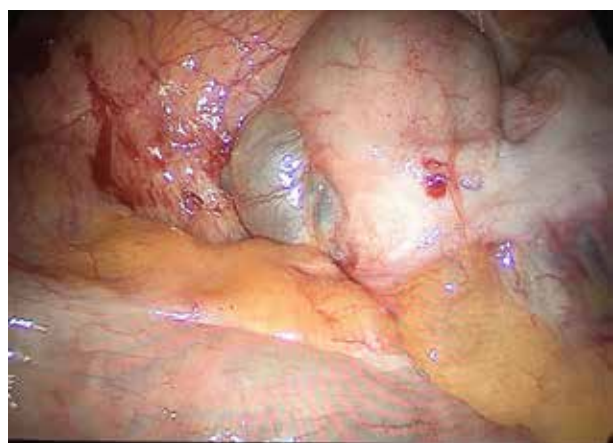

Fig 4: Recurrent mass five months after laparoscopic appendectomy of AM with postoperative diagnosis of LAMN and positive surgical margin (patient #4) (this patient was subsequently operated by means of laparoscopic right hemicolectomy).

neoplastic mucinous appendiceal lesions tend to have a diameter greater than two centimeters.

The treatment of AM is purely surgical. The intraoperative finding of these lesions is of great importance, so detailed description of the lesion is mandatory. It should include the location of the tumor (tip vs. body vs. base), the distance of tumor from proximal resection margin, the presence or absence of mucin deposits on the serosal surface or in the wall of the appendix, or elsewhere in the abdomen, the presence or absence of adhesions to other structures, and the presence or absence of perforation.

For benign non-neoplastic lesions, laparoscopic appendectomy suffices, while laparoscopic appendectomy with lymphadenectomy, including all the fat from the mesoappendix, is indicated for LAMN and HAMN, and when the appendicular base is not compromised by the dilation and with no peritoneal involvement.

In some cases of LAMN and HAMN where there is involvement of the base or extraappendiceal involvement respectively, a more extended resection such as partial cecectomy is advised; in cases where the latter is not achievable, right hemicolectomy would be more appropriate in combination with medical treatment.

In this case series out of 11 cases of appendeceal cystic lesions, ten patients (90.9%) were diagnosed as LAMN, even though the histopathological diagnoses were the same. The treatment approach varied from laparoscopic appendectomy to laparoscopic cecectomy and even laparoscopic right hemicolectomy.

Laparoscopy is definitely not without drawbacks; rupture and spillage of a mucin containing epithelial cells lesion may lead to catastrophic changes in the management of such patients and even an upstaging of the tumor, which may affect survival negatively. In our study, one patient was reoperated because of the positivity of the surgical margin during her first operation and had laparoscopic right hemicolectomy due to recurrent mass in the ceacum originating from the base of the appendectomy (Figure 4). All patients were managed laparoscopically, six (54.5%) of which had laparoscopic appendectomy, one (9.1%) patient had laparoscopic partial cecectomy, another patient had appendectomy then reoperated due to recurrent mass and had laparoscopic right hemicloctomy, three (27.3%) patients had laparoscopic right hemicolectomy due to large potentially malignant appendeceal mucocle, where one of which showed mucinous adenocarcinoma of the appendix on histopatological examination and the other two subjects showed LAMN.

It was particularly noteworthy that there is a liaison between AM and colonic polyps and hence colonic malignancies, which was previously confirmed by other studies[11,27]. Therefore, we recommend surveillance colonoscopy in patients with a diagnosis of AM. Even though there is no strong evidence showing the transformation of LAMN to mucinous adenocarcinoma, most pathologists consider the adenoma-adenocarcinoma sequence is comparable with the colonic polyp–adenocarcinoma sequence[28].

The relatively small number of patients in this study limited the ability to conclude a universal approach concerning diagnosis, treatment and follow up strategies. The low rate of recurrence can be linked to the short follow-up period; the absence of any spillage or rupture during laparoscopic surgery can be attributed again to the low sample size. However, this study may be considered as a leading point to conduct relatively larger studies with longer follow-up period and in a prospective manner.

CONCLUSION

Appendiceal mass should not be taken for granted, especially for patients in the 6th decade with indistinct pain. It was particularly noteworthy that an appendiceal diameter larger than 2 cm suggests a mucinous lesion of the appendix. So, these patients should be approached with prudence and prompt preoperative investigation with CT, magnetic resonance imaging or even colonoscopy. Once the decision for exploration is taken under elective circumstances, the laparoscopic approach would be the most appropriate in experienced hands and the availability of frozen examination should be ensured to help the intraoperative decision making. Laparoscopic approach would be appropriate for patients with mucocele that can be removed without rupture.

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Original Article

The effects of 'Adequacy of Anesthesia' monitorization in general anesthesia on hemodynamics, recovery, and the cost of anesthetic drugs

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ABSTRACT

Objective: Adequacy of anaesthesia provides information about electrical activity of the brain with entropy, and analgesic response of the body with surgical pleth index (SPI). In this study, we aimed to evaluate the effects of anesthetic management performed using adequacy of anaesthesia monitorization on intraoperative hemodynamics, postoperative recovery and the cost of anesthetic drugs.
Design: Prospective, randomized and controlled study
Setting: Department of Anesthesiology and Reanimation, Necmettin Erbakan University, Meram School of Medicine, Konya, Turkey
Subjects: A total of 120 patients scheduled for thyroidectomy operation under general anesthesia were included in the study.
Intervention: Patients divided into two equal groups as Group Adequacy of Anesthesia (Group AoA, n=60) and Group Control (Group C, n=60). For the induction, Group C was maintained with 1-2 mg/kg propofol and 1 μg/kg remifentanil injection, while based on the entropy and SPI values during the induction, Group AoA was injected with propofol and remifentanil so as to provide state entropy and SPI values of 50±10.
Main outcome measures: Hemodynamic data, times and recovery data were recorded and statistically analyzed.
Results: Extubation and recovery times were significantly shorter in Group AoA (P=0.29, P<0,01, P<<0.01; respectively). The cost of anesthesia calculated based on the amount of drugs used was significantly lower in group AoA (P<0.01).
Conclusion: In this study where we compared the use of adequacy of anesthesia with conventional anesthetic depth monitorization methods, we found that the use of adequacy of anesthesia provided positive contributions to the cost of anesthetic drugs and post-anesthetic recovery.

KEY WORDS: adequacy of anesthesia, cost of anesthesia, depth of anesthesia, general anesthesia, recovery

INTRODUCTION

The term of anesthetic depth has largely changed with the advancement in technology, use of novel pharmacological agents, and modernization of anesthetic monitorizations[1].

General anesthesia has three components including hypnosis, analgesia and immobility[2,3]. Today, among these three components of anesthesia, hypnosis is monitored with entropy, analgesia with surgical pleth index (SPI) and immobility with neuromuscular transition (NMT). Adequacy of anesthesia (AoA) is an anesthetic monitorization software created by combining entropy and SPI.

AoA, a monitorization method used in general anesthesia practice, is helpful in evaluation of the individual responses of patients in administration of

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Fig. 1: Adequacy of Anesthesia chart images from the Aisys CS^2 – GE Healthcare, CARESCAPE-B650 monitor.

intravenous hypnotics, opioids and inhalational anesthetics agents. AoA provides information about electrical activity of the brain with entropy, and analgesic response of the body with SPI. In addition, it shows muscle relaxation adequacy with NMT, providing monitorization of hypnosis, analgesia and immobility that are the three components of general anesthesia. AoA is used in the evaluation of anesthetic depth, providing a combination of these non-invasive methods (Figure 1).

AoA aims to prevent both overuse of drugs by applying anesthesia deeper than needed, and wakefulness and awareness that occur due to superficial anesthesia applications during general anesthesia[4].

In this study, we aimed to evaluate the effects of anesthetic management performed on intraoperative hemodynamics, postoperative recovery and cost of anesthetic drugs using AoA monitorization.

SUBJECTS AND METHODS

This study was conducted after receiving approval from the ethics committee (Ref. No:10643207-511.06-E.24117) in the operating room of our hospital between February 2018 and May 2018 in compliance with the Declaration of Helsinki. A total of 120 patients scheduled for thyroidectomy under general anesthesia with a physical status of American Society of Anesthesiology (ASA) I-II according to the classification by the ASA, who were aged between 18 and 65 years, and gave informed consent were included in the study.

Patients with disrupted orientation and cooperation, severe psychiatric disorders, pregnant or breastfeeding women, emergency cases, patients with a history of cardiac dysrhythmia and heart failure, those with chronic smoking, alcohol or substance abuse, patients who needed intraoperative inotropic drugs, and those who rejected to volunteer were excluded from the study. Patients' demographic data were recorded. Patients were randomized with the sealed envelope method and divided into two equal groups as adequacy of anesthesia group (Group AoA, n=60) and control group (Group C, n=60).

As the standard monitorization, electrocardiography, non-invasive blood pressure, pulse oximetry, NMT, end-tidal carbon dioxide, and temperature were followed up. Patients in Group AoA were additionally monitored with entropy and SPI for AoA monitorization (Aisys CS^2 - GE Healthcare, CARESCAPE-B650-Finland). Recording times of the data are given in Table 1.

Table 1: Recording times of data

	Recording times
T0	Baseline
T1	1 min after induction
T2	1 min after extubation
T3	Case position for surgery
T4	Surgery incision
T5	10 min after surgery incision
T6	20 min after surgery incision
T7	30 min after surgery incision
T8	40 min after surgery incision
T9	50 min after surgery incision
T10	End of surgery
T11	Termination of anesthesia
T12	Extubation

For the induction, Group C was injected with 1-2 mg/kg propofol (bolus) and 1 μg/kg remifentanil (infusion), and Group AoA was injected with propofol and remifentanil so as to provide state entropy and SPI values of 50±10. Rocuronium 0.6 mg/kg was administered for muscle relaxation, 2 mg/kg tramadol for postoperative analgesia, and 0.1 mg/kg ondansetron as antiemetic. Data of the 1st minute following anesthetic induction were recorded. All patients were intubated when the ratio of train-of-four reached to zero, data were recorded post-intubation and after the patient was given the necessary position for thyroid surgery. Data were monitored during the surgical incision, and then with ten-minute intervals.

For the maintenance of anesthesia, both groups were administered intravenous (iv) 0.25 μg/kg/min remifentanil infusion and 1 MAC sevoflurane as the inhalational agent. In Group C, maintenance doses of sevoflurane and remifentanil were given based on

Table 2: Fast-track recovery point scoring table

Parameters	Description of the patient	Score
Level of consciousness	Score awake and oriented	2
	Arousable with minimal stimulation	1
	Responsive only to tactile stimulation	0
Physical activity	Able to move all extremities on command	2
	Some weakness in movement of extremities	1
	Unable to voluntarily move extremities	0
Hemodynamic stability	Blood pressure 15% of baseline MAP value	2
	Blood pressure 15%–30% of baseline MAP value	1
	Blood pressure 30% below baseline MAP value	0
Respiratory stability	Able to breathe deeply	2
	Tachypnea with good cough	1
	Dyspneic with weak cough	0
Oxygen saturation status	Maintains value, 90% on room air	2
	Requires supplemental oxygen (nasal prongs)	1
	Saturation, 90% with supplemental oxygen	0
Postoperative pain assessment	None or mild discomfort	2
	Moderate to severe pain controlled with IV analgesics	1
	Persistent severe pain	0
Postoperative emetic symptoms	None or mild nausea with no active vomiting	2
	Transient vomiting or retching	1
	Persistent moderate to severe nausea and vomiting	0
Total score (max)		14

MAP: mean arterial pressure

clinical follow up, pulse, blood pressure, pupil reflex, and tear monitoring as in the conventional anesthetic applications; in Group AoA, the anesthesia was maintained by providing optimum levels (state entropy: 50±10, SPI: 50±10) of adequacy of anesthesia chart values. During general anesthesia, if the patient's heart rate dropped down under 40/min, it was considered as bradycardic, and 0.5mg atropine (iv) was applied to patients. If patient's systolic blood pressure was lower than 90 mmHg, it was considered as hypotensive and 10 mg ephedrine (iv) was applied to patients. When surgical skin suturing was completed, inhalational sevoflurane and remifentanil infusion were terminated. Fresh gas flow was raised to 10 L/min. Patients were awakened.

Anesthesia time was determined as the time from the initiation of induction to extubation, and extubation time was defined as the time from termination of anesthesia maintenance to extubation. The amount of anesthetic drugs, anesthesia time and extubation time were recorded.

Heart rate, pulse oximetry, non-invasive arterial blood pressure and fast-track recovery scores were monitored in patients taken to the postoperative recovery unit after wakening, and the patient with a fast-track score ≥12, providing none of the criteria were zero point, were referred to the ward (Table 2). The time between the extubation and referral to the ward was determined as the recovery time.

Statistical analysis

Data obtained were analyzed using SPSS v. 20 (Statistical Package for Social Sciences, Inc., Chicago, IL). The continuous variables are expressed as mean ± SD or number (%). The categorical variables are given as number and percentage. Normality of the data was tested using Kolmogorov-Smirnov test. Mann-Whitney U test was used in analysis of the continuous parameters (age, weight, etc.). Chi-square test was used in the comparisons of paired groups and in the evaluation of the categorical variables. P <0.05 values were considered statistically significant.

RESULTS

This study was conducted with a total of 120 patients aged between 20 and 65 years, and no statistically significant difference was found between the groups in terms of the demographic data and ASA scores (P >0.05, Table 3).

No statistically significant difference was found between the groups in terms of anesthesia times.

Table 3: Distribution of the demographics by groups

Demography	Group C (n=60)	Group AoA (n=60)	*P*-value
Age	46.20±11.55	44.48±11.42	0.47
Weight (kg)	77.18±14.50	76.63±11.31	0.73
ASA score (I/II)	43/17	47/13	0.26
Sex (M/F)	14/46	19/41	0.21

ASA: American Society of Anesthesiology

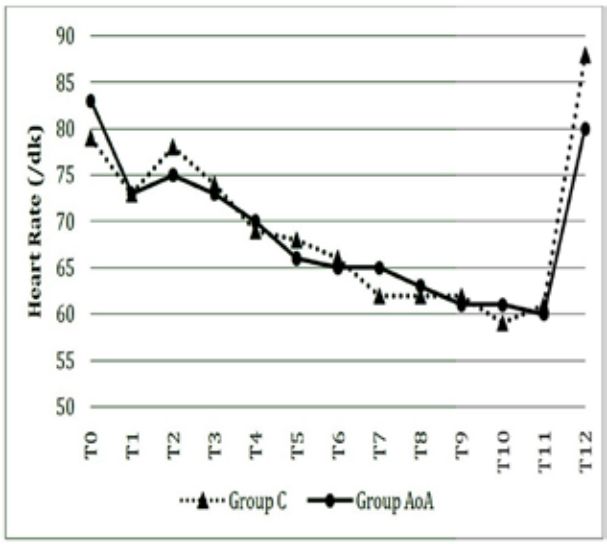

Fig. 2: Mean heart rate values of the groups

Extubation and recovery times were significantly shorter in Group AoA (P <0.01) (Table 4).

Hemodynamic monitoring was performed based on heart rate, and systolic blood pressure and diastolic blood pressures were measured with a non-invasive method. There was no statistically significant difference between the groups in hemodynamic parameters (P >0.05) (Figure 2, 3).

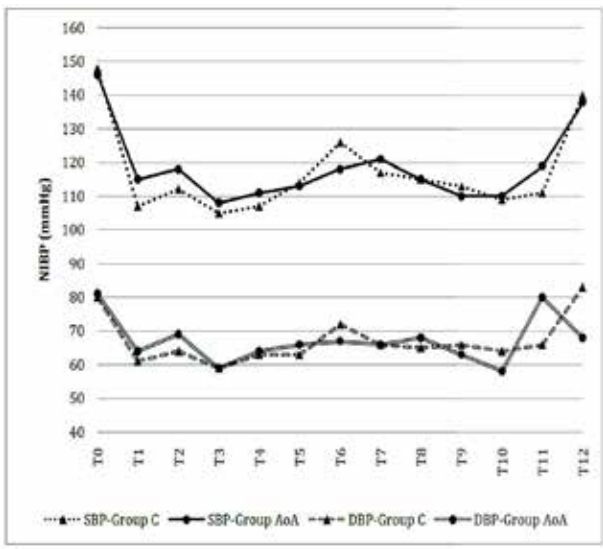

Fig. 3: Mean systolic and diastolic blood pressure values of the groups

Table 4: Mean times calculated according to the groups

Times	Group C	Group AoA	*P*-value
Anesthesia time (min)	90.66±19.51	86.33±19.65	0.29
Extubation time(min)	12.56±2.84	6.58±2.14	<0.01
Recovery time(min)	32.33±8.10	17.83±7.38	<0.01

Table 5: Mean amounts of the drugs used for maintenance of anesthesia

Anesthetic drugs	Group C (n=60)	Group AoA (n=60)	*P*-value
Remifentanil (µg)	1273.33±335.72	932.66±192.11	<0.01
Sevoflurane (ml)	21.56±5.49	16.18±3.80	<0.01
Propofol (mg)	142.83±29.9	129.50±22.43	<0.01

The cost of anesthesia calculated based on the total amount of anesthetic drugs used was significantly lower in Group AoA (P <0.01; Tables 5, 6; Figure 4).

No significant difference was found between the groups in neuromuscular block drugs. The mean entropy and SPI values observed in Group AoA are given in Figure 5.

DISCUSSION

In this study, in which the use of AoA was compared with conventional anesthetic depth monitorization methods, we found that the use of AoA provided positive contributions to the amount of drugs consumed, cost of drugs and post-anesthetic recovery.

Anesthetic depth is determined with the stress response and cognitive changes in a patient under neuromuscular block. According to the traditional

Table 6: Mean costs of the drugs used for maintenance of anesthesia

Anesthetic drugs ($)	Group C (n=60)	Group AoA (n=60)	*P*-value
Propofol	0.52±0.11	0.47±0.08	0.04
Remifentanil	1.54±0.41	1.13±0.23	<0.01
Sevoflurane	5.66±1.44	4.25±1.00	0.01
Total	8.75±1.77	6.76±1.17	<0.01

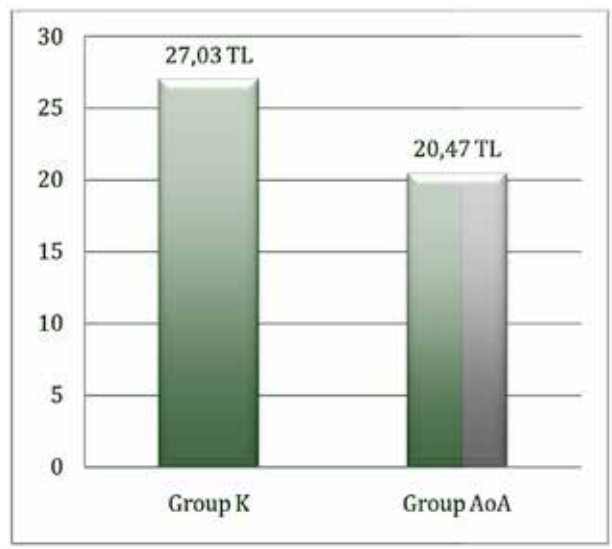

Fig. 4: Mean total cost of the drugs used for anesthesia per one patient

practices, heart rate and blood pressure are guiding in evaluation of the stress response. Eyelash, cornea and conjunctiva reflexes, and the reflexes such as pupillary diameter and light reaction as well as indirect monitorization are used for determination of cognitive changes. However, it has been concluded that these clinical findings show a poor correlation with anesthetic depth[5]. Today, many anesthetists adjust doses of pharmacological agents that they use, by measuring hemodynamic responses and minimal alveolar concentrations of inspired and expired inhaled anesthetic. Unnecessary deep anesthesia may cause hypotension and late recovery, while insufficient anesthesia may lead to complications such as awareness[6]. Although monitorization of anesthetic depth has been shown to decrease the amount of anesthetic drugs used, effectively provide hemodynamic stabilization, and decrease times of wakening and extubation; the benefits that this method would provide in numerous issues including environmental pollution and costs are still underwork[7-9].

Methods based on electroencephalogram findings such as narcotrend, bispectral index (BIS) and entropy are used in the monitorization of anesthetic depth. AoA modul is a current system developed by combining entropy, and SPI which is used for the control of pain and stress response in general anesthesia, and it evaluates anesthetic depth and analgesia together. AoA is open to research in terms of the patient control under general anesthesia, post-anesthetic recovery, consumption and costs of anesthetic drugs.

When designing this study, we planned to apply AoA on thyroidectomy cases in order to prefer a surgery with sufficient time to also evaluate its effects on maintenance anesthesia period, and considering lower intraoperative external impacts. AoA charts were used for monitorization in Group AoA. Anesthetic target in this monitor was defined so as to provide entropy (40-60) values, providing surgical anesthetic depth, and SPI (50±10) values enough to provide adequate analgesia[9,10]. End-tidal inhaler anesthetic concentration was used to adjust entropy values, while the doses of remifentanil infusion were adjusted to achieve SPI target.

Slavlov *et al*[11] examined mobility of patients, hemodynamics and BIS values, and observed increased blood pressure in mobilized patients, while they found no correlation between BIS and hemodynamic data. In a study with pediatric patients, effect of BIS monitorization alone on hemodynamics was not sufficient[12]. In another study in which BIS monitorization was used to monitor anesthetic depth for cranial surgery, monitorization of anesthetic depth had no contribution in the control of hemodynamics[13].

In the present study, we found that AoA monitorization showed similarity with the other monitorization methods, and obtained similar results in the hemodynamic evaluation with the conventional methods. However, systolic arterial pressure was under 90 mmHg in nine patients in Group C, while this finding was observed only in three patients in Group AoA. Significant difference between the groups in terms of the amount of drugs used suggests that hemodynamics was also influenced. In our study, although hypotension was more common in Group C, the difference did not reach statistical significance, and we think that this result was due to the hypotension and bradycardia protocol used.

The relationship between monitorization of anesthetic depth and its effects on drug consumption is a commonly studied subject in anesthesia applications. Drug consumption values were similar in the anesthesia applications performed based on BIS and entropy[14]. In a study with patients who underwent laparoscopic sleeve gastrectomy surgery, the use of BIS was reported to decrease the consumption of desflurane[15]. In a study with elderly Asian population, the use of BIS was shown to provide a reduction in isoflurane consumption by 40%[16]. In a study by Banister *et al*[17], a deeper anesthesia was achieved in the control group which was given sevoflurane and N_2O, and the authors reported reductions by 25-40% in sevoflurane consumption in BIS group[17]. In a study examining effects of anesthesia application using SPI, it was reported that fentanyl consumption was decreased, while sevoflurane consumption was similar[18]. In our study, we used sevoflurane as the anesthetic agents for anesthesia maintenance, and provided analgesia with remifentanil infusion. Looking to the amount of drugs used during the maintenance per patient, the mean amount of remifentanil infusion was found as 1273.33 μg in Group C and 932.66 μg in Group AoA, whereas sevoflurane consumptions were found as 21.56 mL in Group C, and 16.18 mL in Group AoA. Therefore, the use of AoA decreased remifentanil consumption by mean 340.67 μg (26.75%) and sevoflurane consumption by mean 5.38 mL (24.95%). We concluded that the use of drugs for maintenance was significantly lower in Group AoA.

Effects of the monitorization of anesthetic depth on the cost of anesthesia remains controversial. In a review based on 22 studies controlling anesthetic depth with BIS, entropy, and narcotrend, although awareness issue was left disputable, monitorization of

anesthetic depth has been reported to have drug cost reducing effects[19]. In a study investigating effectiveness of SPI on opioid consumption, it was underlined that combined use of SPI and entropy was effective in dose adjustment and decreased both the amount of opioids used and hypnotic levels[4].

Similarly, in our study, we found that reductions in the amount of sevoflurane and remifentanil used significantly decreased the costs. In the calculations of total drug cost, cost per patients was found as 8.75 USD in Group C, and 6.76 USD in Group AoA with a 1.99 USD (22.75%) contribution per patient.

In a study by Punjasawadwong *et al*[20] examining 36 studies, BIS monitorization was found to shorten length of stay in postoperative recovery unit by 6.75 minutes[21]. In addition, it was reported that BIS was not effective on time to discharge. Chhabra *et al*[21] reported that effects of the use of spectral entropy on weakening time has moderate reliable evidence, while Shepherd *et al* reported shortened recovery time[19]. In a study examining 170 patients who underwent SPI guided day case anesthesia, remifentanil and propofol infusion doses were decreased and recovery times were shortened[4].

AoA, which we found to have positive reflections on consumption and costs of drugs, also has effects facilitating post-anesthetic recovery. In the present study, no statistically significant difference was found between total anesthesia times. The mean extubation time was found as 6.58 minutes in Group AoA and 12.56 minutes in Group C, while the mean recovery time was found as 17.83 minutes in Group AoA and 32.33 minutes in Group C. Our results indicate that patients monitored with AoA experienced a more rapid recovery process.

CONCLUSION

This study has some limitations. We could not demonstrate effective results in hemodynamics with significant decrease in drug consumption, which we found. Also, at postoperative patient visit time, none of our patients presented similar information to intraoperative awareness, but we did not perform any test postoperatively.

Further controlled studies are needed to compare AoA and the other monitorization methods for anesthetic depth to evaluate hemodynamics, drug costs and recovery.

In conclusion, the use of AoA for the management of general anesthesia decreases the amount of drug, thus cost of anesthetic drugs, providing a more rapid recovery process in patients. We believe that development of targeted anesthetic management systems will provide a more controllable and more economical anesthetic management.

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Conflict of Interest: None

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Original Article

End-tidal carbon dioxide levels under surgical drapes during local eye surgery: Retrospective study

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ABSTRACT

Objectives: To investigate the end tidal carbon dioxide pressure values in order to determine carbon dioxide accumulation under surgical drapes and it's hemodynamic effects based on anesthetic and surgical records in eye surgeries under local anesthesia
Design: Retrospective study
Setting: Department of Anesthesiology and Reanimation, Düzce Medical Faculty, Düzce, Turkey
Subject: The data were collected from anesthetic records of patients (n=42) who were followed with noninvasive capnography in the operating room at Düzce University Hospital during the period of January 2016 to December 2016. Systolic, diastolic and mean arterial pressure, operation time, heart rate, ST segment analysis, $ETCO_2$ pressure, pulse oximetry values were recorded. Time periods were determined as: after the anesthesia and before drape closure (baseline level), at 10th, 15th, 20th, 45th of the surgery and 5 minutes after drape removal.
Intervention: Non-interventional
Main outcome measure: C a rbon dioxide accumulation under drapes and it's hemodynamic effects in eye surgeries under local anesthesia.
Results: The comparisons were made with basal status and time periods statistically. No differences were found between mean arterial pressures, heart rates, arrhythmias and pulse oximetry values of pati ents between time periods. We observed significant di fferences for $ETCO_2$ levels between basal and the other ti me periods, except when the drapes were removed (P=0.001).
Conclusion: Routine mo nitorisation of $ETCO_2$ with noninvasive capnograph yprovides early detection of CO_2 accumulation and CO_2 rich air breathing during ophthalmic surgery.

KEY WORDS: ambient air quality monitoring, carbondioxide accumulation, end-tidal carbondioxide, eye surgery, surgery drapes

INTRODUCTION

The patients who undergo ophthalmic operations with spontaneous breathing may be exposed to exhaled carbon dioxide accumulation because of covering with ophthalmic drapes. This elevated carbondioxide level may aggravate the haemodynamic and cardiac changes of the patients. These changes also cause significant changes in cerebral blood volume and intracranial pressure[1].

Cerebral blood flow (CBF) is controlled by arterial blood pressure, arterial carbon dioxide (CO_2), arterial O_2 and brain activity, and is largely constant in the awake state. Although small changes in arterial CO_2 are particularly potent to change CBF (1 mmHg variation in arterial CO_2 changes CBF by 3-4%), the coupling mechanism is incompletely understood[2-3]. Elevated CO_2 blood levels have a depressant effect on the central nervous system and can lead to coma in adults. Less is known about the effect of CO_2 on the neurological function of infants[4].

The aim of this retrospective study is to determine the accumulation of CO_2 under cover and to investigate its side effects based on anesthetic records in eye surgeries under local anesthesia.

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SUBJECTS AND METHODS

After approval from the Düzce Faculty of Medicine Noninvasive Researches Ethics Committee (02.01.2017), data of all patients who underwent eye surgery in the operating room at Düzce University Faculty of Medicine Hospital during the period of 01 January 2016 to 31 December 2016 was collected. Of the 586 patients recorded, 79 had sterile surgical cotton fabric drapes, 501 had sterile plastic drape and six had no records. Patients whose anesthetic forms were followed with capnograph (Capnostream 20 p, Oridion, Israel) + sterile 3M plastic drape (n=42 patients) by the anesthesiology department were included in the study. All other patients were excluded. It was observed that 42 patient records met the retrospective study criteria. Demographic and clinical data were abstracted from anesthetic and clinical records.

When the cases were evaluated in terms of CO_2 accumulation, it was observed that most of the patients were not followed up with carbon dioxide. It was also found that two types of sterile drapes (sterile cotton fabric surgical drape and 3M sterile drape) were used during these operations. It was determined that the CO_2 measurements were done either by attaching the end of the capnograph sample line near the mouth of the patients or using the capnostream capnography device (n=42). For this reason, only the capnostream capnographic device and the data of the patients using plastic 3M sterile drape were evaluated in order to obtain the correct data. Capnostream capnograph records were taken from memory USB device.

Age, weight, height of the patients, operation type, duration of operation, types of local anesthetic used, noninvasive systolic, diastolic and mean arterial pressure, heart rates and ST segment analysis (Datex Ohmeda monitor, GE HealthCare, Finland) were recorded. Systolic, diastolic and mean arterial pressure measurements, end tidal carbon dioxide levels ($EtCO_2$) and pulse oximeter values were extracted from anesthetic forms retrospectively.

Arrhythmia recordings were evaluated as (yes / no) over time periods. Surgical field was covered with reusable cotton fabric drape or disposable surgical adhesive plastic drape (SteriDrape, 3M). We included only the records of patients who were covered with the same kind of drapes (SteriDrape, 3M). We excluded records with other types of drape usage or without drape usage to provide homogenization and clarity of the results.

Data were collected from the anesthetic forms at the baseline, before closing drape, at 10^{th}, 15^{th}, 20^{th}, 45^{th} minutes after covering and 5 minutes after drape removal. Records with pulmonary disease, diabetes mellitus, sedative usage and alcohol usage were excluded from the study.

The comparisons were made with patients basal status and time periods statistically.

Statistical analysis

Descriptive statistics (mean, standard deviation, median, minimum, maximum, percent) of all variables included in the study were calculated. The normality assumption for quantitative variables was examined by the Shapiro Wilk test. Variables that did not provide a normality assumption were subjected to Box-Cox transformation. Repeated Measures ANOVA (post hoc Fisher's LSD test) was used to compare time-dependent quantitative variables. The Cochran Q test was used to compare categorical variables measured at different periods. SPSS 22 program was used for statistical evaluations and P <0.05 was considered as statistically significant.

RESULTS

Between January and December 2016, the cases who had undergone local eye operation were examined from the Düzce University Hospital records. A total of 586 patients who had undergone local eye surgery at the specified time interval were identified. Of these patients, 79 had sterile surgical cotton fabric drapes, 501 had sterile plastic drape and six had no records.

Of the 107 patients with end-tidal CO_2 measurements, monitoring was performed by placing the tip of the capnograph sample line by the patient's mouth (n=65) or using a noninvasive capnography device (n=42).

The 42 records that used a noninvasive capnography device provided search criterias as follows: cataract surgery was performed via phacoemulsification in 36 of the 42 records (86%), and extracapsular cataract extraction (14%) was applied to the remaining six records. Thirty-nine (93%) of the records were given topical and three (7%) were subjected to retrobulbar anesthesia. The mean duration of operation was 30.45±14.48 (range: 10-60 minutes). It was observed that the duration of the operation was under 20 minutes in ten patients. Only one patient had under 10 minute duration time. The duration of the operation was equal to or longer than 20 minutes in approximately ¾ of the 42. Twenty-five of the 42 patients were female and 17 of them were male.

We deducted that 2 l/min oxygen delivery was performed in all 42 patients from digital consumption data records of our hospital.

Systolic arterial pressure (SAP) values at different periods were found to change significantly with time (P=0.006). SAP values were fo und to decrease from basal levels on SAP 10^{th} minu te (P=0.016), SAP 15^{th} minute (P=0.025), SAP 20^{th} minute (P=0.031), SAP 30^{th} minute (P=0.004) and SAP after drapes were removed

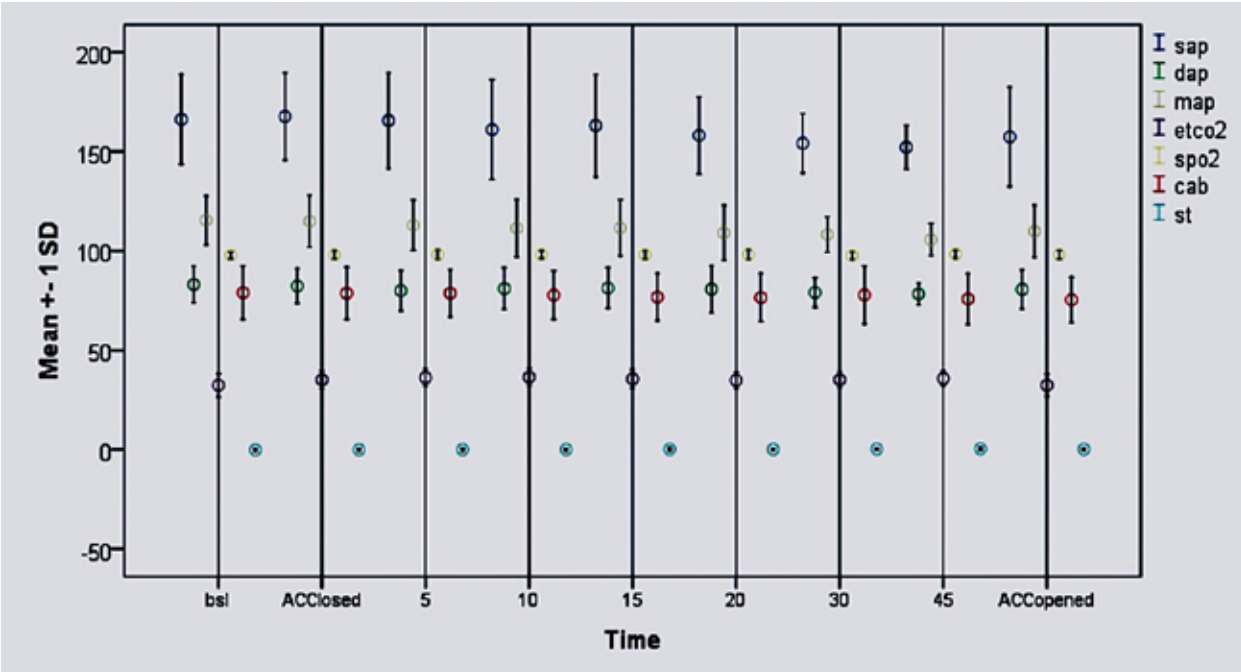

Figure 1: Non-invasive Systolic (SAP), diastolic (DAP), mean (MAP) arterial pressure, end-tidal carbondioxide ($EtCO_2$), pulse oximeter (SpO_2), ST segment (ST) and heart rate (CAP) level changes of the patients. Bsl: basal levels, ACClosed: after drapes were covered, 5, 10, 15, 20, 30, 45 min after drapes were covered, ACCopened: 2 minutes after drape removed. There were no differences between mean arterial pressures, heart rates, arrhythmias and pulse oxymeter values of patients in time periods. We observed significant differences for end-tidal carbon dioxide levels between basal and the other time periods, except remove the drapes. (P=0.001)

(P<0.001). Additionally, SAP values were found to decrease from after the drapes covered the operation area levels on SAP 10th minute (P=0.012), SAP 15th minute (P=0.018), SAP 20th minute (P=0.023), SAP 30th minute (P=0.003) and SAP values after drapes were removed (P <0.001)

It was determined that the mean arterial pressure values measured at different periods did not change significantly depending on the time (P=0.129, Figure 1). It was found that the end-tidal carbondioxide ($EtCO_2$) values measured at different periods changed significantly with time (P=0.001). $EtCO_2$ values were found to increase from basal levels on $EtCO_2$ values after drapes were covered, $EtCO_2$ values 5th minute (P <0.001), $EtCO_2$ values 10th minute (P <0.001), $EtCO_2$ 15th minute (P <0.001), $EtCO_2$ values 20th minute (P <0.001), $EtCO_2$ values 30th minute (P <0.001) and $EtCO_2$ values after drapes were removed (P <0.001; Table 2). Additionally, SAP values were found to decrease from after the drapes covered the operation area levels on SAP 10th minute (P=0.012), SAP 15th minute (P=0.018), SAP 20th minute (P=0.023), SAP 30th minute (P=0.003) and SAP after drapes were removed (P<0.001; Figure 1).

The SpO_2 values measured at different periods were found not to change significantly with time (P=0.863). It has been determined that the heart rate values measured at different periods did not change significantly with time (P=0.076).

It has been determined that ST values measured at different periods change significantly with time (P=0.021). ST segment analysis was found to increase from basal levels on 10th minute (P=0.019), 15th minute (P=0.013), 20th minute (P <0.001), 30th minute (P <0.001) and after drapes were covered (P <0.001). Additionally, ST segment analysis was found increased when compared with after drapes covered levels on 15th minute (P=0.036), 20th minute (P=0.003) and 30th minute (P=0.002). ST values were also shown to decrease nearly to basal levels after drapes were removed. It was observed that the arrhythmia state examined at different periods was not significantly different (P=0.429). It has been determined that the respiratory rate values measured at different periods changed significantly depending on the time (P<0.001).

It was observed that the arrhythmia status was not differentiated significantly at different periods (P=0.429; Table 1).

DISCUSSION

The vast majority of cataract operations are performed between 70-90 years old[5]. Fifty percent of cataract operations are performed with local anesthesia while spontaneously breathing[6].

Table 1: Distribution of arrhythmia status at different periods

Distribution of arrhythmia	n	Percent
Basal		
Yes	4	9.5
No	38	90.5
Total	42	100.0
Before drape closure		
Yes	4	9.5
No	38	90.5
Total	42	100.0
5th minute		
Yes	4	9.5
No	38	90.5
Total	42	100.0
10th minute		
Yes	4	9.5
No	38	90.5
Total	42	100.0
15th minute		
Yes	4	11.1
No	32	88.9
Total	36	100.0
20th minute		
Yes	2	8.0
No	23	92.0
Total	25	100.0
30th minute		
Yes	0	0.0
No	17	100.0
Total	17	100.0
45th minute		
Yes	0	0.0
No	6	100.0
Total	6	100.0
After drapes removed		
Yes	5	11.9
No	37	88.1
Total	42	100.0

In this age group, the incidence of one or more comorbidities such as diabetes, hypertension, coronary artery disease, heart failure or chronic renal failure is high[5]. The medical records of these high-risk patients should be reviewed before operation to ascertain intraoperative monitoring methods for the early diagnosis and prevention of hemodynamic and cardiovascular complications that may occur during the operation. Recommendations state that all patients undergoing major eye surgery under local anesthesia should have careful monitoring including pulse oximetry, electrocardiogram, noninvasive blood pressure and $EtCO_2$ measurement[7].

Several studies have shown that hypercapnia leads to coronary vasodilatation and has cardiac depresant effects[8]. In addition, it was demonstrated that administration of a gas mixture containing 20% CO_2 caused marked depression of myocardial contractility in cats[8-12]. Abnormal ST-T segment changes were identical to those of ischemia. The patient whose coronary blood flow does not increase adequately with an increase in cardiac work demand is under risk of impared contractility of the heart, hypotension, arrhythmias and death[13].

Conventional facial masks make the surgical procedure difficult because they are so close to the operating area that they are used to provide oxygenation in eye surgery[14].

Various methods have been developed to detect CO_2 accumulation under drapes[14-19]. In studies where nasal sampling line was connected to Datex Capnomac Ultima monitor, $EtCO_2$ accumulation was not detected[14]. In another study, $EtCO_2$ was measured with the help of an anesthesia monitor device (Cardiocap Datex, Helsinki, Finland) which has a special apparatus placed between the drapes and the faces of the patients. In this study, transcutaneous partial carbon dioxide was also measured.

Also in this study, it is stated that this increase in the $EtCO_2$ values cannot be measured by routine monitoring methods and that the applied oxygen supplement does not prevent CO_2 accumulation[15].

Microstream technology was used on Capnostream 20p capnograph for con t inuous view of ventilation adequacy on intubated a nd non-intubated patients from neonate to adult.

These devices are used for eye surgery in our clinic and all of the $EtCO_2$ recordings in our surveys have been observed to be ob tained by means of a nasal cannula extending to t he mouth and measuring the pulse oximetry and $EtC O_2$ measurement allowing both oxygen delivery. The four parameters measured

Table 2: End tidal carbondioxide records in time periods

Time period	n	Mean (mmHg)	Standard Deviation (mmHg)	Minimum (mmHg)	Maximum (mmHg)
Basal	42	32.38	5.85	17	49
Before drape closure	42	35.17	4.66	28	47
5th minute	42	36.21	4.16	28	46
10th minute	42	36.48	4.33	29	47
15th minute	35	35.57	4.70	26	47
20th minute	25	34.92	4.13	26	43
30th minute	17	35.18	4.11	28	46
45th minute	6	35.83	3.76	29	39
After drape removal	42	32.36	5.62	21	44

by this device, $EtCO_2$, oxygen saturation, respiratory rate and pulse rate, are integrated to give one number called integrated pulmonary index[19]. It has been observed that the records of the integrated pulmonary index are not available in our records.

In our records, there was no statistically significant change in noninvasive, mean, diastolic arterial blood pressure and heart rate as a function of time compared to baseline levels of the patients, but noninvasive systolic arterial pressure increased statistically significantly during operation compared to baseline values.

A meaningful and statistically significant increase that was observed in the $EtCO_2$ levels indicates the accumulation of carbon dioxide under the cover. However, no new arrhythmia patterns was observed in any of the patients in our records. When the ST segment changes were examined in our records, it was found that there was an increase in the ST segment in the positive direction, that is, statistically and clinically significant ST elevations were observed.

In this sense, we think that the effects on the cardiovascular system can be evaluated more clearly by examining the serial electrocardiogram records to be taken in future prospective studies together with the increase of the underlying $EtCO_2$ levels.

The Joint Working Party on Anesthesia in Ophthalmic Surgery by the Royal College of Ophthalmologists report in February 2012 recommended monitoring methods include: communication, clinical observation, pulse oximetry, electrocardiogram and non-invasive blood pressure. $EtCO_2$ measurements are not included in this schema yet. Our aim in this study is to investigate the accumulation of carbon dioxide under drapes in eye surgery under local anesthesia and to raise awareness of the potential hazards of this accumulation. At the same time, we think that $EtCO_2$ monitoring must be included in the necessary and basic monitoring techniques in these kind of operations.

CONCLUSION

End-tidal carbon dioxide levels should be monitored in patients in whom sedation is performed, the airway is not secured and the anesthesiologist is difficult to reach, in the patient group who can accumulate carbon dioxide under the cover and cannot tolerate hypercarbia.

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Original Article

Efficacy of lamotrigine for seizures, dysexecutive symptoms, anger and sadness rumination in patients with epilepsy

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ABSTRACT

Objectives: To compare epilepsy patients and healthy individuals on dysexecutive symptoms, sadness and anger rumination and to assess efficacy of lamotrigine on seizure frequency, dysexecutive symptoms, sadness and anger rumination in patients with epilepsy
Design: Comparative cross-sectional research study
Setting: Department of Neurology at Sheikh Zayed Hospital, Rahim Yar Khan and Nishter Hospital, Multan, Pakistan
Subjects: Forty patients with epilepsy and forty healthy individuals participated in the study from 1st August 2017 until 29th March 2018.
Intervention: Healthy individuals had single whereas patients had two testing sessions (baseline vs. post- six months lamotrigine therapy as part of treatment). Patients completed Rumination on sadness scale, Anger Rumination Scale and Dysexecutive symptoms questionnaire during baseline and post-lamotrigine therapy. On contrary, healthy individuals completed these measures in baseline session only.
Main outcome measure: Rumination on Sadness Scale, Anger Rumination Scale and Dysexecutive symptoms questionnaire
Results: Baseline scores showed that patients with epilepsy had dysexecutive symptoms (22.17±1.43 vs. 8.47±1.99), rumination on sadness (40.12±2.82 vs. 11.10±2.55), and anger (66.17±6.17 vs. 19.60±3.39) in contrast with healthy individuals. Post-treatment performance showed significant reduction in seizure frequency (7.37±1.58 vs. 1.95±0.78), dysexecutive symptoms (22.17±1.43 vs. 17.57±2.01), sadness (40.12±2.82 vs. 23.50±3.35) and anger (66.17±6.17 vs. 41.15±4.88) rumination in adults with epilepsy.
Conclusion: Lamotrigine therapy is effective in reducing seizures, dysexecutive symptoms, anger and sadness rumination in adults with epilepsy.

KEY WORDS: antiepileptic drugs, cognition, emotion

INTRODUCTION

Epilepsy is a noncommunicable neurological condition which is diagnosed in 2.4 million people each year around the world. Among this number, 80 percent of people live in low- and middle-income countries. Epilepsy is characterized by recurrent seizures, cognitive and emotional disorders[1]. A large disparity occurs in treatment and care of epilepsy patients in the world, with treatment gap of 75% in low income and 50% in middle income countries[2]. The situation is equally alarming in Pakistan, where the number of people diagnosed with epilepsy has crossed 2 million and management of epilepsy is poor due to several reasons, for instance lack of awareness and belief in supernatural phenomenons[3]. Though treatment of epilepsy is available in Pakistan, unfortunately only 25% of the affected population get treatment[4]. Studies with Pakistani population have suggested that patients with epilepsy are at high risk of developing psychological distress, anxiety, depression and social problems in marriage and daily activities[5]. It was also found that non-compliance of medication was associated with poor clinical result in Pakistani patients with epilepsy[6]. Another study demonstrated that patients with epilepsy had weaker prefrontal cortical functioning and emotion recognition as compared with healthy individuals[7].

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There are many treatment options available for epilepsy. Lamotrigine (6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine), a phenyltriazine is a popular antiepileptic drug of unique characteristics[8]. Lamotrigine is associated with improved cognitive status and quality of life in epileptic patients[9]. Lamotrigine exerts antiseizure activity by preventing presynaptic release of excitatory neurotransmitters (glutamate) through blocking activated channels of sodium and stabilizing neuronal membrane[10]. In recent years, its' effectiveness as a mood stabilizer has been explored. In vivo studies have demonstrated that lamotrigine down regulates responses of adenyl cyclase in brain mediated by cortical serotonin ($5\text{-}HT_{1A}$)-receptor[11]. Studies examining behavioral and cognitive functioning of individuals with epilepsy have indicated presence of impaired inhibitory control and emotional intelligence in these patients[12].

To our knowledge, effect of lamotrigine on dysexecutive symptoms, sadness and anger rumination in adults with epilepsy has not been examined in existing literature. Specifically, with reference to Pakistani subjects, no study has yet explored effectiveness of lamotrigine on clinical and social cognition parameters such as seizure frequency, dysexecutive symptoms and emotional rumination. Therefore, the current study was designed to examine efficacy of lamotrigine on these parameters. It was hypothesized that (i) patients with epilepsy would show dysexecutive symptoms in contrast with healthy adults; (ii) patients with epilepsy would show higher sadness and anger rumination contrary with healthy adults; and (iii) lamotrigine would be beneficial in reducing seizures, dysexecutive symptoms, sadness and anger rumination in patients with epilepsy. The objective of this study was to compare patients and healthy individuals on dysexecutive symptoms, sadness and anger rumination and assessment of efficacy of lamotrigine on seizure frequency, dysexecutive symptoms, sadness and anger rumination in patients with epilepsy.

SUBJECTS AND METHODS

This study has a comparative cross-sectional research design and was conducted at the Department of Neurology Nishter Hospital, Multan, and Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan from 1st August 2017 until 29th March 2018. Forty newly diagnosed patients with partial epilepsy were included having no history of treatment with lamotrigine and neurological disease excluding epilepsy. Their age range was 20-45 years and were prescribed lamotrigine as monotherapy for at least six months with dose range of 50-200 mg per day. Patients with epilepsy were excluded if they were prescribed any antiepileptic drug except lamotrigine and were using any other medication at the time of diagnosis. Forty healthy counterparts took part in the study from the local community with age range of 20-45 years. They were included if they had no history or present symptoms of any neurological disease and psychiatric disorder. Healthy individuals were excluded if they were using any medication and had cognitive complaints. The study was ethically approved by The Islamia University of Bahawalpur, Pakistan and was conducted according to the declaration of Helsinki.

Instruments

A revised version of Dysexecutive Questionnaire (DEX)[13] was used to assess dysexecutive symptoms, inhibition and social regulation. The questionnaire contains 15 items which are scored on Likert scale (0 = never – 4 = very often), for example "I am lethargic or unenthusiastic about things". Average completion time is lesser than five minutes. The questionnaire has good psychometric properties. Rumination on Sadness Scale (RSS)[14] is a thirteen self-report item scale with five response categories, high score shows greater sadness rumination. RSS has good reliability, convergent and discriminant validity. Anger Rumination Scale (ARS)[15] has 19 statements to be responded on four response categories. High score reflects greater anger rumination. The scale has good reliability, convergent and discriminant validity. All participants gave written informed consent. Testing of DEX, RSS and ARS were completely randomized across participants. In the baseline session, participants were asked to complete DEX, RSS and ARS. The follow-up session was conducted post six months of lamotrigine therapy. In follow-up session, patients were tested on DEX, RSS and ARS.

Statistical analysis

Data on demographic and clinical characteristics were analyzed through descriptive statistics. Scores pertaining to patients and healthy individuals were compared on ANOVA with Factor 6 (dysexecutive symptoms, inhibition, social regulation, total DEX scores, RSS, ARS) as within subjects x Group 2 (healthy individuals vs. patients with epilepsy) as between subjects group. Baseline and post-lamotrigine therapy scores of patients on DEX, RSS and ARS through repeated measures ANOVA with testing session as with-in subject factor 2 (pre vs. post- Lamotrigine treatment). Seizure frequency on baseline and post-treatment was compared between patients and healthy individuals through *t*-test.

Table 1: Demographic and clinical characteristics of the sample (N=80)

Characteristics	Adults with epilepsy (n=40) M ± SD	Healthy individuals (n=40) M ± SD	t (df), *P*-value
Age (20-45 years)	33.30±7.06	32.05±6.69	t (39)=1.14, P=0.25
Gender male/female (n)	20/20 (50%)	20/20 (50%)	
Dose (50-200 mg/day)	99.97±53.27		
Seizure/month(n) during last 3 months at baseline (4-10)	7.37±1.58	-	t (39)=18.12, P<0.001
Seizure/month(n) during last 3 months at 6 months of Lamotrigine treatment (1-3)	1.95±0.78	-	

RESULTS

Eighty participants (40 patients and 40 healthy individuals) took part in this study as shown in Table 1. The age range for participants was 20 to 45 years whereas patients (33.30±7.06) and healthy individuals (32.05±6.69) were of similar age groups t (39)=1.14, P=0.25. Patients and control group were matched on gender (50% male and 50% female). There was significant decrease in seizure frequency post- six months of lamotrigine treatment t (39)=18.12, P <0.001. Seizure frequency per month for the last three months at baseline testing session was four to ten with mean 7.37±1.58. Post-treatment testing session showed that number of seizures per month was reduced t (39)=18.12, P <0.001 with mean 1.95±0.78 (range 1-3).

Table 2 showed that there were significant main effects of Factor F (5,78) = 2529.80, P <0.001, ηp2=0.97 and Group F (5,78) = 5336.31, P <0.001, ηp2=0.98. Factor x Group F (5,78) = 742.36, P <0.001, ηp2=0.90 interaction was significant. Patients with epilepsy showed higher scores than healthy individuals on dysexecutive symptoms (22.17±1.43 vs. 8.47±1.99), inhibition (24.87±1.97 vs. 8.35±1.23), social regulation (7.50±0.50 vs. 2.95±0.81), DEX total (54.55±2.63 vs. 19.77±2.65), RSS (40.12±2.82 vs. 11.10±2.55), and ARS (66.17±6.17 vs. 19.60±3.39).

Table 3 showed that compared with baseline, post-lamotrigine treatment showed lesser scores on dysexecutive symptoms F(1,39) = 163.73, P <0.001, ηp2=0.80, 22.17±1.43 vs. 17.57±2.01; inhibition F(1,39) = 644.52, P <0.001, ηp2=0.94, 24.87±1.90 vs. 16.22±2.05; social regulation F(1,39)= 454.60, P <0.001, ηp2 =0.92, 7.50±0.5 vs. 5.42±0.50; total DEX scores F(1,39) = 831.20, P <0.001, ηp2 =.95, 54.55±2.63 vs. 39.22±3.12; RSS F(1,39) = 642.21, P <0.001, ηp2=0.94, 40.12±2.82 vs. 23.50±3.35 and ARS F(1,39) = 490.19, P <0.001, ηp2=0.92, 66.17±6.17 vs. 41.15±4.88.

DISCUSSION

This study showed that patients with epilepsy were deficient in executive abilities and exert rumination on sadness and anger in contrast with healthy individuals. Patients had lower inhibition and social regulation skills as compared with healthy individuals. In contrast, they had higher dysexecutive symptoms than healthy adults. Patients had higher anger and sadness rumination contrary with healthy adults. However, there was significant improvement in these parameters post lamotrigine medication in patients. Compared with baseline performance, patients showed significant reduction in seizures frequency. Dysexecutive symptoms, inhibition and social skills were improved. It was found that anger and sadness rumination were reduced in patients after lamotrigine therapy.

These results are consistent with previous reports of cognitive decline and executive function deficits in patients with epilepsy[16,17]. Rather, findings of this study provided detailed results pertaining to executive function deficits. All components of dysexecutive symptoms were present in epilepsy

Table 2: Mean scores of healthy individuals and adults with epilepsy on subscales of Dysexecutive questionnaire (DEX), Rumination on sadness scale, and Anger rumination scale (N=80).

Variables	Healthy individuals (n=40) M ± SD	LB-UB	Adults with epilepsy (n=40) M ± SD	LB-UB
DEX Dysexecutive symptoms	8.47±1.99	7.92-9.02	22.17±1.43	21.62-22.72
DEX inhibition	8.35±1.23	7.83-8.86	24.87±1.97	24.35-25.39
DEX Social Regulation	2.95±0.81	2.73-3.16	7.50±0.50	7.28-7.71
DEX Total	19.77±2.65	18.94-20.60	54.55±2.63	53.71-55.38
Rumination on Sadness Scale	11.10±2.55	10.25-11.94	40.12±2.82	39.27-40.97
Anger rumination scale	19.60±3.39	18.03-21.16	66.17±6.17	64.60-67.74

DEX: Dysexecutive Questionnaire; LB-UB: lower bound-upper bound

Table 3: Baseline and Post-treatment scores from Repeated Measures ANOVA of adults with epilepsy on subscales of Dysexecutive questionnaire (DEX), rumination on sadness scale, and Anger rumination scale (n=40).

Variables	Baseline M ± SD	LB-UB	Post-treatment M ± SD	LB-UB
DEX Dysexecutive symptoms	22.17±1.43	21.62-22.72	17.57±2.01	16.93-18.21
DEX inhibition	24.87±1.97	24.35-25.39	16.22±2.05	15.56-16.88
DEX Social Regulation	7.50±0.50	7.28-7.71	5.42±0.50	5.26-5.58
DEX Total	54.55±2.63	53.71-55.38	39.22±3.12	38.22-40.22
Rumination on Sadness Scale	40.12±2.82	39.27-40.97	23.50±3.35	22.42-24.57
Anger rumination scale	66.17±6.17	64.60-67.74	41.15±4.88	39.58-42.71

DEX: Dysexecutive Questionnaire; LB-UB: lower bound-upper bound

patients such as lack of inhibition and social regulation in patients with epilepsy. This illustrates that patients with epilepsy are deficient in cognitive skills, for example planning, switching and social skills. The underlying pathological factors include abnormal functional connectivity between cognition related brain areas[18], changes in neurogenesis and excitatory –inhibitory balance due to seizures[19], amygdala enlargement[20], and overlap of functional connectivity between hemisphere and epileptogenic zone[21]. These results are consistent with previous reports of increased comorbidity of temporal lobe epilepsy with obsessive-compulsive symptoms[22]. Previous research has shown the presence of obsessive-compulsive behaviors, maladaptive rumination and obsessive thoughts as a biological predisposition in patients with temporal lobe epilepsy. These psychiatric symptoms are unrelated to clinical characteristics of epilepsy such as medication, etiology, seizure severity and control etc[23]. The conduction of automated behaviors which are often ritualistic and repetitive in nature are facilitated by the connection of amygdala with the striatum in obsessive-compulsive disorder. Apart from this, these characteristics arise due to the dysfunction of the collateral loop (*i.e.*, striatal-orbitofrontal-thalamic) mediated by dopamine, serotonin, and gamma-amino butyric acid which results in the inhibition of input into the frontal cortex by the thalamic nucleus[24].

Findings of the present study showed that patients had higher frequency of emotion rumination compared with healthy individuals. This result is consistent with previous studies of epilepsy patients in Pakistan which showed that psychiatric problems such as anxiety, depression, distress and social functioning deficits were common in patients with epilepsy[5]. It was also found that deficient social cognition was due to impaired inhibitory control in patients with epilepsy[7]. This suggests that patients have lesser regulatory control on emotions. In this context, results of the present study are in line that patients ruminate when they feel sad and angry.

Antiepileptic drugs are used to treat seizures whilst are associated with toxicity. Among these pharmacological agents, lamotrigine has the potential to control seizures and enhances cognition in epileptic patients[25]. Efficacy of lamotrigine on executive abilities and rumination in the present study is in line with previous studies which highlight lamotrigine not only as a cognitive enhancer rather a mood stabilizer which acts through inhibiting glutamate, modifying neuronal excitation, and controlling ion channels[26,27]. Long term effects in epileptic patients showed improvement in higher order cognitive functioning[28]. Lamotrigine as a monotherapy is efficacious in reducing seizures, behavioral and cognitive problems in epileptic patients[29]. Likewise, lamotrigine is beneficial in the treatment of behavioral problems comorbid with other psychiatric disorders. For instance, small doses of lamotrigine (*i.e.*, 10 mg/less per day) were found useful in the reduction of behavioral problems in patients with severe mental retardation[30]. In complex elderly patients with behavior problems and psychiatric syndromes, a modest improvement in agitation and aggression was also observed with lamotrigine treatment[31]. In geriatric patients with bipolar disorder, lamotrigine treatment delayed depression related mood relapse[32]. Results of this study are constrained by few limitations. Lamotrigine related changes on executive functions could differ with other cognitive measures. Effects of lamotrigine therapy on executive abilities and rumination must be assessed on long term basis. Thus, results must be considered as preliminary evidence which should be further examined.

Limitations

The efficacy of lamotrigine must be examined for all basic emotions and cognitive abilities other than executive tasks. Results of this study must be taken as preliminary evidence due to small sample size and inclusion of partial epilepsy patients only.

Implications and future research

Results of this study are beneficial in clinical practice for better rehabilitation of patients with

epilepsy. Lamotrigine therapy could be administered to treat cognitive and emotion deficits. Future research must examine whether lamotrigine would be beneficial in the treatment of behavioral disorders.

CONCLUSION

Lamotrigine is efficacious in reduction of dysexecutive symptoms, seizure frequency, sadness and anger rumination in patients with epilepsy.

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Author's contribution: Amara Gul: manuscript writing, conception of idea, data collection, data analysis, interpretation of results. Saima Mehreen: data collection, literature review, data analysis.

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Original Article

Arthroscopic assisted percutaneous figure of eight tension band wiring of patellar fractures

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ABSTRACT

Objective: Different techniques have been reported involving combinations of K-wires, screws and cerclage wiring for the surgical treatment of patellar fractures in the case of disruption in the extension mechanism or articular incongruence of 2 mm or more. The aim of this study was to describe a new and easy arthroscopic assisted reduction and percutaneous tension band wiring technique for displaced fractures of the patella that combines the advantages of minimally invasive surgery and stable internal fixation.
Design: Retrospective study
Setting: Department of Orthopaedics and Traumatology, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey
Subjects: Seventeen patients were treated with arthroscopic assisted reduction
Intervention: Arthroscopic assisted reduction and percutaneous tension band wiring technique for transvers patella fracture
Main outcome measures: Patients evaluated according to evidence of radiological union and articular incongruence, range of motion and activity level
Results: The mean follow-up period was 18 months and the mean patient age was 41 years. Nonunion, articular incongruence or reduction loss were not detected in any case.
Conclusion: The described technique is minimally invasive and cosmetically pleasing, permits ideal image of the reduction and stability of the fracture, allows concomitant intraarticular pathology to be exposed, and facilitates early rehabilitation. It should be considered as an alternate method of treatment in displaced transverse patella fractures with an altered joint surface.

KEY WORDS: arthroscopic assisted reduction, cerclage wiring, patella fracture, tension band

INTRODUCTION

Patella fractures account for 1% of all fractures[1]. Surgery is indicated if there is disruption of extensor mechanism or articular incongruence of 2 mm and more[2,3]. Several techniques involving combinations of K-wires, screws and cerclage wiring are reported for surgical treatment of patella fractures[1,4-12].

Conventionally, the treatment of a displaced patella requires a wide incision to expose fracture fragments and joint surface[1,5]. Such incisions may lead to adhesions, prolonged disability for work and cosmetically unpleasant scar tissue[5,13]. On the other hand, percutaneous surgical techniques preserve the vascular supply of patellar fragments, which may improve fracture consolidation[6]. With the use of arthroscopy, it is possible to evaluate the articular surface reduction without performing an arthrotomy, making it possible to perform a closed reduction and a percutaneous treatment of the fracture[5,7]. We describe a new and easy arthroscopic assisted reduction and

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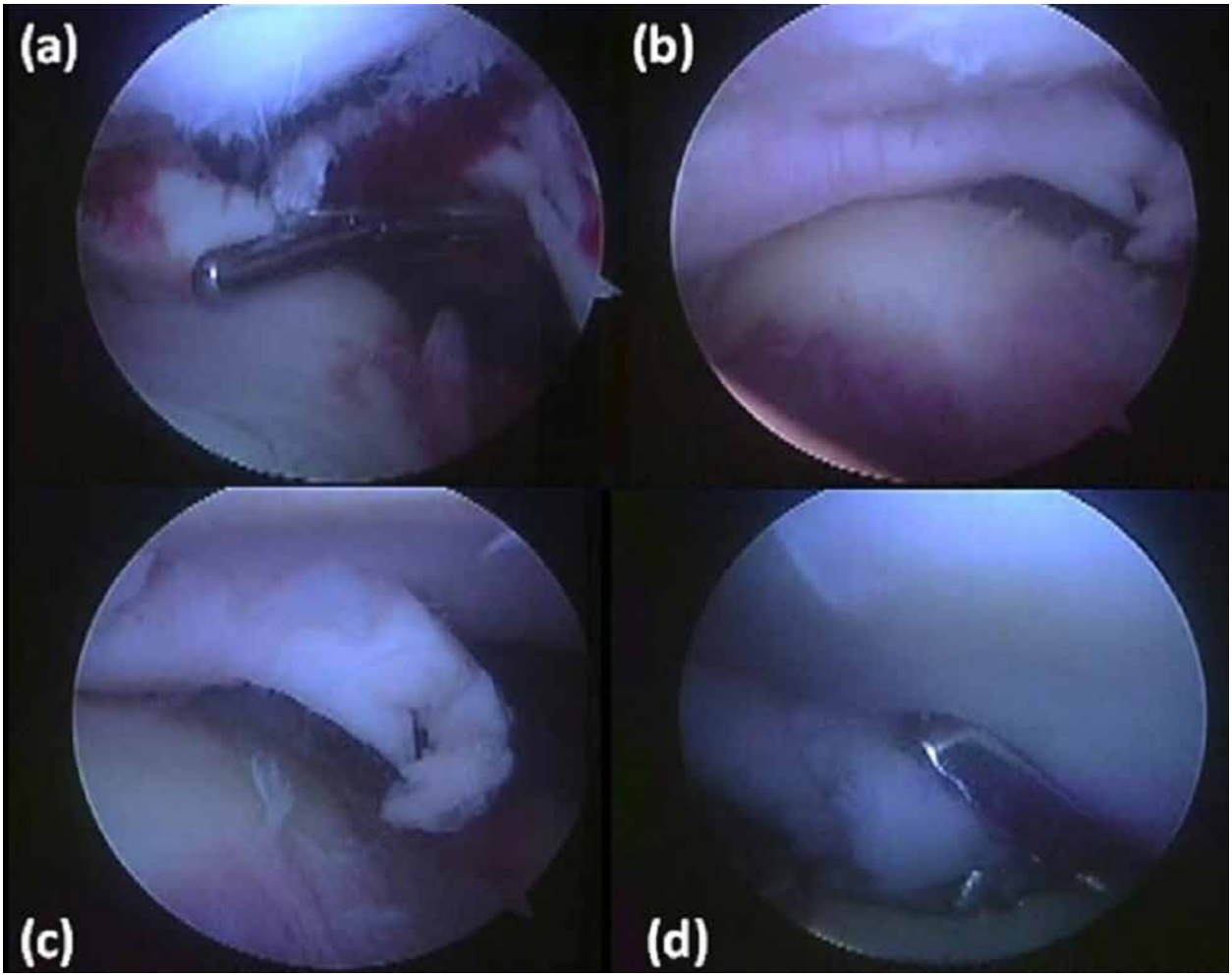

Figure 1: (a) An osteochondral fragment captured by punch; (b) arthroscopic view of chondral lesion of patella; (c) the magnified image of the same lesion; (d) the lesion is debrided by punch

percutaneous tension band wiring technique for displaced fractures of the patella that combines the advantages of minimally invasive surgery and stable internal fixation. This may lead to less morbidity, a short hospitalization period and an accelerated knee recovery. This technique is not indicated for fractures with laceration of patellar retinaculum that need open repair of soft tissue to mend extensor mechanism.

SUBJECTS AND METHODS

We performed the surgery with the patient in the supine position and the knee extended. One gram of Cefazolin sodium was administered intravenously and then the tourniquet was inflated to 300 mmHg. Superolateral and superomedial arthroscopic portals were used to drain the hematoma and to visualize fracture lines clearly. The chondral and osteochondral fragments were taken out by shaver and punch (Fig 1a-d).

We reduced the fracture by percutaneously applied towel clips under arthroscopic visualization of fracture lines (Fig 2a). After the reduction, we inserted two 3.0 mm Kirschner (K) wires in a caudocranial direction, under the arthroscopic control of precise reduction. The reduction was also checked by C scope. Four stab incisions were done to assign the inferolateral (IL) and inferomedial (IM) (Fig 2b), superolateral (SL) and superomedial (SM) (Fig 2c) portals besides the entrance and exit points of K wires for cerclage wiring. A trocar was inserted with its cannula from SL portal to SM portal under the K wires. The trocar was taken out and the cannula was left inside. An 18-gauge cerclage wire was run through the cannula in SL to SM direction. The cannula was then taken out. We inserted the trocar together with the cannula from SM portal through IL portal over the patella. The trocar was taken out and the cannula was left inside. Then, 18-gauge cerclage wire was run through the cannula in SM to IL direction (Fig 2d).

The cannula was taken out. The exact same steps were performed directed from IL portal to IM portal and from IM portal to SL portal (Fig 3a & b). Finally,

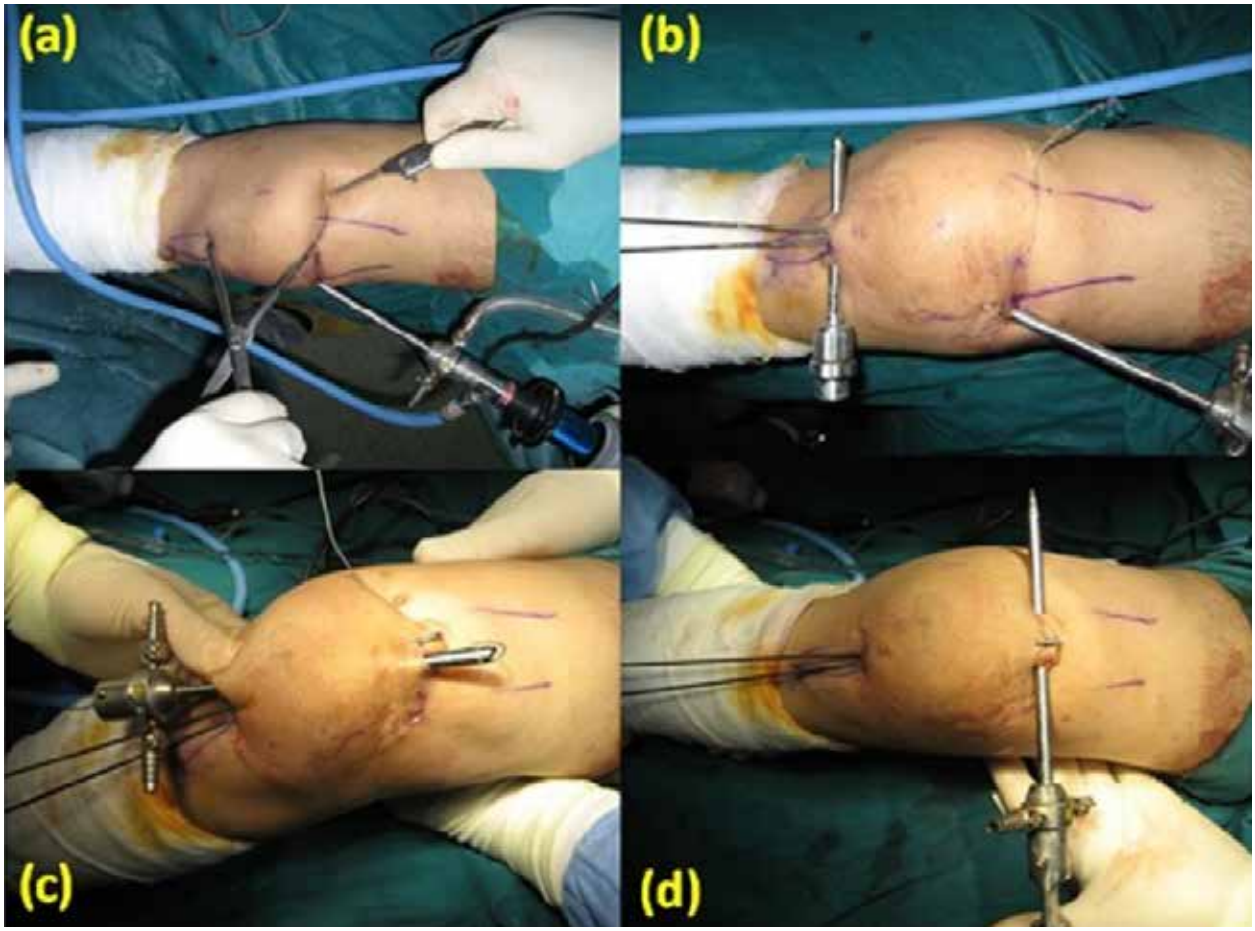

Figure 2: (a) Percutaneous fracture reduction under arthroscopic control; (b) inferolateral and inferomedial portals for cerclage wiring; (c) superolateral and superomedial portals for cerclage wiring; (d) cerclage wire applied through the cannula in superomedial to inferolateral direction

near the SL portal, both wires are tensed and secured to each other with a single knot (Fig 3c).

C scope was used to check figure of eight tension band wiring fixation (Fig 4a & b). Reduction was controlled by arthroscope during the operation.

Stab incisions were closed. The operation time ranged from 40 minutes to 64 minutes with an average of 51 minutes. In all patients, quadriceps setting exercises were encouraged immediately after the operation. An immobilizer brace was applied for two days. Patients were permitted to walk with crutches without weight bearing on the third day. Range of motion exercises were begun on the third day. Partial weight bearing was allowed three weeks

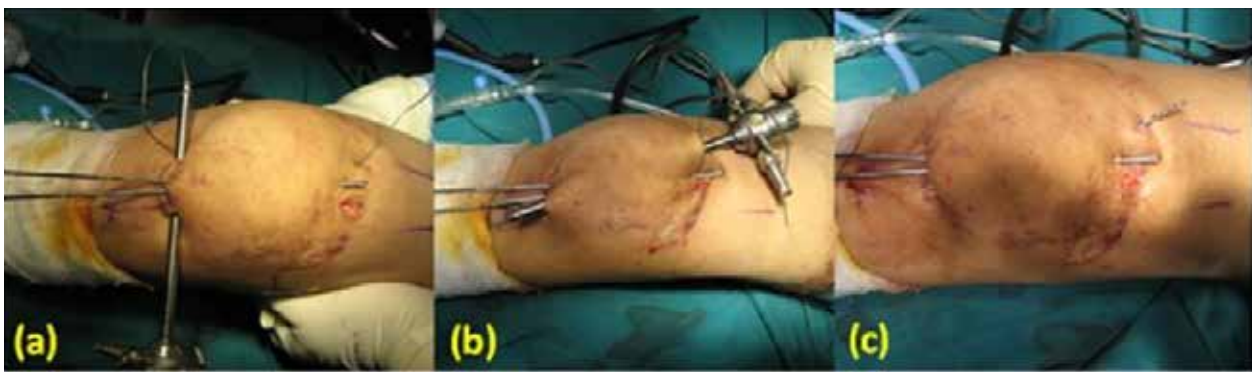

Figure 3: (a) Cerclage wire applied through the cannula in inferolateral to inferomedial direction; (b) cerclage wire applied through the cannula in inferomedial to superolateral direction; (c) wires are knotted near the superolateral portal

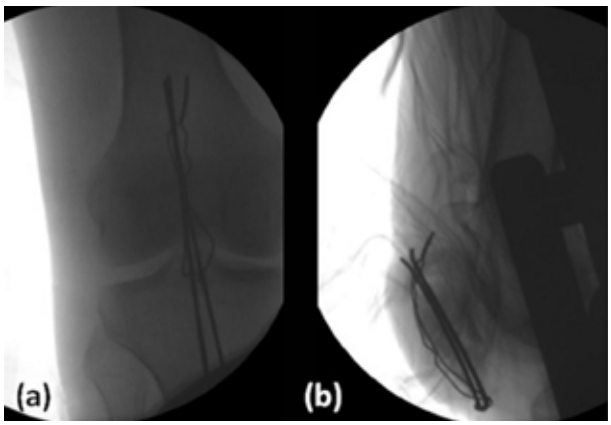

Figure 4: (a) Anteroposterior view of reduction by C-scope; (b) lateral view of reduction by C-scope

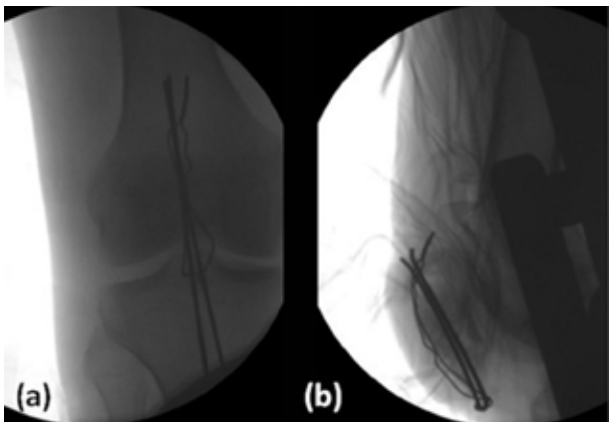

Figure 5: (a) Postoperative two month AP; (b) lateral radiographs present fracture healing

postoperatively. In all patients, full weight bearing was allowed after the fracture was healed radiographically. This time varied from 6 to 8 weeks.

RESULTS

The described technique was applied in 17 patients (average age: 41 years). All cases presented displaced but not multifragmented simple transverse patella fractures with an altered joint surface. The average follow-up of this series was 18 months. Radiographic consolidation was achieved in all patients at an average of two months (Fig 5a-b).

The range of motion was similar to the contralateral knee. All patients returned to the activity level previous to the fracture.

DISCUSSION

Patella fractures are operated to provide a smooth articular surface and to sustain rigid fixation while initiating early knee range-of-motion[1-3]. In intra-articular fractures, irregularity of articular surface results in post-traumatic arthritis, and prolonged immobilization of the knee may cause joint stiffness[1]. We performed percutaneous tension band wiring for displaced patella fractures under arthroscopic control to achieve perfect articular congruence. This new, easy and minimally invasive rigid fixation technique encouraged us for early aggressive rehabilitation.

For displaced patella fractures, a variety of internal fixation techniques have been recommended; including screw fixation, cerclage wiring, tension-band wiring with or without transfixing screws, and external fixation[1,4-12]. The stability of several techniques has been compared[14-16]. Benjamin *et al* compared the stability of screw fixation, modified AO tension-band wiring, Magnusson wiring and Lotke longitudinal anterior band in cadaver knees[14]. The authors recommended screw fixation for patients with adequate bone stock and modified tension-band wiring those with osteopenic bone and comminuted fracture[14]. Carpenter *et al*[15] compared the stability of three different techniques: modified tension-band wiring, two parallel interfragmentary lag screws, and tension-band wiring with two cannulated lag screws. The authors concluded that combining interfragmentary screw fixation with the tension-band principle appears to provide the best stability.

Minimally invasive surgery is increasing its popularity in orthopaedic and trauma surgery[17-19]. Lessened surgical trauma means less postoperative pain, earlier rehabilitation and shortening of hospitalization[17-19]. Authors studied for percutaneous fixation of patella fractures for years[5-12,20,21]. Percutaneous techniques have gained popularity as they tend to decrease skin adhesions and complications such as infections[6,8-10]. According to Leung *et al*[20], the mechanical effect of a tension band loop is well maintained whereas the soft tissue damage is reduced to a minimum. Recently, Luna-Pizarro *et al*[6] introduced a new device (percutaneous patellar osteosynthesis system) for percutaneous tension band wiring of displaced patella fractures. They compared this technique with conventional open surgery in a randomized controlled trial. They found significantly reduced surgical time, less pain at 4 and 8 weeks after the operation, and better knee function 8 weeks and 12 months after the procedure with percutaneous fixation, as compared with patients undergoing conventional open surgery. This technique was further improved by Kose *et al* with the addition of arthroscopy[22]. They performed arthroscopic examination to expose intra-articular lesions and to assess the quality of reduction. Authors recommended percutaneous patellar osteosynthesis system to overcome technical difficulty, to be sure about the reduction, and for parallel placement of the K-wires. We did not need such a custom-made device. By the help of trocar, we think that it is technically easier to pass away the cerclage

wires percutaneously and to be sure about the reduction and fixation, we used C-scope and arthroscope.

Sattler and Schikorski were first to report the arthroscopic-assisted treatment of patella fractures[23] in 1987. They treated 11 cases of transverse patellar fractures by closed screw osteosynthesis under arthroscopic guidance. In 1993, Appel and Siegel[5] described an arthroscopic-assisted percutaneous, cannulated screw fixation technique and other authors reported good results with similar technique[8,11]. Turgut *et al*[7] treated 11 cases well by percutaneous, arthroscopic-assisted osteosynthesis using two crossing K-wires augmented by a circumferential cerclage wire loop. Modified tension band technique, which we performed, has biomechanical advantages over these arthroscopic-assisted techniques. However, Makino *et al*[10] reported excellent preliminary results with arthroscopic-assisted reduction and fixation of five fractures by two cannulated lag screws with tension band wiring. They used two cerclage wires and so two knots to achieve figure of eight wiring. This may be an alternative technique but we have some concerns. Firstly, we are not sure if it provides the same stability as the one cerclage figure-of-eight wiring of Carpenter *et al*[15]. Another comparative biomechanical study should be done to quantify the stability of two cerclage figure-of-eight wiring. Also, two knots may cause more irritation. Finally, considering the screws, it may be hard to apply without a good bone stock, especially in elderly patients with osteopenia[14,8]. Confirming this opinion, Tandogan *et al*[8] performed percutaneous cannulated screw fixation in five patients, but they felt the need for circumferential cerclage wire loop in two elderly patients with osteopenic bone.

The most apparent advantage of the arthroscopic technique is the precision of controlling the articular surface reduction without the need for large surgical incisions. It is also useful to detect intraarticular chondral and osteochondral fragments, to evaluate the cruciate ligaments, the menisci, the tibial plateau, and the femoral condyles that can potentially be injured during the initial trauma[7,8,10,22]. The stability of fixation can also be verified arthroscopically[8]. No motion should be visible in the fracture line while flexing and extending the knee[8]. Postoperative pain control and rehabilitation are easier because large incisions are avoided[8]. Early mobilization is beneficial for articular cartilage nutrition, prevents muscle atrophy and the formation of intraarticular adhesions[1,24].

Some authors reported irritation of the anterior knee area because of wires and wire knots[4,7]. This may be a disadvantage of this technique. Yanmis *et al*[9] advocated the application of a circular external fixator to overcome this problem. However, in closed and noncommunited patellar fractures, we think that to charge the patient with that device until union is hard to tolerate and sustains pin-tract infection risk. Besides, the results in the previous reports were good or excellent, even some patients needed extraction of the wires[4,7].

The major limitation of this technique is that the retinacular tears cannot be repaired simultaneously as in an open technique. Also, as seen in radiological picture of postoperative view, Fig 4 presents K wires that are too close to each other and the figure of eight loop that seems to be not tight enough to provide firm fixation. Since no extra incision and portal are made by using a minimally invasive technique, soft tissue cannot be cleared to the bone for the figure of eight tension band wires. We can provide adequate tension and control it with C scope peroperatively. It may be technically demanding in the beginning, but we have no complications from this situation.

CONCLUSION

Arthroscopic-assisted percutaneous figure-of-eight tension band wiring of patellar fractures is a new technique that presents important advantages over open techniques. The technique is minimally invasive and cosmetically pleasing, permits ideal image of the reduction and stability of the fracture, allows concomitant intraarticular pathology to be exposed, and facilitates early rehabilitation. Our technique may be used for not multi-fragmented simple transverse patella fractures. It can be very hard to apply in comminuted fractures where direct reduction and strong fixation are difficult without requiring visualization of the fracture site. Although we have not attempted it yet, we believe that even comminuted fractures can be fixed with the improvement of this technique.

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Original Article

Computed tomography findings of organizing pneumonia

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ABSTRACT

Objective: In this study, we aimed to present computed tomography (CT) findings of 100 patients with histopathologically confirmed organizing pneumonia.
Design: Retrospective study
Setting: Ankara Atatürk Chest Diseases And Chest Surgery Training And Surgery Hospital, Ankara, Turkey
Subjects: One hundred histopathologically confirmed organizing pneumonia patients between 2009 and 2013 admitted to our clinic.
Intervention: A chest CT scan and the histopathological examination of the lung lesions of the patients were performed.
Main outcome measure: The frequency and the types of CT findings of the patients with proven organizing pneumonia were examined.
Results: Among 100 patients, 73 were male and 27 were female, and the mean age of the patients was 60±11 (range:19-90) years. Pulmonary consolidation was detected in 87 patients and ground-glass opacity was seen in 76 patients. Multiple nodules were seen in 20 patients while a solitary nodule was seen in 15 patients. Acinar nodular pattern was detected in 29 patients, micronodular pattern in 28 patients, bronchocentric pattern in 33 patients, perilobular pattern in 14 patients, progressive fibrotic pattern in 8 patients and reversed halo sign in 12 patients. Lymph node enlargement was seen in 80 patients.
Conclusion: Computed tomography is very important for the diagnosis of organizing pneumonia which has various radiological findings.

KEY WORDS: computed tomography, cryptogenic organizing pneumonia, organizing pneumonia

INTRODUCTION

Organizing pneumonia (OP) is a nonspecific response to pulmonary damage. 50% of the cases of OP are idiopathic and are termed as cryptogenic organizing pneumonia (COP), which is a well described clinical and pathological condition[1,2].

In the histopathological evaluation of OP, the discrimination of alveolar structure is difficult. The most prominent finding of granulation is the polyps, which are also known as Masson bodies (Fig. 1). They are interstitial infiltrates located in the granulation tissue which protrude into alveoli and bronchi[3].

Computed tomography (CT) is a very important diagnostic method for the examination of diffuse parenchymal disease, identify the type of lesion, follow-up and determine the optimal biopsy site[4]. While CT findings of OP are various, the most characteristic features are subpleural patchy consolidation sites and usually accompanying ground-glass opacities[5].

In this study, we aimed to analyze the CT findings of OP in a relatively larger case series.

SUBJECTS AND METHODS

CT findings of a total of 100 patients (73 males and 27 females) with histopathologically proven OP (Fig. 1) who were admitted to a tertiary Chest Disease Training Hospital, were retrospectively screened and

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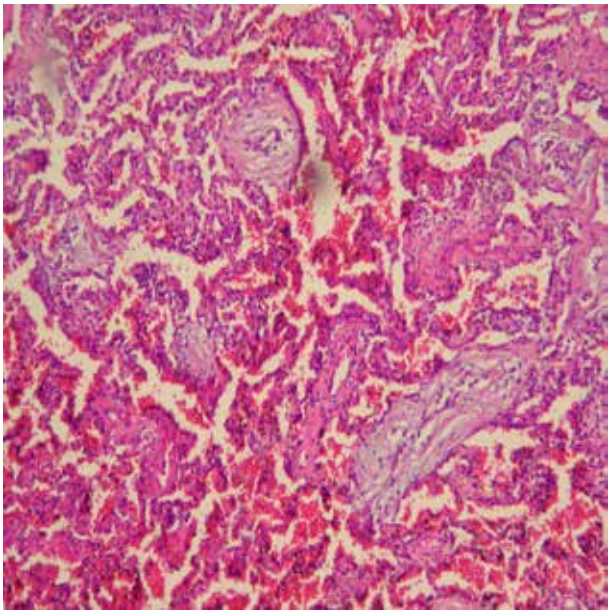

Figure 1: Masson bodies were seen (HEx100)

the findings were interpreted by an experienced thoracic radiologist. The study was approved by the local Ethic Committee.

CT examinations of all the patients were performed by using a Somatom Emotion 6 computed tomography system (Siemens Medical Systems, Forchheim, Germany) with 1 mm collimation at 10-mm intervals, high resolution reconstruction algorithm and adjusted milliamperage-kilovoltage values for the weight of the patients.

Defined radiological findings included consolidation sites, ground-glass opacification, multiple nodular lesions, solitary nodule, acinar type nodular pattern, micronodular pattern, bronchocentric pattern, perilobular pattern and progressive fibrotic pattern. Consolidation sites were classified according to unilateral or bilateral distribution and central or peripheral localisation. Consolidation sites and multiple-solitary nodular lesions were compared as having air bronchograms or cavity and as locating in upper or lower lobes. Mediastinal or hilar lymph node enlargement was also recorded. The presence of lymph node with a short axis transverse diameter >10 mm was defined as lymph node enlargement[6]. The control scans of the patients were compared when available. The radiological response to the treatment was classified as disappearance lesion, as regression (a decrease in size >10% of the lesion), as no difference or as progression (an increase in size >10% of the lesion).

Statistical analysis of data of all 100 patients was performed by using IBM SPSS Statistics version 20. Categorical variables were presented as frequency distribution and continuous variables were calculated as mean ± standard deviation.

Table 1: The rates of organizing pneumonia etiology

Etiology	N (%)
COP	58 (58)
Secondary OP	42 (42)
Infection	13 (13)
Lung malignity	12 (12)
Drug induced	9 (9)
Wegener granulomatosis	3 (3)
Aspiration pneumonia	1 (1)
Radiation induced	1 (1)
Rheumatoid arthritis	1 (1)
Tuberculosis	1 (1)
Cyst hydatic	1 (1)

OP: organizing pneumonia; COP: cryptogenic organizing pneumonia

RESULTS

Female/male rate was 0.37 (27/73) and the mean age of the patients was 60±11 (range: 19-90) years. OP diagnosis was made by the histopathological examination of the specimens which were taken by transthoracic tru-cat biopsy in 75 patients, transbronchial biopsy in 10 patients and excisional biopsy in 15 patients. While in 58 patients there was no systemic disease, radiation therapy or medication history which can be associated with OP, a diagnosis of COP was made for these patients. The remaining 42 patients were accepted as having secondary OP because of presence of systemic disease and medication anamnesis which can be responsible for OP (Table 1).

Data of observed parenchymal findings and the presence of lymph node is detailed in Table 2. The most common radiological finding was parenchymal consolidation sites (Table 3) and the second most common was ground-glass opacification.

Multiple nodules were detected in 20 patients and solitary nodule in 15 patients. The features of nodules

Table 2: Computed tomography findings of organizing pneumonia

CT findings	N (%)
Parenchymal findings	
Consolitadion	87 (87)
Ground-glass opacification	76 (76)
Solitary nodule	15 (15)
Multiple nodule	20 (20)
Acinar nodular pattern	29 (29)
Micronodular pattern	28 (28)
Bronchocentric pattern	33 (33)
Perilobular pattern	14 (14)
Progressive fibrotic pattern	8 (8)
Reversed halo sign	12 (12)
Lymph node enlargement	80 (80)
Mediastinal and hilar	60 (60)
Only mediastinal	15 (15)
Only hilar	5 (5)

CT: computed tomography

Table 3: Features of consolidation in organizing pneumonia

Distribution		Localisation		Structure	
Right lung		Bilateral	49 (56.3%)	Air bronchograms	56 (64.4%)
Upper lobe	47 (54%)	Unilateral	38 (43.7%)	Cavity	2 (2.3%)
Medial lobe	38 (43.7%)			Air bronchogram+cavity	19 (21.8%)
Lower lobe	52 (59.7%)			Only consolidation without air bronchogram and cavity	10 (11.5%)
Left lung					
Upper lobe	49 (56.3%)				
Lower lobe	47 (54%)				
		Central	2 (2.3%)		
		Periferic	58 (66.7%)		
		Central +periferic	27 (31%)		

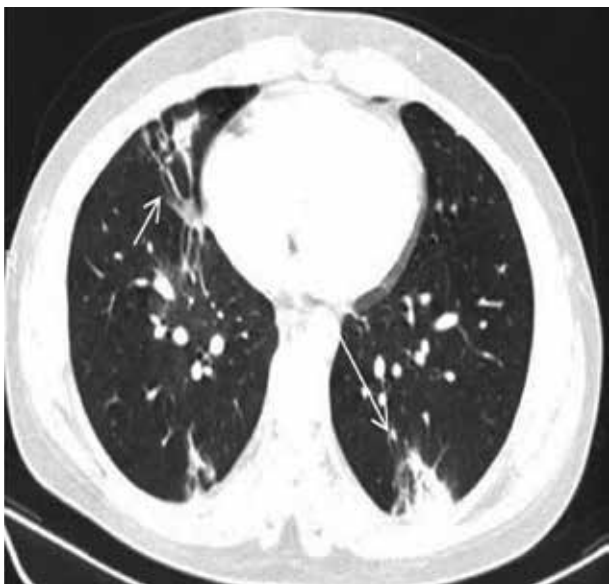

Figure 2: Bilateral peripheral consolidation sites containing air bronchograms (white arrow).

and accompanying parenchymal findings were summarized in Table 4.

Acinar type nodular pattern was detected in 29 patients and micronodular pattern in 28 patients. In all 67 patients with micronodular or acinar pattern, there was also one or more other CT patterns which are seen in Table 2. The association of nodular patterns with the other CT findings are shown in Table 5.

Bronchocentric pattern was detected in 33 patients, perilobular pattern in 14 patients and progressive fibrotic pattern in 8 patients. Reversed halo sign was seen in 12 patients.

Follow-up CT scans of 65 patients were available. Mean duration between initial and follow-up CT scans was 10±8.6 months (range: 1-39 months). Among these

Table 5: Parenchymal findings acompanying nodular patterns

Parenchymal findings	Acinar nodular pattern (n=29)	Micronodular pattern (n=28)
Consolitadion	29 (100%)	23 (82.1%)
Ground-glass opacificity	27 (93.1%)	22 (78.5%)
Solitary nodule	-	4 (14.2%)
Multiple nodule	10(34.5%)	7 (25%)
Bronchocentric pattern	13 (44.8%)	17 (60.7%)
Perilobular pattern	5 (17.2%)	8 (28.6%)
Progressive fibrotic pattern	2 (6.9%)	5 (17.8%)
Acinar nodular pattern	-	6 (21.4%)
Micronodular pattern	6 (20.7%)	-

Table 4: Features of solitary multiple nodules in organizing pneumonia

Features	Solitary Nodule n=15 (15%)		Multiple nodule n=20 (20%)	
Size (cm)	3.8 (1-9)		1.2 (1-2)	
Location	Right lung		Right lung	
	Upper lobe	2 (13.3%)	Upper lobe	15 (75%)
	Medial lobe	2 (13.3%)	Medial lobe	16 (80%)
	Lower lobe	1 (6.7%)	Lower lobe	17 (85%)
	Left lung		Left lung	
	Upper lobe	6 (40%)	Upper lobe	15 (75%)
	Lower lobe	4 (26.7%)	Lower lobe	18 (90%)
Structure	Air bronchograms	4 (26.7%)	Air bronchograms	8 (40%)
	Cavity	1 (6.7%)	Cavity	1 (5%)
	Only nodule without bronchograms and cavity	10 (66.6%)	Only nodule without bronchograms and cavity	11 (55%)
Concomittant parenchymal findings	Consolidation	5 (33.3%)	Consolidation	20 (100%)
	Groud-glass opacificity	3 (20%)	Groud-glass opacificity	19 (95%)
	Micronodular pattern	4 (26.7%)	Micronodular pattern	7 (35%)
	Acinar nodular pattern	0 (0 %)	Acinar nodular pattern	10 (50 %)
	No additional finding	6 (40%)	No additional finding	0 (0%)

Table 6: Changes in the lesions of the patients in follow-up.

Changes in the lesions	Total resolution	Regression	No change	Progression
COP (n=32)	12 (66.66%)	17 (62.96%)	1 (12.5%)	2 (16.6%)
Secondary OP (n=33)	6 (33.34%)	10 (37.04%)	7 (87.5%)	10 (83.4%)
Total (n=65)	18 (27.7%)	27 (41.5%)	8 (12.3%)	12 (18.5%)

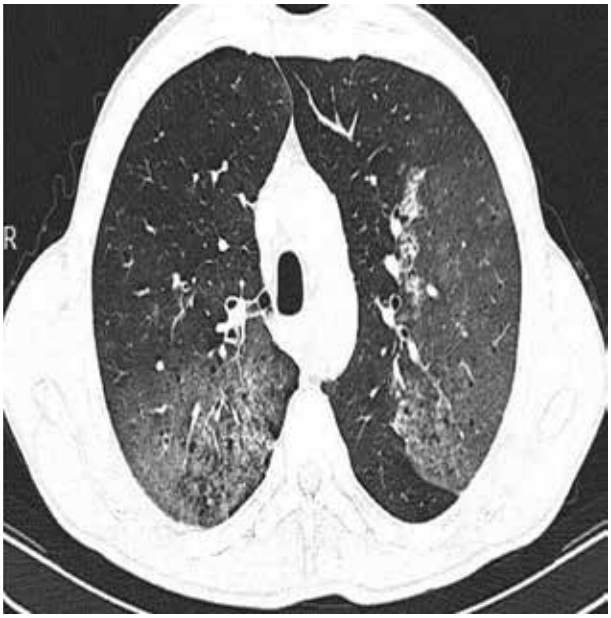

Figure 3: Ground-glass opacification in both lungs.

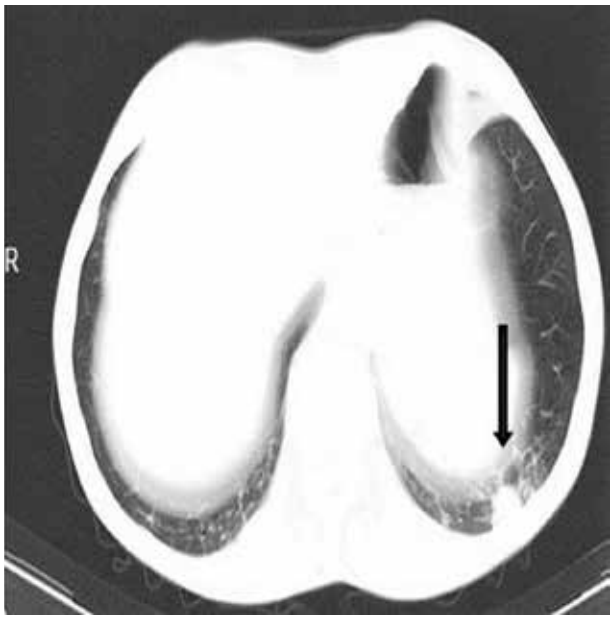

Figure 4: A solitary nodule in the posterobasal segment of the left lower lobe (black arrow).

65 patients, total resolution in radiological findings was observed in 18 (27.7%), regression in 27 (41.5%), no changes in 8 (12.3%) and progression in 12 patients (18.5%; Table 6).

DISCUSSION

Consolidation sites and ground-glass opacification are the most common CT findings of OP. Consolidations tend to be located in lower lobes and the distribution

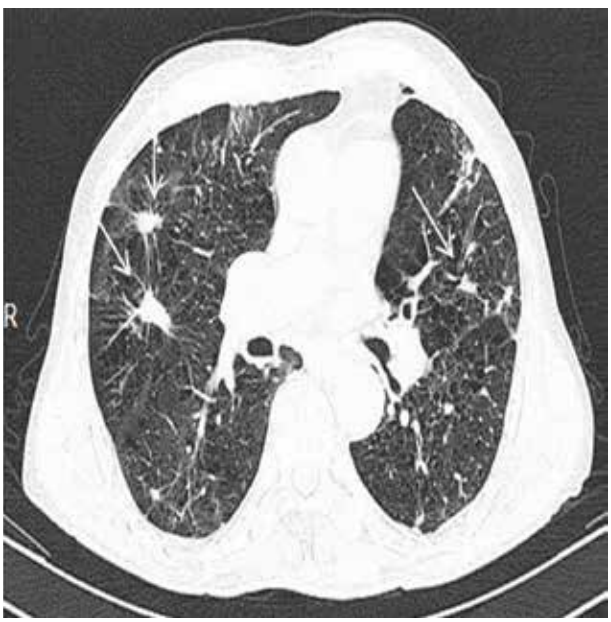

Figure 5: Multiple nodules in both lungs (white arrows).

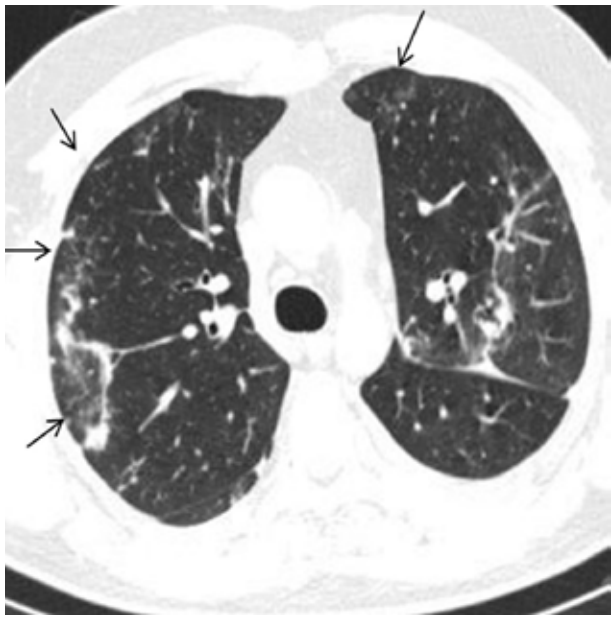

Figure 6: Micronodular pattern (black arow).

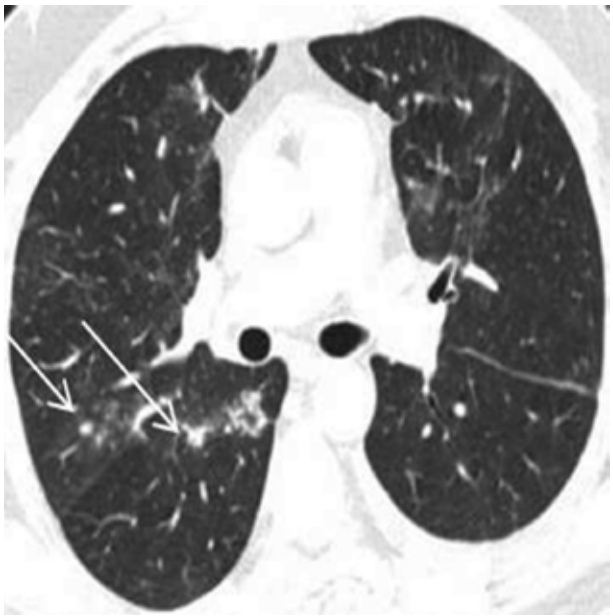

Figure 7: Acinar nodular pattern (white arrow).

of lesions is usually bilateral and periferic[7,8]. While consolidation is detected in 87 (87%) of our patients, among them 49 (56.3%) have bilateral lesions. Consolidation was located in periferic parenchymal areas in 58 patients (66.7%) (Fig 2). Although all the lobes were involved by consolidation with similar rates, these lesions were found mostly in right lower lobe (Table 3). Air bronchograms and bronchial dilation can be seen in consolidation sites[5]. Among the 87 patients with consolidation, 75 (86.2%) were in air bronchograms and in 21 (24.1%) patients, cavitation was detected in consolidation (Table 3).

Consolidation areas are usually seen with ground-glass opacification. Ground-glass opacification frequency in the patients with OP was reported as 60%-86% in various studies[7,9-11]. We found a frequency of 76% (76/100 patients), which is consistent with previous studies (Fig. 3).

Solitary focal mass or nodule can be detected in OP. These lesions usually locate in upper lobes and can contain air bronchograms or cavities. Since radiological findings are sometimes not adequate to discriminate these lesions from malignant lesions, biopsy or surgical excision of the lesion is required[8]. In this study, solitary nodule was detected in 15 patients (Fig. 4). Mean diameter of the lesion was 3.8 cm (range: 1-9 cm). Solitary nodules are most commonly located in left upper lobe.

The diagnosis is difficult when a patient presents with multiple nodules with a diameter >1 cm because differential diagnosis includes various and complex conditions such as metastasis, lymphoma, infections, Wegener's granulomatosis and Kaposi sarcoma[8,12]. Air bronchograms and cavity formations may be present within the nodules. Akira *et al* searched 59 patients with histopathologically proven COP and they found multiple nodules in 20% of their patients[12]. We also detected multiple nodules with a diameter of >1 cm in 20 patients (20%) in our study. Mean diameter of these nodules was 1.2 cm (range: 1-2 cm). While the nodules were located in each lobe with similar rates, the lower lobes were mostly involved (Fig. 5). The

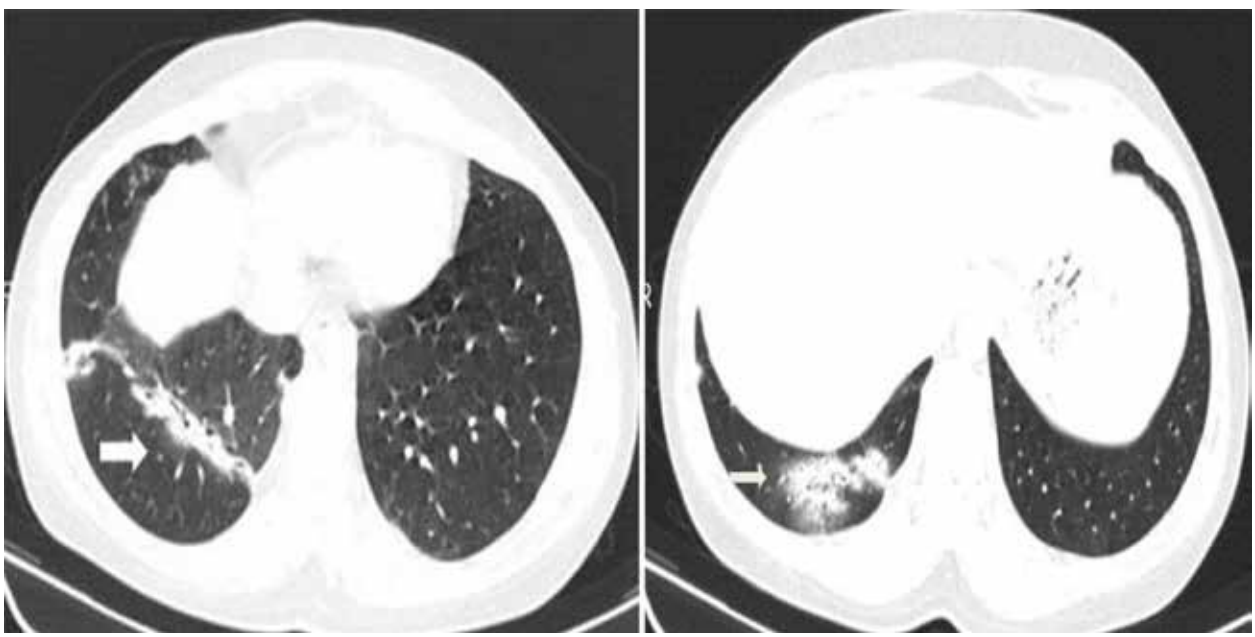

Figure 8: Bronchocentric pattern (white arrow).

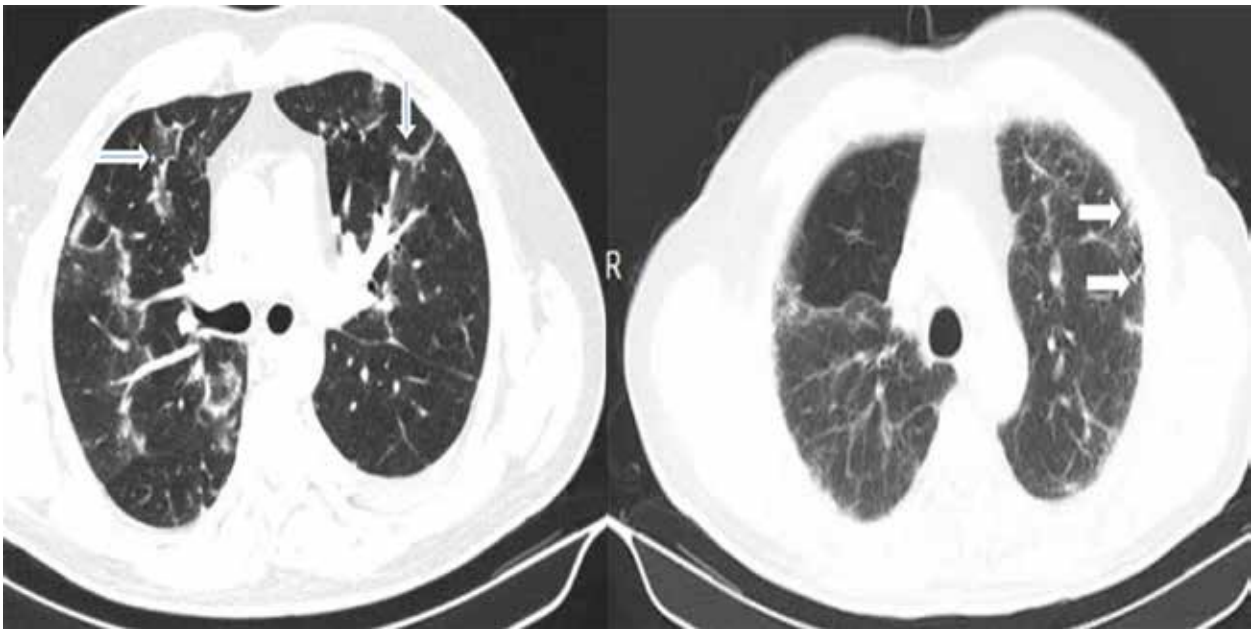

Figure 9: Perilobular pattern (white arrow).

characteristics of solitary and multiple nodules are detailed in Table 4.

Two nodular patterns are defined in OP. The first, micronodular pattern is characterised by the location of lesions <5 mm along bronchovascular bundles (Fig 6). The second, acinar nodular pattern is characterised by the lesions <10 mm located in periferic and peribronchovascular areas (Fig 7)[1,13]. Nodular pattern can be seen in one third of the patients and usually accompanies other CT findings of OP[14]. In our study, acinar nodular pattern was seen in 29 patients. Also, micronodular pattern was detected in 28 patients. As suggested in Table 5, other CT findings accompanied the nodular patterns in these 57 patients.

Bronchocentric pattern is characterised by parenchymal consolidation areas around the bronchovascular bundles, which extend to lung parenchyma[8]. Müller *et al*[13] and Lee *et al*[14] reported bronchocentric pattern in about one third of the patients with OP in their studies. In our study, we also detected bronchocentric pattern in 33 patients with OP (Fig 8).

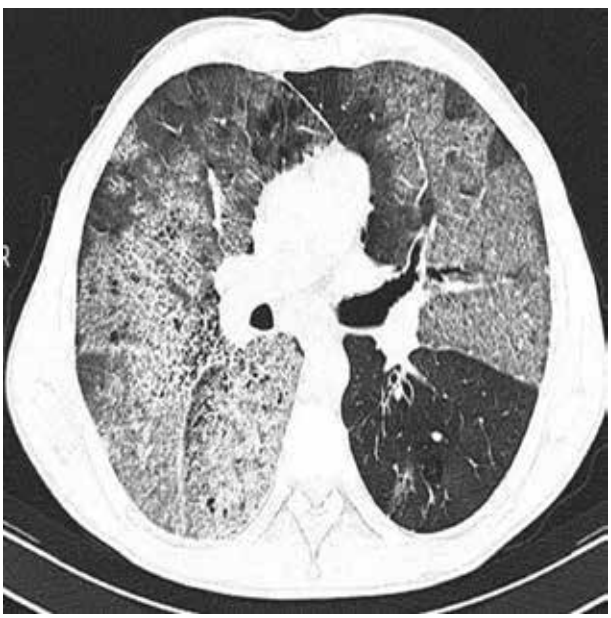

Figure 10: Progressive fibrotic pattern.

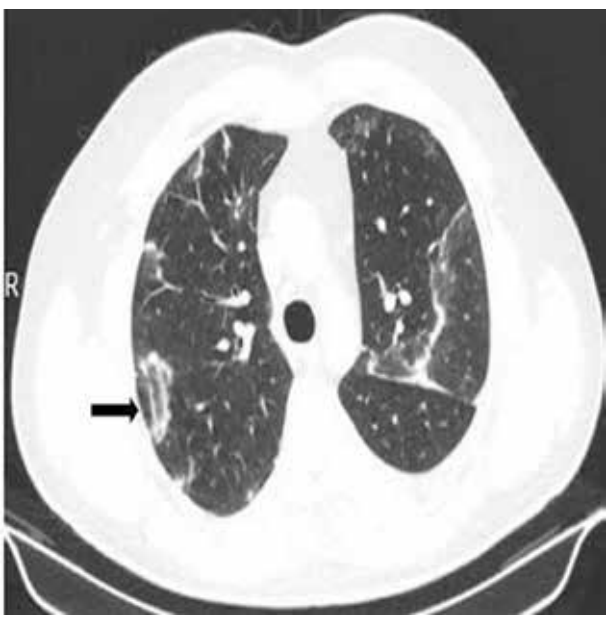

Figure 11: Reversed halo sign (black arrow).

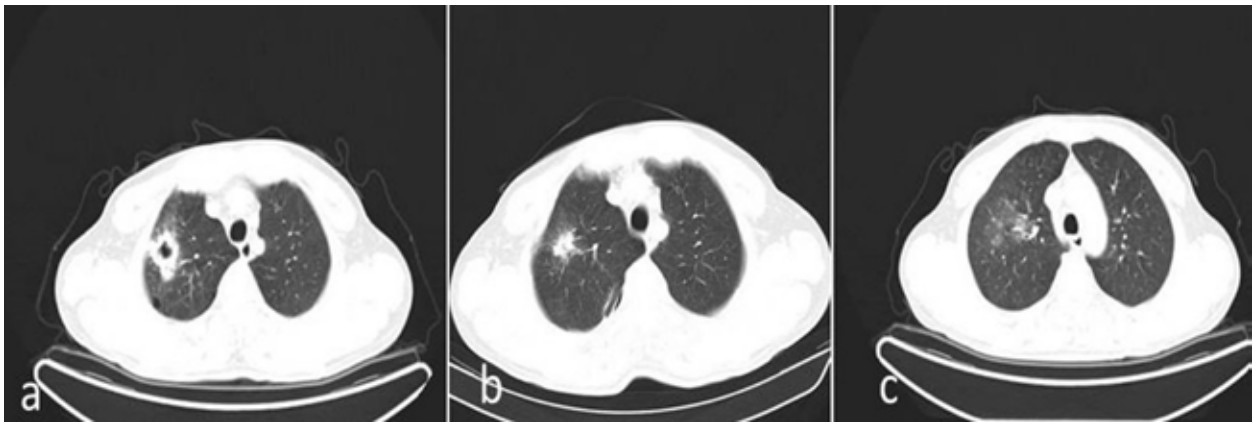

Figure 12: (a) Initial CT scan shows consolidation containing air bronchogram and a cavity in the right upper lobe. In the second examination; **(b)** after 3 months from initial CT scan, cavity disappeared with regression of consolidation; **(c)** the last scan (6 months after first CT) suggests marked regression in consolidation. Consolidation site transformed to ground-glass opacification.

Perilobular pattern is defined as thick, irregular polygonal opacities in the periphery of the secondary pulmonary lobules[15,16]. Ujita *et al* detected a perilobular pattern in 12 of 21 (57%) patients with COP[10]. In our study, perilobular pattern was seen in only 14 patients (14%; Fig 9).

Progressive fibrotic patterns have a relatively poor prognosis than typical opacification accompanied by irregular interlobular septal thickening and fibrosis[17,18]. Bouchardy *et al* reported progressive fibrotic pattern in three of their 12 patients with bronchiolitis obliterans organizing pneumonia[19]. Ujita *et al* reported progressive fibrotic pattern in 5 of 21 patients with COP[10]. In our study, we observed a relatively lower rate of 8% (n=8) of progressive fibrotic pattern than previous studies (Fig 10).

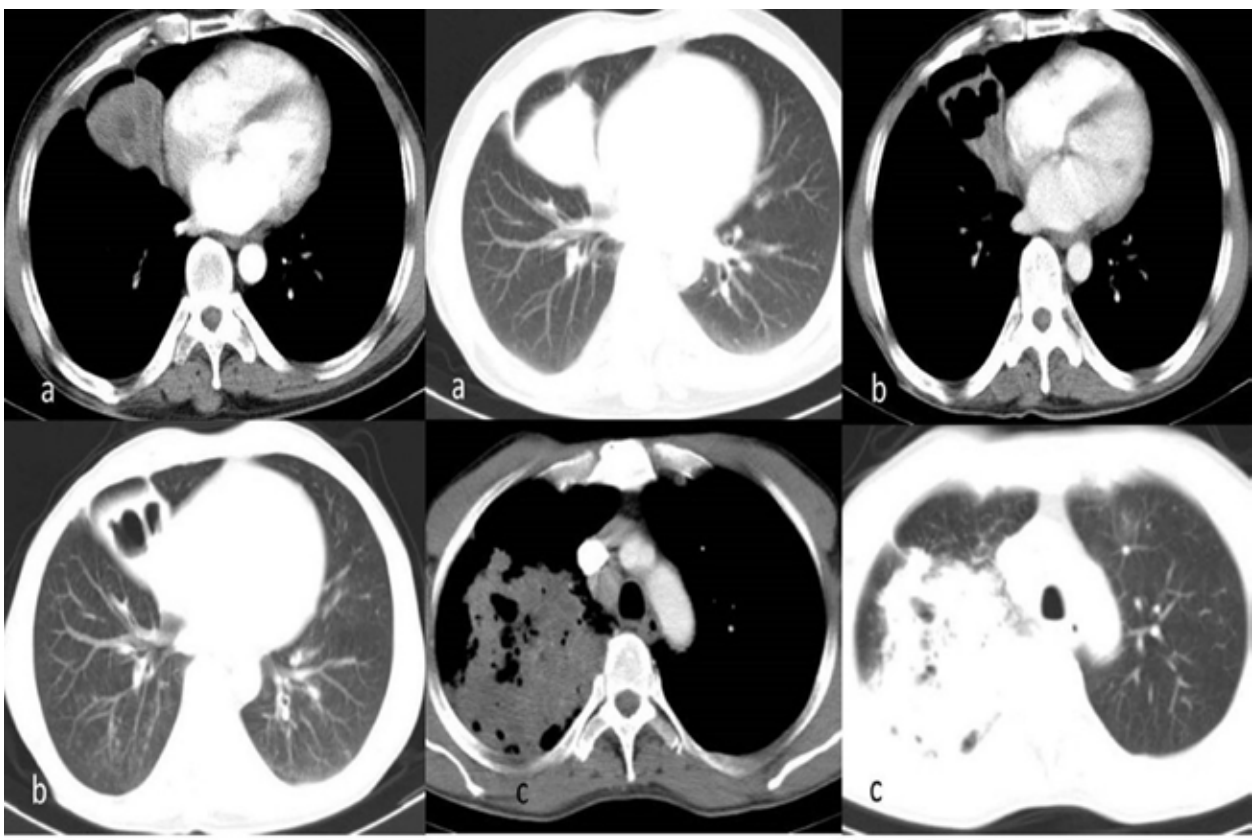

Figure 13: (a) Initial CT scan shows a necrotic consolidation in right middle lobe in initial scan; **(b)** 15 months after initial scan, cavity formation in the consolidation with no marked changes in sizes is seen; **(c)** in the same examination irregular consolidation areas present in right upper lobe.

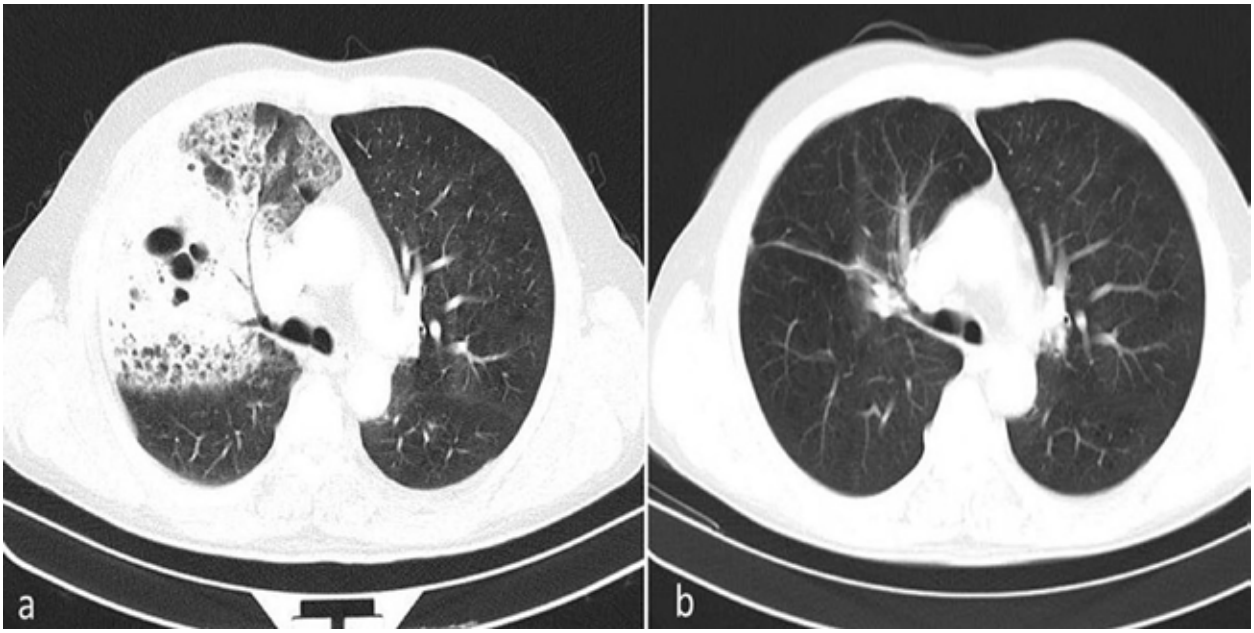

Figure 14: (a) Initial CT scan shows consolidation containing air bronchogram and a cavity in the right upper lobe in initial scan (secondary OP associated with infection); **(b)** After 6 month from initial scan, the lesions completely disappeared.

Reversed halo sign is defined as a ring or cresent shaped opacification which surround ground-glass opacification[20]. Murphy *et al* reported reversed halo sign in 19% of their patients and suggested that this finding is specific for OP[21]. Subsequently, some authors reported that this finding may be seen in various conditions, including infectious and non-infectious diseases[20]. Saberon *et al* detected reversed halo sign in 4 of 34 (12%) cases with OP[9]. Similarly, we found reversed halo sign in 12% (12 of 100) of patients with OP (Fig 11) .

Lymph nodes can be associated with OP. In a study by Greenberg-Wolff *et al*[22], they found mediastinal enlarged (1-1.5 cm) lymph nodes in all their patients with COP. We detected mediastinal lymph node enlargement in 80 patients (80%; Table 2) .

Although OP is usually responsive to corticosteroid treatment, relapse and progression may be

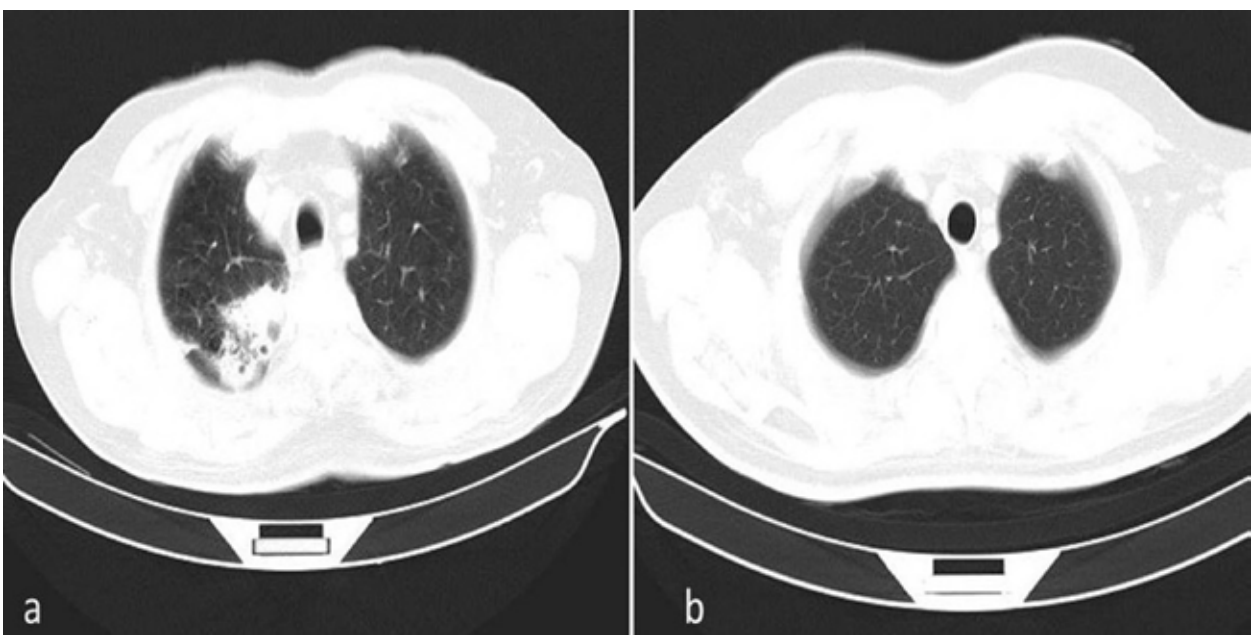

Figure 15: (a) Initial CT scan shows consolidation with air bronchograms in right upper lobe apical and posterior segment (COP); **(b)** After 4 month from initial scan, the lesions completely disappeared.

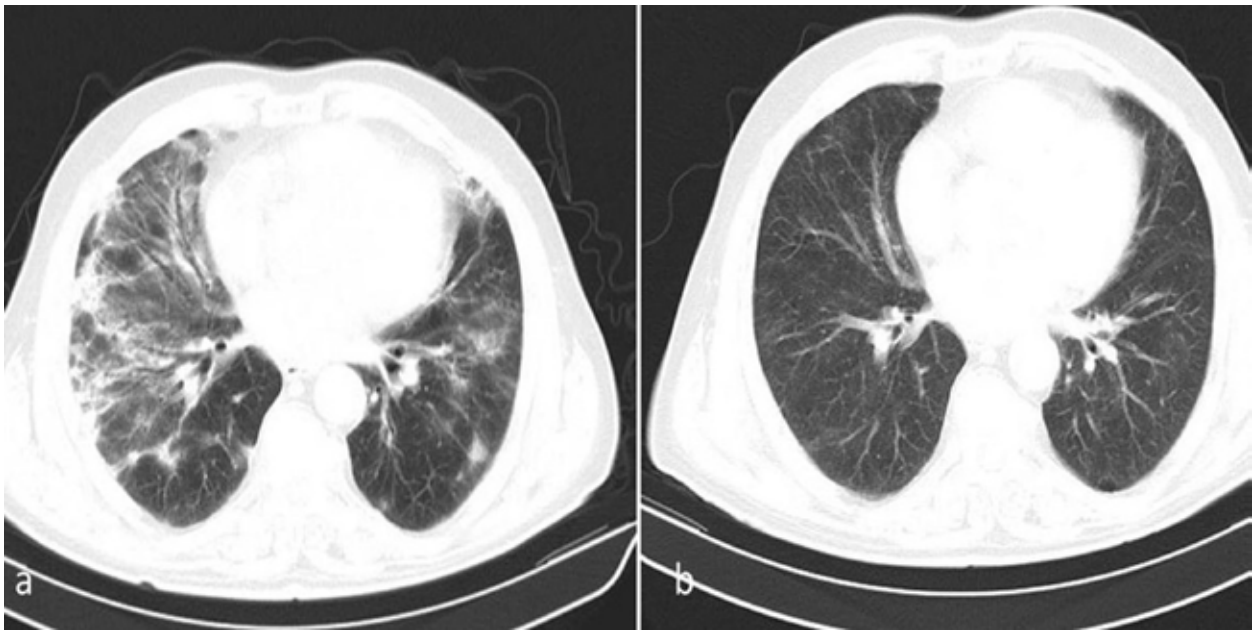

Figure 16: (a) Initial CT scan shows concolidation, ground-glass opacification and multiple nodules in both lungs (COP); **(b)** After 6 month from initial scan, the lesions completely disappeared.

reported[8,17,23]. In a study by Lee *et al*, they reported complete resolution in 6 (27%) and regression in 15 (68%) among their 22 COP patients with steroid treatment, while no patient showed progression and in one patient, the lesion was stable with no changes[7]. Among our 65 patients who had follow-up scans, we observed regression (Fig 12) in 27 (41.5%), progression (Fig 13) in 12 (18.5%) and no changes in 8 (12.3%) patients with steroid treatment. In 18 (27.7%) patients, the lesions completely disappeared (Figs. 14-16; Table 6). We suggest that the number of the patients with progression and no changes in follow up scans is relatively higher because we did not only examine patients with COP, but also secondary OP patients.

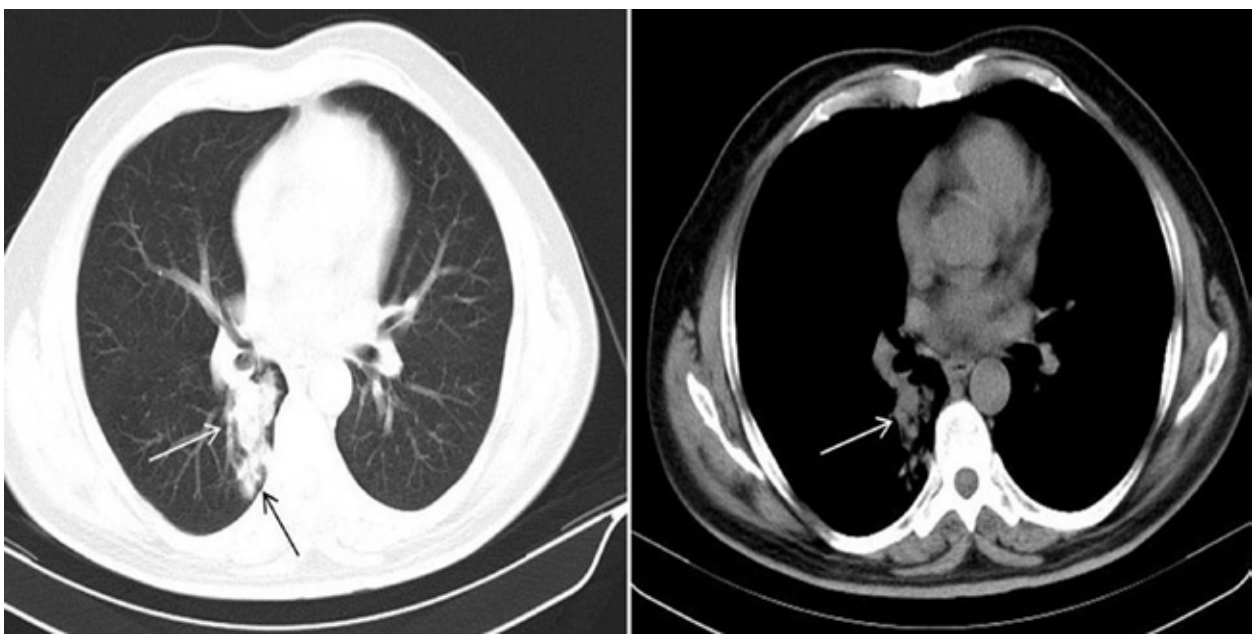

Figure 17: The histopathological examination of the specimen which was taken by a transthoracic biopsy from peripheral zone (black arrow) of the lesion demonstrated organizing pneumonia. A squamous cell lung carsinoma was identified by a subsequently a transbroncial biopsy which obtained the sample at the center (white arrow) of the lesion

Differentiation of COP and secondary OP is essential because the management of secondary OP does not include only treatment of OP, but also treatment of underlying disease and avoiding drugs or agents which are associated with OP[24]. Histopathological features of OP may be reported in association with infectious pneumonia, drugs, lung abscess, connective tissue diseases, lung malignities, bronchiectasis, Wegener granulomatosis, chronic pulmonary fibrosis, pulmonary infarct, aspiration pneumonia and adult respiratory distress syndrome[25]. The most common reason of secondary OP is infection as suggested in our study[25]. In our study, the second most common cause of OP was lung cancer (Table 1). The OP secondary to lung cancer may be seen as a lesion located adjacent to the tumor tissue or far away from the neoplastic lesion anywhere in the lung[26]. Among our 12 patients with OP secondary to lung cancer, the OP lesion located in lung parenchyma was adjacent to the neoplastic tissue in eight patients (Fig 17). The OP lesion was seen simultaneously in a different lobe of the cancer tissue presented in our remaining four patients with lung cancer. For this reason, follow-up and additional diagnostic methods are very important, and repeat biopsy must be considered in the patients who have suspicious clinical and radiological findings.

The limitation of the study was the lack of some of the patients' follow-up scans that did not permit to search the course and to compare initial and susequent radiologic findings.

CONCLUSION

As OP has various radiological findings, CT is very important for the diagnosis of this condition. Even when the disease is histopathologically proven, the follow-up these patients is essential because secondary OP must be kept in mind for the lesions which do not regress despite treatment. The radiological and clinical findings of the conditions which are associated with secondary OP must be well known for making the diagnosis and planning the management.

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Authors' contribution: Yeliz Dadali developed the protocol/project and collected, analysed and managed the data; Sercan Ozkacmaz analysed the data and wrote/edited the manuscript; Yurdanur Erdogan, Havva Akmaz Unlu and Ilke Bursali collected the data and reviewed the manuscript; Funda Demirag analysed the data and reviewed the manuscript.

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Original Article

Influence of neonatal care advancement on mortality and the incidence of bronchopulmonary dysplasia in very low birth weight (VLBW) Saudi infants: two period's comparison

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ABSTRACT

Objectives: To examine the influence of advanced neonatal care on mortality and incidence of bronchopulmonary dysplasia (BPD) in very low birth weight infants
Design: Retrospective observational study
Setting: Neonatal intensive care unit at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia
Subjects: All infants admitted to our unit with birth weight below 1500 grams in two periods (1999-2007 and 2011-2018).
Interventions: Mortality and BPD incidence rates were compared between the two groups.
Main outcome measures: Mortality and development of BPD.
Results: Infants born during the later time period were 2.8 times more likely to die compared with the first period. Higher birth weight was associated with decreased odds of infant death (OR=0.997, P <0.001). Incidence of BPD was lower in the later period (P <0.05).
Conclusions: Advancement in neonatal care in our institute led to decreased incidence of BPD. Mortality rate increased in later period, which might be a result of changes in unit admission policy.

KEY WORDS: advancement in neonatal care, bronchopulmonary dysplasia, mortality, very low birth weight infants

INTRODUCTION

Premature delivery carries a great risk of neonatal mortality and increases the risk of morbidities and future neurodevelopmental delay. Neonatal care, especially for very low birth weight (VLBW) infants, is ever-changing over the past years. In many countries worldwide, advancement in neonatal, as well as antenatal care, led to increased survival in neonate, and VLBW newborns in particular[1-4]. Bronchopulmonary dysplasia (BPD) remains a major challenge in the care of premature infants, despite improvement in neonatal care over the years. The increased survival of VLBW infants proportionally increased the number of surviving sick babies who require advanced care to manage the evolving morbidities in such infants. BPD is one of the most studied topics in the field of neonatology, and most of the research and advancement in neonatal care is directed over the past decades on preventing or minimizing the development of BPD. An estimated 15 million babies are born premature worldwide. Premature infants are at a higher risk of death in comparison with full term babies due to complications of prematurity, mainly neonatal respiratory distress syndrome (NRDS) and BPD. The use of antenatal steroids has been globally adopted as a standard

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obstetric care provided to pregnant ladies with anticipated premature delivery in efforts to prevent NRDS and consequently BPD. There is strong evidence showing that prenatal corticosteroids reduce infant mortality and the incidence of NRDS. However, data suggest that they are not as effective in reducing the incidence of BPD as they do for NRDS, probably due to the multifactorial nature of BPD pathogenesis[5]. Over the past years, many strategies have been developed which resulted in altering the ventilation approach in managing preterm infants with respiratory distress syndrome. The main aim of these strategies is to decrease invasive and prolonged ventilation, trying to decrease mortality and the incidence and/or severity of BPD. The approach of early surfactant replacement therapy with extubation to nasal continuous positive airway pressure is associated with lesser need for mechanical ventilation, lower incidence of BPD and fewer air leak syndromes compared with later selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support[6].

Outcomes are expected to change based on changes in care provided. King Khalid University Hospital (KKUH) birthing center is handling an increasing number of deliveries with increased complexities. Our unit is one of the main tertiary centers in Saudi Arabia with every updated neonatal care in terms of policies and standard neonatal practices.

Comparing outcomes over time is a standard method to achieve some insight regarding efficacy of interventions and policy changes. The aim of this study is to see the effect of advancement in our unit on mortality and development of BPD in VLBW infants.

SUBJECTS AND METHODS

This is a retrospective analysis of data obtained from KKUH neonatal intensive care unit (NICU) data base. This study was approved by Institutional Research Board at KKUH. Infants included in this study were the VLBW infants weighing less than 1500 grams at birth. We compared mortality and incidence of BPD between two periods of time (first period: 1999-2007, and second period: 2011-2018). Still births were excluded from this study as well as any newborn with gestational age less than 24 weeks and/or birth weight less than 500 grams. Total of 1,078 infants were included (481 in first period and 597 in second period). Mortality was defined as death prior to hospital discharge and BPD was defined as oxygen requirement at 36 weeks corrected gestational age.

Statistical procedures

Prior to conducting primary analyses, exploratory analyses were conducted to assess the nature of the obtained data. No significant problems with statistical assumptions were noted; however, assumptions were minimal due to the use of nonparametric analyses as the highest level of analysis. Evaluation of data across time points, indicated some missingness by design (*i.e.*, some data collected in later time points was not assessed in earlier time points). Data that were treated as continuous (*i.e.*, birth weight, gestational age and length of hospital stay), normality was assessed by examining the mean ± standard deviation ratio, skewness and kurtosis. Additionally, within parametric analyses, the assumption of homogeneity of variance was assessed. No significant concerns with normality or homogeneity was noted. Frequencies of births

Table 1: Comparisons of key variables across time points

Infant's characteristics	1999-2007			2011-2018		
	n	**M**	**SD**	**n**	**M**	**SD**
Gestational age	481	27.60	2.46	597	28.75	3.10
Birth weight (g)	475	991.44	284.59	597	1078.97	283.31
Hospital stay	451	71.32	53.30	490	66.98	84.41
	n	%		n	%	
Male	249	51.9		315	52.9	
Booked	332	69.7		404	69.2	
Antenatal steroid	105	22.2		481	86.2	
Antenatal antibiotic	162	33.8		186	32.1	
Emergency c-section	209	43.5		355	61.2	
Spontaneous vaginal birth	250	52.1		206	35.5	
Elective c-section	21	4.4		19	3.3	
Surfactant	378	80.4		348	61.9	
Periventricular leukomalacia	6	1.3		13	2.4	
Bronchopulmonary dysplasia	145	31.0		122	22.3	
Patent ductus arteriosus	129	27.6		157	28.5	
Postnatal steroid	132	28.0		42	8.0	

Percentages shown are relative proportions; means/proportions shown in boldface were significantly greater across columns, $P < 0.05$.

Table 2: Comparisons of key variables by mortality

Infant's characteristics	Survived			Infant death		
	n	M	SD	n	M	SD
Gestational age	864	28.52	2.66	164	26.45	3.29
Birth weight (g)	862	1076.97	268.76	161	830.18	293.09
Hospital stay	796	76.10	70.85	139	26.24	48.34
	n	%		n	%	
Male	141	48.0		70	42.7	
Booked	602	70.4		104	63.8	
Antenatal steroid	463	55.6		92	57.5	
Antenatal antibiotic	268	31.3		67	41.6	
Emergency c-section	481	56.2		57	35.0	
Spontaneous vaginal birth	343	40.1		99	60.7	
Elective c-section	32	3.7		7	4.3	
Surfactant	560	66.8		141	89.8	
Periventricular leukomalacia	15	1.8		4	2.6	
Bronchopulmonary dysplasia	233	27.8		28	18.8	
Patent ductus arteriosus	246	29.4		34	23.0	
Postnatal steroid	139	17.1		28	18.2	

Note: Percentages shown are relative proportions; means/proportions shown in boldface were significantly greater across columns, $P < 0.05$.

across the two time periods was relatively similar (Time 1: n=481, 44.6%; Time 2: n=591, 55.4%), suggesting that comparisons across groups were statistically feasible. Across the years, births ranged from 36 (2005) to 100 (2016), and percentages of births by year generally ranged from 3.3% of the total births to 9.3% of all births included in the study. There was no significant difference in the number of births across the two time points, $P > 0.05$.

In order to assess for differences across independent groups, including comparisons of time and infant mortality, independent samples *t*-tests were used to assess differences in continuous variables, and crosstabulations with Pearson's chi square were used to test relationships between categorical variables. In the first set of analyses, differences across time points were examined. The next phase of analysis examined significant relationships between key variables and infant mortality. Lastly, based on preliminary analyses, the primary analysis utilized binary logistic regression to predict infant mortality from variables identified as being significantly related to infant mortality. All analyses were conducted in SPSS v. 25 and significance was determined at the 0.05 level.

RESULTS

Comparisons across time

A summary of the differences across time are shown in Table 1. At later time points, statistically significant differences were noted for gestational age and birth weight, indicating that in subsequent years, infants tended to be born at older gestational age (28.75 vs. 27.60 weeks) and weighed more (10078.97 vs 991.44 grams). During the earlier time period, higher rates were noted for spontaneous vaginal births, surfactant and postnatal steroid use. At later time periods, higher rates were noted for antenatal steroid use, emergency caesarean-sections and BPD.

Comparisons across infant mortality

A summary of the differences across infant mortality are shown in Table 2. As shown, infants who survived had a higher gestational age (28.52±2.66 weeks) and birth weight (107.97±268.76 grams) compared to infants that died. A greater proportion of infants born via an emergency caesarean section survived compared to those who died. A greater proportion of infants with BPD survived compared to those who died. Among infants born via spontaneous vaginal birth, a greater proportion died. Similarly, among infants who received surfactant, a greater proportion died. There was a trend towards more death in female infants, administration of surfactant and antenatal antibiotics. Caesarean section and death were significantly correlated.

Predicting mortality

A summary of the final model predicting infant mortality is shown in Table 3. As shown, the overall predictive model was significant, $\chi^2(5) = 138.17$, $P < 0.001$, Nagelkerke $R^2 = 0.226$. Infants born during the later time period were 2.8 times more likely to die compared with the first period. Higher birth weight was associated with decreased odds of infant death (OR=0.997, $P < 0.001$). Having an emergency caesarean section was associated with decreased odds of infant death (OR=0.564, $P = 0.007$). When controlling for other predictors, gestational age and surfactant were not

Table 3: Binary logistic regression predicting infant death

Characteristics	β	SE	OR	*P*
Time	1.013	0.201	2.755	<0.001
Gestational age	0.027	0.061	1.027	0.663
Birth weight (g)	- 0.003	0.001	0.997	<0.001
Emergency c-section	- 0.573	0.211	0.564	0.007
Surfactant	0.606	0.338	1.833	0.073

Model summary: $\chi 2(5) = 138.17$, $P < 0.001$, Nagelkerke $R^2 = 0.226$
SE: standard error; OR: odds ratio

significantly associated with infant death. Interestingly, birth weight was more predictive of outcome than gestational age was.

DISCUSSION

NICU at KKUH is one of the major units in the capital city of Saudi Arabia. The unit underwent tremendous advancement in the care of newborns as well as antenatal care provided to pregnant women. Care of sick neonates was up to date with standard international management approach and policies in terms of medications, equipments, ventilators and respiratory management, newborn resuscitation, adoption of Kangaroo care strategy and establishment of neonatal follow-up program[7]. In the second period of this study (2011-2018), the unit's bed capacity eventually expanded to reach 44 beds, with deferent levels of care intensity, from 23-27 beds in the first period. Even admission policy changed as a result of unit expansion in the second period, as we started to accept out-born babies and admissions from emergency room as well as readmissions (in the first period, admissions were restricted to in-born babies only with no re-admission after discharge and babies who are born before entering our emergency room will be admitted to pediatric intensive care unit). The number of certified consultants increased in the second period (7 consultants vs. 3 consultants in first period). With this advancement and dramatic change in the unit structure and policy, we started accepting more high-risk pregnancies to deliver in our hospital, especially after the establishment of feto-maternal unit in our obstetrics department, which is one of the major tertiary referral units in Riyadh. This might explain the increment in mortality rate over the second period in comparison to first period (2.8 times increased rate). Death due to sepsis remained the major cause of mortality in both periods (37% in first period and 47% in second period). Another factor which might contribute to increased mortality in second period is the increment in the number of multiples (mainly triplets which increased by almost 3-fold) as more cases of in vitro fertilization were accepted either from within the hospital or as un-booked pregnancies.

In the second period, our unit strategy and antenatal care changed dramatically in many aspects regarding dealing with anticipated premature delivery. The use of antenatal steroids significantly increased to 86% in the second period in comparison to 22% only in the first period. Eventually, there was significant decrease in the use of surfactant (62% in second period vs. 80% in first period). Over the past 20 years, many substantial changes occurred in respiratory management of the neonates worldwide. Target values of arterial oxygen saturation, carbon dioxide and pH has changed. Non-invasive ventilation modalities are replacing invasive ventilation strategies, which is currently reserved for infants who failed noninvasive modes of ventilation. Also, current evidence-based interventions are applied during neonatal transition (delivery room and first postnatal hours of life) to prevent BPD in extremely preterm infants; they include continuous positive airway pressure, sustained lung inflation, supplemental oxygen use during neonatal resuscitation and surfactant therapy including less-invasive surfactant[8-10].

With advancement in neonatal care in our institute, there was a trend towards non-invasive modes of ventilation and adherence to current recommended approach in delivery room care and resuscitation of newborn babies aiming to decrease the incidence of BPD. Interestingly, there is no increase in BPD rates during the second period of this study, despite less frequent use of surfactant and postnatal steroids. The higher birth weight and gestational age in the second group, and increased use of antenatal steroids along with modified respiratory management practices may led to decreased incidence of BPD in the later time period.

Higher rates of emergency caesarean section deliveries (61.2%) and decreased rates of elective ones in the second period probably reflects reluctance of obstetrician and/or patients to proceed for caesarean section deliveries when indicated. Finally, the doubling rates of periventricular leukomalacia incidence in the second period seems an alarming finding, which deserves further investigation.

Limitations of the study

This study is limited by being of retrospective nature and representing the experience of one center only.

CONCLUSION

Advancement in our neonatal and antenatal care led to decreased incidence of BPD. However, mortality rate has unexpectedly increased in the later time period. We speculate that NICU expansion and

changing our unit admission policy, which permitted accepting out-born babies, pediatrics emergency room admissions and re-admission of discharged infants, as well as the establishment of feto-maternal unit, dealing with high risk pregnancies and accepting referred cases with congenital anomalies and potentially lethal conditions to be followed and delivered in our center, played a major role in increased mortality in later period, despite advancement in neonatal care.

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Conflict of interest: None

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Case Report

Cesarean scar pregnancy: Review and case reports

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ABSTRACT

Cesarean scar pregnancy (CSP) is one of the rarest forms of ectopic pregnancy with devastating complications. It occurs due to the implantation of gestational sac into the myometrial defect of previous cesarean scar, the niche. We are presenting a series of three case reports of CSP who were diagnosed and treated in Alorf hospital over a two-year duration. Painless vaginal bleeding during the first trimester was the most common symptom. Methods of diagnosis and mode of treatment were described and discussed in relation to various medical literatures.

KEY WORDS: cesarean scar pregnancy, ectopic pregnancy, magnetic resonance imaging, methotrexate

INTRODUCTION

Cesarean scar pregnancy (CSP) is one rare form of ectopic pregnancies[1]. The overall prevalence of ectopic pregnancy is approximately 2% relative to all pregnancies. About 97% of cases is in the fallopian tubes[2]. CSP is a condition in which the gestational sac is implanted within the previous hysterotomy scar[3,4]. The estimated incidence ranges from 1/1008 to 1/2500 of all pregnancies[5] and 72% of the patients had more than two cesarean sections[6].

CSP develops following injury to the endometrium and myometrium because of cesarean section, uterine curettage, myomectomy, hysterotomy, hysteroscopy or manual removal of the placenta[6]. It is thought to occur due to the implantation of the blastocyst in the fibrous scar tissue within the wedge- shaped myometrial defect 'niche' in the anterior wall of lower uterine segment following cesarean section[6,7]. This increases maternal morbidity and mortality due to placenta previa, placenta accreta, uterine rupture and hemorrhage[8].

Three patients of CSPs who were diagnosed and treated in our hospital are reported in detail.

CASE REPORT

Case 1

A 28-year-old female patient was G6 P5+0 with a history of five recurrent previous cesarean sections. The last three cesarean deliveries were one year apart, and the last cesarean delivery was on April 19, 2018.

Six months following the last cesarean section, she was misdiagnosed as having incomplete miscarriage that was treated conservatively without surgical intervention. She continued complaining of irregular uterine bleeding for one-month duration. Transvaginal ultrasound revealed irregular shaped cavity with hetero-echoic mass about 5×5 cm at the uterine isthmus. βhCG was 489.8 IU/L. Pelvic magnetic resonance imaging (MRI) showed irregular shaped cystic collection at lower uterine segment and complete myometrial discontinuity, intact serosa and there was no evidence of pelvic collection (Fig 1). The patient was diagnosed as having ectopic disturbed CSP. The hemoglobin level was 8.4 gm/dl and the patient was hemodynamically stable. Exploratory laparotomy was decided. Two units of cross matched packed red blood cells were transfused preoperatively.

After taking informed consent, transverse laparotomy was done. There was no intrabdominal bleeding. The uterus was bulky, myometrium was dehiscent at the site of previous scar with formation of hematoma size about 5×5 cm. With removal of hematoma, cystic tissue was found under the hematoma at the dehiscent myometrium (Fig 2A - 2D). The cystic tissue was excised (Fig 2E), sent to the pathology lab, and suction curettage for the uterine

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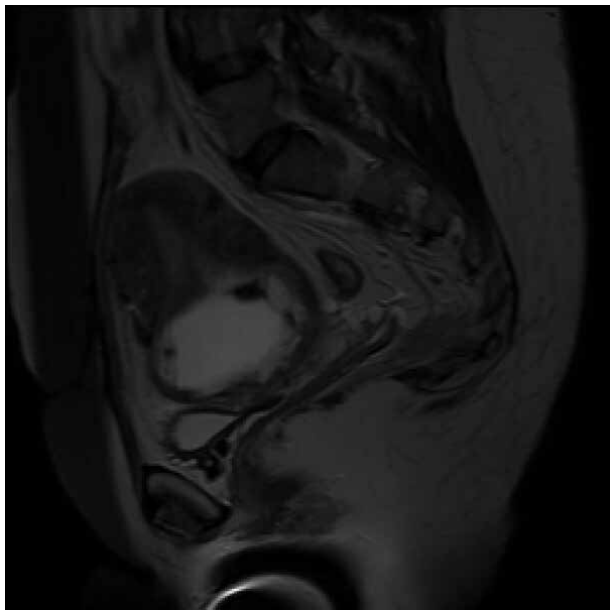

Fig 1: MRI pelvic with stain. The endometrium looks empty clear, cystic collection at lower uterine segment and complete myometrial discontinuity with intact serosa.

cavity was done to ensure removal of all remnants of conception (Fig 2F). Good hemostasis was insured, the uterus was closed in two layers.

Post-operative period passed smoothly. Two days post-operative, the βhCG was 69 IU/L. The pathology report returned as having blood clots containing chorionic villi, fetal membranes, trophoblasts and decidua. In one week, the scar was healed with primary intention. After one-month, pelvic transabdominal sonography showed non gravid uterus, intact myometrium between the uterine isthmus and the bladder.

Case 2

The second case was a 32-year-old female G4 P3+0 with one previous cesarean section two years before the current pregnancy. The last menstrual period was on 28/03/2018.

On 06/05/2018, the patient complained of threatened miscarriage; she was 5 weeks gestation. Pelvic sonography revealed indefinite sac and the βhCG was 9561mIU/mL.

On 13/05/2018 (one week later), the patient sought medical advice. Pelvic sonography revealed bulky uterus with gestational sac implanted within the uterine isthmus at site of previous cesarean scar with marked thinning of myometrium (not measured), intact serosal lining and intrauterine fluid collection in the upper uterine segment. No pelvic mass nor fluid collection were found. These data highly suggested ectopic scar pregnancy. The patient was hemodynamically stable. Exploratory laparotomy was decided. The surgical option was discussed with the patient, explaining the procedures and taking an informed consent.

Laparotomy was done through transverse abdominal incision. There was no intra-abdominal bleeding. The peritoneum over the lower uterine segment was intact under which there was a collection of coagulated blood. After removal of the hematoma, the underlying myometrium was dehiscent with the presence of cystic bloody structure. The structure was removed, the previous scar was trimmed assuring good hemostasis and the uterus was closed in two layers.

The pathology report came out as soft tissue measuring 35×20×10 mm, diagnosed as remnants of conception.

The patient was followed up using the βhCG. Ten days postoperative, it was 138.6 mIU/mL. At the end of four weeks from the operation, it was 15.06 mIU/mL

Case 3

The third case is a 40-year-old female patient G2 P1+0 with a previous cesarean delivery in 2006. Eleven years later, she was pregnant at 7 weeks gestation by last menstrual period, which was on 24/08/2017. Pregnancy was confirmed by pelvic sonography with positive fetal pulsation. One week later, she complained of vaginal spotting, sonography revealed missed miscarriage and CSP was suspected. Repeated pelvic sonography confirmed the diagnosis of CSP. Open laparotomy was decided and informed consent was taken. The βhCG was 10450 mIU/mL. The laparotomy was done through transverse abdominal wall incision, products of conception were removed, and the uterus was closed in two layers. Three days postoperative, the βhCG was 810.6 mIU/mL. Ten days later, it was 33.62 mIU/mL.

The pathology of the excised tissues was tissue mass of about 55×30×15 mm with decidual hypersecretory endometrium and placental tissue identified as products of conception.

DISCUSSION

The increased incidence of cesarean section delivery leads to the uprising of a new type of ectopic pregnancy, the CSP. This condition is following the breach of endometrial and myometrial continuity either from inside the uterus as in uterine curettage or outside due to cesarean delivery or myomectomy[6]. In this article, a series of three case reports is presented between the period of August 2017 and October 2018.

Many risk factors have been accused for the development of CSP. In the Kuwaiti community, there

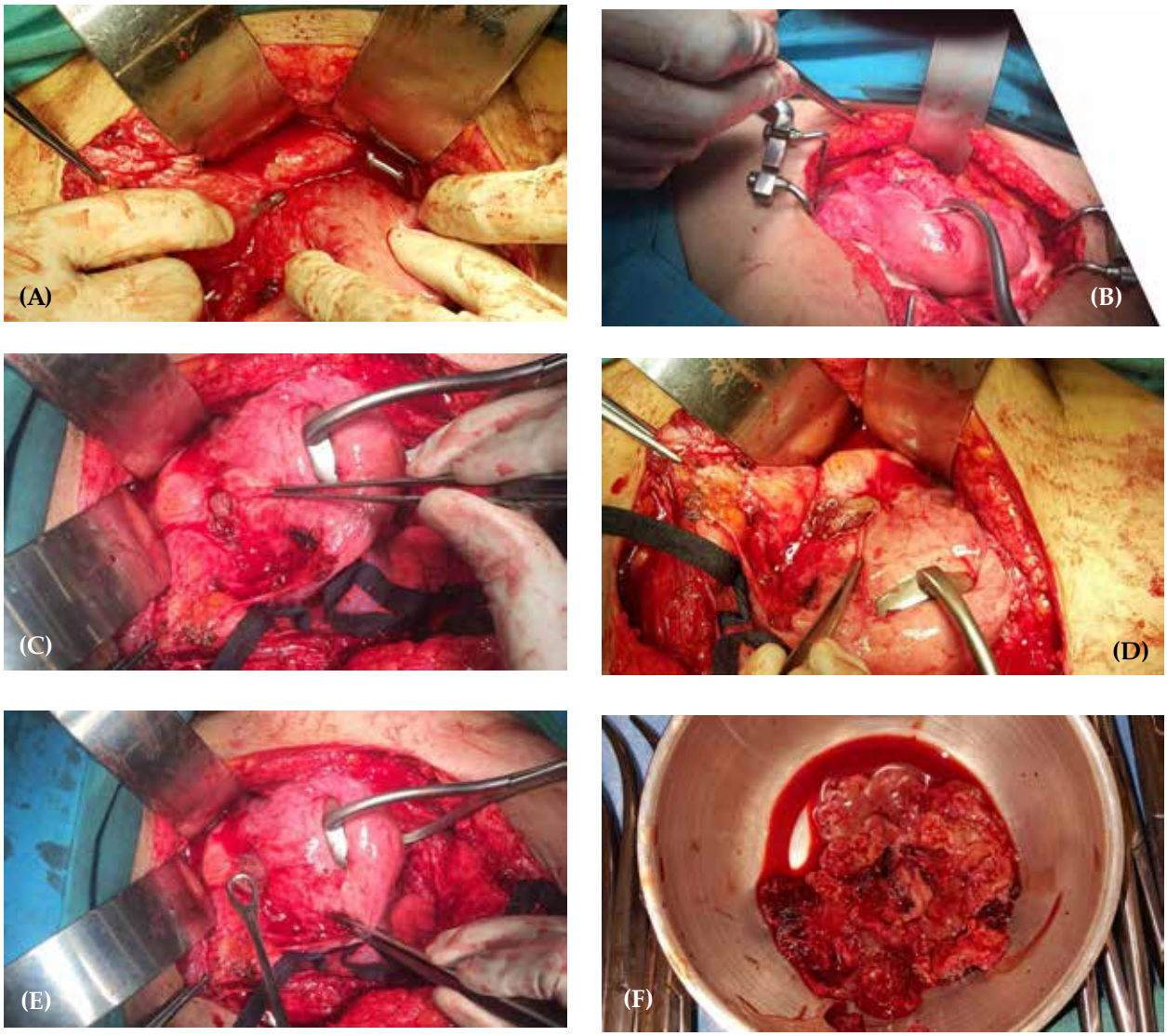

Fig 2: Intra-operative finding. Discontinuity of the myometrium (Fig 2A, 2B), the remnants of conception within the lower uterine segment scar (Fig 2C, 2D), extraction of the contents (Fig 2E), and the whole contents that were excised from the uterus (Fig 2F).

are some specific high-risk factors such as high parity, high number of recurrent caesarean section and non-spacing interval between pregnancies, especially following cesarean deliveries. The patients' age ranged from 28 to 40 years old, gravidity from second to sixth gravida and number of previous caesarean section from one to five previous sections. The time intervals between the last delivery by caesarean section and the incident CSP were 6 months, 2 years and 11 years respectively.

According to different literatures, none of these factors proved to be the cause of occurrence of CSP[6]. No definite relation was found between number of previous cesarean delivery, indication for cesarean section, time interval between CSP and the previous uterine surgical procedure, and the surgical technique for closure of uterus[6]. However, a relation was found between uterine scar defect and the technical aspect of closure of myometrium during cesarean delivery. With a full thickness closure of the myometrium including the decidual endometrium, it will produce weak scar healing and uterine scar defect[9].

Diagnosis of a CSP is relatively easy early in pregnancy, but as the pregnancy progresses, it becomes more difficult. It is frequently misdiagnosed as normal intrauterine pregnancy, different forms of first trimester miscarriages, gestational trophoblastic disease and cervical pregnancy[2]. 37% of cases may be discovered accidentally by ultrasound examination during the first trimester in asymptomatic patients, 39% may present in form of light vaginal bleeding. In extreme cases, the patient may complain of exaggerated abdominal pain associated with collapse or hemodynamic instability, which indicates uterine

rupture[3,6]. The three patients presented during the first trimester complaining of mild vaginal bleeding and mild lower abdominal pain. They were provisionally diagnosed as threatened or missed miscarriage and abnormal uterine bleeding.

Vaginal ultrasound of the sagittal view of the uterus is the primary tool of diagnosis in the first trimester. The criteria for diagnosis are empty uterine cavity and cervical canal, the presence of gestational sac in the anterior wall of uterine isthmus at the presumed site of the cesarean scar, negative organ sliding sign and may be a defect in the myometrium between the bladder and the uterus[6,7]. A combined abdominal approach with full bladder gives a panoramic view of the uterus, exact relation to the bladder and absent sliding organ sign[6]. MRI is useful when sonography is inconclusive before intervention. It measures the myometrium thickness and pictures the lower uterine segment discontinuity[6,7]. In the first case report, vaginal ultrasound was indecisive and MRI diagnosed the empty uterine cavity and the cystic fluid collection at the lower uterine segment and complete myometrial discontinuity with intact serosa.

When CSP is diagnosed, termination of pregnancy during the first trimester is the appropriate management. Variable treatment modalities were presented as case reports in the literature and there is no full consensus on the mode of termination[6,1].

The low-tech laparotomy with wedge resection of the lesion and excision of the old scar and repair may be considered the best primary treatment especially in disturbed pregnancy. It completely removes the lesion and microtubules within the old scar, decreasing recurrence with quick return of βhCG to normal level within 1-2 weeks[10].

All three cases were treated by open laparotomy. This was the suitable choice for the patients' clinical presentations. The first patient is diagnosed as disturbed CSP. In the second case, the gestational sac was found to be implanted within the cesarean scar with marked thinning of the myometrium. During laparotomy, the injured tissues and old scar were removed. In the first patient, βhCG declined more than 85% within two days postoperative. In the second patient, it took four weeks postoperative for βhCG to decline to normal level after excision of the sac surgically. In the third patient, there was a rapid decline of the βhCG from 10450 mUI/ ml to 33.6 mUI/ ml within 10 days postoperative.

Operative hysteroscopy with suction curettage was described for CSP treatment[11]. Lee *et al*[12] was the first to describe using operative laparoscopy in the removal of CSP. Using endoscopy requires general anesthesia, operative skills and facilities, and a surgical setting that enables conversion to emergency laparotomy should treatment fails[13].

Methotrexate is used as a medical treatment for ectopic tubal pregnancy. Accordingly, it can be used as well for CSP in the same dose with undisturbed pregnancy in hemodynamically patient. The medical treatment may need meticulous follow up for 16 weeks. The patient may have heavy bleeding and the scar may dehiscent and rupture with intraabdominal bleeding, which may end up with emergency surgical treatment[14].

An interesting new-generation procedure helpful in CSP management is a surgical method that utilizes high-intensity focused ultrasound. It has been used only for the treatment of prostate pathologies but proves 100% successful in the analyzed cases of CSP[2].

CONCLUSION

Cesarean scar pregnancy is a new challenging clinical condition with catastrophic complications. The three reported cases were diagnosed and operated upon during the first trimester, leading to early recovery and preservation of patient fertility. High index of suspicion, mental awareness and correct early diagnosis will lead to favorable outcome. Once diagnosed, proper selection of mode of pregnancy termination should be according to clinical picture and available medical facilities.

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Author contribution: Mansour B Alorf performed the surgical procedures; Hala F Elsharaky collected patients' data, reviewed literature and wrote the manuscript; Muntaha H Al-Salem suggested the idea and concept and collected patients' data.

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Case Report

Successful management of patient with fulminant myocarditis related refractory ventricular fibrillation by veno-arterial extracorporeal membrane oxygenation

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ABSTRACT

Myocarditis could be a life-threatening clinical condition producing severe symptoms such as refractory arrythmia, cardiogenic shock or cardiac arrest. A 47-year-old female with a medical history of mild mitral stenosis was admitted to a hospital with flu-like symptoms followed by ventricular fibrilation (VF), and multiple organ dysfunction syndrome developed. Bedside transthoracic echocardiogram assessment revealed global left ventricle systolic dysfunction, thrombus in left atrium. Due to myocarditis related persistent VF and cardiogenic shock, the patient was consulted to cardiovascular surgery department in order to perform peripheral venoarterial extracorporeal membrane oxygen application. Cardiovascular surgery team decided to perform mitral valve replacement for mitral stenosis and thrombectomy for left atrial mass. After surgery, the patient was discharged 15 days later without any neurologic deficit. VF could be persistent, unresponsive to medical treatment and defibrillation, and this is a life-threatening condition.

KEY WORDS: intensive care unit, malignant arrhythmia, myocarditis, veno-arterial extracorporeal membrane oxygenation, ventricular fibrilation,

INTRODUCTION

The incidence of myocarditis is not known evenly, given that most patients aren't admitted to the hospital and healed without noticing. Myocarditis could be a life-threatening clinical condition while severe symptoms occur such as refractory arrythmia, cardiogenic shock or cardiac arrest[1].

In this case report, we aim to draw attention to fulminant myocarditis related ventricular tachiarrythmia and how physicians can manage hard and severe clinical conditions.

CASE REPORT

A 47-year-old female, with mild mitral stenosis in her medical history, was admitted to a hospital with flu-like symptoms and she was discharged on medical treatment, but her symptoms increased. She was then admitted to the hospital again. Arrythmia was detected in her physical examination and she was referred to a cardiologist. On her electrocardiography (ECG), high ventricular response atrial fibrillation was detected and left ventricular ejection fraction (LVEF) was 45%. Left ventricular (LV) wall motion abnormality, left atrial dilatation, advanced mitral stenosis, first or second degree mitral insufficiency, first degree tricuspid insufficiency, and first or second degree aortic insufficieny were determined on her transthoracic echocardiographical image (TTE) by the cardiologist. Hence, the patient was treated with enoxaparine sodium, warfarin sodium and metaprolol medication at the hospital. Two days after her discharge, owing to chest pain and tachycardia, the patient was re-admitted

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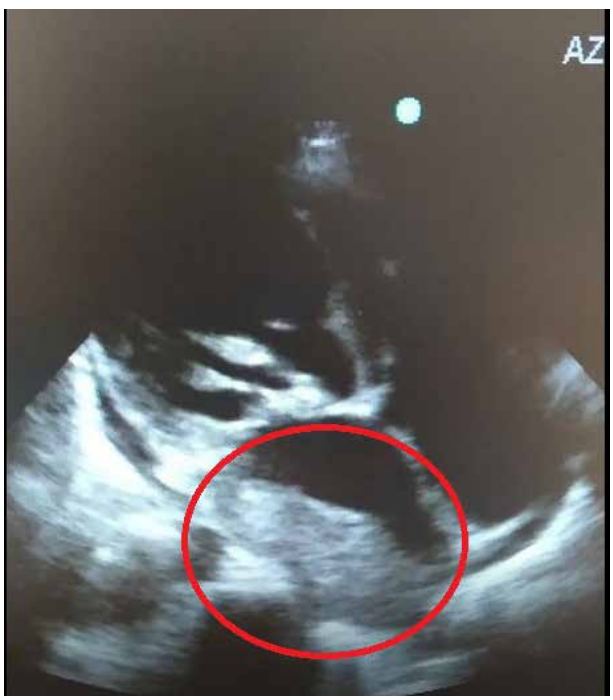
to another hospital. Immediately coronary angiography (CAG) was done and after the procedure, LVEF was 25% and LV global hypokinesia was detected on her control TTE. Although her CAG was normal, ventricular tachycardia (VT) and ventricular fibrilation (VF) developed after the procedure. She was defibrillated and medications were given, which were amiodarone and lidocaine infusion, to recover. At the same time, the patient was intubated because her Glasgow Coma Score (GCS) was 4 and we accepted the patient to our tertiary level intensive care unit (ICU) with multiple organ dysfunction syndrome. Her initial laboratory findings showed metabolic acidosis, arterial blood gas analysis was pH: 7.2, pCO_2: 40 mmHg, pO_2: 86 mmHg, HCO_3: 13mEq/L while fraction inspired oxygen was 40%. Elevated liver enzymes (aspartate aminotransferase: 3691 U/L (<35), alanine aminotransferase: 1956 U/L (<35), gamma glutamil transferase: 1164 U/L (<38), lactate dehydrogenase: 8423 U/L (<247)) were compatible with shock liver. Myocardial markers were troponin I: 3.54 ng/mL (<0.04), creatinine kinase MB: 48.9 ng/mL (0.6-6.3), myoglobin >3950ng/mL (14-66), brain natriuretic peptide: 1836 ng/mL, D-dimer: 39438 ng/mL (0-243), and fibrinogen: 2.44 g/L (2-3.93). There were pathological findings on her first examination at ICU; GCS 4, cardiac murmur was auscultated on diastolic phase in mitral area and crackles were audible in the middle and lower lung zones bilaterally. Bedside TTE assessment revealed global LV systolic dysfunction, ejection fraction 30%, LV global hypokinesia, 5.4 x 3.1 cm size thrombus in left atrial, and mitral valve area of 1.1 cm^2 (Figure 1, 2). We excluded intracranial pathology by means of cranial computed tomography. On account of prolonged QT interval on ECG (corrected QT: 600msec), amiodarone infusion was stopped. On the second day of ICU stay, cardiac arrest developed and cardiopulmonary resuscitation (CPR) was initiated for three minutes. Post-CPR, due to myocarditis related persistent VF and cardiogenic shock, the cardiovascular surgery (CVS) department were consulted to perform peripheral venoarterial extracorporeal membrane oxygen (VA-ECMO). VA-ECMO was inserted via canulations of right femoral artery-17 French (F) size cannulla- and vein-24 F cannulla- bedside by CVS team. During ECMO run, the patient was heparinized to prevent coagulation and it was monitored by activated clotting time (ACT) Target (ACT range: 180-220 second) and according to ACT level, heparin infusion dose was adjusted. During VA-ECMO and mechanical ventilation period, multiple short-term VF attacks developed. Thus, automatic external defibrillator paddle was placed on her chest. While VF time was longer than 15-20 seconds, we performed defibrillation shock at 200-360 Joules. The patient was defibrillated approximately hundred times. During this VF period, lidocaine infusion (2 mg/kg/h) was given, and electrolytes levels such as potasium and magnesium were checked and replaced when their levels were lower than normal range (potassium: 4.5 mEq/L, magnesium: 2.5 mEq/L). On second day after VA-ECMO and arrythmia



Fígure 1: Thrombus in left atrium

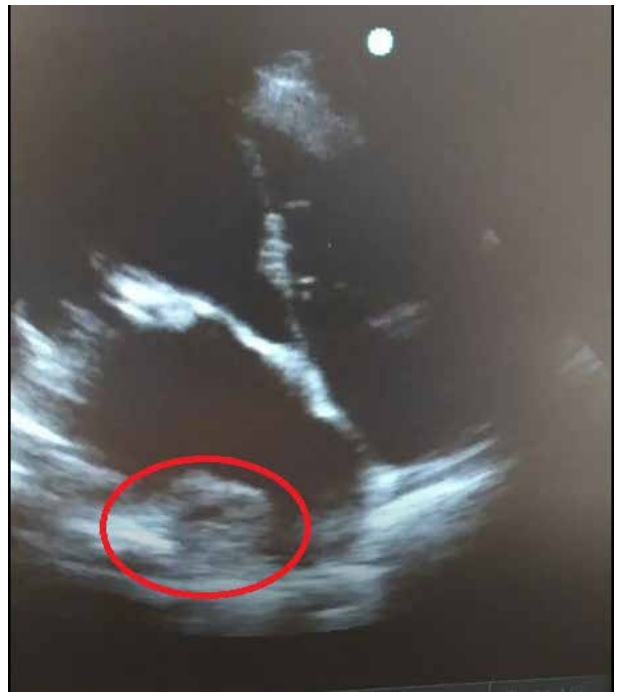


Figure 2: 5.4 x 3.1 cm size thrombus in left atrium

therapy, VF recovered to normal sinus rhythm. Due to a GCS of 10+ when intubated and normal sinus rhythm, sedative agents were stopped and the patient was extubated. After the extubation, oxygen support was continued through mask oxygen (5-7 L/sec). During follow-up, disorientation and non-cooperation occured; so she was re-intubated, just after generalized tonic-clonic seizures. To control and avoid convulsion, propofol infusion (2 mg/kg iv bolus in two minutes, 1-3 mg/kg/h) and antiepileptic agent (levetirasetam, 30 mg/kg iv bolus in ten minutes, maintenance dose 20 mg/kg iv, twice per day) were applied. Sedation level was checked by bedside electroencephalography (Philips MX/800). Although ACT level was optimum, cranial computed tomography was taken to exclude intracranial pathology, and neither hemorraghe nor ischemia was detected. On day six of ICU stay, the sedative agent was discontinued and convulsions were under control. On day seven, VA-ECMO was weaned. Fluid balance and cardiac output were followed by hemodynamic monitorization (Philips MX/800, PİCCO). On day twelve, she was extubated and oxygen was supplied by nasal cannula (2-4 L/min). On her control TTE, LVEF improved to 45% and LV contraction was better now than the prior measure. CVS team decided to perform mitral valve replacement for mitral stenosis and thrombectomy for left atrial mass. After surgery, the patient was discharged to home 15 days later without any neurologic deficit.

DISCUSSION

Myocarditis is an inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria. Myocarditis could be associated with severe cardiac dysfunction, life-threatening arrythmias such as VT/VF or cardiogenic shock[1].

According to Extracorporeal Life Support Organization (ELSO) guidelines, myocarditis is one of the indications for VA-ECMO in adult cardiac failure, and at the same time, VA-ECMO is a bridge to recovery from myocarditis[2]. The other indications are refractory ventricular tachyarrhythmias, acute coronary syndromes, post-cardiotomy cardiogenic shock, acute pulmonary embolism, cardiogenic shock caused by acute mitral regurgitation, septal rupture, right ventricular failure, and pericardial tamponade secondary to the myocardial infarction. Other common causes of cardiogenic shock suitable for VA-ECMO may relate to acute deterioration of chronic heart failure, valvular disease and stress-induced cardiomyopathy[3]. Although the etiology of myocarditis often remains undetermined, a large variety of infectious agents, systemic disease, drugs and toxins can cause the disease[1]. Presented in this case report, the patient had no severe cardiac pathology in her previous medical history. After the flu-like symptoms, she had chest pain and tachycardia. We couldn't detect any viral or bacterial agents, systemic disease, drugs or toxins; hence acute coronary syndrome was excluded by CAG, which was normal. Thereby, we diagnosed myocarditis according to these criteria: acute chest pain, unexplanied arrythmia and unexpected cardiogenic shock, VF and asystole on ECG, elevated myocardial markers, global systolic abnormality and endocavitary thrombi[1]. Ventricular arrythmia such as VT/VF is a severe and life-threatening form, and defibrillation and/or medical therapy are used to reverse these arrythmia. Adegbala *et al* have revealed that VT/VF was most common arrhythmia in acute myocarditis and mechanical circulatory support was required in 8.79% of arrythmia patients[4]. Recently, particularly in company with advanced technology, extracorporeal life support devices have been used as rescue strategy for patients with cardiac arrest who could not treated by defibrilation and/or medical therapy. In this case, cardiac arrest developed due to VF and it was unresponsive to the conventional CPR. Hence, in a short span of time, our team decided to insert VA-ECMO. Upon checking the literature, there are many case reports where VA-ECMO was used in refractory VF; however, many of them had refractory VF owing to acute myocardial infarction. Unlike those cases, CAG of our case was normal and VF developed in our patient after the CAG procedure; it was myocarditis-related persistent VF[5-7].

Echocardiography is essential in the evaluation of patients with cardiovascular disease. In the course of these conditions, TTE helped us to determine pathological findings and the bedside ultrasound guided the initiation of VA-ECMO. The ELSO guideline has suggested the use of bedside echocardiography and ultrasound, particularly while performing canullation and for rechecking placement of canullation[8]. Nevertheless, performing ultrasound depents on user's experience, as the ultrasound is fundamental imaging method in experienced hands. In patients on VA-ECMO, numerous complications could occur such as heamatological, vascular and neurological, associated with VA-ECMO device. Ischemic stroke or intracranial bleeding are common ECMO-related neurological complications, but convulsion is not common and its causes aren't clear. Dimmitt *et al* have revealed that sezuires were more common in VA-ECMO patients (12.3%)[9]. Our patient had generalized convulsion and we thought that it was associated with hemodynamic instability and temporary hypoxemia.

CONCLUSION

In this case report, we would like to highlight a few important points. First, bedside ultrasound plays a key role in ICU, either to diagnose cardiac pathology or as a guide to invasive procedures and for the follow up of the patients' condition fastly and quickly. Secondly, VF could be persistent, unresponsive to medical treatment and defibrillation, leading to a life-threatening condition. However, physicans should not give up treatment and should think to apply VA-ECMO as a rescue therapy for both myocarditis-related severe arryhtymia and cardiogenic shock.

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Conflict of Interest: None

Financial Disclosure: None

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Case Report

First case of bloodstream infection caused by *Clostridium saccharolyticumin* in the Middle East

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ABSTRACT

In this report, we describe a rare case of bacteremia caused by an unusual *Clostridium* species, *Clostridium saccharolyticum*, an environmental anaerobic spore-forming gram-variable bacillus. The clinical significance in humans remains poorly known. This is the first documented report of human infection by this organism in the Middle East.

KEY WORDS: clostridium, emerging pathogen, environmental flora

INTRODUCTION

Clostridium species are spore-forming, almost always Gram-positive bacilli, though a few gram variable anaerobic bacilli have been described. They are ubiquitous in the environment and some species are part of the human gut microbiota. The most common Clostridium species in the intestinal microbiota are those from cluster IV such as *Clostridium leptum* and from cluster XIVa (*Clostridium coccoides*, *Clostridium celerecrescens*, *Clostridium sphenoides*, *Clostridiumclostridioforme*)[1]. In this communication, we report a rare case of severe bacteremia caused by *C. saccharolyticum* in our hospital, representing the first of such reported infection in this region.

CASE REPORT

A 45-year-old Indian female presented to the emergency room of Mubarak Al Kabeer hospital, Jabriya, Kuwait on September 21, 2019 with a four-day history of vomiting, constipation, abdominal pain mainly in the left iliac fossa and left flank. There was a history of laparotomy done six years back for a ruptured ovarian cyst as well as closure of an atrial septal defect done four years back in India. On examination, she was afebrile and vitally stable, with tenderness over the left lower quadrant of the abdomen. A computed tomography scan was done for the patient, which suggested adhesive small bowel obstruction. She was admitted for emergency laparotomy and lysis of the adhesions. The surgery was complicated by the development of multiple enterotomies which were closed with vicryl. Intraoperative findings included multiple bands looping around the small and large intestines and a dilated proximal bowel. Post-operatively, she was shifted to the intensive care unit for observation and started on intravenous piperacillin-tazobactam 4.5g eight-hourly. The following day, she became hypotensive with severe tachypnea and complained of severe abdominal pain at the site of the wound. In addition, she had not passed any flatus or feces. Blood gas analysis showed metabolic acidosis with anion gap of 40 IU/L. A central internal jugular line was fixed for nor-epinephrine 1 µg/kg/min infusion and her antibiotic therapy was changed to meropenem 1g eight-hourly. At this time, a repeat computed tomography scan showed free intraperitoneal air and fluid levels suggestive of perforation of the bowel, bilateral pleural effusion and underlying collapse of the lung bases. These findings prompted an immediate second laparotomy. Intra-operatively, there were two perforations at the site of previously stitched enterotomies which were leaking air along with turbid fluid in the pelvis. These perforations were closed with

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Figure 1: Organism on blood agar growing anaerobically *i.e.* incubated for 48h at 37 ºC in an Anoxomat Anaerobic W5800 system (MART Microbiology BV, Lichtenvoorde, Netherlands), in an atmospheric condition of 85% N_2, 10% CO_2, 5% H_2 with zone of inhibition around the 5µg metronidazole disc.

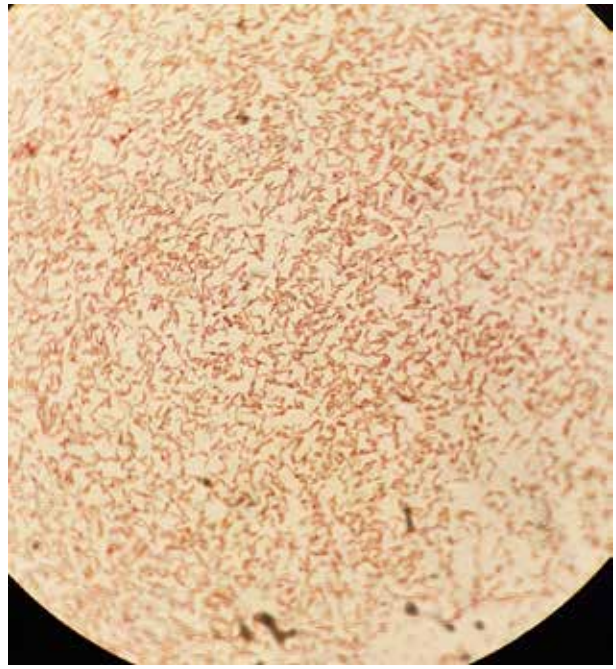

Figure 2: Gram stain appearance of the organism showing gram-negative bacilli with subterminal spores using standard operation procedure.

second layer enforcement. She was moved from the operating room directly to the intensive care unit for close monitoring. A full septic workup including blood culture and urine culture was ordered. In the meantime, post-operatively, she developed high grade fever (temperature of 38.9 ºC). On day 2 post-op, she complained of pain at the site of the incision. A wound swab was taken for culture and sensitivity. The blood culture ordered during the febrile episode yielded an anaerobic gram-negative bacillus with spores (Figures 1, 2) after 20 hours of incubation. The organism was unidentifiable by conventional and rapid automated methods, such as API AN (bioMérieux, L'Etoile, Marcy, France), VITEK 2 (bioMerieux) and MALDITOF MS (bioMerieux). The bacterium was finally identified by 16s rRNA gene sequencing method, using SeqStudio genetic analyzer (Applied BioSystems, Thermo Fisher Scientific, USA), as *Clostridium saccharolyticum*[2]. Phylogenetic relationship between the isolated strain and the type strain of the species is shown in Figure 3. It was susceptible to all antibiotics including penicillin, piperacillin, piperacillin-tazobactam, amoxicillin-

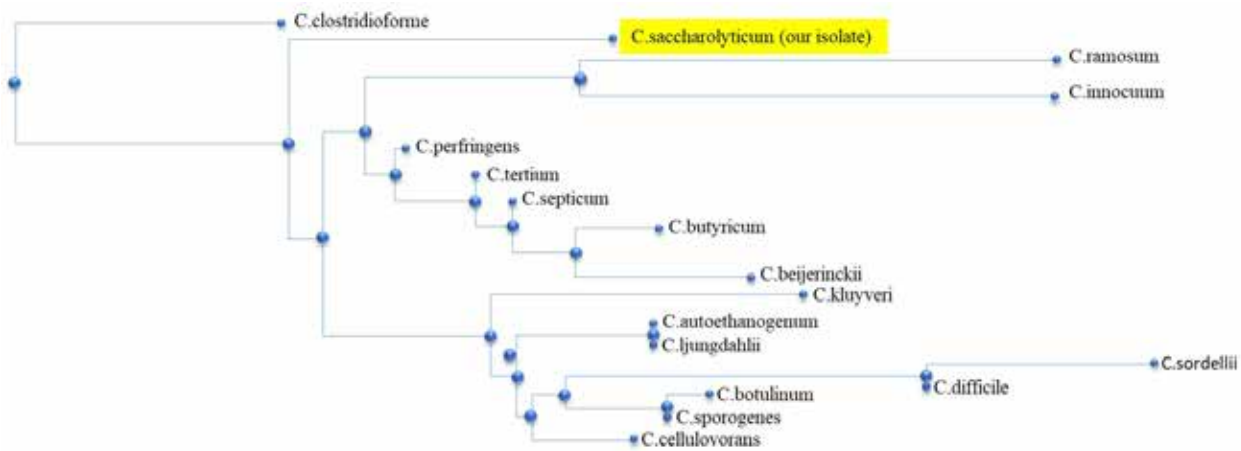

Figure 3: Phylogenetic tree showing the 16S rRNA relationship of our *Clostridium saccharolyticum* isolate with various *Clostridium* species.

clavulanic acid, clindamycin, meropenem and imipenem. Consequently, her antimicrobial therapy was switched to IV amoxicillin-clavulanic acid 1.2g eight-hourly. All the clinical parameters improved, and the patient was shifted to the surgical ward on day 3 post-op. On the 10th day after admission, the antibiotic was switched to the oral formulation of the same drug. She received 18 days of antibiotics in total and was discharged home well. Her post-hospital admission follow-up four weeks after was uneventful and was consequently discharged from the outpatient clinic.

DISCUSSION

In this communication, we report an unusual Gram-negative *Clostridium* spp. rarely involved in systemic infections. It is conceivable to speculate that this bacterium probably invaded the systemic compartment of this patient via the gut as a consequence of the laparotomies. The genus *Clostridium* has a wide environmental distribution, existing primarily in soil, sewage sediments or as part of the gastrointestinal bacterial flora of living beings. A majority of species are characteristically and morphologically gram-positive. There are more than 160 recognized species, but only a few species have been implicated in human illnesses. In general, toxigenic species are recognized as causative agents of food poisoning, gas gangrene, tetanus, botulism, ulcerative colitis, intractable diarrhea, septicemia, and postoperative infections in humans[3]. Although most of the environmental clostridia are considered seemingly harmless and nonpathogenic, there are a few species of these bacteria that have already been implicated in a serious human infection[4]. It seems that there are many unidentified spore-forming anaerobic bacteria that have been isolated from clinical specimens[5]. The correct identification of such bacterium is often a tedious process as seen in our case. Penicillin is the drug of choice for treating most clostridial infections, but the use of high dose amoxicillin-clavulanic acid was adequate and achieved complete resolution in our patient.

There are multiple species which belong to the *C. saccharolyticum* group like *Clostridium indolis*, *Clostridium sphenoides*, *Clostridium celerecrescens*, *Clostridium methoxybenzovorans* and *Desulfotomaculum guttoideum*. First case of *C. indolis* chronic osteitis was published in 2016 from France[5] and in another case report, it was isolated only once from a blood culture of a patient presenting without sepsis syndrome[6]. The clinical significance of *C. saccharolyticum* species group in humans is not well established. Till date, only four cases of infections due to *C. sphenoides* have been reported, including two gastro-intestinal infections, one bacteremia and one osteomyelitis[7–10]. In addition, three cases of *C. celerecrescens* infections have been described including an osteomyelitis, an abscess secondary to an open fracture and a post traumatic wound infection[11,12].

In this report, 16S rRNA was used for the final identification of the bacterium when all the conventional routine laboratory methods available in our laboratory failed. This method has been proven to be more accurate than the API 20 E or 20 NE, VITEK-2 and even MALDITOF as in this case, and has demonstrated a genus-level concordance rate of 96% and species-level concordance rate of 87.5%[2,13]. However, this method has its own limitations, such as difficulties sometimes encountered in obtaining a genus and species identification, which include the recognition of novel taxa, too few sequences deposited in nucleotide databases, species sharing similar and/or identical 16S rRNA sequences, or nomenclature problems arising from multiple genomovars assigned to single species or complexes. In this case, 88% concordance specific for *C. saccharolyticum* was obtained in the absence of any other *Clostridium* spp.

CONCLUSION

The bacterium is considered a non-pathogenic organism and data concerning *C. saccharolyticum* or its infections is scarce in the literature. Hopefully, the use of new tools, such as MALDI-TOF MS and 16S rRNA sequencing, in diagnostic laboratories for routine bacterial identification of difficult-to-identify organisms will provide a better understanding of the clinical significance of some clostridia in human infections. Our case report highlights a unique bloodstream infection caused by a rare gram-negative *Clostridium* sp. normally regarded as innocuous and of little clinical importance. It is pertinent to emphasize the importance of *C. saccharolyticum* as a potential pathogen capable of causing bloodstream infection in immuno-compromized as well as immuno-competent patients was the case of our patient. As far as we know, this is the first case report of systemic infection caused by a gram-negative *Clostridium* spp. in the Middle East.

ACKNOWLEDGMENT

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Conflict of interest: None

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Case Report

Adenomatoid tumor of the adrenal gland synchronous with clear cell papillary renal cell carcinoma: Report of an unusual case

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ABSTRACT

Adenomatoid tumors are benign neoplasms with a mesothelial origin that may be seen especially in the genital system and in many organs, but rarely in the adrenal gland.

A male aged 30 years presented to the gastroenterology clinic complaining of abdominal pain and diarrhea. In abdominal computed tomography, a well-circumscribed hypodense (+50 HU) lesion was observed in the right adrenal gland with a size of 37x25x15 mm. In the upper pole of the right kidney, a well-defined solid mass with a size of 19x15x14 mm was observed that showed contrast involvement in the contrast-enhanced series and a 33 HU density in the contrast-unenhanced series. Right partial nephrectomy and right adrenalectomy were applied to differentiate between non-functional adrenal mass and metastatic carcinoma. The renal tumor was diagnosed as clear cell papillary renal cell carcinoma (CCPRCC) and the adrenal mass was diagnosed as an adenomatoid tumor.

CCPRCC synchronous with adrenal adenomatoid tumor is unusual. Reviewing the literature for adenomatoid tumors, we report a case with an adenomatoid adrenal tumor accompanied by a CCPRCC. To the best of our knowledge, this is the first study in English literature reporting this kind of co-occurrence.

KEY WORDS: adenomatoid tumor, adrenal gland, clear cell papillary renal cell carcinoma

INTRODUCTION

Adenomatoid tumors (AT) are benign neoplasms with a mesothelial origin mostly seen in the genital system and in many organs, including the adrenal gland[1-3].

While some cases are reported by abdominal pain and hypertension, most of the patients are detected incidentally as asymptomatic conditions during routine imaging tests.

Clear cell papillary renal cell carcinoma (CCPRCC) is a relatively uncommon renal neoplasm characterized by an indolent biological behavior, described recently in the World Health Organization 2016 renal tumor classification.

In this study, summarizing the literature for AT, we report a case with an adenomatoid adrenal tumor accompanied by a CCPRCC.

CASE REPORT

Clinical history and radiological findings

A male patient aged 30 years presented to the gastroenterology clinic complaining of abdominal pain for a long time and diarrhea for the last week. The patient had no history of illness or enduring medicine usage. After the clinical evaluation, a contrast-enhanced abdominal computed tomography was ordered with the preliminary diagnosis of chronic pancreatitis. In computed tomography, a

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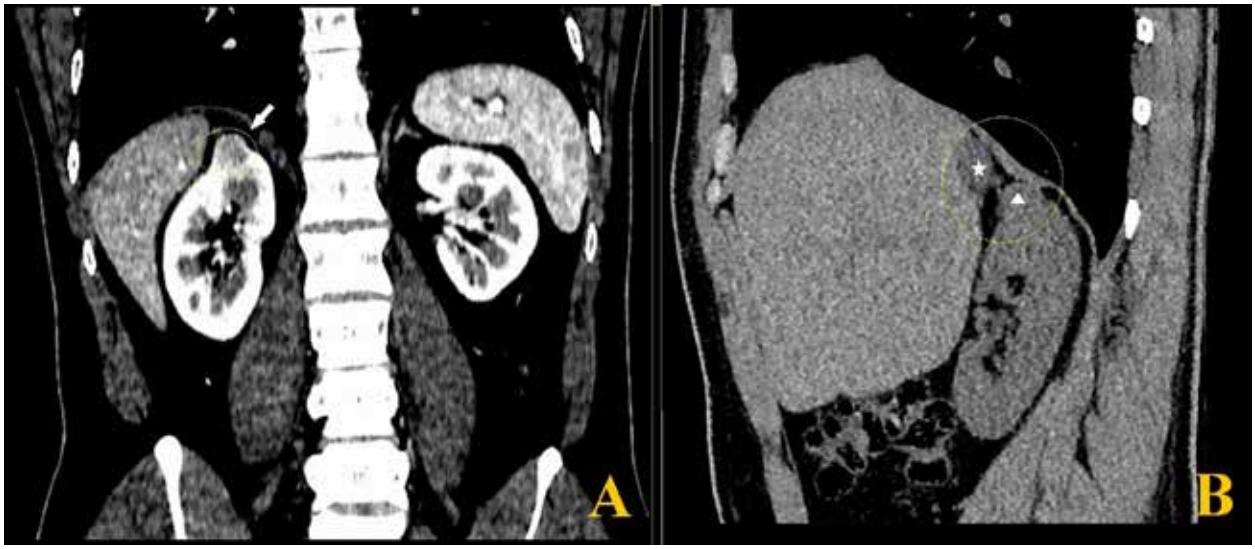

Figure 1 (Abdominal CT examination): A 2 cm mass in the upper pole of the right kidney (arrow) revealed in contrast-enhanced CT (A). In contrast-unenhanced CT, the same kidney mass (arrowhead) and adrenal mass adjacent to the liver (star) are seen together (B).

well-circumscribed hypodense (+50 HU) lesion was observed in the right adrenal gland with a size of 37x25x15 mm. In the upper pole of the right kidney, a well-defined solid mass with a size of 19x15x14 mm was observed that showed contrast involvement in the contrast-enhanced series and a 33 HU density in the contrast-unenhanced series (Fig. 1). The condition was assessed radiologically as a malignant kidney tumor. Further studies revealed 24-hour urine metanephrine as 51.40 μg/24h (50-250), 24-hour urine normetanephrine as 123.30 μg/24h (100-500), plasma renin activity as 9.25 ng/ml/hour, plasma aldosterone as 30.60 ng/dl, aldosterone/renin ratio as 3.3 (<20), basal cortisol as 16.68 μg/dl (3-22), cortisol after low-dose dexamethasone suppression test as 0.8 μg/dl (<1.8), and dehydroepiandrosterone-phosphate as 311 μg/dl. The patient's current hormonal scan was normal. Right partial nephrectomy and right adrenalectomy were applied to differentiate between non-functional adrenal mass and metastatic carcinoma.

Pathologic findings

Kidney

During the macroscopic evaluation of the right partial nephrectomy material, a well-circumscribed, encapsulated mass with focal hemorrhage and a size of 2.5x2x1.9 cm was seen in a yellow-brown color, located beneath the intact renal capsule.

Microscopically, a neoplasm with varying proportions of papillary, tubular and cystic epithelial structures without solid components separated from the normal parenchyma by a thick fibrous capsule, was observed. The tumor cells were cuboidal cells with clear cytoplasms and apical snouts. The nuclei of these cells had inconspicuous nucleoli and mild membrane irregularities and tended to align linearly, away from the cell's basal and apical edges (Fig. 2). Some cystic spaces were filled with eosinophilic secretions. There was no tumor necrosis, perinephric invasion or lymphovascular invasion. Also, foamy histiocytes, psammoma bodies and hemosiderin depositions were not observed.

Immunohistochemically, the tumor cells were positive for CK7, EMA, CAIX, and 34β12, whereas negative for CD117, CD10, AMACR, and GATA 3 (Fig. 2).

The case was diagnosed as CCPRCC. Nuclear properties were consistent with ISUP grade 1, and the patient's stage was pT1.

Adrenal gland

Macroscopic examination revealed a well-circumscribed, unencapsulated, yellow-grey colored mass with a size of 4.5x2.5x15 cm, adjacent to a normal-appearing right adrenalectomy material with a size of 2x0.7x0.5 cm and orange-brown color.

On microscopic examination, a neoplasm composed of cystic, lymphangioma-like angiomatous or microtubular compositions distributed in a fibrous connective tissue stroma lined by flattened endothelial-like cells without atypia (Fig. 3). Extra-capsular spread, hemorrhage and necrosis were not observed. There were clusters of focal lymphoplasmacytic infiltrates in the stroma. Immunohistochemically in islands with endocrine morphology, inhibin and melan-a were positive, while CK7, synaptophysin, chromogranin-a, calretinin, and vimentin were negative. However, at the angiomatoid and microtubular areas, CK7, calretinin and vimentin were positive, while synaptophysin, chromogranin-A, CD117, CD31, S100, inhibin and

CD10 were negative (Fig. 3). The Ki-67 proliferation index was evaluated as ~1%.

Based on these findings, the right adrenal mass was diagnosed as an AT.

DISCUSSION

Clear cell papillary renal cell carcinoma

CCPRCC is a renal epithelial neoplasm with an indolent course that constitutes 1-4% of renal tumors[4,5]. The tumor may develop sporadically or with end-stage renal disease and Von Hippel-Lindau syndrome syndrome[4,5]. It can be seen between the ages of 18-88[4]. Typically, it is encountered incidentally in asymptomatic patients. The tumor is generally well-circumscribed and encapsulated macroscopically[4]. More than 95% is pT1 during the diagnosis, without necrosis.

Our patient was a 30-year-old male with normal kidney functions and no features of polycystic kidney or Von Hippel-Lindau syndrome. The renal cortical neoplasm was encountered incidentally.

Papillary, tubular, acinar and cystic structures formed by cuboidal-columnar cells with clear cytoplasm, which have nuclei that tend to show linear sequencing, away from the cell base, form the basis of CCPRCC morphology[4]. Luminal eosinophilic secretions, which are frequently seen, may be useful in the differential diagnosis.

Immunohistochemically, CK7, 34β12, EMA, CA-IX, Pax2, Pax8 and vimentin are positive, while CD10, AMACR, CD117, TFE3 and TFEB are negative[4]. The value of GATA-3 was demonstrated in the differential diagnosis, which is positive in 76% of the cases[6].

The differential diagnosis includes papillary renal cell carcinoma (RCC), clear cell RCC (CCRCC), MiT Family Translocation RCC, and multilocular cystic RCC with low malignancy potential. Our case had the morphological and immunohistochemical features of CCPRCC.

Our patient's tumour is different from CCRCC for being immunohistochemically CK7 and 34β12 positive and for being AMACR and CD10 negative and

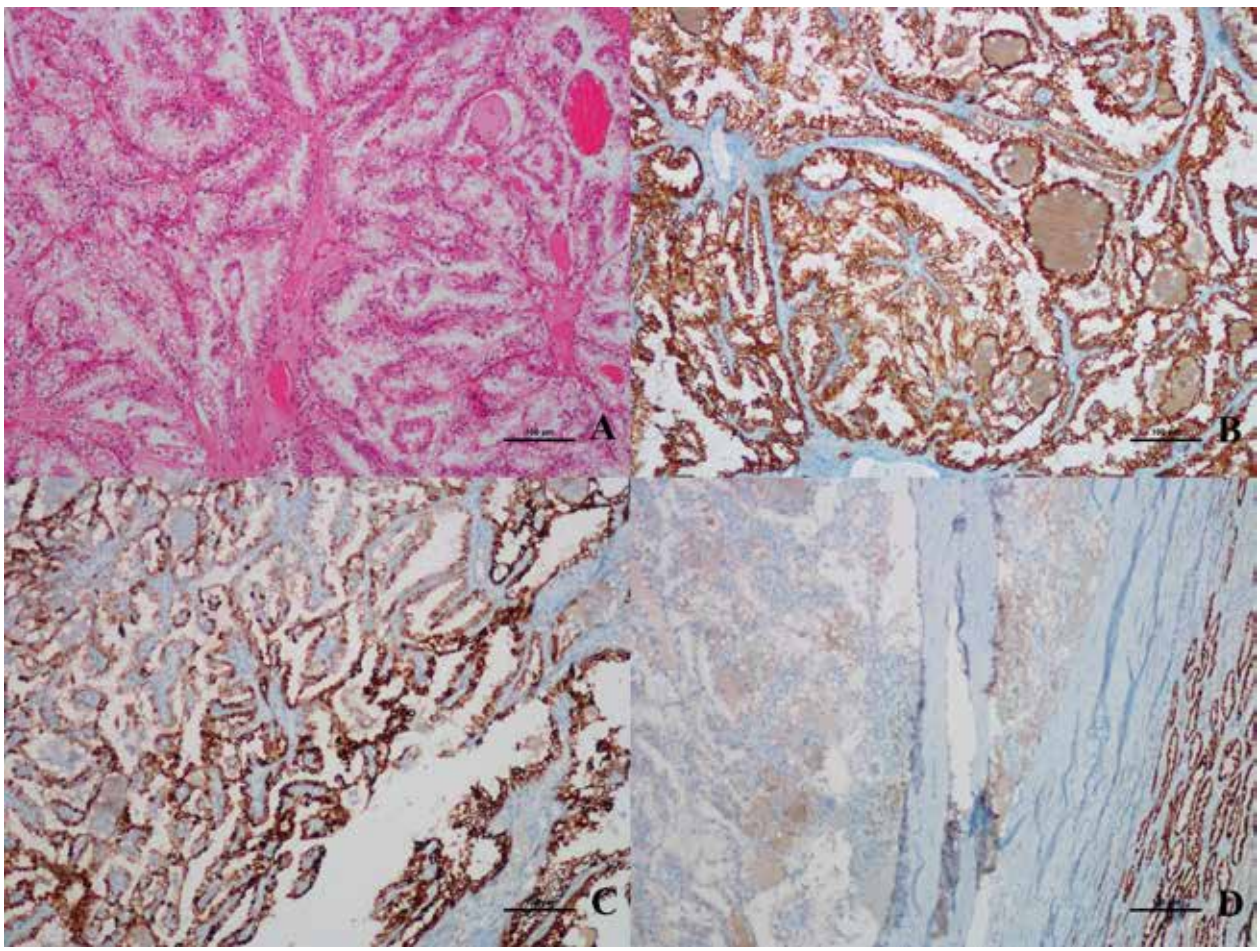

Figure 2 (Kidney): A tubulopapillary neoplasm with a thin fibrovascular core, lined by cuboidal cells with clear cytoplasm is seen. Also, focal luminal eosinophilic secretion is remarkable (A, H & E, 100x Magnification). Strong and diffuse staining was observed in tumor cells with CK7 (B, IHC, 100x Magnification) and 34β12 (C, IHC, 100x Magnification), whereas AMACR (D, IHC, 100x Magnification) was negative.

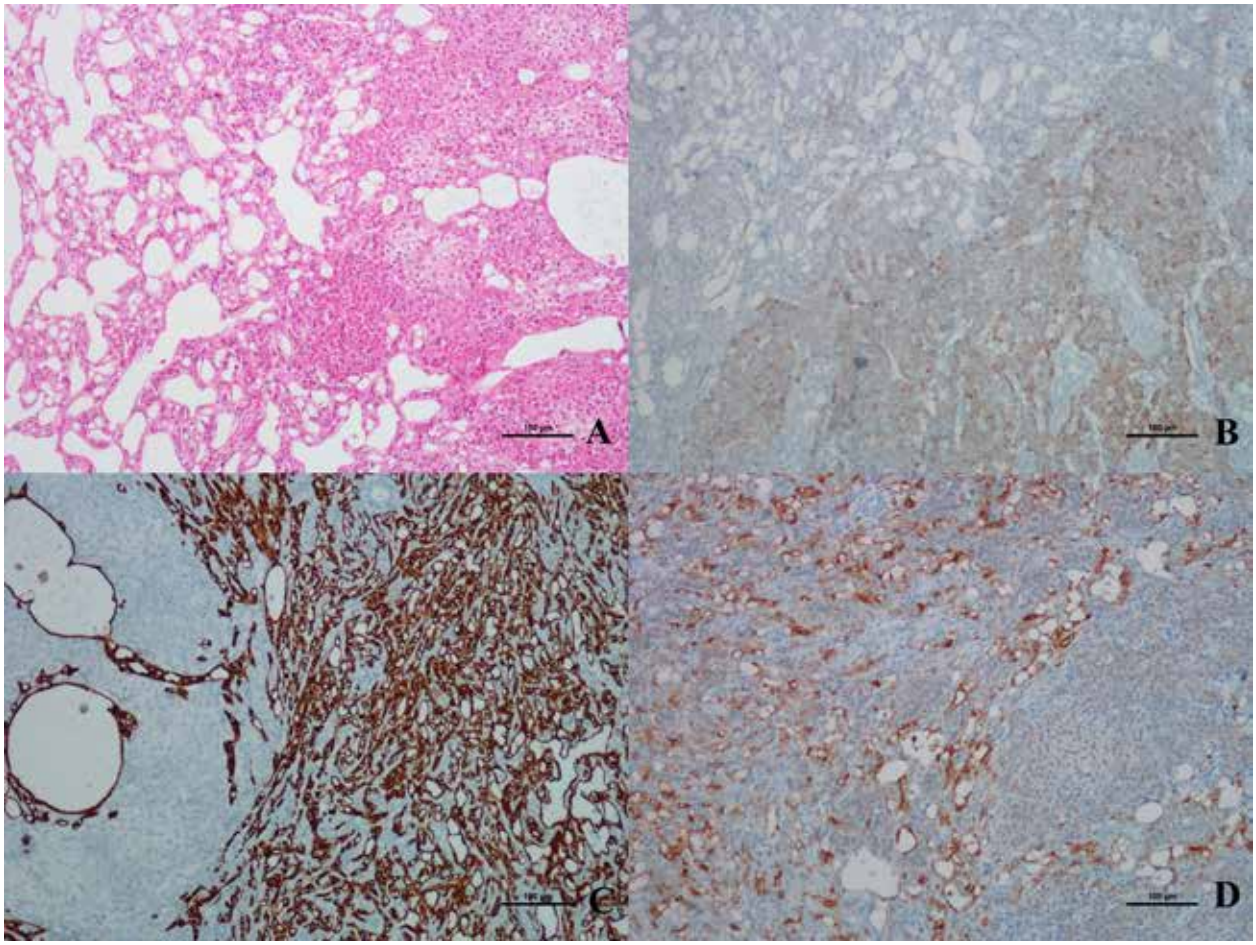

Figure 3 (Adrenal Gland): Among the adrenal parenchymal cell islands, a tumor with microcystic and tubular structures lined by flattened endothelial-like cells is observed (A, H & E, 100x Magnification). Immunohistochemically, inhibin (B, IHC, 100x Magnification) was positive in adrenal parenchymal cell islands while negative in tubular microcystic areas, whereas CK7 (C, IHC, 100x Magnification) and calretinin (D, IHC, 100x Magnification) were positive in tubular microcystic areas, whereas negative in the adrenal parenchymal cell areas.

morphologically containing no necrosis or high nuclear grade; it differentiates from papillary RCC for being immunohistochemically CA-IX positive and AMACR negative. Also, it differentiates from MiT family translocation RCC for being immunohistochemically strongly CK7 positive, TFE3 and TFEB negative and containing no psammoma bodies and hyaline nodules. Finally, it differentiates from multilocular cystic RCC with low malignancy potential for being immunohistochemically CD10 negative. No recurrence or metastasis was observed in our patient within a one-year follow-up.

Adenomatoid tumor

A search on PUBMED and Google Scholar revealed only 41 articles that reported a total of 52 adrenal AT cases in the English-language literature between 1988-2021. Including our case, 47 of the 52 cases were male, while the other five were female, and contrary to general knowledge, most of the cases (27/48) were located in the right adrenal gland. The patients were between the ages of 22 and 73 (mean: 40.3 years). A cystic morphology was prominent in 8 cases. Clinical information on these studies is summarized in Table 1 (adapted from Phitayakorn *et al*[2]).

The differential diagnosis of AT includes primary adrenal tumors, vascular tumors, malignant mesothelioma, liposarcoma and metastatic carcinomas. Microcystic structures lined with endothelial-like flattened cells mimic vascular tumor morphology. In our case, calretinin and CK7 positivity and CD31-negativity exclude vascular tumors. Since synchronous RCC was also observed in our case, we had to exclude metastatic carcinoma. Both morphological and immunohistochemical findings do not match CCPRCC metastasis. Clear cell morphology forming papillary structures, lack of atypia and increased mitotic activity, and immunohistochemically vimentin and calretinin positivity are in favor of an AT.

Malignant mesothelioma (MM) and AT have similar immunohistochemical profiles. However, contrary to MM, calretinin is only positive in flattened cells

Table 1: Clinical features of ATs reported in the literature

Case	Age	Gender	Localization	Clinical presentation	Additional data
1 [1]	51	M	L	Incidental	
2 [2]	22	M	R	Incidental	HIV
3 [3]	37	M	L	Incidental	
4 [3]	31	M	R	Incidental	
5 [3]	31	M	NDA	Syncope	
6 [3]	64	M	L	Incidental	
7 [7]	36	M	L	Painless hematuria	
8 [8]	44	M	L	HTN	
9 [9]	24	M	L	Cushing syndrome	
10 [10]	49	M	R	Incidental	
11 [10]	57	M	L	Incidental	
12 [10]	50	F	R	Incidental	
13 [10]	40	M	L	Incidental	Cystic morphology
14 [11]	34	M	R	Incidental	AIDS
15 [12]	28	M	R	Abdominal pain	
16 [13]	54	M	L	Epigastic pain	
17 [14]	31	M	R	Abdominal pain	
18 [15]	51	M	R	HTN	Micronodular AC hyperplasia
19 [16]	33	M	L	HTN	
20 [17]	42	M	L	HTN	
21 [18]	54	M	L	Incidental	Heterotophic Oscification
22 [19]	55	F	R	NDA	
23 [20]	65	M	NDA	NDA	
24 [21]	46	M	R	Right flank pain	Cystic morphology
25 [21]	33	M	L	Incidental	
26 [21]	33	M	R	HTN	
27 [22]	42	M	L	HTN	Nephrolithiasis and renal cyst
28 [23]	30	M	L	Incidental	
29 [24]	32	M	R	Fever and renal pain	
30 [25]	26	M	R	Incidental	Liver ecchinococ cyst
31 [26]	47	M	R	Incidental	Myelolipoma
32 [26]	52	M	R	HTN	Myelolipoma
33 [27]	73	F	R	Incidental	Lung Carcinoid
34 [28]	39	M	R	Incidental	Lymphangioma-like Cystic Morp.
35 [29]	44	M	L	Incidental	
36 [30]	29	M	R	Incidental	Germline SDHD mutation
37 [31]	24	M	L	Incidental	Cystic morphology
38 [32]	32	M	L	Incidental	Cystic morphology
39 [33]	62	M	R	Incidental	Cystic morphology
40 [34]	40	F	R	Incidental	Cystic morphology
41 [35]	40	M	R	Incidental	
42 [36]	47	M	R	Incidental	AC Adenoma
43 [37]	30	F	R	Incidental	
44 [38]	52	M	L	Incidental	
45 [39]	48	M	L	Incidental	Ganglioneuroma, myelolipoma, AC hyperplasia
46 [40]	26	M	R	Incidental	
47 [41]	27	M	NDA	Incidental	Lympangioma-like Cystic Morp.
48 [42]	30	M	R	Incidental	
49 [42]	31	M	L	Incidental	
50 [43]	28	M	R	NDA	
51 [43]	50	M	R	NDA	
52 pc.	30	M	R	Incidental	CCPRCC, AC adenoma

HTN: hypertension; CCPRCC: clear cell papillary renal cell carcinoma; AC: adrenocortical, PC: presented case, NDA: no data available; L: left; R: right

and is negative in fusiform stromal cells in AT cases. EMA is mostly positive in MM. In our case, EMA was negative. Additionally, the gross and radiologically well-circumscribed and microscopically composite structure not destroying the adrenocortical cell islands favor AT in the differential diagnosis.

In some areas of the tumor, there are vacuolated, flat to low cuboidal cells that have formed microtubules within the fibrous stroma, giving the impression of metastatic adenocarcinoma or signet-ring cell carcinoma invasion into the desmoplastic stroma. Minimal atypia in these cells, no mitotic activity, negative musicarmine, and positive calretinin exclude the metastasis of signet-ring cell carcinoma. In addition, S100 negativity, as well as keratin and calretinin positivity, do not match liposarcoma.

No metastasis and recurrence were reported in adenomatoid tumors.

CONCLUSION

In our case, no recurrence or metastasis was observed in the 18-month follow-up. CCPRCC synchronous with adrenal adenomatoid tumor makes this an unusual case. To the best of our knowledge, this is the first study in English literature reporting this kind of co-occurrence.

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Conflicts of interest: The authors declared no conflict of interest.

Author contribution: Abdulkadir Yasir Bahar was a major contributor in writing the manuscript and performed the histological examination. Murat Sahin analyzed and interpreted the patient data regarding the endocrine disease. All authors read and approved the final manuscript.

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Case Report

Breast hamartoma: a series of variable clinical presentation

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ABSTRACT

Introduction: Breast hamartoma is a breast within the breast. Hamartoma is a relatively rare entity that may become large and cause breast asymmetry. It contains normal breast parenchyma including glandular, fibrous, and fibrocystic and adipose tissue surrounded by pseudo-capsule which can be under diagnosed or misdiagnosed, with a reported incidence range of 1.2% to 4.8% of all benign breast pathology
Methods: Prospective study collecting all the patients with breast mass suspected by ultrasound or mammogram to have hamartoma with exclusion of other causes of breast mass by true cut biopsy starting January 2012 to January 2019 and to assess the clinical presentation and the fate of the hamartoma.
Result: Breast hamartoma is a rare benign breast lesion with variable clinical presentation. Over a period of seven years, only four patients were diagnosed to have breast hamartoma. Small number of patients indicate rarity of the disease or under diagnosis.
Conclusion: Breast hamartoma is a rare pathology that can present as breast asymmetry, painful breast mass. It can also increase in size during pregnancy and be misdiagnosed as breast lipoma. Surgical excision is the treatment of choice. It can be affected by all pathology that affects normal breast tissue.

KEY WORDS: hamartoma breast

INTRODUCTION

Hamartoma (from Greek, hamartia, meaning fault, defect, and oma denoting tumor or neoplasm)[1] was initially defined as mastoma. Hamartoma is a relatively rare entity that may become large and cause breast asymmetry[2]. It contains normal breast parenchyma including glandular, fibrous, fibrocystic and adipose tissue[3,4]. It is a fibro glandular tissue intermixed predominantly with fatty tissue surrounded by compressed connective tissue, forming a pseudo-capsule. Arrigoni *et al* were the first to use the term hamartoma in 1971. Breast asymmetry from nipple to infra mammary fold are found in 59.6%[5]. Minor breast asymmetry is quite common, but significant breast asymmetry need to be investigated carefully to rule out underlying pathologies. Large hamartoma having the same texture of the other breast can be mistaken as normal larger asymmetric breast. Hamartoma may be discovered during imaging performed for other reasons[6]. The increasingly widespread use of mammographic screening for the diagnosis of breast hamartoma is on rise[6]. Small hamartoma can be detected by physical exam as a breast mass. Hamartoma by ultrasound resembles normal breast tissue; it may be seen as solid with hypoechoic and hyperechoic components and the lesions are soft and easy to compress[2] or defined as lipoma with pseudo-capsule. Mammogram is diagnostic (breast within a breast) and magnetic resonance imaging of the breast is of great help in diagnosis. Fine needle aspiration cytology and core biopsy has no role in such cases[7], but can exclude other cause of breast mass

Methods

This prospective study was conducted over a period of seven years starting in January 2012 to January 2019 in King Khalid University hospital - Riyadh College of Medicine King Saud University. Total number of patients were four. Patients were diagnosed radiologically (by using breast ultrasound,

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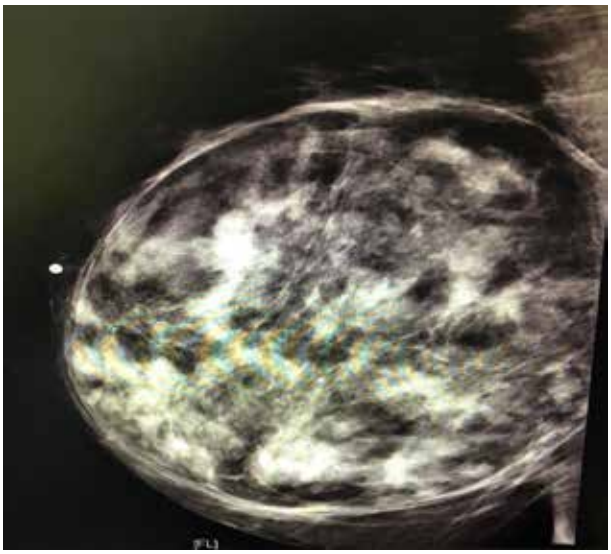

Fig 1: Case 1 mammogram of large breast hamartoma.

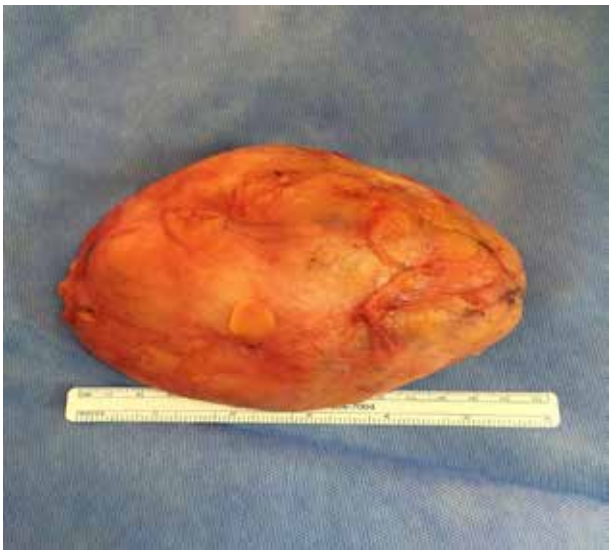

Fig 2: Case 1 right breast hamartoma of size 15x12.5 cm.

mammogram as age indicates) and pathologically by ultrasound guided true-cut biopsy to diagnose hamartoma and to exclude other causes of breast mass. The 4th patient was excluded because biopsy was not done and she was lost to follow-up.

CASE REPORT

CASE 1

A 38-year-old female sought medical advice several times for nine years for her right breast asymmetry. She was assured by her physician every time that there is no pathology and her ultrasound reported as normal breast tissue.

With increase in her breast size, she was referred to our clinic for a second opinion. In the young woman with clear breast asymmetry, her right breast was double the size of her left breast with a soft mobile mass almost occupying all her right breast. The patient was sent for breast ultrasound, which was reported as normal. The case was discussed with the breast imaging radiologist. Mammogram was performed, which shows clear mass occupying the whole breast (Fig 1) with a feature suggestive of hamartoma (breast within the breast). Patient underwent surgical excision of her right well circumscribed breast mass of size 15x12 cm (Fig 2) with a pathology report of encapsulated fibrocystic changes. Apocrine metaplasia had no malignant feature. Post-operative follow-up of the patient showed almost symmetric breast. Hamartoma presented clinically in this case as breast asymmetry.

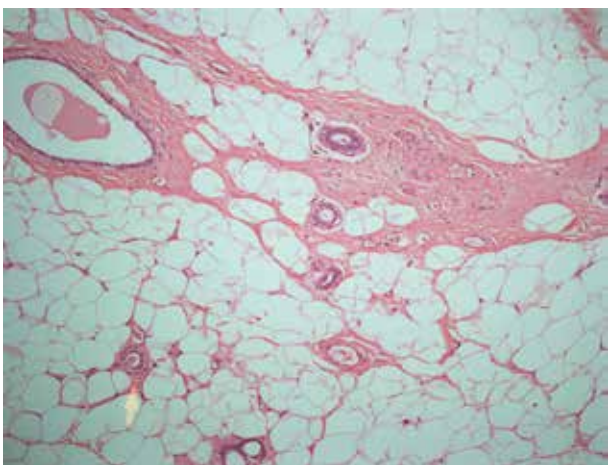

Image 1 A (5561-100): Histopathology of case 2. Low power view showing feature of mammary hamartoma. Note the presence of disorganized lobular structure with dilated ducts and fatty infiltration. Haematoxylin eosin x100

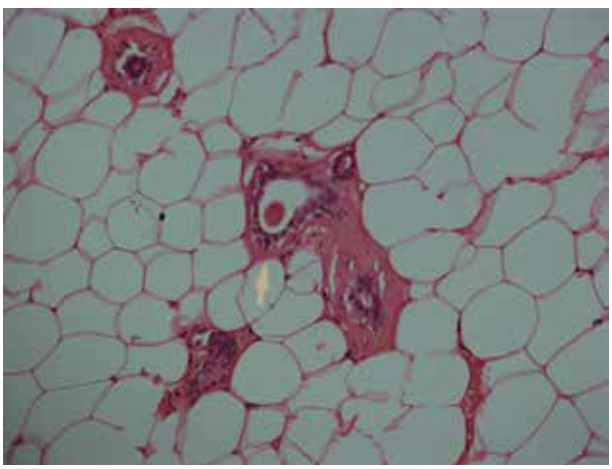

Image 1 B (5561-200): Histopathology of case 2. Mammary hamartoma showing disorganized ducts and ductules with prominent fatty infiltration. Haematoxylin and eosin x200

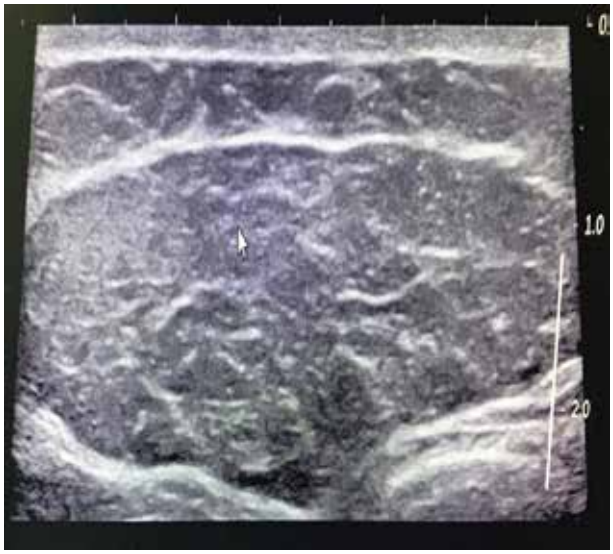

Fig 3: Case 2 ultrasound of left breast hamartoma (isoechoic circumscribed mass with pseudo capsule).

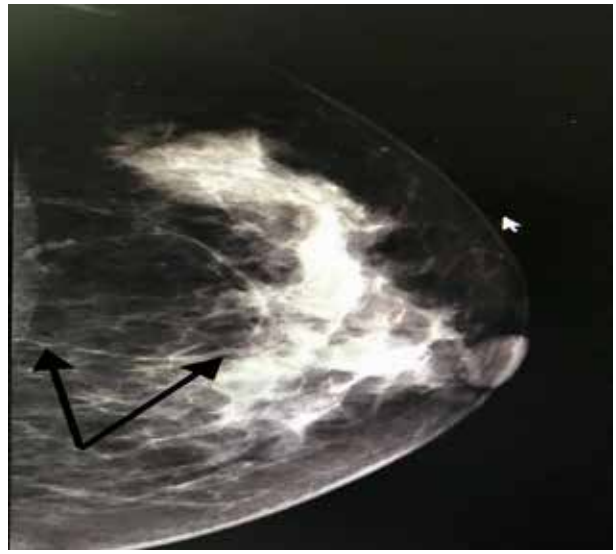

Fig 4: Case 2 mammogram of left breast hamartoma with pseudo capsule black arrow.

CASE 2

A 46-year-old female complained of left breast mass for one year that was increasing in size and associated with cyclic pain. Breast examination revealed a deep mobile soft mass at 5 o'clock position with the initial impression of breast lipoma. Fig 3 shows the left breast ultrasound and Fig 4 shows the mammogram. Both ultrasound and mammogram reported as lipoma with pseudo-capsule. Mass lumpectomy was done for her. Histopathology report revealed an encapsulated 5.5x4x2 cm hamartoma of adenolipoma type. Hamartoma in this case presented as painful breast mass mimicking lipoma (histopathology image 1 A and 1 B).

CASE 3

A 31-year-old female complained of left breast mass at 2 o'clock position which increased in size during her pregnancy. Left breast examination revealed a mass of same breast texture about 5x2 cm in size. Breast ultrasound reported a benign looking mass (Fig 5). Ultrasound guided core biopsy was done, which is reported as benign breast fibroepithelial proliferation intermixed with adipose tissue. Patient

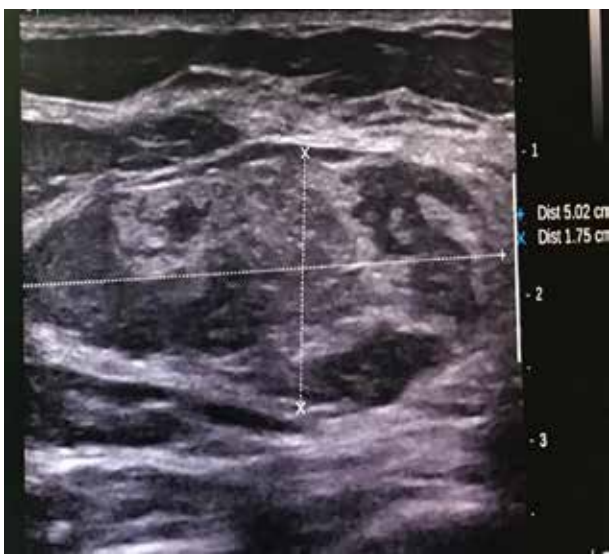

Fig 5: Case 3 ultrasound of left breast hamartoma in pregnant woman (circumscribed mixed hyperechoic and hypoechoic texture benign oval mass with no posterior feature).

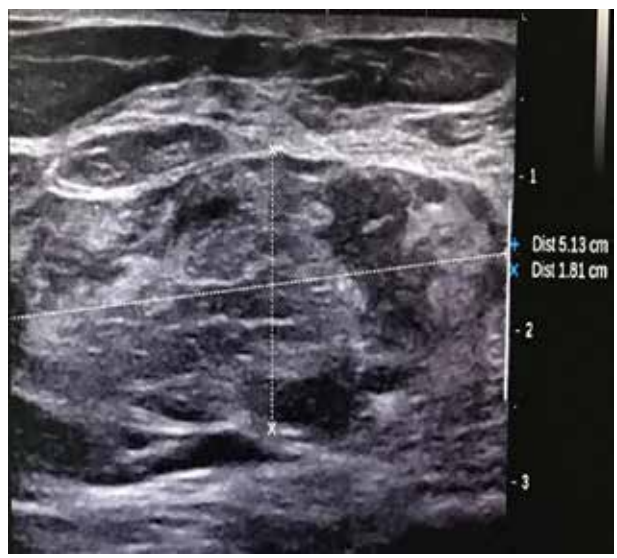

Fig 6: Case 3 ultrasound of left breast hamartoma increase in size in 6/12

was followed clinically by breast ultrasound with slight increase in the size of her breast mass (Fig 6). Hamartoma increased in size during pregnancy, which may indicate hormonal influence to hamartoma as the rest of her breast tissue.

CASE 4

A 33-year-old patient was diagnosed with deep vein thrombosis, pulmonary embolism and cerebro vascular accidents with no neurological deficit. She was diagnosed to have protein c deficiency on anticoagulant medication and was found to have right breast mass. Her ultrasound reported a hamartoma 3x2 cm in size (Fig 7). Biopsy was not done and she was lost to follow-up. She was excluded from the study.

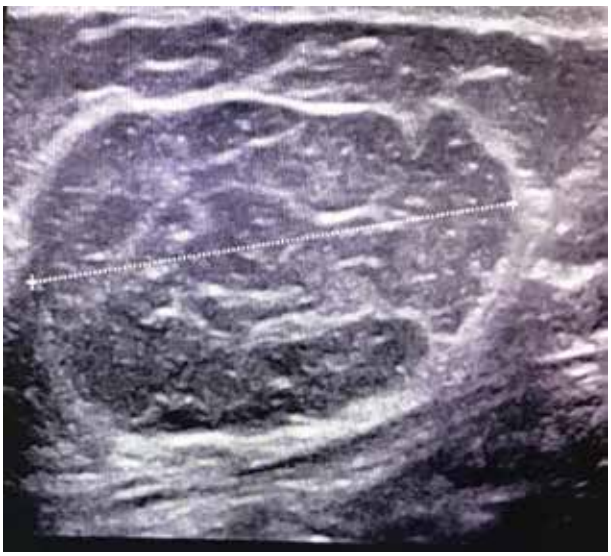

Fig 7: Case 4 ultrasound of right breast hamartoma (oval circumscribed heterogeneous mass with parallel oriented, no posterior features)

RESULT

Hamartoma is a breast within the breast which represents benign proliferation of fibrous, glandular, and fatty tissue (fibro-adeno-lipoma) surrounded by a thin capsule of connective tissue. All components are found in normal breast tissue and this is why the lesions are considered hamartomatous. It is a rare benign breast lesion that is detected in the breast during screening of breast asymmetry or discovered pathologically in combination with other breast pathologies. Large hamartoma can be considered as one of the differential diagnosis of breast asymmetry, especially for young women where mammogram is not frequently ordered as in case 1. It can be suspected if the patient complains of significant breast asymmetry with no clearly evident breast mass by physical exam. It can mimic lipoma in the breast as in case 2 or can present as a slow growing mass as in case 3. It can be affected by all pathologies that affect the breast tissue. Hamartomas can increase in size if not removed surgically. Ultrasound can diagnose small, localized hamartoma as a well-circumscribed lesion resembling normal breast tissue often mixed with both hyperechoic and hypoechoic components which are soft and easy to compress. The margins are often difficult to delineate. Mammogram is diagnostic (breast within a breast). Clinical correlation with radiological imaging and histopathology will lead to early diagnosis and treatment of breast hamartoma. Table I indicates the duration of complaint and the size of hamartoma as well the clinical presentation .

DISCUSSION

Breast hamartoma is a relatively rare entity and some authors report 1.2% to 4.8% incidence of all benign breast masses. It may become large and cause breast asymmetry[8], which is a common complaint among young woman. Physical examination and clinical evaluation are assuring, but significant breast asymmetry or presence of mass indicates full clinical, radiological and pathological evaluation. Hamartoma doesn't possess specific diagnostic histological feature. The role of fine needle aspiration cytology and core needle biopsy in making the diagnosis is limited and requires clinical and radiological correlation to avoid under diagnosis[4,7]. Case 1 hamartoma presented as breast asymmetry undiagnosed for nine years. The pathogenesis of breast hamartoma is still poorly understood[4]. Our patient falls histologically into the encapsulated fibrocystic changes type, which can be missed histologically and sonographically as normal breast. Both ultrasound and histopathology will be variable and nonspecific[4,9].

Table 1: Duration of complaint, size of hamartoma and the clinical presentation

Case No.	Age	Duration of complain	Presenting symptom	Size of hamartoma
1	38 y	9 years	Right breast asymmetry	15x12.5 cm
2	46 y	One year	Painful breast mass	5.5 x4 cm
3	31 y	3 years	Mass increasing in size during pregnancy	5.8x3cm
4	33 y	7 months	Breast mass	3x2 cm

Hamartoma can be misdiagnosed as lipoma, fat necrosis[3], as in case 2. Breast hamartoma was soft like lipoma by examination and the association of cyclic pain supports the diagnosis of hamartoma (adenolipoma type). Trials to classify hamartoma into specific categories (fibroadenolipoma, lipoadenofibroma, adenolipoma or encapsulated fibrocystic changes) based on their histological appearance are not generally accepted by most authorities[3,9-12]. This is due to benign proliferation of fibrous glandular and fatty component of the breast surrounded by connective tissue capsule[8]. Mammogram has the characteristic feature of "breast within the breast'' or "a slice of the sausage" appearance[4].

The radiological feature by mammogram is a well circumscribed rounded or oval mass surrounded by thin capsule, comprising of both fat and soft tissue internal densities[4,8,13]. Association of hamartoma with other pathologies e.g. phylloides or lipoma or even malignancy[10-12] can make the diagnosis easier. The change in size during pregnancy and lactation could be secondary to hormonal effects similar to case 3, which increased in size. Many authors consider hamartoma to be underdiagnosed[7,12,13].

CONCLUSION

Breast hamartoma is a rare benign breast disease that mandate clinical, radiological and pathological correlation. It varies in clinical presentation; however, all of the patients had increase in size of their breast mass if not removed surgically.

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Conflict of interest: None

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Case Report

Thyroglossal cyst fistulized to the skin accompanying multinodular goiter in an adult: A case report

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ABSTRACT

Thyroglossal duct cyst (TGDC) consists of remnants of the thyroglossal duct during embryological development. It usually appears during childhood. A 56-year-old female patient presented with swelling and discharge in the midline of the neck. The patient underwent Sistrunk's procedure and total thyroidectomy through a single incision transversely to the cyst. Cysts, which are unnoticed and cannot be diagnosed in childhood, rarely show up complicatedly in adulthood. These major complications are papillary carcinoma, squamous cell carcinoma and fistulization to the skin. TGDC, which can gain a malignant characteristic in adulthood, should be surgically treated during childhood.

KEY WORDS: multinodular goiter, Sistrunk's procedure, skin fistulization, thyroglossal cyst, total thyroidectomy

INTRODUCTION

Thyroglossal duct cyst (TGDC) consists of remnants of the thyroglossal duct during embryological development[1]. Although the incidence of its coexistence with malignancy in childhood is low[2], it can be seen with malignancies as age progresses[1,3,4]. The cases reporting the complication of fistulization of the cyst in adult patients are only a few in the literature[5,6]. In this case, we planned to present the operation of a complicated thyroglossal cyst fistulized to the skin, which was seen with multinodular goiter, using a single incision line.

CASE REPORT

A 56-year-old female patient presented to the General Surgery Outpatient Clinic of Antalya Training and Research Hospital with the complaint of swelling and discharge in the midline of the neck in January 2018. On examination, she was diagnosed with TGDC fistulized to the skin and multinodular goiter (Figure 1). Magnetic resonance image is shown in Figure 2. Her neck ultrasonography showed hypoechoic nodular appearance with a heterogeneous internal structure and no significant Doppler flow signal measuring ~14x6.5 mm in the midline of the neck and multiple isoechoic nodular appearances with a heterogeneous internal structure in both lobes and at the isthmus level in the thyroid parenchymal areas, the largest of which measured as 21x13 mm (Figure 3). The fine-needle aspiration biopsy of the thyroid was reported as insignificant atypia. Sistrunk procedure and thyroidectomy were simultaneously performed on the cystic structure and multinodular goiter mass with no malignant findings in the pathology report, using a single incision transversely to the cyst. No complication developed. The patient was discharged on the second postoperative day. Figure 4 shows the postoperative first month image and Figure 5 shows one year after surgery.

DISCUSSION

TGDC is relatively a childhood disease because of being a defect that occurs during embryological development[1]. Cysts, which are unnoticed and cannot be diagnosed in childhood, rarely show up complicatedly in adulthood. This disease brings about some complications. These major complications

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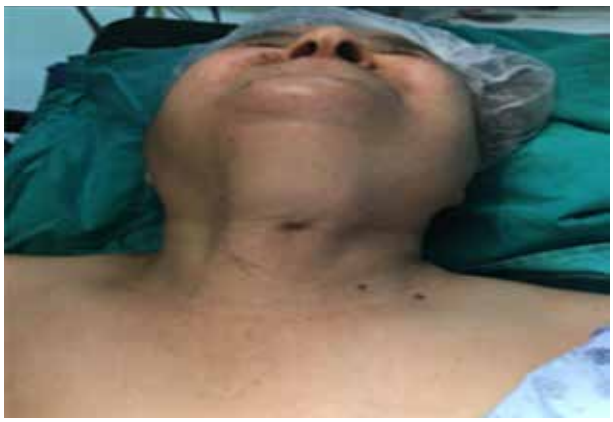

Figure 1: Thyroglossal cyst fistulized to the skin

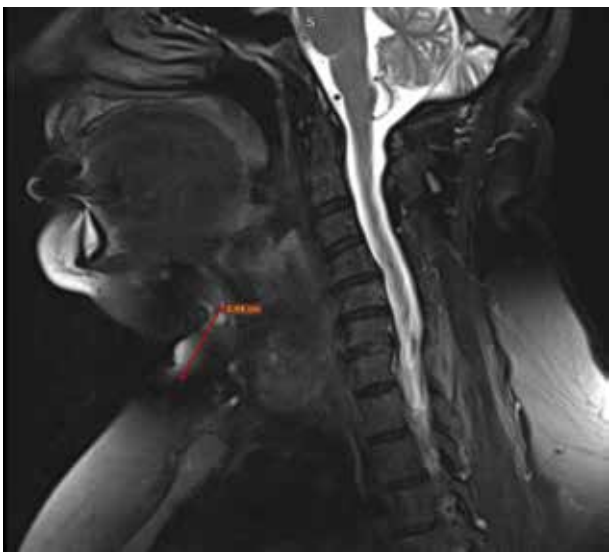

Figure 2: Magnetic resonance imaging of the thyroglossal cyst

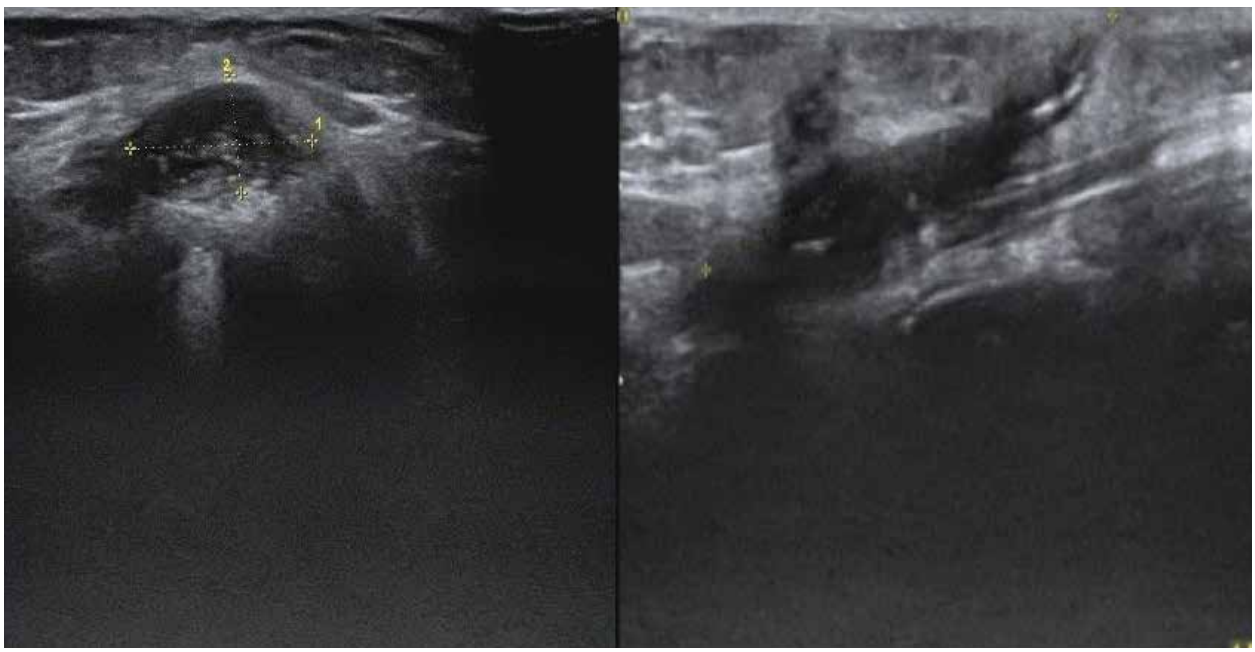

Figure 3: Multinodular goiter and fistulized thyroglossal cyst ultrasonography image

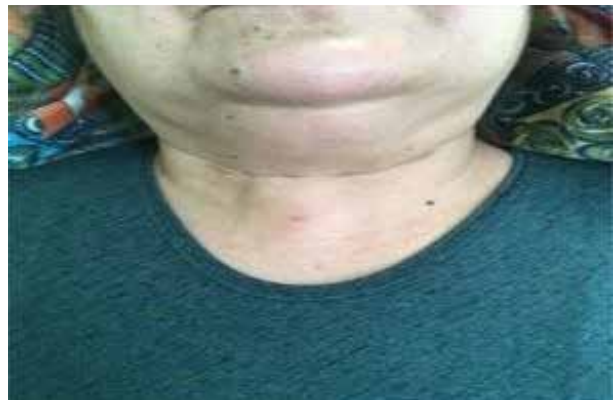

Figure 4: Postoperative first month image

are papillary carcinoma[1,3,4,7], squamous cell carcinoma[8-10] and fistulization to the skin[5,6]. Tissue remnants forming during embryological development may gain a malignant characteristic over time. In our case, no evidence of malignancy was found except for atypical cells as a result of fine needle aspiration biopsy of the thyroid. It is not surprising that cystic formations become infected over time, for this reason, the infected cyst in our case became complicated by fistulizing to the skin along with malodorous discharge. It is noteworthy that Sistrunk procedure and total thyroidectomy were performed through the same incision line. In addition to reducing the complication rate, this surgical technique produced positive cosmetic results in the patient.

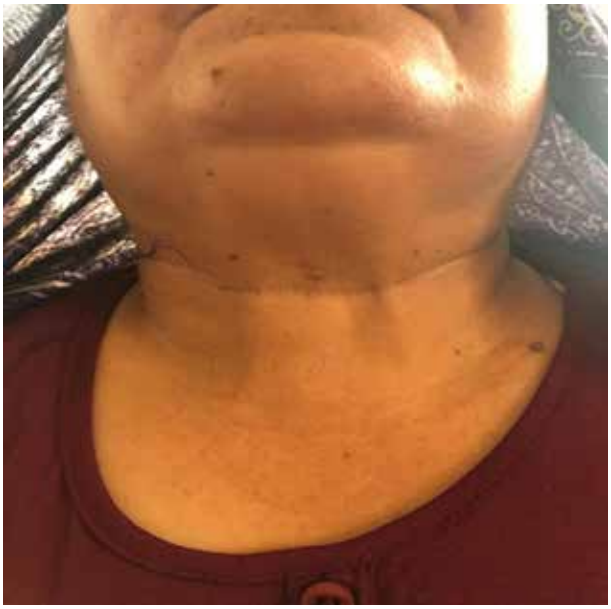

Figure 5: One year after surgery

CONCLUSION

TGDC is a common embryonic developmental defect in children. Besides, it may develop malignant characteristics over the years, it can fistulize to the skin and other tissues. Its surgical treatment in childhood will reduce the complication rate.

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Authors contribution: Ozkan Gorgulu authored the article and Mehmet Nuri Kosar was the organizer.

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Short Communication

Understanding the context of COVID-19 pandemic; lessons learnt for a long-term sustainable healthcare system

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ABSTRACT

Since COVID-19 invaded the globe, healthcare systems and economies have been crippled in various places. COVID-19 cases have been reported in 223 out of 232 countries, territories and regions named in the world, with a total count reaching 234,073,401 million, as of 30th September 2021. As of that day, the total number of cases in Oman reached 303,738 affecting 6% of the total population. The pandemic had overwhelming implications on the healthcare sector, and this will likely have a lasting impact on health ventures and delivery models for years to come.

This article will review the highlights of COVID-19 pandemic in the Sultanate of Oman, with particular attention to the impacts on the healthcare sector. The aim is to discuss the lessons learnt from managing the pandemic and use this experience for improving management of future healthcare quandaries. The objective is to educate health care workers and the public about the lessons learnt from handling the pandemic, to ensure sustainability and endurance of the healthcare sector.

KEY WORDS: corona virus, global pandemic, health services administration, Ministry of Health, World Health Organization

INTRODUCTION

It has been a grim twenty-two months since COVID-19 invaded the globe. The pandemic impacted multiple aspects of our lives. It severely challenged governments, health systems, economies and has devastated millions of lives and livelihoods all over the world. Out of 232 countries, territories and regions named in the world, COVID-19 cases have been reported in 223, with the total count reaching 234,073,401 million, as of September 30th 2021[1]. As of that day, the total number of cases in Oman reached 303,738, affecting 6% of the total population[1]. The World Health Organisation (WHO) reported a few surges in the number of cases, but since September 1st 2021, a global slowdown in the number of cases and death tolls has been noted. Despite that, the overwhelming implications of the pandemic on healthcare will likely have a lasting impact on health ventures and delivery models for years to come[2].

The WHO reported the first case of COVID-19 disease in Wuhan city, Hubei Province of China on December 31st 2019. This was followed up by a series of declarations, initially declaring its highest level of alarm and labelling the situation as a public health emergency of international concern. This was followed up by the identification of the causative agent, then labelling the situation a global pandemic. In March 2020, an international trial named 'The Solidarity trial' was launched by the WHO and its partners. The aim of this trial was to generate robust information about the disease from around the globe, in an attempt to identify the most effective treatment option for it[3]. Following detection of the first case of the virus in Oman, His Majesty issued royal orders to stipulate the formation of the Supreme Committee to study scopes for a mechanism to handle developments resulting from COVID-19 pandemic. As this was the first time to report ailments in the human race from this strain of novel agents, it incurred the need to take hasty measures. Following rapid assessments of the

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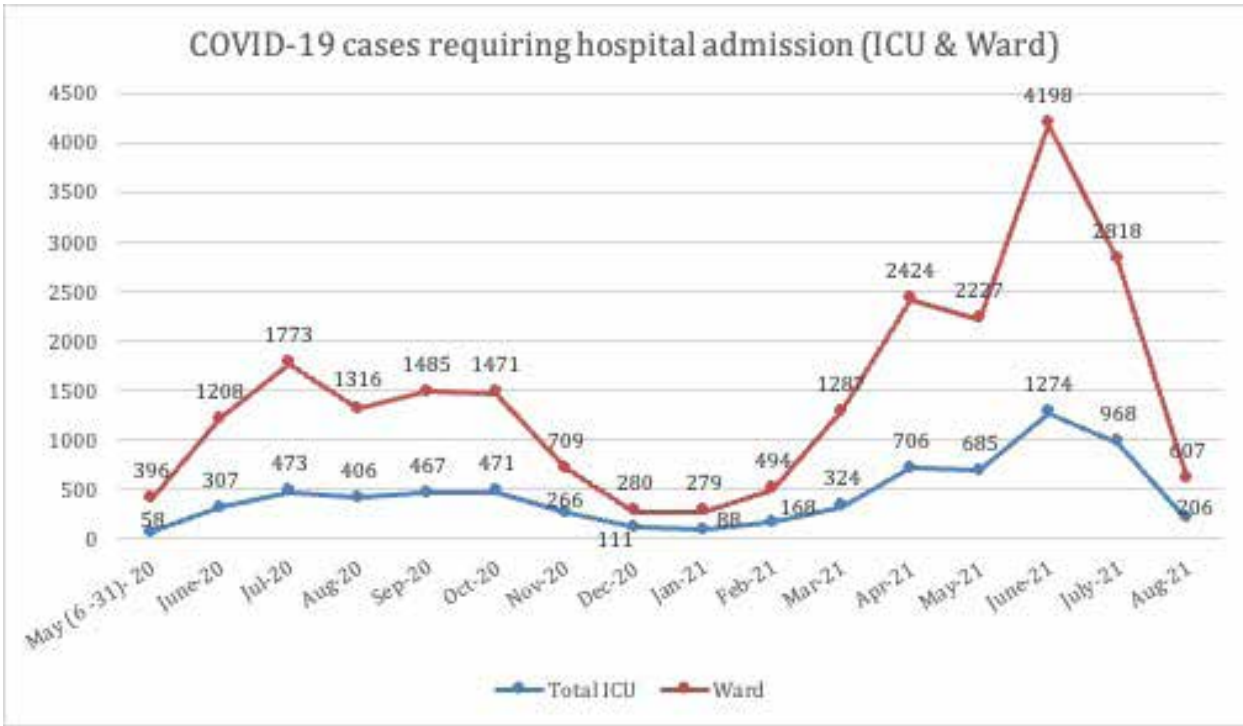

Figure 1: Graph representing the total number of COVID-19 cases admitted to hospitals per month, between May 2020 and August 2021. The blue line represents the total number of cases admitted to the Intensive Care Unit, while the red line depicts the total number of cases admitted to the ward. Note that recording of admitted cases in Oman ensued in May 2020.

situation, the Supreme Committee issued a decision to establish a field hospital for COVID-19 cases.

This article will review the highlights of COVID-19 pandemic in the Sultanate of Oman, with particular attention to the impacts on the healthcare sector. The aim is to highlight the lessons learnt from managing the pandemic, and use this experience for improving management of future healthcare quandaries. The objective is to educate health care workers and the public about lessons learnt from handling the pandemic, to ensure sustainability and endurance of the healthcare sector. Figures represented in this article have been retrieved from United Nations Data, WHO global dashboard, National Surveillance Data Reports and Ministry of Health e-Health Portal.

DISCUSSION

During the year 2020, the total number of confirmed cases across the globe reached 83,900,384, while in 2021, the total count jumped to 218,572,732 as of August 31st. The rate of spread and case load has been more expeditious in certain countries compared to others, namely the USA, India and Brazil. In the year 2020, the total number of confirmed cases in the Sultanate of Oman reached 128,867, and as of 31st August 2021, the count outstretched to 302,300[1]. People aged 15-59 years constituted 89.9% of cases, while 69.9% involved males[3,4].

The majority of patients infected with COVID-19 showed uneventful recovery from the illness (80%), without requiring further medical care. Out of every 5 cases infected, 1 case showed progression and worsening in clinical symptoms[1]. Among the subgroup that required hospital admission, 80-85% required ward care, while the remaining percentage required high level of care in the intensive care unit[1]. Figure 1 shows the total number of cases admitted to the hospital starting from May 2020, up until August 2021.

In the period between February 2020 and August 2021, the Sultanate of Oman reported 4,064 deaths related to COVID-19. Among those, 54% were patients aged 60 and above, 68% were males and 67% were Omanis[1,4]. Figure 2 represents the total number of deaths reported per month during the period specified.

The biggest burden arising from the pandemic fell on the healthcare system, as it created a significant additional load on the tertiary hospitals following the increase in the number of confirmed and admitted cases. The surplus of patients requiring medical care created a challenge in terms of providing care for patients with COVID-19 along with the usual care for other patients with long-term illnesses. This necessitated the need to make healthcare services more resilient and sustainable.

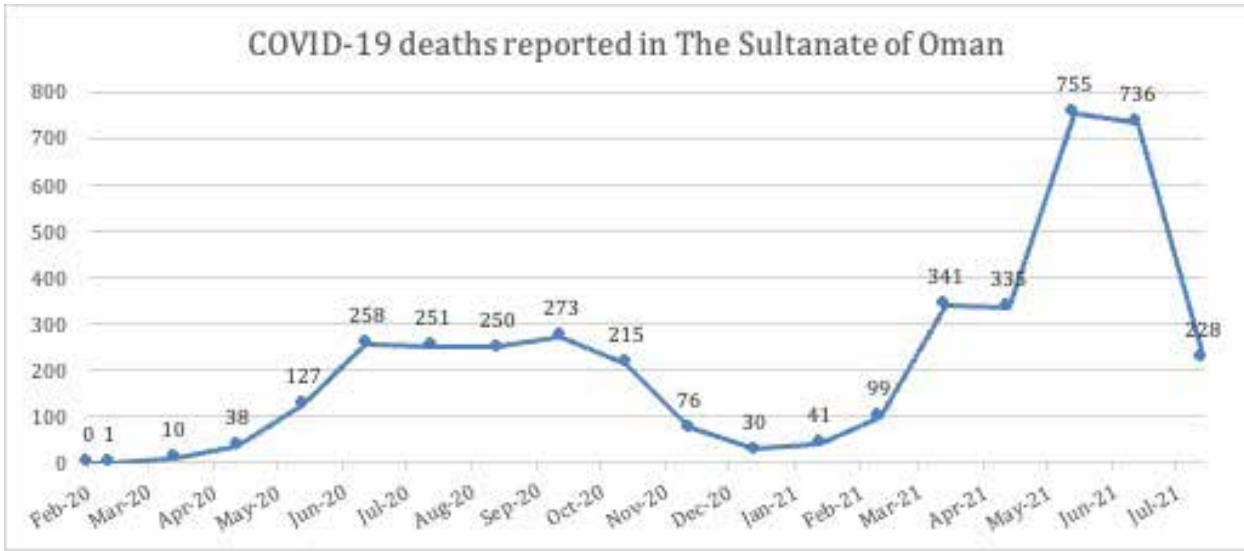

Figure 2: Graph representing the total number of COVID-19 deaths reported per month in Oman, between February 2020 & July 2021. The lowest total number of COVID-19 deaths was reported in February 2020, while the highest count was reported in May 2021.

Looking into the total count of cases across the gulf countries, it can be noted that the United Arab Emirates had the highest number of confirmed cases, with 735,727 reported as of September 30th 2021. Kingdom of Saudi Arabia came second, with a total count of 411,605 cases. Qatar showed the smallest number of cases, being 236,558[1]. The table below summarizes the figures reported in Oman and the rest of the gulf countries (Table 1).

The government and supreme committee regularly evaluated the situation. Policies were evaluated and immediate measures were implemented to strengthen the emergency response plans, expand aptitude of case detection and screening, optimize care delivered, restrict extent of impacts, ensure sufficient availability of personnel and equipment and finally implement life-saving interventions[4,5].

Measures implemented were of two aspects; containment strategies and suppression interventions. The former included closure of borders and travel restriction, case finding and contact-tracing, isolating positive cases, and secluding exposed ones. The latter encompassed lockdowns of various intensities and scopes, social distancing, closure of educational institutions, and dissolution of large-scale gatherings. Despite the reallocation of services and expansion of existing wards, the current hospital capacity was not sufficient to meet the anticipated need. A decision was consequently made to establish a field hospital for COVID-19 cases, as a step-down unit, for providing intermediate care for recovering cases[4-6].

The total capacity of the field hospital was set at 312 beds. It was inaugurated on October 5th 2020, with an initial capacity of 100 beds. The hospital was set to function over three phases, with the capacity to be gradually incremented as the need arose. The highest occupancy rate reached around 202 inpatients during June 2021. Following that, case numbers gradually declined, and the hospital was closed on the 12th of September 2021 until further notice[4,7]. The table below outlines the main mitigation steps taken by the Country along with the outcomes achieved (Table 2).

Over the past two years, handling the unaccustomed COVID-19 pandemic has been eye opening and fueled with learning lessons. It has raised attention to aspects in need of assessment and improvement. In this report, seven lessons will be highlighted. The first lesson is the significance of emergency contingency plans, with a

Table 1: Information pertaining to COVID-19 pandemic in the Gulf countries. Aspects covered entail population size, date of first detection in the country, total number of confirmed cases and deaths in each country during the study period, and finally the percentage of the population fully vaccinated.

S.No	Component	Oman	UAE	Kuwait	Qatar	KSA	Bahrain
1	Population size (/ million)	4.975	9.771	4.206	2.832	34.27	1.641
2	Date of first detection in the Country	24.2.20	02.02.20	24.02.20	01.03.20	02.03.20	24.02.20
3	Confirmed cases as of 30/09/21	303,738	735,727	411,605	236,558	547,090	274,981
4	Confirmed deaths as of 30/09/21	4,096	2,095	2,448	605	8,713	1,389
5	Percentage of population fully vaccinated (%) as of 30/09/21	40.62	82.40	No data available	81.7	52.73	63.84

Table 2: Summary of the key mitigation steps taken by Oman during the COVID-19 pandemic. The table reviews the main approaches adopted by the country since the date of first detection, lockdown measures implemented, along with the maximum number of beds occupied by patients at the hospitals.

S.No	Component	Oman
1	Population size (/ million)	4.975
2	Date of first detection in the Country	24/02/20
3	Approach	Screening, testing, monitoring, Mandatory self-quarantine, Expansion of existing wards, Construction of a field hospital, Restriction on activities involving large-scale gathering Limiting use of services to 50% of full capacity,
4	Duration of lockdown	Night time lockdown – interrupted periods Complete lockdown – 4 days (Al Adha Eid Holiday July 2021)
5	Total number of beds at MOH hospitals in Oman	5262 (Including field hospital)
6	Total number of beds at the private hospitals in Oman	1054
7	Maximum number of admission beds utilized for COVID-19 cases (all hospitals in Oman)	1650 (Figure reported on 28.06.21)
8	Maximum number of ICU beds utilized for COVID-19 cases (all hospitals in Oman)	538 (Figure reported on 03.07.21)
9	Confirmed cases as of 30.09.21	303,738
10	Confirmed deaths as of 30.09.21	4,096

designated taskforce, each having clear roles, to enable early preparation for unwonted situations[8]. The preparation phase also encompasses selection of site for the provision of additional care, as the environment has a marked impact on optimizing care provided[2,5]. A field hospital is defined by the WHO as a "mobile, self-contained, self-sufficient health care facility capable of rapid deployment and expansion or contraction to meet immediate emergency requirements for a specified period of time, can be set up in an existing structure or in a structure, tent or similar"[5]. The establishment and operation of the field hospital was a major milestone towards culminating the impact of the pandemic. Cases were first detected in the country in February 2020. They reached their highest peak in June 2020, and the field hospital started to operate in October 2020. The WHO, however, states that a field hospital established in response to an adversity should be effective within 24 hours of the event, in order to cover the urgent healthcare needs. Along with the premises, ensuring availability of adequate facilities is vital to meet the anticipated requirements, and the equipment offered should be usable by both local and national members of the healthcare field[2,9].

Lesson number two is the significance of accelerating innovation, when possible, using strategic partnerships. This enables the utilization of innovative products and artificial intelligence in managing mishaps[2,5]. An official COVID-19 electronic application system was launched in June 2020, with the aim of providing information on the current disease situation, providing guidelines and best practices, in addition to tracking the movement and spread of COVID-19 cases, for citizens of all nationalities residing in the country[4,6]. The initiative was supported by Oman ITC Group, eMushrif Company and Oman Broadband Company[6]. To validate its effectiveness, further studies and auditing are essential to assess the effectiveness of the tracking system and the extent to which isolation measures were adhered to.

The third lesson learnt is the importance of learning from the experience of other countries in handling the pandemic, by implementing the lessons learnt and taking action on gaps highlighted applicable to the current situation. This is particularly relevant as the pandemic has not yet run its course, and the chance of another wave arising looms in the horizon[8]. Some examples include:

1. Contact tracing of cases

The country adopted a manual approach for contact tracing. This greatly relies on cases recalling where they went, who they went with and most importantly whether they are prepared to share this information with the verifier. SARS-Cov-2 virus was however noted to have a very fast course with high death rates, rendering this method slow-moving, labour-intensive and subject to flaws. On the other hand, digital contact tracing applications adopted in countries like China, South Korea, Switzerland and Singapore have shown potential with regards to tracking confirmed cases. It relies on bluetooth low energy beaconing technology, to keep record of when phones come in close proximity to each other, enabling self-isolation instructions to be sent immediately to people who come into close contact with a confirmed case[8].

2. Closure of services

In June 2021, the local figures along with the total death toll were reaching their highest peak since the start of the pandemic. However, that period accorded with restricted lockdown measures, limited to the night period only. This was topped up with deferment in arrival and distribution of vaccines in the country,

rendering Oman with the second highest overall death rates among the gulf countries. The global experience has shown that insufficient or delayed enactment of lockdown measures impacted the efficiency of hindering the spread of infection, the former seen in USA and India and the latter in the United Kingdom, Russia and France[8,9].

Lesson number four is the importance of instigating coping strategies. The preceding period witnessed a marked rise in implementing telemedicine in the delivery of care. This service decreased the need for space required and the burden of commuting on patients, especially the ones following up on a regular basis for chronic conditions[2].

The fifth lesson learnt is the significance of effective communication and information management, as employee engagement is the driver of productivity. This encompasses both the clinical staff and the community. Implementation of non-pharmaceutical interventions have shown to be of valuable impact in controlling the disease spread, and ensuring reliable and smooth access to updated information about the situation will ultimately generate public cooperation in implementing the steps agreed on[2,5].

The sixth lesson learnt is the significant impact agile leadership has in times of crisis. It is the main driver of productivity and among the main influencing parameters in employee retention, both of which are vital during onerous periods. Four agile leadership skills that were vital before, during and will continue to be important after this pandemic are: humility (eliminating the need to know everything), adaptability (willing to revise own opinion, open to new ideas), visionary (having a clear long-term plan, despite short-term qualms) and remaining engaged during difficult periods[10].

The final lesson to be raised in this report is the need to think of creative solutions and utilise talents accordingly. Right from the start of the pandemic, shortage of emergency supplies, including ventilation devices and personal protective equipment, surfaced in multiple regions across the globe. Despite the lesson learnt, there appears to be no straight forward solution for this issue; the current pandemic mainly affected the respiratory system, and the next pandemic could target a different system, rendering storage of respiratory equipment in vain. Moreover, storing supplies in large quantities is neither feasible financially nor logistics wise, necessitating the need for alternative answers to future pandemics[9].

The experience Oman has witnessed with regards to responding to this pandemic has emphasized some of the strategies that should be accentuated in the sector of healthcare management, along with the role of technology and telemedicine in healthcare, which in turn will strengthen and integrate the system, and enable rapid reorganization of services, ensuring that it remains robust, sustainable and innovative during onerous periods[9].

LIMITATIONS

This review is limited by the internal validity and accuracy of figures reported, as the reporting of cases may have been controlled or filtered in the regions reported.

CONCLUSION

This retrospective review provided a concise summary of COVID-19 pandemic in Oman. It has highlighted the main events involved, steps taken to mitigate it, and the impact it has had on the healthcare system, highlighting areas in need of attention and improvement. The lessons learned include preparing contingency plans, incorporating artificial intelligence, learning from the experience of other countries, implementing innovative strategies, communicating effectively, maintaining agile leadership and implementing creative solutions.

A significant proportion of the information reported was obtained from news agency reports. Such an article is therefore vital to corroborate and document the information stated. The urgent steps taken during COVID-19 pandemic to make the health care system innovative and robust should not be forgotten once the storm passes, and instead should be implemented within the health care system. The battle against this virus will continue to exist, but with global solidarity and national unity, the light at the end of the tunnel will continue to brighten, bringing hopes for a nearby liberty and resumption to normality.

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DISCLOSURE

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and an approval certificate was deemed unnecessary in view of the data being retrieved from openly available resources.

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Short Communication

How to understand the "Stealth" Omicron subvariant and prepare for its challenge

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ABSTRACT

BA.2, nicknamed "stealth omicron", is one of three known subvariants of Omicron. BA.2 differs from BA.1 (the original Omicron variant) in some mutations, including in the spike protein. This mutation makes it more difficult to identify as Omicron subvariant on several tests, and BA.2 is more infectious and more likely to infect vaccinated people compared to BA.1. BA.2 has been detected in at least 40 countries and in all continents except Antarctica, and the World Health Organization is continuing to monitor its spread, while BA.2 is beginning to replace the original Omicron strain in many countries. This commentary provides an overview of current knowledge and unknowns about this new variant and summarizes the important study findings for the purpose of informing experts.

KEY WORDS: coronavirus, COVID-19, SARS-CoV-2, stealth Omicron variant

INTRODUCTION

The first case of an unidentified form of viral pneumonia were reported in Wuhan city, Hubei province in China, in December 2019[1]. This virus infection of pneumonia was identified as the novel coronavirus (SARS-COV-2) by the scientific research institution in China, and later it was named "COVID-19" by the World Health Organization (WHO)[2].

This unknown virus gradually spread over the whole world. The mortality rate of COVID-19 is lower than other coronaviruses such as severe acute respiratory syndrome and Middle East respiratory syndrome[3]. However, COVID-19 is highly transmissible and rapidly spread, as it can be transmitted by respiratory droplets and contact and several unknown ways[4].

Though several vaccines have been developed to treat and prevent COVID-19 infections, the world has not ended its struggle with these viruses.

At this time, the new variant was discovered in South Africa and threatened the world concerning new pandemic coming from this variant[5]. WHO first reported the new strain on November 24, 2021, after a case was reported in South Africa in November, later designated it as one of "variants of concern" which showed a marked degree of mutation (Fig 1), with 20I (Alpha, V1) or B.1.1.7, 20H (Beta, V2) or B.1.351, 20I (Gamma, V3) or P.1, 21A (Delta).

Following the discovery of the SARS-CoV-2 Omicron variant (B.1.1.529), the global COVID-19 outbreak has resurfaced after appearing to be relentlessly spreading over the past two years. This new Omicron variant became a major dominant virus in COVID-19 pandemic everywhere (Fig 2)[6].

Cases of the Omicron variant are on the decline worldwide, but a different version of Omicron is now gaining traction. This is called as "stealth" variant, officially known as BA.2, armed with even higher transmission potential, and possibly a greater ability to evade the immune response, than the original Omicron, leading experts to fear it could further prolong the COVID-19 pandemic[7].

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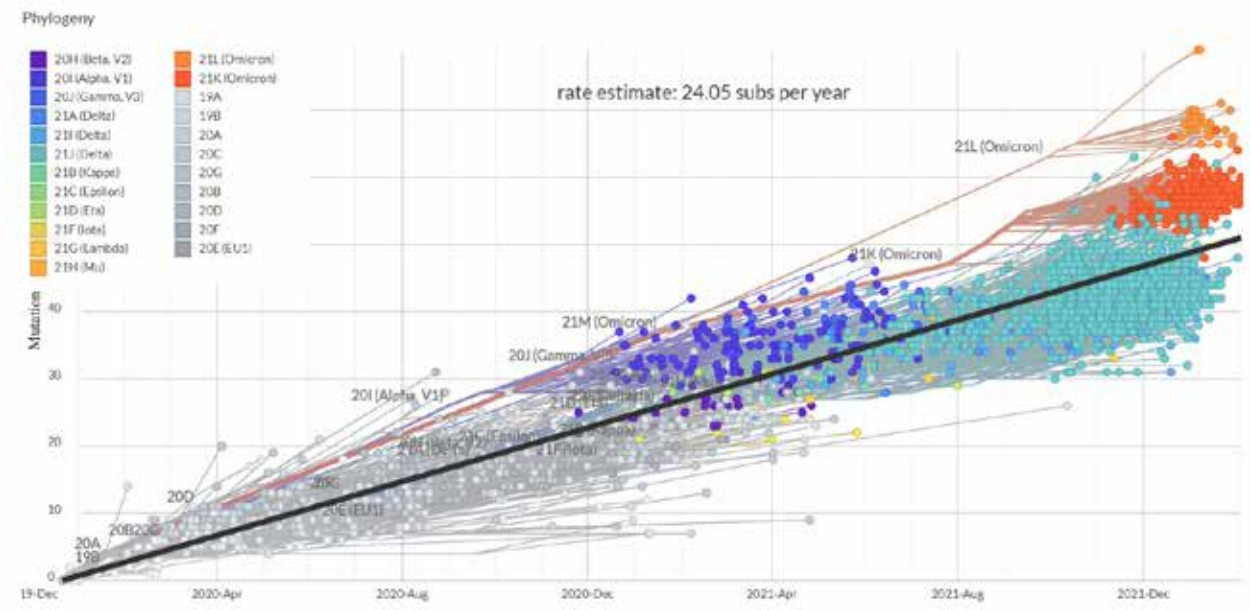

Fig 1: The mutations according to time in every variant of SARS-CoV-2 between Dec 2019 and Feb 2022.

The World Health Organization is continuing to monitor its spread. BA.2 is beginning to replace the original Omicron strain in many countries. It has now become the dominant variant in many countries such as Denmark, India, the Philippines and the United States.

About "stealth" Omicron subvariant (BA.2)

What makes BA.2 different?

Most of the differences between BA.2 and BA.1 are in the spike protein of the virus, which it uses to anchor to and infect human cells. BA.2 also has a large number of mutations in other parts of its viral sequence that are not well understood.

Early estimates by Denmark's State Serum Institute suggest BA.2 is about 50 percent more transmissible than the previous BA.1 strain. The Danish study looked into the way COVID-19 spread in more than 8000 patients between late December and early January. About a quarter were BA.2 cases and the data show that even fully vaccinated people are more susceptible to catching BA.2 than BA.1[8].

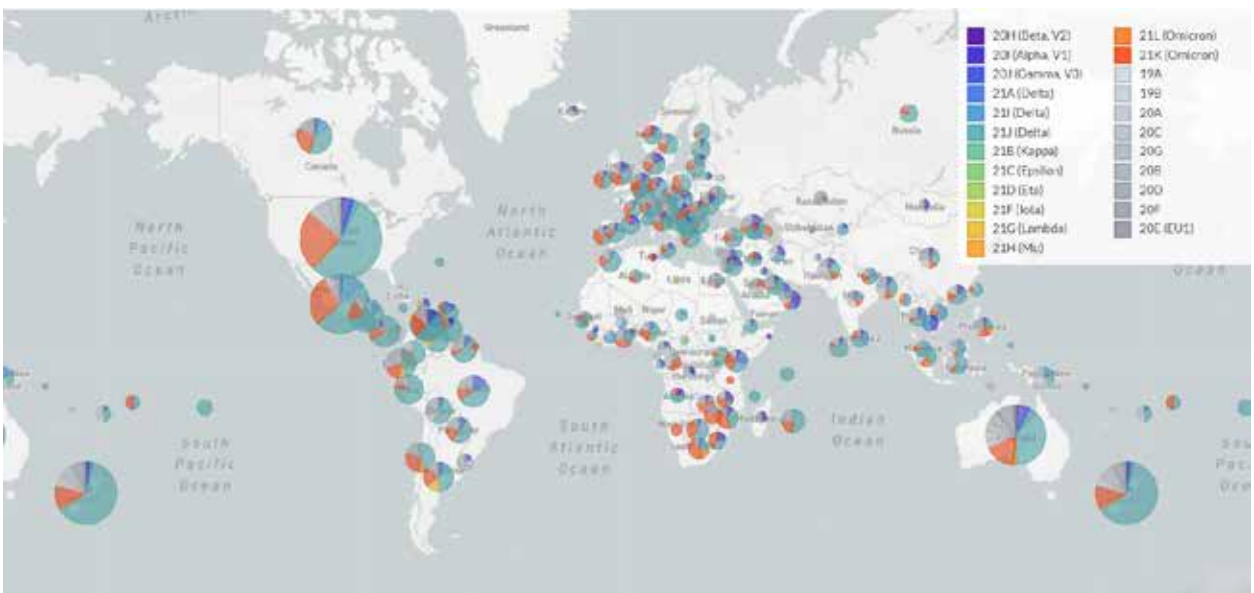

Fig 2: The global geographical infection status of SARS-CoV-2 variants according to countries between Dec 2019 and Feb 2022.

Does BA.2 increase transmissibility compared with BA.1?

When comparing BA.2 relative to BA.1, there was an increased risk of infection in BA.2 regardless of the vaccination status of the potential secondary case, indicating an inherent increased transmissibility of the BA.2 subvariant. In addition, comparing the risk of patient members being infected in BA.2 relative to BA.1, was higher in vaccinated and booster vaccinated than in unvaccinated, which suggests immune evasive properties of the BA.2 variant.

Moreover, the study found that the unvaccinated BA.2 cases transmitted infection to both the vaccinated and booster vaccine vaccinated patients with higher levels than the BA.1 cases[8].

The United Kingdom Health Security Agency also estimates that BA.2 is more transmissible, though it puts the figure at roughly 30 percent higher than BA.1. Although BA.2 looks quite different from the original Omicron, there is no evidence yet to suggest it is any more severe than the previous variant.

Will vaccines protect against BA.2?

The results from preliminary data are mixed as to whether current vaccines will be more or less protective against BA.2 compared to BA.1, which has experts concerned about more potential breakthrough infections.

For context, BA.1 is already very efficient at dodging previous immunity. It also reduces the efficacy of two doses of the Pfizer-BioNtech mRNA vaccine, though a third dose at least partially restores it[9-11].

The U.K. Health Security Agency estimates that existing vaccines are equally effective at preventing symptomatic disease caused by BA.2 and BA.1, though their data are based on a relatively small number of cases. The U.K. data showed that a booster dose administered two weeks after the second shot of a vaccine was 63 percent effective at preventing symptomatic disease from BA.1 and 70 percent effective for BA.2.

Preliminary studies with lab-synthesized versions of the coronavirus also suggest that neutralizing antibodies collected from the blood of vaccinated people are equally capable of blocking BA.1 and BA.2.

Fred Hutchinson's Bloom and others have done modelling based on the subvariant's specific mutations, and they predict that BA.2 won't be as good as BA.1 at evading antibodies from vaccines. By contrast, the Danish study is based on a larger case sample, and their data suggest the BA.2 subvariant is even better at evading immune protection provided by vaccines than the original version. Therefore, the progressive study is needed for the more understanding and answer this question of vaccine efficacy.

Preparing for the "stealth" Omicron variant challenge

The most important point of research in preparing for its challenge is whether you can use the current vaccines for Omicron subvariant, which can give you an answer what will be the first choose to control this variable pandemic in the future. As these issues have not yet been clarified, but the health experts do not have a clear idea how effective the vaccines are in preventing illness. There is a potential that COVID-19 vaccines might not be as effective with new variants. However, the more antibodies a person has, the more protected they will be. That is why everyone is encouraged to get a COVID-19 booster shot once you are eligible. Preliminary evidence suggests that vaccines are less effective against the spread of omicron, compared with delta. However, vaccines still protect well against serious illness such as hospitalization. National and global vaccinations are still considered as one of the most efficient approaches in the prevention of pandemics.

Following the vaccination, personal defenses such as washing hands, wearing masks, keeping social distances etc., are fundamental to prevention of Omicron subvariant infection and transmission. Omicron variants are incredibly infectious. Everyone should be masking (covering both the mouth and nose) when indoors around anyone not in their household and outdoors when in crowded settings. Several studies indicate how effective masks can be in protecting yourself and others. It's important to remember that you may be asymptomatic and not know you are infected but still able to spread COVID-19. Wearing a mask in these situations helps protect vulnerable people you could unknowingly infect.

Currently, health experts and medical practitioners are conducting research projects to reduce the burden on health care and treatments during the pandemic, for example, the containment measure and the failure to carry out health care services during the first outbreak of coronavirus in many countries, and Remdesivir and monoclonal antibody therapy being used to control viral infection (or replication) with using dexamethasone to control the immune response to infection in the treatment[12].

CONCLUSION

In conclusion, vaccination and personal defense should be thoroughly established before the measures against variant virus are accurately revealed. We need to promote the rate of vaccination and the accuracy of

the variant virus test to find the infected persons and treat them in time. There is an urgent need to explore the virology and biology of Omicron subvariants, define clinical phenomes and therapies, monitor dynamics of genetic changes, and protect people from this subvariant. It is up to every country to make common efforts and compliance with all health requirements.

ACKNOWLEDGMENT

Ethics: Not applicable.

Conflict of interest: All authors have substantially contributed to conducting the underlying research and drafting this manuscript. To the best of our knowledge, none of the authors have a conflict of interest, financial, or otherwise.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2022; 54 (2): 287 - 290

Sodium–glucose cotransporter-2 inhibitors induced euglycemic diabetic ketoacidosis: Two case reports and a review of the literature

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Clin Case Rep. 2022;10:e05440. https://doi.org/10.1002/ccr3.5440

If not detected early, euglycemic diabetic ketoacidosis can be a serious adverse effect of sodium–glucose cotransporter-2 (SGLT2) inhibitors. Unfortunately, euglycemic diabetic ketoacidosis is underreported in recent trials and missed because of normal blood sugar levels and nonspecific symptoms on presentation. We present two patients with type 2 diabetes mellitus who developed dapagliflozin-associated euglycemic diabetic ketoacidosis followed by hyperglycemic ketoacidosis. The second patient had euglycemic ketoacidosis twice despite instructions to stop using the medication dapagliflozin.

Protein/Creatinine ratio versus 24-hours urine protein in preeclampsia

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Ginekol Pol. 2022 Feb 14. doi: 10.5603/GP.a2021.0233. Online ahead of print.

OBJECTIVES
Proteinuria is one of the diagnostic criteria of preeclampsia (PE). Measurement of 24-hour urine protein is the gold standard method for detection of proteinuria in PE. The 24-hour urine sampling is time-consuming, and inconvenient. To evaluate the accuracy of protein/creatinine (P/C) ratio in detection of significant proteinuria (> 1 g/24-hours urine) in PE.

MATERIAL AND METHODS
One hundred and ten (110) preeclamptic women were included in this study and admitted for blood pressure monitoring, 24-hour urine collection, fetal well-being assessment and spot urine sample for measuring of P/C ratio. After thorough history and clinical examination, routine antenatal investigations were done for the women included in the study according to the hospital protocol, and to excluded

pre-existing chronic renal disease. Twenty-four-hour urine collection started on the morning following hospital admission. Spot urine samples were obtained shortly before the 24-hour urine collection for measuring of P/C ratio. Collected data statistically analyzed to evaluate the accuracy of P/C ratio in detection of significant proteinuria in PE.

RESULTS

The P/C ratio of 1.35 ± 2.54 had 94.4% sensitivity, 94.9% specificity, 97.1% positive predictive value (PPV), 90.2% negative predictive value (NPV), and 94.5% overall accuracy in detection of significant proteinuria (> 1 g/24-hour urine) in PE.

CONCLUSIONS

The P/C ratio of 1.35 ± 2.54 had 94.4% sensitivity, 94.9% specificity, 97.1% PPV, 90.2% NPV, and 94.5% overall accuracy in detection of significant proteinuria (> 1 g/24-hour urine) in PE. This study suggests the use of P/C ratio as an alternative to 24-hour urine protein to detect significant proteinuria in PE.

The Pediatric COVID-19 Registry in Kuwait (PCR-Q8): Methodology and Results of Pilot Phase

Sarah Qabazard, Dalia Al-Abdulrazzaq, Hessa Al-Kandari, Mariam Ayed, Ayed Alanezi, Nufoud Al-Shammari, Zaid Alharbash, Muna Al-Khabbaz, Khaled Kalander, Saadoun Bin-Hassan, Abdulla Alfraij, Mohammad Alghounaim, Khaled Alsaeid, Hashem Al-Hashemi

Med Princ Pract. 2022 May 20. doi: 10.1159/000524756. Online ahead of print.

OBJECTIVE

Establishing a pediatric COVID-19 registry in Kuwait (PCR-Q8) deemed imperative during the pandemic to study children infected with severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) focusing on mode of presentation, therapeutic interventions, disease severity and early outcomes. This manuscript describes the rapid establishment of the PCR-Q8 registry showcasing an infrastructure of the development process and presents the results of the pilot phase.

SUBJECT AND METHODS

The registry was developed and implemented using the general key steps from Gliklich et al. resource titled "Registries for Evaluating Patient Outcomes: A User's Guide" as a guide for best practice, experience from a previously established pediatric diabetes registry in Kuwait and several other COVID-19 registries developed globally. During the pilot phase, a convenience sample of 120 children were included, of those 66 (55%) were male.

RESULTS

Experience and expertise from other COVID-19 registries, guidance provided by the World Health Organization (WHO) and effective collaboration and cooperation between the stakeholders, study group and data enterers during these challenging times were critical for the development and implementation of the registry. Our results were similar to international reports where most children presented with mild disease (69.2%), majority (70.2%) had normal chest X-ray, and the most common symptom at presentation was fever (77%).

CONCLUSION

We anticipate the PCR-Q8 development to be a steppingstone for more in-depth investigation of SARS-CoV-2 infection in children in Kuwait and further other registry establishments.

Estimated incidence, prevalence, mortality, and registration of childhood cancer (ages 0-14 years) in the WHO Eastern Mediterranean region: an analysis of GLOBOCAN 2020 data

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Lancet Child Adolesc Health. 2022 May 20;S2352-4642(22)00122-5. doi: 10.1016/S2352-4642(22)00122-5. Online ahead of print.

Background

There is little evidence about childhood cancer burden in the WHO Eastern Mediterranean region (EMR). We aimed to provide an estimate of childhood cancer burden in the EMR, examine the connection between age-standardised mortality rate and level of income (gross domestic product [GDP] per capita), and reflect on the current status of childhood cancer registration in the EMR.

Methods

Using the GLOBOCAN 2020 data from the Cancer Surveillance Unit of the International Agency for Research on Cancer, we extracted data for childhood cancer (at ages 14-0 years) incidence, prevalence, and mortality for 22 countries in the EMR, the EMR as a whole, and other WHO regions, and categorised by main cancer types. Childhood cancers were classified according to the 10th revision of the International Classification of Diseases. We also searched MEDLINE, Google Scholar, and the grey literature between May 17 and Aug 2, 2021, for English-language articles and reports about the status of childhood cancer registration in the EMR. We further examined the connection between age-standardised mortality rate and GDP per capita for the 22 countries in the EMR.

Findings

The total estimated number of incident childhood cancer cases in the EMR was 847 23 in 2020, with an age-standardised incidence rate of 10·1 per 100 000 children at risk, ranging from 7·3 per 100 000 children at risk in Pakistan to 13·8 per 100 000 children at risk in Iran. The estimated number of incident cases was 7451 (age-standardised incidence rate 3·10 per 100 000 children at risk) for leukaemia, 3006 (1·30 per 100 000 children at risk) for brain and CNS tumours, 2222 (0·92 per 100 000 children at risk) for non-Hodgkin lymphoma, 1569 (0·67 per 100 000 children at risk) for kidney cancers, and 1420 (0·58 per 100 000 children at risk) for Hodgkin lymphoma. In 2020, the number of total estimated childhood cancer deaths in the EMR was 10 535, with an age-standardised mortality rate of 4·4 (per 100 000 children at risk, ranging from 0·8 per 100 000 children at risk in Qatar to 7·2 per 100 000 children at risk in Somalia. A negative correlation was found between countries' GDP per capita (income level) and mortality rates (r=-0·77, p<0·0001). The scarcity of data and quality of cancer registries in EMR countries prevented further analysis.

INTERPRETATION

Given the variable quality and coverage of cancer registries in EMR countries, these findings are likely to be underestimates. Nevertheless, these data, especially the high mortality rates, reflect a need for effective national childhood cancer plans in line with the WHO Global Initiative for Childhood Cancer to improve survival.

Increased expression of advanced glycation endproducts in the gingival crevicular fluid compromises periodontal status in cigarette-smokers and waterpipe users

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BMC Oral Health. 2022 May 25;22(1):206. doi: 10.1186/s12903-022-02240-z.

BACKGROUND

The aim was to assess the association between levels of advanced glycation endproducts (AGEs) in the gingival crevicular fluid (GCF) and periodontal parameters among cigarette-smokers and waterpipe-users.

METHODS

Self-reported cigarette-smokers; waterpipe-users and never-smokers were included. Demographic data was recorded using a questionnaire. Periodontal parameters (plaque index [PI], gingival index [GI], clinical attachment loss [AL], probing depth [PD], and marginal bone loss [MBL]) were assessed in all groups. The GCF samples were collected using standard techniques and assessed for AGEs levels using enzyme-linked immunosorbent assay. Sample-size estimation was done and group-comparisons were done. Correlation between levels of GCF AGEs levels and periodontal parameters was assessed using a logistic regression model. Level of significance was set at $P < 0.01$.

RESULTS

Eighty-two individuals (28 cigarette-smokers, 28 waterpipe-users and 26 never-smokers) were included. There was no difference in mean ages of all patients. Cigarette-smokers had a smoking history of ± 5.1 0.2 pack years and waterpipe-users were using waterpipe for 0.6 ± 4.4 years. There was no statistically significant difference in PI, GI, clinical AL, PD and MBL in all groups. Levels of AGEs were significantly higher among cigarette-smokers ($P < 0.001$) and waterpipe-users ($P < 0.001$) than never-smokers. There was no significant correlation between levels of GCF AGEs levels and periodontal parameters in all groups.

CONCLUSION

Clinical periodontal status of individuals with a short history of cigarette-smoking and waterpipe-usage may appear similar to never-smokers. On a molecular level, cigarette-smoking and waterpipe-users express raised levels of AGEs than never-smokers that sirens about the ongoing yet latent periodontal inflammatory process.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2022; 54 (2): 291 - 297

International Conference on **Nutrition & Health** (ICNH)
Jun 01, 2022
Canada, Montreal
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/25265/ICNH/

International Conference on **Medical and Health Sciences** (ICMHS)
Jun 02, 2022
Singapore, Singapore
Conference End Date :2022-06-02
Event Website: http://academicsconference.com/Conference/18704/ICMHS/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Jun 02, 2022
United Arab Emirates, Dubai
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/10837/ICHCG/

International Conference on **Medical and Biological Engineering** (ICMBE)
Jun 03, 2022
United Kingdom, Edinburgh
Email: papers.techno@gmail.com
Event Website: http://technoarete.com/Conference/6869/ICMBE/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Jun 04, 2022
Korea (South), Busan
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/10945/ICHCG/

International Conference on **Medical and Health Sciences** (ICMHS)
Jun 05, 2022
Turkey, Istanbul
Email: papers.academicsconference@gmail.com

International Conference on **Cell and Tissue Science** (ICCTS)
Jun 05, 2022
Netherlands, Rotterdam
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/31841/ICCTS/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Jun 06, 2022
Australia, Adelaide
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/11101/ICHCG/

International Conference on **Cell and Tissue Science** (ICCTS)
Jun 07, 2022
Germany, Stuttgart
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/31889/ICCTS/

International Conference on **Medical and Health Sciences** (ICMHS)
Jun 07, 2022
United Kingdom, Oxford
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/20557/ICMHS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Jun 09, 2022
Singapore, Singapore
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/18542/ICRAMMHS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Jun 12, 2022
Qatar, Doha
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/18654/ICRAMMHS/

International Conference on **Nursing Ethics and Medical Ethics** (ICNEME)
Jun 17, 2022
United States, New York
Email: info.wrfase@gmail.com
Event Website: http://wrfase.org/Conference2022/6/USA/ICNEME/

1317th International Conference on **Medical and Health Sciences** (ICMHS)
Jun 19, 2022
Italy, Florence
Email: info@iserd.co
Event Website: http://iserd.co/Conference2022/Italy/6/ICMHS/

1318th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Jun 19, 2022
United Kingdom, Edinburgh
Email: info@iastem.org
Event Website: http://iastem.org/Conference2022/UK/4/ICMBPS/

1312th International Conference on Recent Advances in **Medical and Health Sciences**
Jun 19, 2022
Malaysia, Putrajaya
Email: info@academicsworld.org
Event Website: http://academicsworld.org/Conference2022/Malaysia/8/ICRAMHS/

World Conference on **Pharma Industry and Medical Devices** (WCPIMD)
Jun 19, 2022
India, Hyderabad, Telangana
Email: info.iferp@gmail.com
Event Website: http://iferp.org/Conference/6973/world-conference-on-pharma-industry-and-medical-devices/

International Conference on **Medical and Health Sciences** (ICMHS)
Jun 20, 2022
United Kingdom, Cambridge
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/20565/ICMHS/

1297th International Conference on **Science, Health and Medicine** (ICSHM)
Jun 21, 2022
Czech Republic, Prague
Email: info@iser.co
Event Website: http://iser.co/Conference2022/CzechRepublic/1/ICSHM/

1319th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Jun 21, 2022
Turkey, Antalya
Email: info@iastem.org
Event Website: http://iastem.org/Conference2022/Turkey/2/ICMBPS/

International Conference on **Medical and Health Sciences** (ICMHS)
Jun 25, 2022
United Arab Emirates, Dubai
Email: papers.academicsconference@gmail.com
Event Website: http://academicsconference.com/Conference/19736/ICMHS/

International Conference on **Medical, Medicine and Health Sciences** (ICMMH)
Jun 26, 2022
Greece, Crete
Email: contact.iierd@gmail.com
Event Website: http://iierd.com/Conference/1693/ICMMH/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Jun 27, 2022
Canada, Montreal
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/6/Canada/2/ICMPH/

International Conference on **Medical and Biological Engineering** (ICMBE)
Jun 28, 2022
Indonesia, Bali
Email: papers.techno@gmail.com
Event Website: http://technoarete.com/Conference/6996/ICMBE/

1312th International Conference on **Medical and Biosciences** (ICMBS)
Jun 28, 2022
United States, Philadelphia
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2022/USA/9/ICMBS/

1324th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Jun 29, 2022
Italy, Milan
Email: info@iastem.org
Event Website: http://iastem.org/Conference2022/Italy/4/ICMBPS/

1320th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Jul 01, 2022
United Arab Emirates, Dubai
Email: info@academicsworld.org
Event Website: http://academicsworld.org/Conference2022/UAE/5/ICRAMHS/

World **Disability & Rehabilitation** Conference (WDRC)
Jul 01, 2022
Canada, Montreal
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/25275/WDRC/

1303rd International Conference on **Science, Health and Medicine** (ICSHM)
Jul 02, 2022
Germany, Berlin
Email: info@iser.co
Event Website: http://iser.co/Conference2022/Germany/3/ICSHM/

1353rd International Conference on Recent Advances in **Medical Science** (ICRAMS)
Jul 02, 2022
United Arab Emirates, Abu Dhabi
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/UAE/3/ICRAMS/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Jul 03, 2022
Germany, Berlin
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/7/Germany/ICMPH/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Jul 03, 2022
India, Hyderabad, Telangana
Email: papers.issrd@gmail.com
Event Website: http://issrd.org/Conference/14869/international-conference-on-medical-health-science-pharmacology--bio-technology/

International Conference on **Medical and Health Sciences** (ICMHS)
Jul 04, 2022
United Kingdom, London
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/21458/ICMHS/

1316th International Conference on **Medical and Biosciences** (ICMBS)
Jul 05, 2022
Sweden, Stockholm
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2022/Sweden/1/ICMBS/

International Conference on **Obesity and Chronic Diseases** (ICOCD)
Jul 07, 2022
United Arab Emirates, Dubai
Email: info.iared.org@gmail.com
Event Website: http://iared.org/Conference/168/ICOCD/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Jul 08, 2022
New Zealand, Christchurch
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/13545/ICMEP/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Jul 09, 2022
Japan, Kitakyushu
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/13560/ICHCG/

World **Disability & Rehabilitation** Conference
Jul 14, 2022
India, Pune, Maharashtra
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/31234/WDRC/

International Conference on Recent Advances in **Medical Science** (ICRAMS)
Jul 15, 2022
United States, Massachusetts
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/US/62/ICRAMS/

International Conference on **Cell and Tissue Science** (ICCTS)
Jul 15, 2022
South Africa, Durban
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/32664/ICCTS/

International Conference on **Medical and Health Sciences**
Jul 17, 2022
United States, Boston
Email: papers.academicsconference@gmail.com
Event Website: http://academicsconference.com/Conference/23291/ICMHS/

International Conference on Advances in **Health and Medical Science** (ICAHMS)
Jul 19, 2022
Singapore, Singapore
Email: info.saard.org@gmail.com
Event Website: http://saard.org/Conference2022/7/Singapore/2/ICAHMS/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Jul 20, 2022
Malaysia, Kuala Lumpur
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/13700/ICMEP/

1187th International Conference on **Pharma and Food** (ICPAF)
Jul 21, 2022
Turkey, Antalya
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/Turkey/3/ICPAF/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Jul 24, 2022
Italy, Rome
Email: papers.issrd@gmail.com
Event Website: http://issrd.org/Conference/14206/international-conference-on-medical-health-science-pharmacology-&-bio-technology/

1368th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Jul 25, 2022
South Africa, Johannesburg
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/SouthAfrica/2/ICRAMS/

1369th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Jul 27, 2022
Japan, Kyoto
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/Japan/7/ICRAMS/

1321st International Conference on **Science, Health and Medicine** (ICSHM)
Aug 01, 2022
Ireland, Dublin
Email: info@iser.co
Event Website: http://iser.co/Conference2022/Ireland/1/ICSHM/

1344th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Aug 02, 2022
Germany, Berlin
Email: info@iastem.org
Event Website: http://iastem.org/Conference2022/Germany/4/ICMBPS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Aug 04, 2022
Switzerland, Geneva
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/21005/ICRAMMHS/

1158th International Conference on **Medical & Health Science** (ICMHS)
Aug 08, 2022
Australia, Brisbane
Email: info@researchfora.com
Event Website: http://researchfora.com/Conference2022/Australia/6/ICMHS/

1199th International Conference on **Sports Nutrition and Supplements** (ICSNS)
Aug 10, 2022
Bahrain, Manama
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/Bahrain/1/ICSNS/

1350th International Conference on **Medical and Health Sciences** (ICMHS)
Aug 11, 2022
Spain, Barcelona
Email: info@iserd.co
Event Website: http://iserd.co/Conference2022/Spain/4/ICMHS/

1366th International Conferences on **Medical and Health Science** (ICMHS)
Aug 12, 2022
France, Paris
Email: info@theires.org
Event Website: http://theires.org/Conference2022/France/3/ICMHS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Aug 17, 2022
United States, Cambridge
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/21127/ICRAMMHS/

1204th International Conference on **Pharma and Food** (ICPAF)
Aug 18, 2022
United States, Los Angeles
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/USA/11/ICPAF/

1351st International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Aug 21, 2022
Turkey, Antalya
Email: info@academicsworld.org
Event Website: http://academicsworld.org/Conference2022/Turkey/3/ICRAMHS/

International Conference on **Oncolytic Virus Therapeutics** (ICOVT)
Aug 21, 2022
United Kingdom, London
Email: info.conferenceonline@gmail.com
Event Website: http://www.conferenceonline.net/Conference/311/ICOVT/

International Conference on **Nutrition & Health** (ICNH)
Aug 22, 2022
Malaysia, Kuala Lumpur
Email: info.conferenceonline@gmail.com
Event Website: http://www.conferenceonline.net/Conference/315/ICNH/

1349th International Conference on **Medical and Biosciences** (ICMBS)
Aug 23, 2022
Luxembourg, Luxembourg City
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2022/Luxembourg/1/ICMBS/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Aug 25, 2022
Japan, Tokyo
Email: papers.issrd@gmail.com
Event Website: http://issrd.org/Conference/14283/international-conference-on-medical-health-science-pharmacology-&-bio-technology/

International Conference on **Medical, Medicine and Health Sciences (**ICMMH)
Aug 27, 2022
United Arab Emirates, Dubai
Email: contact.iierd@gmail.com
Event Website: http://iierd.com/Conference/1857/ICMMH/

International Virtual Conference on **COVID-19 and its Effect** (IVCCE)
Aug 29, 2022
Russian Federation, Moscow
Email: info.conferenceonline@gmail.com
Event Website: http://www.conferenceonline.net/Conference/310/IVCCE/

International Conference on **Medical and Health Sciences** (ICMHS)
Aug 30, 2022
Canada, Montreal
Email: papers.academicsconference@gmail.com
Event Website: http://academicsconference.com/Conference/22587/ICMHS/

1362nd International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Sep 01, 2022
Ireland, Dublin
Email: info@iastem.org
Event Website: http://iastem.org/Conference2022/Ireland/1/ICMBPS/

International Conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Sep 02, 2022
Canada, Ottawa
Email: papers.issrd@gmail.com
Event Website: http://issrd.org/Conference/14297/international-conference-on-medical-health-science-pharmacology-&-bio-technology/

1213th International Conference on **Pharma and Food** (ICPAF)
Sep 04, 2022
Germany, Frankfurt
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/Germany/5/ICPAF/

International Conference on Recent advancement in **Medical Education, Nursing, and Health Sciences** (ICRAMNH)
Sep 07, 2022
Japan, Kobe
Email: info.irfconference@gmail.com
Event Website: http://irfconference.org/Conference/14585/ICRAMNH/

International Conference on **Cell and Tissue Science** (ICCTS)
Sep 09, 2022
United States, San Jose
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/33607/ICCTS/

1369th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Sep 12, 2022
Morocco, Marrakesh
Email: info@iastem.org
Event Website: http://iastem.org/Conference2022/Morocco/2/ICMBPS/

International Conference on **Medical, Medicine and Health Sciences** (ICMMH)
Sep 15, 2022
Australia, Sydney
Email: contact.iierd@gmail.com
Event Website: http://iierd.com/Conference/1901/ICMMH/

1367th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Sep 16, 2022
Switzerland, Zurich
Email: info@academicsworld.org
Event Website: http://academicsworld.org/Conference2022/Switzerland/1/ICRAMHS/

International Conference on **Cardiology and Diabetes** (ICCD)
Sep 16, 2022
United States, New York
Email: info.iared.org@gmail.com
Event Website: http://iared.org/Conference/214/ICCD/

International Research Conference on **COVID-19** and its Impact on Mental Health (IRCCIMH)
Sep 16, 2022
India, Ernakulam, Kerala
Email: info.researchconferences@gmail.com
Event Website: http://researchconferences.in/Conference/2669/international-research-conference-on-covid-19-and-its-impact-on-mental-health/

1267th International Conference on **Food Microbiology and Food Safety** (ICFMFS)
Sep 19, 2022
United Kingdom, Edinburgh
Email: info@theires.org
Event Website: http://theires.org/Conference2022/UK/6/ICFMFS/

World **Disability & Rehabilitation** Conference (WDRC)
Sep 20, 2022
New Zealand, Auckland
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/29412/WDRC/

1404th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Sep 21, 2022
Italy, Venice
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/Italy/5/ICRAMS/

International Conference on **Science, Health and Medicine** (ICSHM)
Sep 24, 2022
Canada, Calgary
Email: info@iser.co
Event Website: http://iser.co/Conference2022/Canada/43/ICSHM/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Sep 24, 2022
Hong Kong, Hong Kong
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/13328/ICMEP/

1369th International Conference on **Medical and Biosciences** (ICMBS)
Sep 25, 2022
France, Paris
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2022/France/3/ICMBS/

International Conference on **Oncolytic Virus Therapeutics** (ICOVT)
Sep 27, 2022
United States, New York
Email: info.conferenceonline@gmail.com
Event Website: http://www.conferenceonline.net/Conference/392/ICOVT/

International Video Conference on **Healthcare** (IVCH)
Sep 28, 2022
Turkey, Istanbul
Email: info.conferenceonline@gmail.com
Event Website: http://www.conferenceonline.net/Conference/407/IVCH/

1230th International Conference on **Sports Nutrition and Supplements** (ICSNS)
Oct 01, 2022
Ireland, Dublin
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2022/Ireland/2/ICSNS/

International Conference on **Medical and Health Sciences** (ICMHS)
Oct 02, 2022
United Kingdom, Glasgow
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/20811/ICMHS/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Oct 05, 2022
Japan, Tokyo
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/10/Japan/1/ICMPH/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Oct 09, 2022
Qatar, Doha
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/10/Qatar/ICMPH/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Oct 10, 2022
Australia, George Town
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/21666/ICRAMMHS/

1281st International Conference on **Food Microbiology and Food Safety** (ICFMFS)
Oct 12, 2022
Oman, Muscat
Email: info@theires.org
Event Website: http://theires.org/Conference2022/Oman/2/ICFMFS/

International Conference on **Medical, Medicine and Health Sciences** (ICMMH)
Oct 13, 2022
Japan, Tokyo
Email: contact.iierd@gmail.com
Event Website: http://iierd.com/Conference/1976/ICMMH/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Oct 17, 2022
Switzerland, Bern
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/10/Switzerland/ICMPH/

1420th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Oct 18, 2022
United Kingdom, London
Email: info@theiier.org
Event Website: http://theiier.org/Conference2022/UK/7/ICRAMS/

2nd Edition of **International Vaccines** Congress
Oct 19, 2022
United States, Orlando, Florida
Email: vaccines@magnusconference.com
Event Website: https://vaccinescongress.com/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Oct 20, 2022
Korea (*South*), Seoul
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference2022/10/SouthKorea/ICMPH/

1386th International Conference on **Medical and Biosciences** (ICMBS)
Oct 21, 2022
Italy, Venice
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2022/Italy/8/ICMBS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Oct 22, 2022
Hong Kong, Hong Kong
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/21178/ICRAMMHS/

1388th International Conference on **Medical and Biosciences** (ICMBS)
Oct 24, 2022
Australia, Melbourne
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2022/Australia/7/ICMBS/

WHO-Facts Sheet

1. Dracunculiasis (guinea-worm disease)
2. Hypertension
3. Monkeypox
4. Oral health
5. Rehabilitation

Compiled and edited by
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Kuwait Medical Journal 2022; 54 (2): 298 - 309

1. DRACUNCULIASIS (GUINEA-WORM DISEASE)

KEY FACTS

- Dracunculiasis is a crippling parasitic disease on the verge of eradication, with 27 human cases reported in 2020.
- From the time infection occurs, it takes between 10–14 months for the transmission cycle to complete. About this time, a mature female worm emerges from the body.
- The parasite is transmitted mostly when people drink stagnant water contaminated with parasite-infected water fleas.
- Dracunculiasis was endemic in 20 countries in the mid-1980s.

Dracunculiasis is rarely fatal, but infected people become non-functional for weeks and months. It affects people in rural, deprived, and isolated communities who depend mainly on open stagnant surface water sources such as ponds for drinking water.

Scope of the problem

During the mid-1980s an estimated 3.5 million cases of dracunculiasis occurred in 20 countries worldwide, 17 countries of which were in Africa and the 3 others in Asia. The number of reported cases fell to fewer than 10 000 cases for the first time in 2007, dropping further to 542 cases (2012). Over the past eight years, human cases have stayed at double digits (54 in 2019 and 27 human cases in 2020). These human cases were reported from four countries: Angola (1), Chad (12), Ethiopia (11), Mali (1), South Sudan (1) and Cameroon (1) - likely imported from Chad.

Transmission, life-cycle and incubation period

About a year after infection, a painful blister forms – 90% of the time on the lower leg – and one or more worms emerge accompanied by a burning sensation. To soothe the burning pain, patients often immerse the infected part of the body in water. The worm(s) then releases thousands of larvae (baby worms) into the water. These larvae reach the infective stage after being ingested by tiny crustaceans or copepods, also called water fleas.

People swallow the infected water fleas when drinking contaminated water. The water fleas are killed in the stomach, but the infective larvae are liberated. They then penetrate the wall of the intestine and migrate through the body. The fertilized female worm (which measures 60–100 cm long) migrates under the skin tissues until it reaches its exit point, usually at the lower limbs, forming a blister or swelling from which it eventually emerges. The worm takes 10–14 months to emerge after infection.

Prevention

There is no vaccine to prevent the disease, nor is there any medication to treat patients. Prevention is possible, however, and successful implementation of preventive strategies have driven the disease to the verge of eradication. Prevention strategies include:

- heightening surveillance to detect every human case and infected animal within 24 hours of worm emergence,
- preventing transmission from each worm by treatment, and regular cleaning and bandaging of affected areas of skin until the worm is completely expelled from the body;
- preventing contamination of drinking-water by preventing infected people and infected animals

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(dogs and cats) with emerging worms from wading into water;
- ensuring wider access to improved drinking-water supplies to prevent infection;
- filtering water from open water bodies before drinking;
- implementing vector control by using the larvicide temephos; and
- promoting health education and behavioural change.

The road to eradication

In May 1981, the Interagency Steering Committee for Cooperative Action for the International Drinking Water Supply and Sanitation Decade (1981–1990) proposed the elimination of dracunculiasis as an indicator of success of the Decade. In the same year, WHO's decision-making body, the World Health Assembly, adopted resolution WHA 34.25, recognizing that the International Drinking Water Supply and Sanitation Decade presented an opportunity to eliminate dracunculiasis. This led to WHO and the United States Centers for Disease Control and Prevention formulating the strategy and technical guidelines for an eradication campaign.

In 1986, The Carter Center joined the battle against the disease and, in partnership with WHO and UNICEF, has since been at the forefront of eradication activities. To give it a final push, in 2011 the World Health Assembly called on all Member States where dracunculiasis is endemic to expedite the interruption of transmission and enforce nationwide surveillance to ensure eradication of dracunculiasis.

Country certification

To be declared free of dracunculiasis, a country is required to have reported zero instances of transmission and maintained active surveillance for at least 3 consecutive years.

After this period, an international certification team visits the country to assess the adequacy of the surveillance system and to review records of investigations regarding rumoured cases or infected animals and subsequent actions taken.

Indicators such as access to improved drinking-water sources in infected areas are examined and assessments are conducted in villages to confirm the absence of transmission. Risks of reintroduction of the disease are also assessed. Finally, a report is submitted to the International Commission for the Certification of Dracunculiasis Eradication (ICCDE) for review.

Since 1995, the ICCDE has met 15 times and on its recommendation, WHO has certified 199 countries, territories, and areas (belonging to 187 Member States) as free of dracunculiasis.

Kenya, a formerly endemic country, was the last to attain this status in February 2018.

Ongoing surveillance

WHO recommends active surveillance in a country and/or area that has recently interrupted guinea-worm disease transmission to be maintained for a minimum of 3 consecutive years. Ongoing surveillance is essential to ensure that no human cases and infected animals have been missed and to prevent reoccurrence of the disease.

As the incubation period of the worm takes 10–14 months, a single missed emerged worm could delay eradication by a year or more. Evidence of re-emergence was brought to light in Ethiopia (2008) after the national eradication programme claimed interruption of transmission, and more recently in Chad (2010) where transmission re-occurred after the country reported zero cases for almost 10 years.

A country reporting zero cases over a period of 14 consecutive months is believed to have interrupted transmission. It is then classified as being in the pre-certification stage for at least 3 years since the last indigenous case, during which intense surveillance activities must be continued. Even after certification, surveillance should be maintained until global eradication is declared.

Challenges

Finding and containing the last remaining cases and infected animals are the most difficult and expensive stages of the eradication process, as these usually occur in remote, often inaccessible, rural areas.

Insecurity, with the resulting lack of access to disease-endemic areas, is a major constraint, especially in countries where cases and animal infections are still occurring.

Dracunculus medinensis infection in dogs continues to pose a challenge to the global eradication campaign particularly in Chad, Ethiopia and Mali. The phenomenon was noted in Chad in 2012, and since then several dogs with emerging worms, genetically identical to those emerging in humans, continue to be detected in the same at-risk area. In 2020, Chad reported 1508 infected dogs and 63 infected cats; Ethiopia reported three infected dogs, four infected baboons, and eight infected cats. Mali reported infections in nine dogs.

Transmission in animals can be interrupted through enhanced surveillance to detect all infected animals and to contain them (tethering of infected animals and pro-active tethering), provision of health education for community members and animal owners, and implementation of vigorous and comprehensive vector control interventions.

WHO response

In response to dracunculiasis, WHO advocates for eradication, provides technical guidance, coordinates eradication activities, enforces surveillance in dracunculiasis-free areas and monitors and reports on progress achieved.

WHO is the only organization mandated to certify countries as free of the disease transmission following recommendations made by the ICCDE. The ICCDE currently comprises 9 public health experts. The Commission meets as and when necessary to evaluate the status of transmission in countries applying for certification of dracunculiasis eradication and to recommend whether a country should be certified as free of dracunculiasis' transmission.

2. HYPERTENSION

KEY FACTS

- Hypertension - or elevated blood pressure - is a serious medical condition that significantly increases the risks of heart, brain, kidney and other diseases.
- An estimated 1.28 billion adults aged 30-79 years worldwide have hypertension, most (two-thirds) living in low- and middle-income countries
- An estimated 46% of adults with hypertension are unaware that they have the condition.
- Less than half of adults (42%) with hypertension are diagnosed and treated.
- Approximately 1 in 5 adults (21%) with hypertension have it under control.
- Hypertension is a major cause of premature death worldwide.
- One of the global targets for noncommunicable diseases is to reduce the prevalence of hypertension by 33% between 2010 and 2030.

What is hypertension?

Blood pressure is the force exerted by circulating blood against the walls of the body's arteries, the major blood vessels in the body. Hypertension is when blood pressure is too high. Blood pressure is written as two numbers. The first (systolic) number represents the pressure in blood vessels when the heart contracts or beats. The second (diastolic) number represents the pressure in the vessels when the heart rests between beats.

Hypertension is diagnosed if, when it is measured on two different days, the systolic blood pressure readings on both days is ≥140 mmHg and/or the diastolic blood pressure readings on both days is ≥90 mmHg.

What are the risk factors for hypertension?

Modifiable risk factors include unhealthy diets (excessive salt consumption, a diet high in saturated fat and trans fats, low intake of fruits and vegetables), physical inactivity, consumption of tobacco and alcohol, and being overweight or obese.

Non-modifiable risk factors include a family history of hypertension, age over 65 years and co-existing diseases such as diabetes or kidney disease.

What are common symptoms of hypertension?

Hypertension is called a "silent killer". Most people with hypertension are unaware of the problem because it may have no warning signs or symptoms. For this reason, it is essential that blood pressure is measured regularly.

When symptoms do occur, they can include early morning headaches, nosebleeds, irregular heart rhythms, vision changes, and buzzing in the ears. Severe hypertension can cause fatigue, nausea, vomiting, confusion, anxiety, chest pain, and muscle tremors.

The only way to detect hypertension is to have a health professional measure blood pressure. Having blood pressure measured is quick and painless. Although individuals can measure their own blood pressure using automated devices, an evaluation by a health professional is important for assessment of risk and associated conditions.

What are the complications of uncontrolled hypertension?

Among other complications, hypertension can cause serious damage to the heart. Excessive pressure can harden arteries, decreasing the flow of blood and oxygen to the heart. This elevated pressure and reduced blood flow can cause:

- Chest pain, also called angina.
- Heart attack, which occurs when the blood supply to the heart is blocked and heart muscle cells die from lack of oxygen. The longer the blood flow is blocked, the greater the damage to the heart.
- Heart failure, which occurs when the heart cannot pump enough blood and oxygen to other vital body organs.
- Irregular heart beat which can lead to a sudden death.

Hypertension can also burst or block arteries that supply blood and oxygen to the brain, causing a stroke.

In addition, hypertension can cause kidney damage, leading to kidney failure.

Why is hypertension an important issue in low- and middle-income countries?

The prevalence of hypertension varies across regions and country income groups. The WHO African Region has the highest prevalence of hypertension (27%) while the WHO Region of the Americas has the lowest prevalence of hypertension (18%).

The number of adults with hypertension increased from 594 million in 1975 to 1.13 billion in 2015, with the increase seen largely in low- and middle-income countries. This increase is due mainly to a rise in hypertension risk factors in those populations.

How can the burden of hypertension be reduced?

Reducing hypertension prevents heart attack, stroke, and kidney damage, as well as other health problems.

Prevention

- Reducing salt intake (to less than 5g daily).
- Eating more fruit and vegetables.
- Being physically active on a regular basis.
- Avoiding use of tobacco.
- Reducing alcohol consumption.
- Limiting the intake of foods high in saturated fats.
- Eliminating/reducing trans fats in diet.

Management

- Reducing and managing stress.
- Regularly checking blood pressure.
- Treating high blood pressure.
- Managing other medical conditions.

What is the WHO response?

The World Health Organization (WHO) is supporting countries to reduce hypertension as a public health problem.

In 2021, the WHO released a new guideline for on the pharmacological treatment of hypertension in adults. The publication provides evidence-based recommendations for the initiation of treatment of hypertension, and recommended intervals for follow-up. The document also includes target blood pressure to be achieved for control, and information on who, in the health-care system, can initiate treatment.

To support governments in strengthening the prevention and control of cardiovascular disease, WHO and the United States Centers for Disease Control and Prevention (U.S. CDC) launched the Global Hearts Initiative in September 2016, which includes the HEARTS technical package. The six modules of the HEARTS technical package (Healthy-lifestyle counselling, Evidence-based treatment protocols, Access to essential medicines and technology, Risk-based management, Team-based care, and Systems for monitoring) provide a strategic approach to improve cardiovascular health in countries across the world.

In September 2017, WHO began a partnership with Resolve to Save Lives, an initiative of Vital Strategies, to support national governments to implement the Global Hearts Initiative. Other partners contributing to the Global Hearts Initiative are: the CDC Foundation, the Global Health Advocacy Incubator, the Johns Hopkins Bloomberg School of Public Health, the Pan American Health Organization (PAHO) and the U.S. CDC. Since implementation of the programme in 2017 in 18 low- and middle-income countries, 3 million people have been put on protocol-based hypertension treatment through person-centred models of care. These programmes demonstrate the feasibility and effectiveness of standardized hypertension control programmes.

3. MONKEYPOX

Key facts

- Vaccines used during the smallpox eradication programme also provided protection against monkeypox. Newer vaccines have been developed of which one has been approved for prevention of monkeypox
- Monkeypox is caused by monkeypox virus, a member of the Orthopoxvirus genus in the family Poxviridae.
- Monkeypox is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks. Severe cases can occur. In recent times, the case fatality ratio has been around 3–6%.
- Monkeypox is transmitted to humans through close contact with an infected person or animal, or with material contaminated with the virus.
- Monkeypox virus is transmitted from one person to another by close contact with lesions, body fluids, respiratory droplets and contaminated materials such as bedding.
- Monkeypox is a viral zoonotic disease that occurs primarily in tropical rainforest areas of central and west Africa and is occasionally exported to other regions.
- An antiviral agent developed for the treatment of smallpox has also been licensed for the treatment of monkeypox.
- The clinical presentation of monkeypox resembles that of smallpox, a related orthopoxvirus infection which was declared eradicated worldwide in 1980. Monkeypox is less contagious than smallpox and causes less severe illness.

- Monkeypox typically presents clinically with fever, rash and swollen lymph nodes and may lead to a range of medical complications.

Introduction

Monkeypox is a viral zoonosis (a virus transmitted to humans from animals) with symptoms similar to those seen in the past in smallpox patients, although it is clinically less severe. With the eradication of smallpox in 1980 and subsequent cessation of smallpox vaccination, monkeypox has emerged as the most important orthopoxvirus for public health. Monkeypox primarily occurs in central and west Africa, often in proximity to tropical rainforests, and has been increasingly appearing in urban areas. Animal hosts include a range of rodents and non-human primates.

The pathogen

Monkeypox virus is an enveloped double-stranded DNA virus that belongs to the *Orthopoxvirus* genus of the *Poxviridae* family. There are two distinct genetic clades of the monkeypox virus: the central African (Congo Basin) clade and the west African clade. The Congo Basin clade has historically caused more severe disease and was thought to be more transmissible. The geographical division between the two clades has so far been in Cameroon, the only country where both virus clades have been found.

Natural host of monkeypox virus

Various animal species have been identified as susceptible to monkeypox virus. This includes rope squirrels, tree squirrels, Gambian pouched rats, dormice, non-human primates and other species. Uncertainty remains on the natural history of monkeypox virus and further studies are needed to identify the exact reservoir(s) and how virus circulation is maintained in nature.

Outbreaks

Human monkeypox was first identified in humans in 1970 in the Democratic Republic of the Congo in a 9-year-old boy in a region where smallpox had been eliminated in 1968. Since then, most cases have been reported from rural, rainforest regions of the Congo Basin, particularly in the Democratic Republic of the Congo and human cases have increasingly been reported from across central and west Africa.

Since 1970, human cases of monkeypox have been reported in 11 African countries: Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Cote d'Ivoire, Liberia, Nigeria, the Republic of the Congo, Sierra Leone and South Sudan. The true burden of monkeypox is not known. For example, in 1996–97, an outbreak was reported in the Democratic Republic of the Congo with a lower case fatality ratio and a higher attack rate than usual. A concurrent outbreak of chickenpox (caused by the varicella virus, which is not an orthopoxvirus) and monkeypox was found, which could explain real or apparent changes in transmission dynamics in this case. Since 2017, Nigeria has experienced a large outbreak, with over 500 suspected cases and over 200 confirmed cases and a case fatality ratio of approximately 3%. Cases continue to be reported until today.

Monkeypox is a disease of global public health importance as it not only affects countries in west and central Africa, but the rest of the world. In 2003, the first monkeypox outbreak outside of Africa was in the United States of America and was linked to contact with infected pet prairie dogs. These pets had been housed with Gambian pouched rats and dormice that had been imported into the country from Ghana. This outbreak led to over 70 cases of monkeypox in the U.S. Monkeypox has also been reported in travelers from Nigeria to Israel in September 2018, to the United Kingdom in September 2018, December 2019, May 2021 and May 2022, to Singapore in May 2019, and to the United States of America in July and November 2021. In May 2022, multiple cases of monkeypox were identified in several non-endemic countries. Studies are currently underway to further understand the epidemiology, sources of infection, and transmission patterns.

Transmission

Animal-to-human (zoonotic) transmission can occur from direct contact with the blood, bodily fluids, or cutaneous or mucosal lesions of infected animals. In Africa, evidence of monkeypox virus infection has been found in many animals including rope squirrels, tree squirrels, Gambian poached rats, dormice, different species of monkeys and others. The natural reservoir of monkeypox has not yet been identified, though rodents are the most likely. Eating inadequately cooked meat and other animal products of infected animals is a possible risk factor. People living in or near forested areas may have indirect or low-level exposure to infected animals.

Human-to-human transmission can result from close contact with respiratory secretions, skin lesions of an infected person or recently contaminated objects. Transmission via droplet respiratory particles usually requires prolonged face-to-face contact, which puts health workers, household members and other close contacts of active cases at greater risk. However, the longest documented chain of transmission in a community has risen in recent years from 6 to 9 successive person-to-person infections. This may

reflect declining immunity in all communities due to cessation of smallpox vaccination. Transmission can also occur via the placenta from mother to fetus (which can lead to congenital monkeypox) or during close contact during and after birth. While close physical contact is a well-known risk factor for transmission, it is unclear at this time if monkeypox can be transmitted specifically through sexual transmission routes. Studies are needed to better understand this risk.

Signs and symptoms

The incubation period (interval from infection to onset of symptoms) of monkeypox is usually from 6 to 13 days but can range from 5 to 21 days.

The infection can be divided into two periods:

- the invasion period (lasts between 0–5 days) characterized by fever, intense headache, lymphadenopathy (swelling of the lymph nodes), back pain, myalgia (muscle aches) and intense asthenia (lack of energy). Lymphadenopathy is a distinctive feature of monkeypox compared to other diseases that may initially appear similar (chickenpox, measles, smallpox)
- the skin eruption usually begins within 1–3 days of appearance of fever. The rash tends to be more concentrated on the face and extremities rather than on the trunk. It affects the face (in 95% of cases), and palms of the hands and soles of the feet (in 75% of cases). Also affected are oral mucous membranes (in 70% of cases), genitalia (30%), and conjunctivae (20%), as well as the cornea. The rash evolves sequentially from macules (lesions with a flat base) to papules (slightly raised firm lesions), vesicles (lesions filled with clear fluid), pustules (lesions filled with yellowish fluid), and crusts which dry up and fall off. The number of lesions varies from a few to several thousand. In severe cases, lesions can coalesce until large sections of skin slough off.

Monkeypox is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks. Severe cases occur more commonly among children and are related to the extent of virus exposure, patient health status and nature of complications. Underlying immune deficiencies may lead to worse outcomes. Although vaccination against smallpox was protective in the past, today persons younger than 40 to 50 years of age (depending on the country) may be more susceptible to monkeypox due to cessation of smallpox vaccination campaigns globally after eradication of the disease. Complications of monkeypox can include secondary infections, bronchopneumonia, sepsis, encephalitis, and infection of the cornea with ensuing loss of vision. The extent to which asymptomatic infection may occur is unknown.

The case fatality ratio of monkeypox has historically ranged from 0 to 11 % in the general population and has been higher among young children. In recent times, the case fatality ratio has been around 3–6%.

Diagnosis

The clinical differential diagnosis that must be considered includes other rash illnesses, such as chickenpox, measles, bacterial skin infections, scabies, syphilis, and medication-associated allergies. Lymphadenopathy during the prodromal stage of illness can be a clinical feature to distinguish monkeypox from chickenpox or smallpox.

If monkeypox is suspected, health workers should collect an appropriate sample and have it transported safely to a laboratory with appropriate capability. Confirmation of monkeypox depends on the type and quality of the specimen and the type of laboratory test. Thus, specimens should be packaged and shipped in accordance with national and international requirements. Polymerase chain reaction (PCR) is the preferred laboratory test given its accuracy and sensitivity. For this, optimal diagnostic samples for monkeypox are from skin lesions – the roof or fluid from vesicles and pustules, and dry crusts. Where feasible, biopsy is an option. Lesion samples must be stored in a dry, sterile tube (no viral transport media) and kept cold. PCR blood tests are usually inconclusive because of the short duration of viremia relative to the timing of specimen collection after symptoms begin and should not be routinely collected from patients.

As orthopoxviruses are serologically cross-reactive, antigen and antibody detection methods do not provide monkeypox-specific confirmation. Serology and antigen detection methods are therefore not recommended for diagnosis or case investigation where resources are limited. Additionally, recent or remote vaccination with a vaccinia-based vaccine (e.g. anyone vaccinated before smallpox eradication, or more recently vaccinated due to higher risk such as orthopoxvirus laboratory personnel) might lead to false positive results.

In order to interpret test results, it is critical that patient information be provided with the specimens including: a) date of onset of fever, b) date of onset of rash, c) date of specimen collection, d) current status of the individual (stage of rash), and e) age.

Therapeutics

Clinical care for monkeypox should be fully optimized to alleviate symptoms, manage complications and prevent long-term sequelae. Patients should be offered fluids and food to maintain adequate nutritional status. Secondary bacterial infections should be treated as indicated. An antiviral

agent known as tecovirimat that was developed for smallpox was licensed by the European Medical Association (EMA) for monkeypox in 2022 based on data in animal and human studies. It is not yet widely available.

If used for patient care, tecovirimat should ideally be monitored in a clinical research context with prospective data collection.

Vaccination

Vaccination against smallpox was demonstrated through several observational studies to be about 85% effective in preventing monkeypox. Thus, prior smallpox vaccination may result in milder illness. Evidence of prior vaccination against smallpox can usually be found as a scar on the upper arm. At the present time, the original (first-generation) smallpox vaccines are no longer available to the general public. Some laboratory personnel or health workers may have received a more recent smallpox vaccine to protect them in the event of exposure to orthopoxviruses in the workplace. A still newer vaccine based on a modified attenuated vaccinia virus (Ankara strain) was approved for the prevention of monkeypox in 2019. This is a two-dose vaccine for which availability remains limited. Smallpox and monkeypox vaccines are developed in formulations based on the vaccinia virus due to cross-protection afforded for the immune response to orthopoxviruses.

Prevention

Raising awareness of risk factors and educating people about the measures they can take to reduce exposure to the virus is the main prevention strategy for monkeypox. Scientific studies are now underway to assess the feasibility and appropriateness of vaccination for the prevention and control of monkeypox. Some countries have, or are developing, policies to offer vaccine to persons who may be at risk such as laboratory personnel, rapid response teams and health workers.

Reducing the risk of human-to-human transmission

Surveillance and rapid identification of new cases is critical for outbreak containment. During human monkeypox outbreaks, close contact with infected persons is the most significant risk factor for monkeypox virus infection. Health workers and household members are at a greater risk of infection. Health workers caring for patients with suspected or confirmed monkeypox virus infection, or handling specimens from them, should implement standard infection control precautions. If possible, persons previously vaccinated against smallpox should be selected to care for the patient.

Samples taken from people and animals with suspected monkeypox virus infection should be handled by trained staff working in suitably equipped laboratories. Patient specimens must be safely prepared for transport with triple packaging in accordance with WHO guidance for transport of infectious substances.

The identification in May 2022 of clusters of monkeypox cases in several non-endemic countries with no direct travel links to an endemic area is atypical. Further investigations are underway to determine the likely source of infection and limit further onward spread. As the source of this outbreak is being investigated, it is important to look at all possible modes of transmission in order to safeguard public health.

Reducing the risk of zoonotic transmission

Over time, most human infections have resulted from a primary, animal-to-human transmission. Unprotected contact with wild animals, especially those that are sick or dead, including their meat, blood and other parts must be avoided. Additionally, all foods containing animal meat or parts must be thoroughly cooked before eating.

Preventing monkeypox through restrictions on animal trade

Some countries have put in place regulations restricting importation of rodents and non-human primates. Captive animals that are potentially infected with monkeypox should be isolated from other animals and placed into immediate quarantine. Any animals that might have come into contact with an infected animal should be quarantined, handled with standard precautions and observed for monkeypox symptoms for 30 days.

How monkeypox relates to smallpox

The clinical presentation of monkeypox resembles that of smallpox, a related orthopoxvirus infection which has been eradicated. Smallpox was more easily transmitted and more often fatal as about 30% of patients died. The last case of naturally acquired smallpox occurred in 1977, and in 1980 smallpox was declared to have been eradicated worldwide after a global campaign of vaccination and containment. It has been 40 or more years since all countries ceased routine smallpox vaccination with vaccinia-based vaccines. As vaccination also protected against monkeypox in west and central Africa, unvaccinated populations are now also more susceptible to monkeypox virus infection.

Whereas smallpox no longer occurs naturally, the global health sector remains vigilant in the event it

could reappear through natural mechanisms, laboratory accident or deliberate release. To ensure global preparedness in the event of reemergence of smallpox, newer vaccines, diagnostics and antiviral agents are being developed. These may also now prove useful for prevention and control of monkeypox.

4. ORAL HEALTH

KEY FACTS

- Oral diseases, while largely preventable, pose a major health burden for many countries and affect people throughout their lifetime, causing pain, discomfort, disfigurement and even death.
- It is estimated that oral diseases affect nearly 3.5 billion people.
- Untreated dental caries (tooth decay) in permanent teeth is the most common health condition according to the Global Burden of Disease 2019.
- Treatment for oral health conditions is expensive and usually not part of universal health coverage (UHC).
- Most low- and middle-income countries are unable to provide services to prevent and treat oral health conditions.
- Oral diseases are caused by a range of modifiable risk factors, including sugar consumption, tobacco use, alcohol use and poor hygiene, and their underlying social and commercial determinants.

Oral health conditions

Most oral health conditions are largely preventable and can be treated in their early stages. The majority of cases are dental caries (tooth decay), periodontal diseases, oral cancers, oro-dental trauma, cleft lip and palate, and noma (severe gangrenous disease starting in the mouth mostly affecting children).

The *Global Burden of Disease Study 2019* estimated that oral diseases affect close to 3.5 billion people worldwide, with caries of permanent teeth being the most common condition[1]. Globally, it is estimated that 2 billion people suffer from caries of permanent teeth[1] and 520 million children suffer from caries of primary teeth[1].

In most low- and middle-income countries, the prevalence of oral diseases continues to increase with growing urbanization and changes in living conditions. This is primarily due to inadequate exposure to fluoride (in the water supply and oral hygiene products such as toothpaste), availability and affordability of food with high sugar content and poor access to oral health care services in the community. Marketing of food and beverages high in sugar, as well as tobacco and alcohol, have led to a growing consumption of products that contribute to oral health conditions and other noncommunicable diseases.

Dental caries (tooth decay)

Dental caries result when plaque forms on the surface of a tooth and converts the free sugars (all sugars added to foods by the manufacturer, cook, or consumer, plus sugars naturally present in honey, syrups, and fruit juices) contained in foods and drinks into acids that destroy the tooth over time. A continued high intake of free sugars, inadequate exposure to fluoride and a lack of removal of plaque by toothbrushing can lead to caries, pain and sometimes tooth loss and infection.

Periodontal (gum) disease

Periodontal disease affects the tissues that both surround and support the tooth. The disease is characterized by bleeding or swollen gums (gingivitis), pain and sometimes bad breath. In its more severe form, the gum can come away from the tooth and supporting bone, causing teeth to become loose and sometimes fall out. Severe periodontal diseases are estimated to affect around 14% of the global adult population, representing more than one billion cases worldwide[1]. The main causes of periodontal disease are poor oral hygiene and tobacco use.

Oral cancer

Oral cancer includes cancers of the lip, other parts of the mouth and the oropharynx. The global incidence of cancers of the lip and oral cavity is estimated at 4 cases per 100 000 people. However, there is wide variation across the globe, from 0 to around 22 cases per 100 000 people[2]. Oral cancer is more common in men and in older people, and it varies strongly by socio-economic condition.

Tobacco, alcohol and areca nut (betel quid) use are among the leading causes of oral cancer[3]. In North America and Europe, human papillomavirus infections are responsible for a growing percentage of oral cancers among young people[4].

Oro-dental trauma

Oro-dental trauma results from injury to the teeth, mouth and oral cavity. Around 20% of people suffer from trauma to teeth at some point in their life[5]. Oro-dental trauma can be caused by oral factors such as lack of alignment of teeth and environmental factors (such as unsafe playgrounds, risk-taking behaviour, road accidents and violence). Treatment is costly and lengthy and sometimes can even lead to tooth loss, resulting in complications for facial and psychological development and quality of life.

Noma

Noma is a severe gangrenous disease of the mouth and the face. It mostly affects children aged 2–6 years suffering from malnutrition, affected by infectious disease, living in extreme poverty with poor oral hygiene or with weakened immune systems.

Noma is mostly found in sub-Saharan Africa, although cases have also been reported in Latin America and Asia[6]. Noma starts as a soft tissue lesion (a sore) of the gums, inside the mouth. The initial gum lesion then develops into an acute necrotizing gingivitis that progresses rapidly, destroying the soft tissues and further progressing to involve the hard tissues and skin of the face.

According to latest estimates (from 1998) there are 140 000 new cases of noma annually. Without treatment, noma is fatal in 90% of cases[7]. Survivors suffer from severe facial disfigurement, have difficulty speaking and eating, endure social stigma, and require complex surgery and rehabilitation. Where noma is detected at an early stage, its progression can be rapidly halted through basic hygiene, antibiotics and improved nutrition.

Cleft lip and palate

Orofacial clefts, the most common craniofacial birth defects, have a global prevalence of between 1 in 1000-1500 births with wide variation in different studies and populations[8,9]. Genetic predisposition is a major cause. However, poor maternal nutrition, tobacco consumption, alcohol and obesity during pregnancy also play a role[10]. In low-income settings, there is a high mortality rate in the neonatal period. If lip and palate clefts are properly treated by surgery, complete rehabilitation is possible.

Noncommunicable diseases and common risk factors

Most oral diseases and conditions share modifiable risk factors such as tobacco use, alcohol consumption and an unhealthy diet high in free sugars that are common to the 4 leading noncommunicable diseases (cardiovascular disease, cancer, chronic respiratory disease and diabetes).

In addition, diabetes has been linked in a reciprocal way with the development and progression of periodontal disease[11]. There is also a causal link between the high consumption of sugar and diabetes, obesity and dental caries.

Oral health inequalities

Oral diseases disproportionally affect the poor and socially disadvantaged members of society. There is a very strong and consistent association between socioeconomic status (income, occupation and educational level) and the prevalence and severity of oral diseases[12]. This association exists from early childhood to older age and across populations in high-, middle- and low-income countries.

Prevention

The burden of oral diseases and other noncommunicable diseases can be reduced through public health interventions by addressing common risk factors.

These include:

- promoting a well-balanced diet low in free sugars and high in fruit and vegetables, and favouring water as the main drink;
- stopping use of all forms of tobacco, including chewing of areca nuts;
- reducing alcohol consumption; and
- encouraging use of protective equipment when doing sports and travelling on bicycles and motorcycles (to reduce the risk of facial injuries).

Adequate exposure to fluoride is an essential factor in the prevention of dental caries.

An optimal level of fluoride can be obtained from different sources such as fluoridated drinking water, salt, milk and toothpaste. Twice-daily tooth brushing with fluoride-containing toothpaste (1000 to 1500 ppm) should be encouraged[13].

Access to oral health services

Unequal distribution of oral health professionals and a lack of appropriate health facilities to meet population needs in most countries means that access to primary oral health services is often low. Out-of-pocket costs for oral health care can be major barriers to accessing care. Paying for necessary oral health care is among the leading reasons for catastrophic health expenditures, resulting in an increased risk of impoverishment and economic hardship[14,15].

WHO response

The World Health Assembly approved a Resolution on oral health in 2021 at the 74th World Health Assembly. The Resolution recommends a shift from the traditional curative approach towards a preventive approach that includes promotion of oral health within the family, schools and workplaces, and includes timely, comprehensive and inclusive care within the primary health-care system. The Resolution affirms that oral health should be firmly embedded within the noncommunicable disease agenda and that oral health-care interventions should be included in universal health coverage programs.

The World Health Assembly delegates asked WHO: to develop a draft global strategy on tackling oral diseases for consideration by WHO governing bodies in 2022; and by 2023: to translate the global

strategy into an action plan for oral health; to develop "best buy" interventions on oral health; and to explore the inclusion of noma within the roadmap for neglected tropical diseases 2021-2030. WHO was asked to report back on progress and results until 2031 as part of the consolidated report on noncommunicable diseases.

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5. REHABILITATION

KEY FACTS

- Rehabilitation is an essential part of universal health coverage along with promotion of good health, prevention of disease, treatment and palliative care.
- Rehabilitation helps a child, adult or older person to be as independent as possible in everyday activities and enables participation in education, work, recreation and meaningful life roles such as taking care of family.
- Globally, an estimated 2.4 billion people are currently living with a health condition that benefits from rehabilitation.
- The need for rehabilitation worldwide is predicted to increase due to changes in the health and characteristics of the population. For example, people are living longer, but with more chronic disease and disability.
- Currently, the need for rehabilitation is largely unmet. In some low- and middle-income countries, more than 50% of people do not receive the rehabilitation services they require. Rehabilitation services are also amongst the health services most severely disrupted by the COVID-19 pandemic.

What is rehabilitation?

Rehabilitation is defined as "***a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment*".**

Put simply, rehabilitation helps a child, adult or older person to be as independent as possible in everyday activities and enables participation in education, work, recreation and meaningful life roles such as taking care of family. It does so by addressing underlying conditions (such as pain) and improving the way an individual functions in everyday life, supporting them to overcome difficulties with thinking, seeing, hearing, communicating, eating or moving around.

Anybody may need rehabilitation at some point in their lives, following an injury, surgery, disease or illness, or because their functioning has declined with age.

Some examples of rehabilitation include:

- Exercises to improve a person's speech, language and communication after a brain injury.
- Modifying an older person's home environment to improve their safety and independence at home and to reduce their risk of falls.
- Exercise training and education on healthy living for a person with a heart disease.
- Making, fitting and educating an individual to use a prosthesis after a leg amputation.
- Positioning and splinting techniques to assist with skin healing, reduce swelling, and to regain movement after burn surgery.
- Prescribing medicine to reduce muscle stiffness for a child with cerebral palsy.
- Psychological support for a person with depression.
- Training in the use of a white cane, for a person with vision loss.

Rehabilitation is highly person-centered, meaning that the interventions and approach selected for each individual depends on their goals and preferences. Rehabilitation can be provided in many different settings, from inpatient or outpatient hospital settings, to private clinics, or community settings such as an individual's home.

The rehabilitation workforce is made up of different health workers, including but not limited to physiotherapists, occupational therapists, speech and language therapists and audiologists, orthotists and prosthetists, clinical psychologists, physical medicine and rehabilitation doctors, and rehabilitation nurses.

The benefits of rehabilitation

Rehabilitation can reduce the impact of a broad range of health conditions, including diseases (acute or chronic), illnesses or injuries. It can also complement other health interventions, such as medical and surgical interventions, helping to achieve the best outcome possible. For example, rehabilitation can help to reduce, manage or prevent complications associated with many health conditions, such as spinal cord injury, stroke, or a fracture.

Rehabilitation helps to minimize or slow down the disabling effects of chronic health conditions, such as cardiovascular disease, cancer and diabetes by equipping people with self-management strategies and the assistive products they require, or by addressing pain or other complications.

Rehabilitation is an investment, with cost benefits for both the individuals and society. It can help to avoid costly hospitalization, reduce hospital length of stay, and prevent re-admissions. Rehabilitation also enables individuals to participate in education and gainful employment, remain independent at home, and minimize the need for financial or caregiver support.

Rehabilitation is an important part of universal health coverage and is a key strategy for achieving Sustainable Development Goal 3 – "Ensure healthy lives and promote well-being for all at all ages".

Misconceptions about rehabilitation

Rehabilitation is not only for people with long-term or physical impairments. Rather, rehabilitation is a core health service for anyone with an acute or chronic health condition, impairment or injury that limits functioning, and as such should be available for anyone who needs it.

Rehabilitation is not a luxury health service that is available only for those who can afford it. Nor is it an optional service to try only when other interventions to prevent or cure a health condition fail.

For the full extent of the social, economic and health benefits of rehabilitation to be realized, timely, high quality and affordable rehabilitation interventions should be available to all. In many cases, this means starting rehabilitation as soon as a health condition is noted and continuing to deliver rehabilitation alongside other health interventions.

Unmet global need for rehabilitation

Globally, about 2.4 billion people are currently living with a health condition that benefits from rehabilitation. With changes taking place in the health and characteristics of the population worldwide, this estimated need for rehabilitation is only going to increase in the coming years.

People are living longer, with the number of people over 60 years of age predicted to double by 2050, and more people are living with chronic diseases such as diabetes, stroke and cancer. At the same time, the ongoing incidence of injury (such as a burn) and child developmental conditions (such as cerebral palsy) persist. These health conditions can impact an individual's functioning and are linked to increased levels of disability, for which rehabilitation can be beneficial.

In many parts of the world, this increasing need for rehabilitation is going largely unmet. More than half of people living in some low- and middle-income countries who require rehabilitation services do not receive them. Rehabilitation services are consistently amongst the health services most severely disrupted by the COVID-19 pandemic.

Global rehabilitation needs continue to be unmet due to multiple factors, including:

- Lack of prioritization, funding, policies and plans

for rehabilitation at a national level.
- Lack of available rehabilitation services outside urban areas, and long waiting times.
- High out-of-pocket expenses and non-existent or inadequate means of funding.
- Lack of trained rehabilitation professionals, with less than 10 skilled practitioners per 1 million population in many low- and middle-income settings.
- Lack of resources, including assistive technology, equipment and consumables.
- The need for more research and data on rehabilitation.
- Ineffective and under-utilized referral pathways to rehabilitation.

Rehabilitation in emergencies

Natural hazards such as earthquakes or disease outbreaks and human induced hazards including conflict, terrorism or industrial accidents can generate overwhelming rehabilitation needs as a result of injury or illness. They also simultaneously disrupt existing services and have the greatest impact on the most vulnerable populations and the weakest health systems.

While the important role of rehabilitation in emergencies is recognized in clinical and humanitarian guidelines, it is rarely considered as part of health system preparedness and early response. The result is that pre-existing limitations in rehabilitation services are magnified, health service delivery is less efficient, and people directly affected are at risk of increased impairment and disability.

WHO response

For rehabilitation to reach its full potential, efforts should be directed towards strengthening the health system as a whole and making rehabilitation part of health care at all levels of the health system, and as part of universal health coverage.

In 2017, WHO launched the Rehabilitation 2030 initiative, which emphasizes the need for health system strengthening, and calls for all stakeholders worldwide to come together to work on different priority areas, including: improving leadership and governance; developing a strong multidisciplinary rehabilitation workforce; expanding financing for rehabilitation; and improving data collection and research on rehabilitation.

WHO is responding to the identified challenges and promoting health system strengthening for rehabilitation through:
- Providing technical support and building capacity at country level
- Increasing leadership, prioritization and resource mobilization
- Developing norms, standards and technical guidance
- Shaping the research agenda and monitoring progress