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Review Article	5000	200	50	6	10 or total of 20 images
Case Report	1500	200	10	No tables	10 or total of 20 images
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Clinical Imaging/ Visual Diagnosis	400	N/A	5	No tables	3 or total of 6 images
History	900	N/A	10	No tables	3 or total of 6 images
Publication ethics	900	N/A	10	No tables	No media

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Eurasian J Emerg Med. 2022;21(4): 227-33

The Effectiveness of Immature Granulocyte Count for Predicting COVID-19 Severity and Poor Outcomes

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Abstract

Aim: The aim of this study was to examine the relationship between immature granulocyte (IG) counts and the severity of the disease and to evaluate the effectiveness of IG in predicting the poor outcomes in polymerase chain reaction-confirmed Coronavirus disease-2019 (COVID-19) cases.

Materials and Methods: The study was conducted prospectively and observationally at the emergency department. Patients were divided into three groups according to the clinical severity indicators such as mild, moderate and severe. The IG level was measured from the whole blood samples taken at the admission to the emergency department. Intensive care unit admission, ventilation support, and death within the first 28 days after the admission were evaluated as composite outcomes.

Results: The study group consisted of 203 adults, of whom 91 (44.8%) were women. According to the severity of the illness, 40 patients (19.7%) were classified as mild, 67 patients (33.0%) as moderate, and 96 patients (47.3%) as severe. When comparing IG levels between the groups, there was a statistically significant difference between the mild and severe groups ($p=0.047$) and between the moderate and severe disease groups ($p=0.036$). There was no statistically significant relationship between IG counts and the composite outcome ($p>0.05$)

Conclusion: The IG level, which could be measured faster than other laboratory tests without any additional cost, could be used for the determination of the clinical severity of patients with COVID-19. However, we conclude that this parameter is not effective in determining poor outcomes during the admission.

Keywords: COVID-19, emergency department, immature granulocyte, mortality, severity

Introduction

The Coronavirus disease-2019 (COVID-19) pandemic affects nearly every country, with more than 4.0 million confirmed cases and over 280,000 deaths. Although the majority of cases are mild disease (nearly 80%), the prognosis can be more severe; 20% of cases require hospital admission and approximately 5% require intensive care admission (1). The prognosis of COVID-19 is worse in older adults, men and comorbidities such as hypertension, diabetes, cardiovascular disease, malignancy, chronic kidney disease, or chronic obstructive pulmonary disease (2-4). Furthermore, abnormalities in certain laboratory tests, such as lymphocyte count, D-Dimer, ferritin, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and C-reactive protein (CRP) have been associated with the prognosis (5). However, there is still no exactly accepted test for predicting poor outcome and mortality.

The release of immature neutrophils into the bloodstream during infection or sepsis results in an increase in the immature granulocyte (IG)/total granulocyte ratio. This increase in IG rate is widely used in the clinical a diagnostic marker of infection or sepsis (6).

Studies have reported that IG rates are associated with disease severity and mortality related to sepsis or septic shock in patients with various infections such as bacteremia, pneumonia, and peritonitis (6,7). Moreover, recent studies have shown that IG is also associated with the severity and prognosis of non-

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infectious inflammation-related diseases such as acute upper gastrointestinal bleeding and pancreatitis (6,8-11).

The purpose of this study was to examine the relationship between IG values at the time of admission to the emergency department and the severity of the disease in COVID-19 patients and to evaluate the effectiveness of IG in predicting the poor outcome, including intensive careunit admission, ventilation support, and the first 28-day mortality in these patients.

Materials and Methods

The study was conducted prospectively and observationally at an urban hospital in the capital's largest district, with approximately 350.000 emergency room admissions annually, upon approval by the Keçiören Training and Research Hospital Local Ethics Committee (24.11.2020/2192). Polymerase chain reaction-confirmed COVID-19 cases that were over 18 years old were included in the study with an informed consent form. All oropharyngeal and nasopharyngeal swabs were collected at the emergency department. Demographic characteristics, comorbidities, hemodynamic conditions, laboratory and radiological data and 28-day clinical outcomes of patients were recorded on the registration form. Patients were divided into three groups according to the clinical severity indicators such as mild, moderate and severe. The group which was described as severe, consisted of patients with shortness of breath and 30/minute respiratory rate, ≤93% oxygen saturation at rest, PaO_2/FiO_2 ≤300 mmHg, intensive care and mechanical ventilation requirement and shock. Patients with high fever, respiratory symptoms, and radiological findings with pneumonia were included in the second group called "moderate." Besides these, patients with stable vital signs and no signs of pneumonia were classified as "mild." pregnancy, receiving blood transfusions, taking immunosuppressive or steroid medication treatment, having hematologic malignancies, or who had missing data were exclusion criteria for the study.

IG count was obtained from whole blood samples by using the DIFF scattergram method (Mindray BC-6800, China). Blood samples were collected in EDTA-coated tubes immediately after admission to the emergency department. Glucose, blood urea nitrogen (BUN), creatinine, AST, sodium, potassium, LDH, CRP, high sensitivity troponin I, D-Dimer, albumin, lactate levels, complete blood counts, blood gas levels, and erythrocyte sedimentation rates were analyzed in all cases.

Intensive care unit (ICU) admission, ventilation support–and death within the first 28 days after the admission were evaluated as composite outcomes.

Statistical Analysis

All data were analyzed by IBM Statistical Package for the Social Sciences Statistics for Mac, version 25.0 for Mac OS X (IBM Corp., Armonk, N.Y., USA). The normality of the data distribution was determined by the Shapiro-Wilk test, histogram, and Q-Q plots. The categorical values of the patients were expressed as a number and a percentage and were analyzed with a chi-square test. Continued values were presented as a mean and standard deviation or median values and an interquartile range (IQR) of 25-75%. The non-parametric values were analyzed using the Mann-Whitney U and Kruskal-Wallis tests. For post hoc analysis, new p-value level was calculated using Bonferroni correction. The 95% confidence intervals were also calculated when appropriate, and a p-value <0.05 was considered statistically significant.

Results

The study group consisted of 203 adults, of whom 91 (44.8%) were women. The median age of the cases was 61 (49-73), and it was 85 (41.9%) for cases who were over 65 years old. One hundred-one (49.8%) patients were febrile (has a measured body temperature over 38 °C) on admission to the hospital. The fever was the most common reason for hospital admission, followed by dyspnea in 96 patients (47.3%), muscle pain in 92 patients (45.3%), and weakness in 87 patients (42.9%). The most common comorbidities were hypertension in 87 patients (42.9%), diabetes mellitus in 43 patients (21.2%), and coronary heart disease in 40 patients (19.7%) (Table 1).

Laboratory tests determined the median (IQR 25-75) of CRP as 70.49 mg/L (17.37-117.88), D-dimer as 650 ng/mL FEU (340-1215), high sensitivity troponin I as 5.14 ng/L (2.5-19.09), and IG count as 0.01 (0.01-0.02).

According to the severity of the illness, 40 patients (19.7%) were classified as mild, 67 patients (33.0%) as moderate, and 96 patients (47.3%) as severe. The IG median values of the mild, moderate, and severe groups were 0.01 (0.00-0.02), 0.01 (0.01-0.02), and 0.015 (0.01-0.03) respectively. When comparing IG levels between the groups, no significant difference was found between patients with mild and moderate disease ($p=0.7$). There was a statistically significant difference between the mild and severe groups ($p=0.047$) and between the moderate and severe disease groups ($p=0.036$) (Figure 1).

Pneumonia was diagnosed using pulmonary tomography in 152 cases (87.9%). While 72 cases (35.5%) were discharged from the emergency department, 112 cases (55.2%) were hospitalized in various clinics and 19 cases (9.4%) were hospitalized in the ICU (Table 2).

Table 1. Demographic characteristics	
Age, years, median (IQR 25-75)	61 (49-73)
Age groups	**n (%)**
<65	118 (58.1%)
≥65	85 (41.9%)
Female gender n (%)	91 (44.8%)
Comorbidities	**n (%)**
Hypertension,	87 (42.9%)
Coronary heart disease	40 (19.7%)
Congestive heart failure	8 (3.9%)
Diabetes mellitus	43 (21.2%)
Chronic kidney disease	6 (3%)
Malignancy	4 (2%)
Using immunosuppressant	1 (0.5%)
Cerebrovascular disease	7 (3.4%)
Symptoms	**n (%)**
Fever	101 (49.8%)
Dyspnoea	96 (47.3%)
Headache	30 (14.3%)
Sore throat	12 (5.9%)
Muscle pain	92 (45.3%)
Weakness	87 (42.9%)
Loss of smell	4 (2%)
Loss of taste	4 (2%)
Nausea	32 (15.8%)
Vomiting	11 (5.4%)
Diarrhoea	20 (9.9%)
Haemoptysis	1 (0.5%)
Syncope	1 (0.5%)
Back pain	1 (0.5%)
Smoking	**n (%)**
No	86 (42.4%)
Yes, but left more than a year	49 (24.1%)
Yes	68 (33.5%)
Clinical severity	**n (%)**
Mild	40 (19.7%)
Moderate	67 (33.0%)
Severe	96 (47.3%)
Radiological data	
XR pneumonia identified	**n (%)**
CT pneumonia identified	13 (39.4%)
CT percentage of involvement, median (IQR 25-75)	152 (87.9%)
	25 (8-40)
CT percentage of involvement group	
0-25%	56 (29.2%)
25-50%	55 (28.6%)
50-75%	37 (19.3%)
75-100%	5 (2.6%)

IQR: Interquartile range, CT: Computed tomography

Considering the intensive care admission, ventilation support, and death as composite outcomes; there was a significant correlation between age, dyspnea at the time of admission, vital signs, renal and hepatic function tests, CRP, D-Dimer, troponin, albumin levels and the composite outcome. There was no statistically significant relationship between IG counts and the composite outcome ($p>0.05$) (Table 3).

Table 2. Emergency department treatments, respiratory support types, and emergency department outcome	
Emergency department treatments	**n** (%)
Favipiravir	132 (65%)
Steroid	75 (36.9%)
Anticoagulant	74 (36.5%)
Respiratory support types	**n (%)**
No requirement	93 (45.8%)
Nasal	20 (9.9%)
Mask	81 (39.9%)
HFNO	5 (2.5%)
CPAP	1 (0.5%)
IMV	3 (1.5%)
Emergency department outcome	**n (%)**
Discharge	72 (35.5%)
Hospitalized into the services	112 (55.2%)
Hospitalized into the intensive care	19 (9.4%)

HFNO: High flow nasal oxygen, CPAP: Continuous positive airway pressure, IMV: Invasive mechanical ventilation

Discussion

We have two main findings in this study, where we investigated the effectiveness of the IG count as a predictor of disease severity and poor outcomes in patients admitted to the emergency department with a diagnosis of COVID-19. First, we found a significant relationship between the total number of IGs and the severity of the disease. IG counts are significantly higher in patients with severe disease compared to mild and moderate patients. This suggests that it may be used as an indicator of the severity of the disease in the management of patients, as well as levels of CRP and D-Dimer. Although obtaining the IG count quickly from complete blood count without any additional cost is an advantageous aspect compared to other tests, we believe that studies with larger sample sizes are necessary because the level of statistical significance is close to the limit.

Secondly, we also found that there was no statistically significant relationship between IG count and the composite outcome consisting of ICU admission, ventilation support, and 28-day mortality. This finding differs from the previously published research findings on the relationships such as sepsis, pancreatitis, and gastrointestinal bleeding (6,8-10).

Under normal conditions, IG is not present in the peripheral bloodstream. The presence of IGs in peripheral blood shows that the bone marrow has been stimulated by infection, inflammation, or another stimulus. It has been reported that under inflammatory conditions (infection, sepsis vs.), elevation of IG counts was observed much more earlier than other widely used parameters such as CRP or white blood cell count and IG count could be used as an inflammatory marker (8). IG count was found to be substantially higher in inflammatory

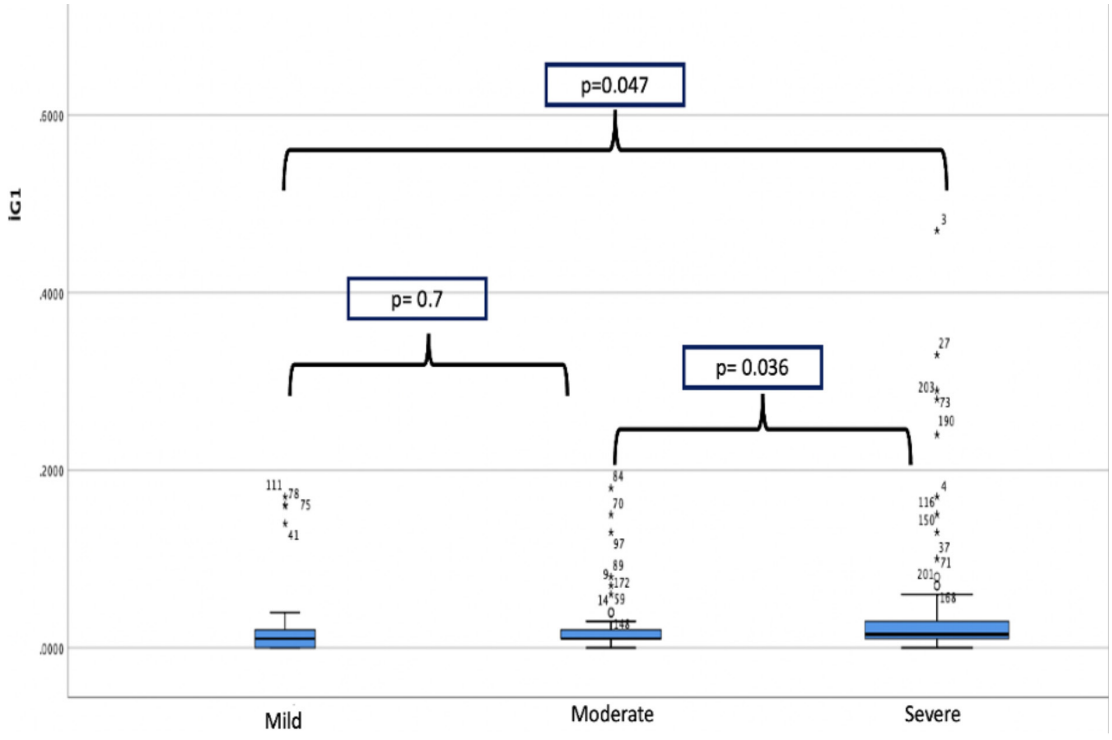

Figure 1. Relationship between immature granulocyte count and severity of the disease

conditions such as acute appendicitis, pancreatitis, liver abscess, and infective complications after cardiac surgery (8,11). It has also been documented that the IG count may be used as an independent mortality marker in patients with pancreatitis and gastrointestinal bleeding (9,10,12).

Even though the most common symptoms of COVID-19 are cough, fever, headache, myalgia and diarrhea. Dyspnea is the most common symptom in patients with serious illnesses and it is associated with hypoxemia. The severe disease picture is progressive, and the disease known as acute respiratory distress syndrome (ARDS) could lead to acute bilateral infiltration in the lungs, severe hypoxemia, heart failure, and unexplained pulmonary edema. Lymphopenia and thromboembolic complications could be commonly develop in these patients. Additionally, severe COVID-19 could cause severe organ damage like acute inflammation in, heart, kidney and liver (13). Therefore, it is extremely important to anticipate the fatal images that may occur and to guide the course of the disease with the measures to be taken.

Huang et al. (12) reported that elevated IG levels in patients with acute pancreatitis could be used to identify patients at high risk of ARDS early on, typically before admission to the ICU. It could be estimated that the assessment of IG level during the admission could reduce the aggravation of the disease by taking adequate measures. In our study, we examined whether IG levels during the admission could be a guide for composite outcomes such as ARDS, intubation and mechanical ventilation requirements in COVID-19 patients, we did not find a relationship between poor outcomes and IG levels, contrary to the findings of Huang et al. (12). However, in our study, IG levels were examined through blood samples that were taken during the hospital admission from the emergency department. The relationship between later the peak IG levels in the later days of patients, and mortality and poor outcomes were not investigated. Therefore, it is still uncertain whether IG count changes could be used for monitoring the prognoses of these patients.

In our study, we found a statistically significant relationship between the parameters defined as poor outcomes and age, including dyspnea during the admission, hypoxemia, abnormal platelet, lymphocyte, BUN, creatinine, AST, LDH, CRP, D-Dimer, troponin I, and albumin levels. Our findings are similar to the literature (3,13). Inflammation, coagulation disorders, and ultimately tissue hypoxia resulting from COVID-19 are among the leading causes of death. Hypercoagulability and tissue hypoxia due to decreased blood flow, which are observed in severe illness, may cause multiple organ failure and death. Older age is accepted as an independent risk factor for mortality (13). The results of our study show that death rates are higher in older people, in accordance with the literature.

Table 3. Factors influencing the composite outcome			
	No composite endpoints	**Composite endpoints exist**	**p value**
Male gender n (%) **Age** median (IQR 25-75)	80 (58.4%) 62.5 (52-72)	17 (65.4%) 72.5 (58.5-78)	0.714 **0.002**
Comorbidities n (%)			
Hypertension	63 (46%)	14 (53.8%)	0.462
Coronary heart disease	29 (21.2%)	7 (26.9%)	0.517
Congestive heart failure	5 (3.6%)	3 (11.5%)	0.117
Diabetes mellitus	29 (21.2%)	8 (21.6%)	0.284
Chronic kidney disease	3 (2.2%)	2 (7.7%)	0.180
Chronic obstructive pulmonary disease	15 (10.9%)	1 (6.3%)	0.472
Malignancy	3 (2.2%)	1 (3.8%)	0.504
Using immunosuppressant	0 (0%)	1 (3.8%)	N/A
Cerebrovascular disease	4 (2.9%)	1 (3.8%)	0.586
Symptoms n (%)			
Fever	67 (48.9%)	11 (42.3%)	0.470
Cough	79 (57.7%)	13 (50%)	0.953
Dyspnoea	73 (53.3%)	20 (76.9%)	**0.026**
Headache	15 (10.9%)	2 (7.7%)	1.000
Sore throat	4 (2.9%)	0 (0%)	N/A
Muscle pain	58 (42.3%)	11 (42.3%)	0.998
Weakness	61 (44.5%)	11 (42.3%)	0.835
Loss of smell and taste	1 (0.7%)	1 (3.8%)	0.294
Nausea	25 (18.2%)	1 (3.8%)	0.081
Vomiting	9 (6.6%)	0 (0%)	N/A
Diarrhoea	12 (8.8%)	3 (11.5%)	0.710
Haemoptysis	1 (0.7%)	0 (0%)	N/A
Vital signs median (IQR 25-75)			
Systolic blood pressure	136 (126-145)	140 (124-147)	0.509
Diastolic blood pressure	83 (70-89)	87 (67-93)	0.104
Pulse	95 (84-102)	101 (93-104)	**0.005**
RR	18 (16-22)	27 (17-30)	**0.001**
Fever	37.6 (36.8-38.1)	37.6 (36-37.8)	0.22
SPO_2	89 (83-94)	77 (50.25-88)	**<0.001**
Laboratory data median (IQR 25-75)			
Glucose	110 (97.5-164)	162 (120-489)	0.255
Urea	35.3 (24-50.9)	51.4 (36.4-125.8)	**0.007**
Creatinine	1 (0.82-1.18)	1.34 (1.07-1.66)	**0.001**
Sodium	136 (132-139)	135 (132-142)	0.293
Potassium	4.24 (4.0.8-4.7)	4.36 (3.89-5.22)	0.505
CRP	98.35 (40.1-130.4)	204.5 (100.4-256.8)	**<0.001**
D-Dimer	855 (465-1850)	1520 (763-3370)	**0.009**
Troponin I	8.82 (2.5-18.25)	46.2 (8.1-112.9)	**<0.001**
AST	34 (24-59)	51 (30-85)	**<0.001**

Table 3. Continued			
	No composite endpoints	**Composite endpoints exist**	**p value**
ALT	19.5 (13-32.5)	32.5 (15.5-49.5)	0.638
LDH	318 (234-459)	377 (324-701)	**0.006**
Albumin	3.4 (3-3.6)	3 (2.4-3.4)	**0.002**
WBC	6.15 (4.7-8.7)	7.9 (4.38-14.38)	0.331
Haemoglobin	13.5 (11.6-14.7)	12.7 (11.2-13.3)	0.055
Platelet	213.5 (164-311)	147 (99-245)	**0.013**
Lymphocyte	1.3 (0.8-2)	0.69 (0.39-1.64)	**0.002**
Neutrophil	4.38 (3.11-6.55)	6.25 (3.15-13.5)	0.068
pH	7.41 (7.34-7.44)	7.42 (7.36-7.44)	0.563
pCO_2	36.5 (33.6-42.7)	35.5 (30.6-40.9)	**0.033**
HCO_3	23.3 (20.7-26)	22.6 (20.3-24.2)	**0.008**
Lactate	1.9 (1.3-2.7)	2.15 (1.8-3.4)	0.05
Immature granulocyte	0.01 (0.01-0.02)	0.02 (0.003-0.03)	0.362
Immature granulocyte %	0.15 (0.0045-0.2)	0.1 (0.027-0.2)	0.347
Radiological data n (%)			
CT involvement **Severity** **0-25%** **25-50%** **50-75%** **75-100%**	 51 (39.8%) 47 (36.7%) 27 (21.1%) 0 (0%)	 3 (12%) 32 (36.0%) 9 (36%) 5 (3.3%)	**<0.001**
CT involvement percentage Median (IQR 25-75)	 12.50 (10-18.75)	 40 (26.25-60)	**<0.001**

IQR: Interquartile range, CT: Computed tomography, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein

Study Limitations

As our study was conducted only in patients who were admitted to the emergency department, the total number of moderate and severe cases was higher compared to the social distribution. Additionally, our study was conducted at a single center and with a limited sample size. Additionally, later IG levels and peak IG values of patients could not be obtained so the relationship between IG levels and the composite outcome, particularly mortality could not have beenanalyzed.

Conclusion

The IG level, which could be measured faster than other laboratory tests without any additional cost, could be used for the determination of the clinical severity of patients with COVID-19. However, we conclude that this parameter is not effective in determining poor outcomes during the admission, and more meaningful results could be obtained with repeated analyses of IG levels during the follow-up. Therefore, more comprehensive studies are necessary.

Ethics

Ethics Committee Approval: The study was approved by the Keçiören Training and Research Hospital Local Ethics Committee (24.11.2020/2192).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.Ç., Concept: Y.Ç., G.F.T., Design: Y.Ç., E.E., Data Collection or Processing: Y.Ç., F.N.K., Analysis or Interpretation: Ş.K.Ç., Literature Search: Y.Ç., F.N.K., Writing: Y.Ç., G.F.T., E.E.

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Retrospective Analysis of Bicycle Accidents at a Referral Pediatric Emergency Department: Mechanisms, Outcomes and Perspectives

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Abstract

Aim: We investigated the characteristics of patients involved in bicycle accidents, along with the mechanisms of accidents and clinical outcomes in children. Our secondary aim was to assess the characteristics of patients with serious clinical consequences, such as traumatic brain injury (TBI) and permanent neurological sequelae.

Materials and Methods: Children admitted to the pediatric emergency department of a tertiary referral hospital during a four-year period due to bicycle accidents were included. The mechanism of the accident was classified into two groups; high-energy trauma and low-energy trauma. Statistical analyses were performed to recognize injury patterns and clinical outcomes associated with the mechanism of the accident.

Results: Three hundred-sixty children were included. Two of the injured patients were using a bicycle helmet. Twenty-nine patients (8.1%) required surgery. Fourteen patients had clinically important TBI. Eighteen patients had handlebar trauma to the abdomen. Eight patients had permanent neurological sequelae (vision loss in three, hearing loss in three, spasticity and hemiparesis in two patients) and two patients had finger amputations. Abrasions/soft tissue injuries, scalp fractures, maxillofacial fractures and TBI were also significantly more common types of injury in high-energy trauma.

Conclusion: Although the recommendation of using helmets while riding was made two decades ago, the rate of helmet use is still very low in our country. In this retrospective cohort with low rate and no obligatory regulation of helmet use, high-energy bicycle accidents have caused significant clinical outcomes, including maxillofacial-scalp fractures, TBI, permanent sensory (visual and hearing) or motor (spasticity and hemiparesis) disability.

Keywords: Bicycle, children, traumatic brain injury, helmet, accident, disability

Introduction

Cycling is a popular activity among children for purposes of transportation, recreation and exercise. Bicycle accidents may result in mild injury, permanent disability, or even mortality. Children have a low awareness of traffic rules and a high tendency toward risky behavior. In the United States (US), bicycle injuries are among the leading causes of non-fatal injuries in children aged 5-17 years. Although bicycle-related deaths have decreased in children since 2001, children are still more prone to bicycle-related deaths than adults (1). In Turkey, 7,518 bicycle accidents occurred in 2017 (2.6% of all traffic accidents), resulting in 126 deaths (3.9% of deaths due to all traffic accidents) (2).

In children with trauma, while assessing trauma severity and making clinical decisions regarding the extent of diagnostic evaluation and patient disposition; the mechanism of accident, anamnesis and physical examination findings should be evaluated carefully (3). Because of their anatomical and physiological characteristics, children may suffer from serious injuries even when the mechanism of the accident seems to be low-risk. Bicycle accidents can occur with the mechanisms of falling off the bicycle, collision with stationary or moving objects, or vehicles (4).

Patients should be carefully evaluated because severe injuries may occur after bicycle accidents, such as blunt abdominal trauma involving bicycle handlebars or head trauma (5). The impact

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of the handlebar may cause injury to the abdominal organs, including the pancreas, duodenum, spleen or liver and to the scrotum (6). Head trauma may be complicated by craniofacial fractures, subdural, epidural, or cerebral hemorrhage and even clinically important traumatic brain injury (ciTBI) and mortality. Traumatic brain injury (TBI) is the leading cause of acquired disability in children. Wearing a helmet reduces the risk and severity of head injury (7). Colliding with a non-stationary motor vehicle while cycling has been associated with severe injuries among children (8). The patient's age, severity of injury, and the degree of structural injury are other factors associated with the neurological and cognitive sequelae of the accident (3,4). Orthopedic injuries mainly involve the clavicle, humerus and the forearm, whereas lower extremity fractures are rare. The most common indication of surgical intervention after bicycle accidents are orthopedic injuries (9).

Our clinical experience has made us concerned about the incidence and severity of bicycle injuries in our practice, especially because of the apparently low rate of helmet use, and the severe clinical consequences even in the absence of a collision with a motor vehicle. Documenting and analyzing the data on bicycle accidents, including the mechanism of the accident, can provide new perspectives into the evaluation and management of affected patients. In this study, we investigated the demographic and clinical characteristics of the patients, and the effect of the mechanism of bicycle accidents on the process of patient assessment and clinical outcomes. Our secondary aim was to assess the characteristics of patients with serious clinical consequences, such as TBI and permanent neurological sequelae.

Materials and Methods

Children (<18 years of age) who presented to the pediatric emergency department of our hospital during a four-year period (June 1, 2014 to May 31, 2018) due to a bicycle accident were included in the study. Patient-related information, including date, age, sex, trauma mechanisms, physical findings, injury localization and patterns, laboratory results, complications, consultations, treatment modalities, surgical interventions, intensive care unit admissions, duration of stay in the hospital and clinical outcomes, was recorded retrospectively using a data acquisition form.

The mechanism of bicycle accidents was classified into two groups, high-energy and low-energy injury mechanisms. Patients in these groups were compared in terms of injured anatomical region, injury type, interventions, disposition and length of stay characteristics.

Our pediatric emergency department cares for approximately 75,000 patients per year, and is part of a tertiary referral academic hospital. Patients are referred from all around the country, and all surgical specialties, and intensive care and operation room facilities are available.

Multiple trauma was defined as clear injury to two or more body areas of any severity (3). Being run over or struck by a motor vehicle, falling from a height with a bicycle, rolling down a cliff, hitting the wall while cycling fast, impingement of an extremity were included in the high-energy injury mechanism group (10). Other accidents were classified as low-energy injury mechanisms. ciTBI was defined as those which result in death, neurosurgical intervention, intubation for more than 24 h, or hospitalization for more than 48 h (11,12) The diagnosis of handlebar trauma was diagnosed according to the trauma mechanism, and the signs and symptoms of the patients.

The study was conducted in accordance with the principles of the Declaration of Helsinki and it was approved by the certified ethics board of the Hacettepe University, which waived the need for informed consent from the participants (approval date: 12.06.2018, approval number: GO 18/540).

Statistical Analysis

Statistical analyses were performed to recognize injury patterns and clinical outcomes associated with the mechanism of bicycle accident. Numerical measurements were presented with mean ± standard deviation, median and range, and qualitative data with numbers and percentages. Cross tables were used in the evaluation of associations between qualitative data. In comparing patients with high- vs. low-energy injury mechanisms, numerical values were analyzed with Student's t-test for parametric data, Mann-Whitney U test for non-parametric data and chi-square or Fisher's Exact tests for qualitative data, as appropriate. The Kolmogorov-Smirnov test was used for the normality distribution. Statistical significance was set as $p<0.05$. Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics 21 data editor software (IBM, Armonk, NY, USA).

Results

22,981 trauma patients were admitted to our pediatric emergency department during the four-year study period, 1,249 of whom were due to traffic accidents. Three-hundred-sixty children presenting with bicycle accidents were included. Their median age at presentation was 9.0 years (range: 1-17 years); 44.2% of whom were between 5 and 9 years of age. 29.4% of patients were classified as high-energy trauma mechanism. Two of the injured patients were using a bicycle helmet at the time of accident, one of whom was a 13-year-old male patient who sustained a medial malleolar fracture and required surgery after a collision with a

motor vehicle, while the other was an 8-year-old boy with minor soft tissue injuries in the extremities. General characteristics of the patients are summarized in Table 1.

At the time of presentation, 337/360 (93.6%) patients had at least one physical finding on physical examination. Eighty-nine (26.4 %) patients had injuries more than two anatomical sites. Injuries were most commonly in the extremities, followed by the head and neck. The most common types of injuries were abrasions and soft tissue swelling (202; 56.1%); 14 (3.8%) patients developed ciTBI. As for disposition and hospital stay, it was found that most patients were discharged from the emergency department and stayed in the hospital for less than 24 h (307 and 309 patients, respectively). Injury localization, patterns and clinical course of patients are provided in Table 2.

Handlebar trauma was diagnosed in 18 patients. All these patients were evaluated with pediatric surgical consultation and abdominal ultrasonography. Notable clinical characteristics and outcomes of these patients were as follows: spleen, kidney, liver laceration (one patient each), deep inguinal laceration sutured in the operating room (two patients), superficial inguinal hematoma (one patient), penile hematoma (one patient), large pubic ecchymosis (two patients), labial, penile and scrotal laceration (one patient each), open wound on abdominal wall (one patient), right periorbital hematoma (one patient), and optic nerve avulsion (one patient). Others reporting handlebar trauma had minor injuries.

The most common medical intervention was wound care and suture (199/360, 55.3%). Twenty nine patients required surgery. Orthopedic operations were the most common (15 patients). Other departments performing surgery were plastic and reconstructive surgery (eight patients), neurosurgery (three patients), pediatric surgery (two patients), otorhinolaryngology (one patient) and ophthalmology (one patient). Two patients had permanent sequela after finger amputation.

Fourteen patients were diagnosed with ciTBI, the details of whom are provided in Table 3. Twelve of 14 ciTBI had high-energy injury mechanism. Six of them were discharged with permanent neurological damage: Two patients had vision loss due to optic trauma, two had hearing loss due to temporal

Table 1. General characteristics of the patients (n=360)

Age* (years)	**9.0 (1-17)**
	n (%)
Age groups (years)	
0-1	5 (1.4)
1-4	41 (11.4)
5-9	159 (44.2)
10-14	117 (32.5)
15-17	38 (10.6)
Sex	
Female	70 (19.4)
Male	290 (80.6)
Mechanism of accident	
Motor vehicle accident	69 (19.1)
Falling off bicycle	242 (67.2)
Rolling downhill with bicycle	21 (5.8)
Falling down from a height with bicycle	16 (4.4)
Other	12 (3.3)
Mechanism of injury	
High-energy	106 (29.4)
Low-energy	254 (70.6)

*Median (range)

Table 2. Injury location, pattern and clinical course of patients (n=360)

Injured body region	**n (%)**
Multiple	89 (26.4)
Extremity	197 (58.5)
Head-neck	185 (54.9)
Trunk	48 (14.2)
Injury type	
Abrasion/soft tissue swelling	202 (56.1)
Laceration	117 (32.5)
Fractures	83 (23.1)
Extremity fracture	54 (15)
Scalp fracture	17 (4.7)
Maxillofacial fracture	12 (3.3)
ciTBI	14 (3.8)
Internal	9 (2.5)
Interventions	
Wound care and suture	199 (55.3)
Splint-cast	66 (18.3)
Surgery	29 (0.8)
Disposition	
Discharged from the emergency department	307 (85.3)
Hospitalization	40 (11.1)
PICU	11 (3.1)
Length of stay	
<24 hr	309 (85.8)
24-48 hr	12 (3.3)
>48 hr	39 (10.8)

ciTBI: Clinically important traumatic brain injury, PICU: Pediatric intensive care unit

Table 3. Clinical characteristics of the patients with clinically important traumatic brain injury

Age/sex	Accident mechanism	GCS on arrival	PTS	Vital signs	Cranial Imaging	Other notable findings	Interventions, disposition and clinical course	Clinical outcome
13, M	Rolling down a cliff with a bicycle	12	10	Unstable	Cranium base, sphenoid, temporal fracture; subarachnoid and extra axial hemorrhage	Femur fracture	Intubated in PED; PICU; operation by neurosurgery and orthopedic	Permanent vision loss
12, M	MVA	6	9	Unstable	Cranium base fracture; subarachnoid hemorrhage; diffuse axonal injury	-	Intubated in PED; PICU; operation by neurosurgery	Right hemiparesis
11, M	Falling off a bicycle	13	9	Stable	Epidural hematoma, mid-line shift	Diffuse abrasions	Ward; non-operative observation	No sequela
5, M	Falling down with a bicycle from a height	9	6	Unstable	Temporal, occipital, sphenoid fractures	Otorrhea and bleeding from the ear, pulmonary contusion and pneumothorax	Intubated in PED; PICU; non-operative observation	Hearing loss
13, F	MVA	8	6	Unstable	Temporal fracture; subarachnoid, extra axial hemorrhage; epidural hematoma; cerebral edema, diffuse axonal injury	Spleen laceration; rib fractures; pneumothorax; pulmonary contusion; humerus fracture	Intubated in PED; PICU; non-operative observation	Spastic motor deficiency
14, M	Falling off a bicycle	15	10	Stable	Parietal, temporal fracture; extra axial hemorrhage	Ear bleeding, clavicula fracture	Ward; non-operative observation	Hearing loss
16, M	Falling down with a bicycle from a height	15	10	Stable	Maxillary, orbital fracture; ethmoid and frontal sinus hemorrhage; retrobulbar air	Eye ecchymosis, loss of light reflex, traumatic ICA dissection; traumatic optic neuropathy	Ward; non-operative observation; medical treatment	Permanent vision loss
13, M	MVA	15	9	Unstable	Occipital fracture; intraparenchymal, subarachnoid hemorrhage	Arm fracture; pulmonary contusion; pneumothorax; spleen laceration; rib fracture	PICU; non-operative observation	No sequela
4, F	Falling down with a bicycle from a height	15	10	Stable	Frontal, orbital fractures	Diffuse abrasions; racoon eyes	Ward; non-operative observation	No sequela
6, M	Rolling down a cliff with a bicycle	15	10	Stable	Cranium base fracture; extra axial hemorrhage; pneumocephaly	Diffuse abrasions and lacerations	Ward; non-operative observation	No sequela
7, M	Falling down with a bicycle from a height	13	10	Unstable	Orbital, ethmoid fracture; intraparenchymal hemorrhage; extra axial hematoma; infraorbital emphysema	Racoon eyes	PICU; non-operative observation	No sequela

Table 3. Continued

Age/sex	Accident mechanism	GCS on arrival	PTS	Vital signs	Cranial Imaging	Other notable findings	Interventions, disposition and clinical course	Clinical outcome
9, F	Rolling down a cliff with a bicycle	13	9	Unstable	Temporal fracture; subarachnoid hemorrhage; pneumocephaly; cerebral edema	Bleeding from ear	PICU; non-operative observation	No sequela
11, M	Rolling down a cliff with a bicycle	14	9	Stable	Parietal, temporal fracture; epidural hematoma	Clavicula fracture	PICU; non-operative observation	No sequela
14, M	Falling off a bicycle	15	11	Stable	Temporal, orbital fracture; subarachnoid, extra axial hemorrhage; infraorbital air and bleeding	Retrograde amnesia	Ward; non-operative observation	No sequela

ciTBI: Clinically important traumatic brain injury, GCS: Glasgow coma scale, ICA: Internal carotid artery, F: Female, M: Male, MVA: Motorized vehicle accident, PED: Pediatric emergency department, PICU: Pediatric intensive care unite, PTS: Pediatric trauma score

bone damage, and two had hemiparesis and spasticity due to diffuse axonal injury. Clinical characteristics of the patients with ciTBI are provided in Table 3. Two patients sustained significant injuries to the sensory organs without ciTBI: one developed optic nerve avulsion and subsequent complete vision loss in the left eye following handlebar impact on the eye; and the other developed hearing loss due to mastoid fracture. There were no deaths during the study period.

The age of the patients in the high-energy trauma group was significantly higher than that in the low-energy trauma group, and there was no difference between the two groups in terms of gender distribution. In high-energy trauma, significantly more commonly affected anatomical areas compared to low-energy trauma were the extremities, head and neck, and multiple injuries. Abrasions/soft tissue swelling, scalp fractures, maxillofacial fractures and ciTBI were also significantly more common types of injuries in high-energy trauma ($p<0.05$). High-energy injuries required significantly more wound care and suture, but there were no significant differences in splint-cast or surgical operations in relation to the mechanism of accident. Patients with low-energy injuries were more frequently discharged from the emergency department, and within 24 h, whereas patients with high-energy injuries were more commonly admitted to the hospital or the pediatric intensive care unit. Clinical characteristics and outcomes with regard to the mechanism of the accident are shown in Table 4.

Discussion

In this study, most of the patients were male, the most common accident mechanism was falling off the bicycle and the most common surgical interventions were orthopedic; all in line with the previously published work on children (9). However, the most common age group involved in bicycle accidents was a different cohort, indicating a younger demographic compared to other studies (5-9 vs. 10-14 years) (8,9). The main finding of this study, performed in a cohort of patients usually not using helmets during cycling, was the demonstrate that in high-energy mechanisms such as motor vehicle accidents, hitting a wall, or rolling down a cliff, children may suffer from ciTBI and permanent neurological disability.

The most common injuries related to bicycle accidents are soft tissue injuries; however, fractures, abdominal injuries and TBI cause emergency admissions and hospitalization (13). TBI and maxillofacial injuries are common in children who do not use helmets; emergency management is important as these can lead to death and permanent disability. Both individual and environmental precautions should be taken together in the prevention of bicycle accidents (13). In a large recent study on 2,219 patients aged five and 17 years old who were treated in emergency departments in the US for injuries after bicycle accidents between 2006 and 2015, it was reported that collisions with a motor vehicle was a factor associated with TBI and injury-related hospitalization (9). The same study also demonstrated that using a helmet decreased hospital admissions and craniocervical injuries (9). In our study, severe clinical outcomes were also observed with mechanisms other than a collision with a motor vehicle. In our country, using a helmet while cycling is not widespread, and not required by law. Consequently, the vast majority of the patients included in our study were not using a helmet, except for two. Since there were too few patients using

Table 4. Clinical characteristics and outcomes with regard to the mechanism of the accident

	High-energy n=106 (%)	Low-energy n=254 (%)	p
Age*	10.0 (1-17)	9.0 (1-17)	0.001
Sex (male)	200 (78.7)	90 (35.4)	0.178
Injured anatomic region			
Multiple	53 (52.4)	36 (15.2)	<0.001
Extremity	73 (72.2)	124 (52.5)	0.001
Head-neck	69 (68.3)	116 (49.1)	0.001
Trunk	15 (14.8)	33 (13.9)	0.834
Injury type			
Abrasion/soft tissue swelling	69 (68.3)	133 (56.3)	0.027
Laceration	35 (34.6)	82 (34.7)	0.892
Extremity fracture	15 (14.8)	39 (16.5)	0.771
Scalp fracture	14 (13.8)	6 (2.5)	<0.001
Maxillofacial fracture	14 (13.8)	4 (0.1)	<0.001
ciTBI	12 (11.8)	2 (0.1)	<0.001
Internal	5 (4.9)	4 (0.1)	0.082
Interventions			
Wound care and sutures	70 (69.3)	129 (54.6)	0.008
Splint-cast	23 (22.7)	43 (18.2)	0.286
Surgery	8 (7.9)	21 (0.8)	0.819
Disposition			
Discharged from the emergency department	83 (82.1)	226 (95.7)	0.008
Hospitalization	12 (11.3)	28 (11.8)	0.008
PICU	11 (10.8)	0	<0.001
Length of stay			
<24 h	83 (82.1)	226 (95.7)	0.008
24-48 hr	3 (2.9)	9 (0.3)	0.731
>48 h	20 (19.8)	19 (0.8)	0.002

*Median (range).
ciTBI: Clinically important traumatic brain injury, PICU: Pediatric intensive care unit

helmets, the association of ciTBI or permanent neurologic sequela with helmet use could not be analyzed. However, the need to wear protective gear to prevent/attenuate head injuries is not new. Previous studies with large numbers of participants have clearly demonstrated that wearing a helmet can reduce cranial injuries, as per the recommendations of the American Academy of Pediatrics (AAP) (14,15). Studies have shown that helmets decrease head, brain and serious brain injuries by 63-88% and prevent upper- and mid-facial trauma by 65% (16). Regardless of the age of the patient or the type of crash, helmets can reduce craniofacial injuries in bicycle accidents (17). In countries such as Australia, New Zealand and Finland, the law requires the use of a helmet while riding a bicycle. In a population-based study conducted in a state where there is no helmet law in the US, it was stated that the use of helmet is rare and causes severe consequences (18). In our study, there were patients with severe clinical consequences, such as TBI, permanent visual loss, permanent hearing loss, spasticity and hemiparesis. In patients with motor deficit diffuse axonal damage; in patients who developed vision and hearing loss, fractures in the skull bones (especially temporal fracture in hearing loss) were detected. There are publications in the literature reporting hearing loss due to temporal bone fracture in bicycle accidents in children (19,20). None of these patients were wearing a helmet at the time of the accident. Considering that helmet use reduces the risk and severity of head trauma, it can be argued that clinical outcomes would have been better if these patients had used helmets.

Twenty-nine percent of patients were injured by a high-energy mechanism. Although helpful as an initial guide, mechanism alone is not a highly accurate predictor of the risk of sustaining significant injuries (3). Physiological parameters (pupils, blood pressure, respiratory rate, heart rate, etc.) that are quickly and easily accessible have great importance in the assessment of patient stability. The decision of immediate intervention (intravenous bolus hydration, intubation etc.) was made according to the physiological findings of our patients who were diagnosed with ciTBI among the patients in our study group. The fact that two patients with ciTBI were in the low-energy group (falling off the bicycle) underlines that the mechanism of accident alone is not an adequate indicator of the assessment and management of pediatric trauma patients. Similarly, patients with mild physical findings and normal physiological parameters were present also in the high-energy mechanism group.

Cycling accidents most commonly affect the upper extremities, followed by the lower extremities, face, head and neck (9). Extremity injuries were common in our study (58.5%), ranging from strains to open fractures. Considering that the extremities are the most commonly affected areas after bicycle accidents, soft tissue injuries amenable to simple medical interventions and fractures of long bones, which may require surgery account for most of the injuries. Both the American Association of Orthopedic Surgeons and the AAP recommend not only helmets, but also extremity-protecting gear while skateboarding (17,21). Similar protective wear may decrease extremity injuries in bicycle accidents.

The impact with bicycle handlebars is an important mechanism to consider. Eighteen patients in this study reported handlebar

trauma, who had a wide array of injuries ranging from inguinal bruising to splenic rupture. Three patients had internal injuries (spleen, liver and kidney laceration), and one suffered from permanent vision loss due to optic nerve avulsion caused by handlebar trauma. This mechanism of vision loss has been reported in only a few cases (22,23). A significant characteristic of handlebar traumas is their propensity to cause a rapidly worsening clinical course (within hours) in the absence of abnormal physical examination findings at the initial evaluation (24). The accuracy of the history of the mechanism of accident taken from the child may vary, depending on the age, pain, anxiety and clinical status of the child. Therefore, the trauma caused by bicycle handlebars cannot be excluded by history alone, especially if the accident was not witnessed by an adult. To prevent abdominal trauma caused by bicycle handlebars, bicycle models with retractable handlebars and wearing protective abdominal pads should be encouraged (25).

Study Limitations

This study is limited by its retrospective nature. Data regarding the mechanisms of accident and the parameters at admission were retrieved from anamnesis and consultation forms. Although it was based in a single centre, it does reflect the experience of one of the largest pediatric trauma centres in the country. The lack of long-term assessment of outcomes is a limitation of the study since the neuropsychological evaluation was not universally performed in follow-up.

Conclusion

Although the recommendation of using helmets while riding was made two decades ago, the rate of helmet use is still very low in our country. In this retrospective cohort with low rate and no obligatory regulation of helmet use, high-energy bicycle accidents have caused significant clinical outcomes, including maxillofacial and scalp fractures, TBI, and permanent sensory (visual and hearing) or motor (spasticity and hemiparesis) disability.

Ethics

Ethics Committee Approval: The study were approved by the Hacettepe University of Local Ethics Committee (approval date: 12.06.2018, approval number: GO 18/540).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: L.A.Y., Ö.T., Design: L.A.Y., A.T., Ö.T., Data Collection or Processing: L.A.Y., A.T., Analysis or Interpretation: L.A.Y., Literature Search: L.A.Y., A.T., Writing: L.A.Y., Ö.T.

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A Pilot Study of Inhaled Low-dose Methoxyflurane to Support Cunningham Reduction of Anterior Shoulder Dislocation

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Abstract

Aim: The Cunningham method allows for the reduction of anterior shoulder dislocations (ASD) without procedural sedation and analgesia (PSA) in some patients. This pilot study evaluates the feasibility of investigating whether the administration of inhaled methoxyflurane (I-MEOF) increases the success rate of Cunningham reduction of ASD.

Materials and Methods: Twenty patients with uncomplicated ASD underwent reduction attempts using the Cunningham method supported by I-MEOF analgesia (Cunningham/I-MEOF). Outcomes included the success rate without the requirement for PSA, emergency department length of stay (LOS), and operator and patient satisfaction.

Results: Of the patients enrolled. 80% were male, median age was 38.6 years (range 18-71) and 55% were the first dislocations. 35% (8/20 patients) were successfully reduced using Cunningham/I-MEOF. The remainder of patients proceeded to successful closed reduction under PSA. 60% of operators reported good to excellent satisfaction with the process. Operators identified the primary cause of failed initial reduction attempts as inadequate muscle relaxation. 80% of patients reported good to excellent satisfaction. Patients whose initial reduction attempt with Cunningham/I-MEOF was successful had an average LOS of 149 min, compared with 216 min for those who proceeded to reduction under PSA.

Conclusion: Success with ASD reduction by the Cunningham technique was marginally increased with the use of I-MEOF, although 65% of patients still required PSA to facilitate reduction. Both providers and patients found the process generally satisfactory, suggesting that early administration of analgesia is appreciated.

Keywords: Methoxyflurane, Cunningham, reduction, shoulder, dislocation

Introduction

Shoulder dislocations comprise 60% of major joint dislocations, 95% of these being anterior shoulder dislocations (ASD) (1). ASD is a medical emergency; treatment involves the reduction to a normal anatomical position as soon as possible, to manage pain and disability and to minimize the chance of poor long-term outcome. It has been reported that from the time of arrival in the emergency department (ED) with an ASD, every 10 min delay in the reduction attempt increased the odds of a failed reduction attempt by 19% (2).

Numerous methods exist to effect reduction (3), most of which are conducted under procedural sedation and analgesia (PSA) that allows the shoulder muscles to relax so that they do not hold the humeral head in a dislocated position. PSA involves administrating intravenous sedatives and narcotic analgesics that carry the risk of respiratory depression and hypotension (4). In the specific population of patients with ASD, the successful reduction of the dislocation to its normal position, immediately removes the painful stimulus that had antagonized the respiratory depression of the sedative and analgesic agents; often resulting in an unopposed respiratory depression that might be unrecognized

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as the crisis appears to have been solved with the restoration of the anatomy of the shoulder joint. The process of PSA thus requires both time and human resources to conduct, with specific expertise of caregivers skilled in the use of the medications and in the resuscitation and support of people who unexpectedly experience adverse events (4).

An ability to reduce even a portion of ASD humanely and efficiently without PSA would be a great advantage to the field of emergency medicine.

Several novel reduction methods for ASD have been described. One such method, the Cunningham technique (5,6) entails the massaging of the shoulder muscles in an attempt to get sufficiently relaxation to painlessly allow reduction without the inconvenience and risks of PSA. Unfortunately, although the method can work, and has been associated with decreased need for PSA, use of the Cunningham method has been limited by success rates as low as 27% (6). Moreover, although described as painless, it is not always so (7) which further limits its routine use. After unsuccessful attempts using the Cunningham technique, the fallback is generally to then provide PSA, increasing the time, and potential pain involved before eventual reduction.

Inhaled methoxyflurane (I-MEOF) offers a rapidly administered, minimally invasive option for short-term analgesia, and has been used to assist shoulder reduction (8). It has also been shown to decrease the length of stay within the ED and provide effective pain relief for patients (9). This pilot study evaluated the feasibility of investigating whether I-MEOF analgesia improves the process and success rate of ASD reduction using the Cunningham method.

Materials and Methods

At the Charles V. Keating Emergency and Trauma Centre, an academic ED where specially trained critical care paramedics are responsible for administering PSA (4), a consecutive sample of 20 patients, identified as having suffered an uncomplicated ASD was given the option of a first reduction attempt using the Cunningham method supported by I-MEOF analgesia (Cunningham/I-MEOF). Emergency physician operators, all of whom had had shown a series of videos demonstrating the Cunningham reduction method, were instructed to limit their initial reduction attempt to the Cunningham method. No other analgesics were used in the initial attempt. The attempt was considered successful if the reduction was achieved within 15 minutes and no other reduction methods, adjuvant analgesics or intravenous PSA were administered. If the reduction was not achieved, standard PSA was conducted. Outcomes measured at the time of discharge included initial success rate, subjective patient and operator satisfaction with the procedure on a scale of 1-5, with 5 representing 'excellent' satisfaction and 1 being 'poor', and ED length of stay (LOS) measured as time from initial registration to discharge from the ED. Institutional ethics approval was obtained. The study was supported by an unrestricted grant from Perdue Pharma, makers of I-MEOF (Penthrox^{R}).

Statistical Analysis

We recorded percentages of patients who achieved successful reduction under I-MEOF and those that subsequently received reduction under PSA.

Results

Twenty patients with ASD were approached, and all gave informed consent for a trial of a reduction attempt with Cunningham/I-MEOF. 80% were male, with a median age of 38.6 years (range 18-71). 60% were first-time dislocations. The Cunningham/I-MEOF approach was successful in 35% (7/20 patients), with a slightly better success rate in patients who had suffered a previous ASD (0.42 vs. 0.33). The remainder (13/20) proceeded to closed reduction under PSA (individual patient outcomes displayed in Table 1).

All patients had eventual successful closed reduction of ASD in the ED. 60% of operators reported good to excellent (4-5/5) satisfaction with Cunningham/I-MEOF, with inadequate muscle relaxation identified as the primary cause of failed initial reduction attempts. 80% of patients reported good to excellent (4-5/5) satisfaction with the process, although this decreased from 100% in successful cases to 69% for those proceeding to PSA.

Patients whose initial reduction attempt with Cunningham/I-MEOF was successful had an average and median ED LOS of 149 and 120 min, respectively, versus 216 and 178 min for those who proceeded to reduction under PSA. In the 12 months before this study, 169 patients presented with shoulder dislocations, with an average and median LOS of 229 and 186 min, respectively.

Discussion

Reported success rates with the Cunningham technique are low. Even with the addition of I-MEOF analgesia, our success rate of 35% was only marginally better than the 27% reported by Gudmundsson and Bjornsson (6). Although success was not significantly improved by adding I-MEOF, the Cunningham/I-MEOF approach was generally satisfactory for both providers and patients, suggesting that the early administration of analgesia for ASD is appreciated. Moreover, one-third of patients achieved atraumatic reduction using this approach and did not require PSA and in patients who did subsequently require PSA, 69% still

Table 1. Individual patient demographics and outcomes

Age	Gender	Previous ASD	Cunningham/I-MEOF success	Patient satisfaction of procedure	Reducer's opinion of procedure	LOS (min)
65	M	Yes	No	Very good	Poor	214
63	F	No	No	Excellent	Very good	117
18	M	No	Yes	Very good	Very good	201
58	F	No	No	Good	Good	361
68	F	No	No	Excellent	Excellent	164
21	M	No	No	Very good	Fair	153
28	M	Yes	Yes	Very good	Very good	81
44	M	No	No	Excellent	Good	94
20	M	No	Yes	Excellent	Excellent	238
21	M	Yes	No	Fair	Poor	120
32	M	Yes	No	Very good	Poor	108
30	M	No	No	Fair	Poor	282
50	F	Yes	No	Poor	Poor	134
27	M	No	Yes	Very good	Excellent	2.88
21	M	Yes	No	Very good	Very good	2.97
21	M	Yes	Yes	Excellent	Excellent	2.00
24	M	Yes	Yes	Good	Excellent	113
20	M	No	Yes	Excellent	Excellent	118
68	M	No	No	Fair	Fair	582
71	M	No	No	Excellent	Fair	199

ASD: Anterior shoulder dislocations, I-MEOF: Inhaled methoxyflurane

reported good to excellent satisfaction. Although we found a higher incidence of success in those with previous ASD (0.42 vs. 0.33), our numbers are too small to conclude in this regard.

The LOS for patients successfully reduced with Cunningham/I-MEOF was 67 min shorter compared to those subsequently requiring PSA. As the LOS in the latter group included the initial reduction attempt under I-MEOF, we also compared LOS in patients with ASD treated in the 12 months before the study period. The average LOS for study patients who required PSA was 13 min shorter than that for patients treated in the previous year. This finding is likely explained by the Hawthorne effect as study enrollment likely improved ED flow for all patients with ASD. Similarly, the LOS for patients with successful Cunningham/I-MEOF reductions may also have been shorter simply because they were enrolled in a study.

In a retrospective chart review, Umana et al. (8) reported that 30 of 152 patients with ASD underwent a reduction attempt using I-MEOF with a success rate of 80%, and a shorter LOS for those successfully reduced with I-MEOF. In their study, the selection of analgesia (I-MEOF or propofol), as well as the reduction technique, was at the discretion of the attending EP. The high success rate reported with I-MEOF-facilitated reductions is likely because EPs could identify and select patients less likely to require PSA (20% of all patients with ASD in their study). 16% of patients presenting during their study period achieved ASD reduction under I-MEOF, suggesting a greater opportunity to avoid PSA had they applied a first attempt at I-MEOF-assisted reduction to all patients (5).

One reason for the limited application of ASD reduction attempts without PSA may be concerned about exposing patients to unnecessary pain. Our findings suggest that the use of I-MEOF appears to manage the pain of reduction attempts even when they are subsequently found to be unsuccessful. Our findings suggest that an attempt at atraumatic reduction under I-MEOF is a reasonable first step in managing ASD.

Another inhalational analgesic that has been described for ASD reduction is nitrous oxide (NO). A study published in 2011 showed the successful reduction of only 10% of the cases using NO compared to 80% with PSA. The use of NO was also associated with increased side effects (80% vs. 8.4% with PSA) and a significant decrease in patient satisfaction (10).

Study Limitations

The aim of this pilot study was to test the feasibility of studying this approach to ASD reduction, and our findings are limited by the small sample size, the specification of a single atraumatic method and a non-randomized study design, which allows for the possibility of a significant placebo effect. Our findings should not, therefore be considered definitive evidence. The Cunningham method was selected because it is most familiar to EPs in our ED. There may have been a significant variation in operator comfort and experience with this method, which may have affected our success rate. Published experience with this technique is limited and some authors have expressed concern that the method is not as painless as initially reported. It is possible that different atraumatic reduction methods (11-13) assisted by I-MEOF may be more successful.

Larger, randomized studies may identify patient characteristics that make the Cunningham technique and other atraumatic reduction methods more likely to be successful. Further studies may also determine whether I-MEOF can be used to facilitate the reduction by methods previously believed to require PSA.

Conclusion

The addition of I-MEOF analgesia to the Cunningham method for reducing ASD does not appear to increase success rates, although the pain of unsuccessful attempts appears to be well controlled. The use of I-MEOF to support the first attempt at ASD reduction appears reasonable and does not seem to increase ED LOS.

Ethics

Ethics Committee Approval: The study was approved by the Nova Scotia Health Authority Research Ethics Board (protocol number: 1024125, date: 15.04.2019).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.C., H.W., R.F., C.C., S.T., P.H., A.S., Concept: S.C., C.C., A.S., Design: S.C., A.S., Data Collection or Processing: S.C., H.W., R.F., C.C., S.T., P.H., A.S., Analysis or Interpretation: S.C., H.W., R.F., C.C., S.T., P.H., A.S., Literature Search: S.C., C.C., A.S., Writing: S.C.

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Diagnostic Value of S100B and Neuron-specific Enolase in Distinguishing Acute Central and Peripheral Vertigo

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Abstract

Aim: Vertigo is a common presenting complaint to the emergency department (ED). Distinguishing between acute central and peripheral vertigo can be challenging. During recent years, several biomarkers have been introduced for use in distinguishing central and peripheral vertigo. The current study determined whether S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE) serum concentrations could effectively predict the central causes of vertigo.

Materials and Methods: This was a prospective study performed on 117 patients with acute vertigo who were admitted to the ED. All patients underwent magnetic resonance imaging (MRI) and the results of the MRI were considered the gold standard. S100B and NSE from blood samples taken <8 h after the onset of symptoms were measured in all patients.

Results: Finally, 117 patients were enrolled in the study, of which 43 patients had central vertigo and 74 patients had peripheral vertigo. The serum levels of S100B and NSE in the central group were significantly higher (60.62 vs 28.01 pg/mL, and 11.86 vs 7 ng/mL, $p<0.001$, respectively). The receiver-operating characteristic analysis demonstrated an AUC of 0.91 [95% confidence interval (CI): 0.84-0.96] and 0.93 (95% CI: 0.87-0.97) for S100B and NSE for predicting central vertigo and reported a sensitivity of 97.7% and 93% and a specificity of 87.8% and 89.2% for detecting the central cause of vertigo with S100B and NSE.

Conclusion: The serum S100B and NSE concentrations in central vertigo were significantly higher, and could be useful markers in screening central from peripheral vertigo in the ED.

Keywords: Neuron-specific enolase, S100B, central vertigo, peripheral vertigo, emergency department

Introduction

Dizziness and vertigo are the most common chief complaints referred to the emergency department (ED), with a prevalence of 1.8% among young adults and more than 30% in the elderly (1,2). Among patients with acute vertigo and dizziness, about 25% have a potentially life-threatening condition, such as a stroke in 4-15% (1,3).

Although vertigo does not usually increase the risk of death, it can affect the quality of life. Central vertigo is the cause of dizziness in approximately one-fourth of patients who experience dizziness (2). Therefore, we need a reliable, safe, and cost-effective method to differentiate between central and peripheral vertigo in the ED (4).

Cerebrovascular diseases such as transient ischemic attack or stroke, cerebellopontine angle tumor (i.e., acoustic neuroma), multiple sclerosis, neurodegenerative disorders, and migraine are the most common central causes of vertigo (5,6). In one case series on fifteen cases of misdiagnosed cerebellar infarction, half of the patients were less than 50 years old, had 40% overall mortality and had disabled deficits in about 50% of all survivors (7).

Brain imaging in patients with acute-onset vertigo is indicated in the following cases: in patients with vertigo that begin suddenly

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and the patient is suspected of having central causes of vertigo, or the patient has signs or symptoms of brainstem dysfunction or the patient cannot stand or walk. Magnetic resonance imaging (MRI) with diffusion weighting (DWI), which reliably detects new infarcts, is the modality of choice (8). DWI is widely considered an important imaging sequence for detecting various brain lesions, especially in the diagnosis of infarct lesions.

Although brain computed tomography (CT) is widely used in the ED setting to rule out potentially life-threatening disorders in patients whose examination is not completely typical of a peripheral vestibulopathy, it is significantly less sensitive in the assessment of a patient in the early phase of infarction, and in subjects with lacunar or posterior fossa infarction and for pathologies affecting the brainstem or vestibular nerve. Therefore, the diagnostic efficiency of brain CT was low in isolated vertigo (9,10). Biomarkers help distinguish central and peripheral vertigo and provide a strategy for identifying a subset of patients for MRI (11-13). Serum biomarkers are useful for distinguishing central from peripheral vertigo because of their association with the cause of central vertigo (11-13). MRI is not always available or cost-effective (14). Biomarkers are a strategy for identifying a subset of patients in need of MRI (12,13).

Neuron-specific enolase (NSE), a neuronal form of the glycolytic enzyme enolase, and the S100 calcium-binding protein B (S100B), a glial cytoplasmic protein, have been studied as useful biochemical markers to indicate brain damage observed under conditions such as head injury, cerebral infarction, cardiac arrest, and heart surgery (11).

Few studies have examined S100B and NSE in subjects with acute vertigo in the ED to differentiate peripheral from central vertigo (12-14). These biomarkers can be effective for emergency physicians in identifying the need for neuroimaging.

This study investigated the screening values of S100B and NSE in distinguishing central from peripheral causes of acute-onset vertigo in the ED.

Materials and Methods

Study Design

This prospective cross-sectional study was performed between January 2015 and March 2016 in the adult ED of Al-Zahra and Kashani Hospitals in Isfahan, Iran. The study was approved with Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.REC.1394.3.049) the and informed consent was obtained from each subject.

Study Setting and Population

Adult patients (>18 years) with the chief complaint of acute-onset vertigo who presented to the ED within 8 h of the onset of symptoms and signed a consent form to participate were eligible for the study.

Patients who had a previous history of vertigo and known cranial or auditory system disorders and a history of recent head trauma or malignancies were excluded. Patients with any persistent neurological deficits at admission and with contraindications for performing MRI were also excluded.

Study Protocol

All participants were examined by an Emergency Medicine Specialist at their arrival and the medical history, examination, and electrocardiograms of each patient were obtained. After the initial evaluation, blood samples for NSE and S100B levels were taken by a trained research assistant nurse at the same venipuncture that was used to measure hemoglobin and electrolytes.

Then brain diffusion-weighted MRI (DWI) was performed for all patients. A radiologist who was blinded to the biomarker results interpreted the MRI.

The patients with abnormal MRI findings related to central vertigo were in the central group, and the others were in the peripheral group. Biomarker levels were compared between the two groups. Emergency care has not been modified in this study. Figure 1 shows a flow chart of the study.

Biomarker Assessments

Peripheral venous blood (10 mL) from the patients with vertigo was sampled in plain tubes containing separation gels. The sampled blood was allowed to clot for 30 min and then centrifuged at 2,500 rotations per minute for 10 min. Serum samples were diluted with 1 mL of distilled water and then transferred to test tubes. The serum was frozen and then stored at -20 °C until further testing.

Electrochemiluminescence immunoassay was used to detect the NSE and S100B proteins serum levels. S100B and NSE levels were measured using a commercial kit (Elecsys® analyzer, Roche Diagnostics, Mannheim, Germany).

Results for NSE and S100B are expressed as nanogram per milliliter (ng/mL) and picograms per milliliter (pg/mL), respectively. Laboratory personnel were blinded to imaging findings and baseline characteristics of the patients.

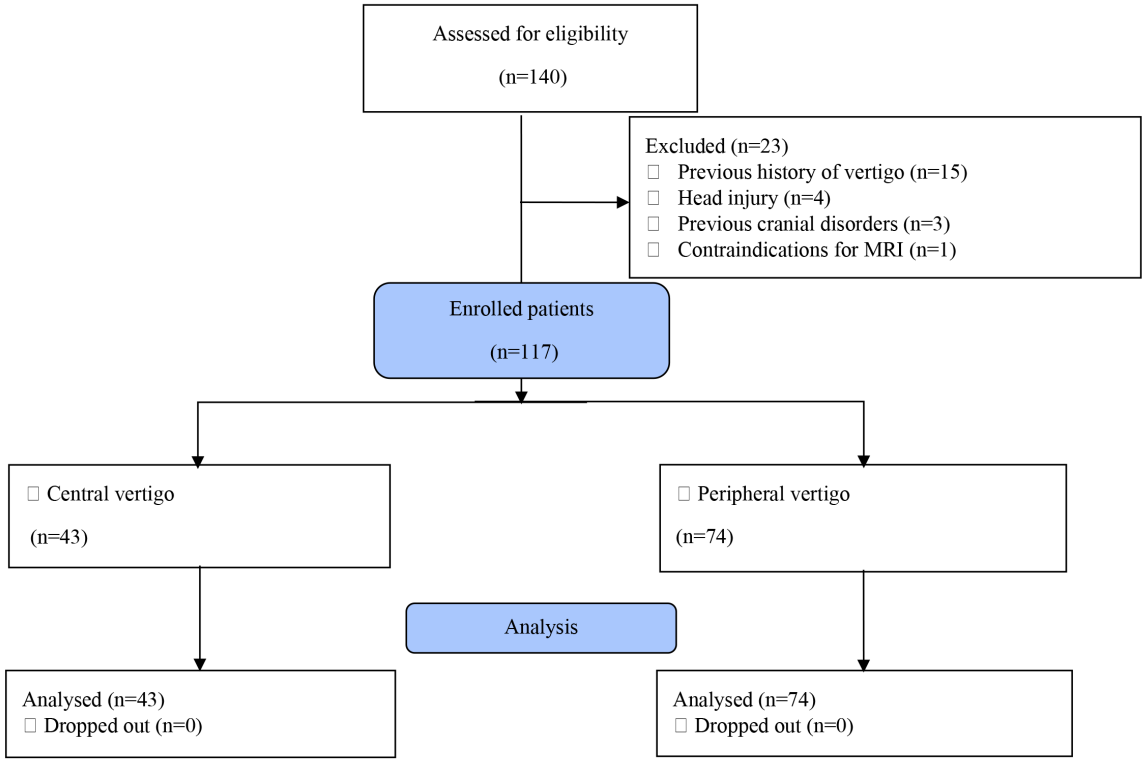

Figure 1. Study flowchart
MRI: Magnetic resonance imaging

Statistical Analysis

Data analysis was performed using the IBM Statistical Package for the Social Sciences software (version 22, NY, USA). Kolmogorov-Smirnov test was performed to check the normal distribution of variables. The chi-square test was used for the comparisons between qualitative variables. Student's t-test and paired t-test were performed for normally distributed variables, and Mann-Whitney and Wilcoxon tests were used for nonparametric data. Receiver-operating characteristic (ROC) analysis was performed to predict the accuracy with 95% confidence interval (CI) of each serum biomarker for differentiating central and peripheral vertigo. The cut values of serum NSE and S100B were calculated according to Youden's index. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Out of 140 eligible patients, 117 subjects with acute-onset vertigo were finally enrolled in the study. Of them, 43 (36.8%) had MRI findings related to central causes of vertigo (placed in the central group) and the MRI findings didn't indicate the central causes of vertigo in 74 (63.2%) patients (placed in the peripheral group). Of the 43 patients with central causes of vertigo, 31 had an acute infarct of posterior circulation, 8 had an ischemic attack of the brainstem due to vertebrobasilar insufficiency, 3 had a cerebellar hemorrhage, and one patient had a cerebellar mass. Serum biomarker levels were not significantly different between these subgroups.

The mean age of the patients was 53.72±11.86 years in the peripheral group and 55.62±10.43 years in the central group. There was no statistically significant difference between the two groups in terms of age, gender, and vital signs ($p>0.05$). The baseline characteristics of the subjects are reported in Table 1.

The S100B serum levels in the central and peripheral groups were 60.62±10.63 pg/mL and 28.01±8.16 pg/mL. The serum level of NSE was 11.86±2.01 ng/mL for the central group and 7.00±1.47 ng/mL for the peripheral group. The serum levels of NSE and S100B in the central group were statistically significantly higher than those in the peripheral group ($p<0.001$).

Serum levels of NSE and S100B were good biomarkers for differentiating central and peripheral vertigo with the sensitivity of 93.0% and 97.7%, the specificity of 89.2% and 87.8%, the PPV of 83.3% and 82.4%, the NPV of 95.7%, and 98.5%, and overall

Table 1. The baseline characteristics in acute vertigo patients				
Group variables		**Brain MRI findings**		**p value**
		Peripheral vertigo (n=74)	**Central vertigo (n=43)**	
Age (year)		53.72±11.86	55.62±10.43	0.43
Sex (male)		35 (47.3%)	24 (55.8%)	0.45
Vital signs	Systolic blood pressure (mmHg)	143.7±26.8	150.6±28.5	0.323
	Diastolic blood pressure (mmHg)	82.4±16.2	82.5±21.3	0.928
	Pulse rate (/minute)	84.5±14.1	81.1±15.3	0.311
	Respiratory rate (/minute)	17.27±2.26	17.01±1.58	0.423
	Peripheral oxygen saturation (%)	98.6±2.1	98.7±2.2	0.756
Biomarker level	S100B (pg/mL)	28.01±8.16	60.62±10.63	<0.001
	Neuron specific enolase (ng/mL)	7±1.47	11.86±2.01	<0.001

Values are expressed as the mean ± standard deviation or number (%).
S100B: S100 calcium-binding protein B, MRI: Magnetic resonance imaging

Table 2. Diagnostic value of S100B and NSE in distinguishing central from peripheral vertigo		
Variables	**S100B**	**NSE**
True positive	42	40
False positive	9	8
True negative	65	68
False negative	1	3
Sensitivity	97.7 (87.7-99.9)	93.0 (80.9-98.5)
Specificity	87.8 (78.2-94.3)	89.2 (79.8-95.2)
Positive likelihood ratio	8.03 (4.35-14.84)	8.61 (4.45-16.64)
Negative likelihood ratio	0.026 (0.004-0.184)	0.078 (0.026-0.234)
Positive predictive value	82.4 (71.6-89.6)	83.3 (72.1-90.6)
Negative predictive value	98.5 (90.3-99.8)	95.7 (88.0-98.5)
Accuracy	91.5 (84.8-95.8)	90.6 (83.8-95.2)
AUC	0.928 (0.865-0.967)	0.911 (0.844-0.956)
Cut-off level	42.65 pg/mL	8.6 ng/mL

Values are expressed with 95% CI.
AUC: Area under the curve, NSE: Neuron specific enolase, S100B: S100 calcium-binding protein B, CI: Confidence interval

accuracy of 90.6% and 91.5%; respectively (Table 2). The cutoff concentration for serum NSE and S100B was 8.6 ng/mL and 42.65 pg/mL, respectively. The ROC analysis demonstrated an AUC of 0.91 (95% CI: 0.84-0.96) for S100B and an AUC of 0.93 (95% CI: 0.87-0.97) for NSE to predicting central vertigo (Figure 2).

Discussion

Finding a quick and accessible method to diagnose central vertigo in the ED is crucial. NSE, and the S100B, have been studied as useful biochemical markers to indicate brain damage observed under conditions such as head injury, cerebral infarction, cardiac arrest, seizure, and heart surgery (11,15). Several studies have evaluated the efficacy of serum biomarkers for differentiating central and peripheral vertigo (11-16). Akinci et al. (16) performed a study on 116 patients who sought treatment for vertigo and showed that serum levels of D-dimer, fibrinogen, and C-reactive protein cannot be significant markers for differentiating central and peripheral vertigo. However, few studies have been performed on the diagnostic accuracy of the S100B and NSE in this area.

In this study, one hundred and seventeen patients with acute-onset vertigo were evaluated. According to our results, the serum levels of NSE and S100B in the central vertigo were significantly higher than those in peripheral vertigo. S100B is found in the nervous system, particularly in astrocytes and NSE is a biomarker of neuronal loss (13). Therefore, NSE and S100B concentrations are elevated in central nervous system disorders. Consistent with this study, it was demonstrated in several studies (12-14).

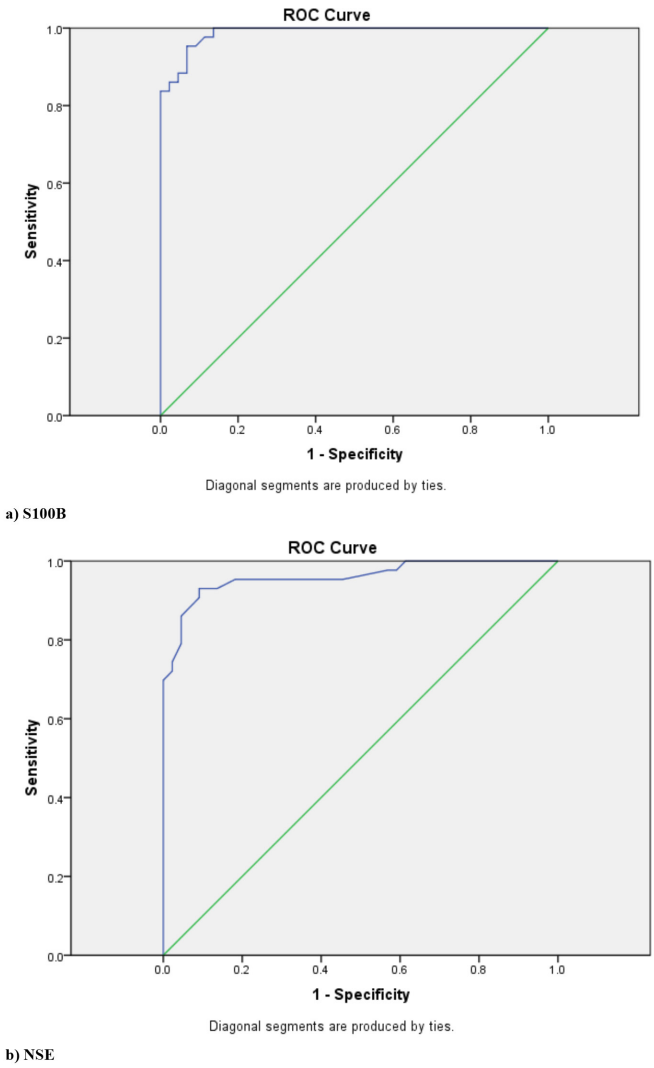

Figure 2. S100B (a) and NSE (b) the ROC curve of biomarkers in distinguishing central from peripheral vertigo

S100B: S100 calcium-binding protein B, NSE: Neuron-specific enolase, ROC: Receiver-operating characteristic

Moreover, S100B with a cut-off point 42.65 pg/mL and NSE with the cut-off point 8.6 ng/mL had high and acceptable sensitivity, specificity, PPV, and NPV for differentiating central and peripheral vertigo etiologies. S100B and NSE had good NPV (98.5% and 95.7%) to rule out central vertigo etiologies. Due to the high sensitivity (93.0% and 97.7%) and NPV, NSE and S100B may be useful diagnostic biomarkers in the diagnosis of central vertigo.

Kartal et al. (12) examined the serum S100B levels in 82 subjects with acute vertigo and demonstrated that the median serum S100B levels were significantly lower in patients with normal MRI compared to cases with abnormal MRI (27.00, vs. 60.94 pg/mL, p=0.04). Moreover, serum concentrations above 30 pg/mL had the sensitivity, specificity, PPV, and NPV of 83.89%, 51%, 51%, and 83.9%, for S100B in predicting the central cause of vertigo. They showed an AUC of 0.774 for S100B for predicting central vertigo. Finally, they reported that serum S100B levels were not sensitive enough to exclude patients for cranial MRI. This finding is contrary to the results of the present study.

Sohn et al. (13) in 77 patients with acute vertigo compared the serum S100B, NSE, glial fibrillary acidic protein (GFAP), brain-derived neurotrophic factor (BDNF), and interleukin-6 levels in to distinguish central from peripheral vertigo. Consistent with the present study, they reported that NSE and S100B levels were significantly higher in central vertigo compared with peripheral vertigo. The serum GFAP and BDNF levels were the same among the central and peripheral vertigo. They showed an AUC of 0.843 (95% CI=0.753-0.932) and 0.787 (95% CI=0.687-0.886) for NSE and S100B for predicting central vertigo. The sensitivity and specificity of NSE were 70.0% and 70.6% at a cut-off concentration of 73.1494 ng/mL and the sensitivity and specificity of S100B were 70.0% and 69.1% at a cut-off level of 766.9938 ng/mL in predicting the central cause of vertigo. The AUC of NSE and S100B to identify patients with central vertigo in this study was higher than that reported by Sohn et al. (13) and Kartal et al. (12).

Mozafari et al. (14) reported that serum S100B and NSE levels were significantly higher in acute central vertigo (217.13±119.28 vs. 77.39±31.67, p<0.001 and 30.90±7.34 vs.10.92±6.34, p<0.001), and could be used as accurate methods in the screening of these patients in the ED. The AUC was 90.3 (95% CI: 80.7-99.8) for S100B and 96.9 (95% CI: 93.7-100.0) for NSE in differentiating acute vertigo cases with a central cause. The serum S100B concentration cut-off of 119.68 pg/l gave sensitivity and specificity of 90.00% and 92.00%. At a cut-off NSE concentration above 18.12 ng/mL, the sensitivity and specificity of the test were 100.00% and 89.47% for detecting the central cause of vertigo. These findings are consistent with the results of this study.

Purrucker et al. (17) found that serum S100B levels were significantly higher in vascular vertigo cases (stroke) than in nonvascular vertigo cases. The sensitivity and specificity of S100B for indicating stroke in patients with acute vertigo were 94.4% and 31.8%.

The study by Zuo et al. (18) demonstrated that increased NSE (>11.85 ng/mL) was significantly higher in patients with cerebral infarction compared with non-infarcted subjects (45.7% vs. 22.5%, p<0.05) when evaluated in patients with acute vertigo.

Consistent with previous studies, we demonstrated that the serum NSE and S100B levels were significantly higher in patients with the central cause of vertigo. This study showed that serum levels

of S100B and NSE had an acceptable sensitivity for diagnosing the causes of peripheral vertigo from the central.

Study Limitations

In this study, biomarkers were measured only once. Repeated measurements at different times may provide a more accurate picture of each biomarker. The wide difference in time between the onset of symptoms and blood sampling may affect our calculated cut-off points.

Conclusion

The serum S100B and NSE concentrations were significantly higher in patients with central vertigo and could be useful markers with acceptable accuracy in screening central from peripheral vertigo in ED. These biomarkers are more cost-effective and easily accessible compared to MRI and provide a strategy for identifying a subset of patients for brain MRI as the gold standard tool.

1. NSE and S100B can serve as suitable screening tools in diagnosing central and peripheral vertigo in the emergency ward.
2. The NSE and S100B are more cost-effective and easily accessible as compared to MRI.
3. NSE and S100B do not need to be interpreted by a radiologist and the result is easily available to the physician.
4. NSE and S100B do not require the patient to leave the ED and can also be used in critically ill patients.

Ethics

Ethics Committee Approval: The study was approved with Ethics Committee of Isfahan University of Medical Sciences (approval no: IR.MUI.REC.1394.3.049, date: 30.06.2016).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.M., R.B., F.H., A.M., B.A., M.N-E., Concept: B.M., R.B., F.H., A.M., B.A., M.N-E., Design: B.M., R.B., F.H., A.M., B.A., M.N-E., Data Collection or Processing: B.M., R.B., F.H., M.N-E., Analysis or Interpretation: B.M., R.B., F.H., A.M., B.A., M.N-E., Literature Search: B.M., R.B., F.H., M.N-E., Writing: B.M., R.B., F.H., A.M., B.A., M.N-E.

Conflict of Interest: No conflict of interest was declared by the authors.

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Content and Adequacy of Emergency Medicine Point of Care Ultrasound Training: Evaluation of Turkey

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Abstract

Aim: With its widespread use for emergency patient care, point-of-care ultrasound (PoCUS) is included in postgraduate education in Turkey, but its practice may vary depending on the training program. Our study aimed to determine the content of practices regarding PoCUS training in Turkey, and to present a future perspective by revealing the relationship between years of education and competence perceptions.

Materials and Methods: This is a descriptive study conducted on emergency medicine students who were still residents approximately 2018-2019. The first part includes demographic data, theoretical and practical training content. The second part is created according to the Likert scale for self-assessment that questions the competence. The survey was conveyed to.

Results: In our study, including 249 residents, the participants reported their practical training hours for emergency ultrasound (US) use as 12.5 h, and theoretical training hours as 12.1 h. For all sonographic evaluations, it was found that 10.1% of the practices were performed under the supervision of an academic member.

Conclusion: It was found that Emergency Medicine clinics in Turkey had adequate equipment for the use and training of US, residents had a certain level of competence to using US, but there was no regular training with curriculum and assessment criteria in clinics.

Keywords: Ultrasound education, PoCUS, medical education, emergency room

Introduction

The use of ultrasound (US) in emergency departments has significantly increased in the last thirty years. The US increases the quality of patient care in the emergency department, shortens the duration of discharge, increases quality and value in terms of diagnostic accuracy and cost reduction and contributes to patient safety in interventional procedures (1). In parallel with this, the US has started to be included in the emergency training curricula over the last 20 years.

The US has taken been included into all levels of medical education, integrated into the medical school curriculum, entered postgraduate education after postdoctoral education, and started to be included in the training of nurses and prehospital care providers. In the United States of America (USA), which has a pioneering position in the field of clinical US use, and around the world, the content of both undergraduate and postgraduate US training has been described in detail, especially in the field of emergency medicine (1).

After the recognition of the value of the US in the emergency department, studies on the use of US have been conducted in many countries such as the UK (UK College of Emergency Medicine-CEM), Australia (Australasian College for Emergency Medicine-ACEM), Canada (Canadian Association of Emergency Physicians-CAEP), especially the USA (American College of Emergency Physicians-ACEP) (2). Because of these studies, training curricula on the use of US were created for emergency department personnel. In these curricula, minimum qualification criteria and contents, which differ on country basis, were determined to ensure the standardization of US training (1).

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In emergency departments, especially the use point-of-care ultrasound (PoCUS) is well known. Although PoCUS was previously used for managing patients with blunt trauma, it has been used for diagnostic and interventional purposes in non-trauma cases with the training and increased experience (1).

In the USA, ACEP states that the clinician should recognize the indications and contraindications for each PoCUS area as a prerequisite for 11 titles (trauma, intrauterine pregnancy, abdominal aortic aneurysm, cardiac, biliary, urinary, DVT, soft tissue and musculoskeletal, thoracic, ocular, interventional), which are defined as the core. To acquire adequate images and to provide this in different cases, it must understand the US physics to make an appropriate and accurate sonographic evaluation in patients with different body characteristics. Simultaneously with the image acquisition, the clinician should interpret the imaging by distinguishing between normal anatomy, common variants, as well as a range of obvious and indistinct pathologies. Finally, the clinician should be able to integrate emergency sonographic evaluation findings into individual patient care plan and management. It is stated that effective integration includes proper documentation, quality assurance, and immediate US reimbursement, as well as accurate information provided by each assessment (1).

In the core program of US training, emergency US rotation 2 weeks in the first year, in the following period 1 week for each year, and 80 h of emergency US training for each student are required during the residency period. These rotations should focus on the integration of the US into daily clinical practice in small groups, as well as device use, evaluation protocols, image optimization, interpretation, and recording. In addition to emergency US turn of duty under the supervision of a lecturer, weekly case discussions and simulations of less common cases are recommended (1). Numerous researchers have shown that simulation results in image acquisition, interpretation and practitioner confidence with equivalent success compared to traditional practical training (3,4). Simulation allows the practice of new skill in a safe environment before actual clinical performance. ACEP has also drawn attention to the weekly paper hours and according to the need, assessment in the form of question/answer in small groups, and the definition of assessment processes at the end of emergency US imaging periods and rotation (1).

In the evaluation of US training, ACEP recommends exam methods such as supervised question-answer, objective structured clinical exams (OSCE), one-to-one standardized direct observation tools, simulation (1).

In the first Emergency Medicine Specialization Training Curriculum approved by the Board of Medical Specialties (TUK) in 2008, emergency US was included with the content of Focused Assessment with Sonography for Trauma (FAST) under the title of trauma/orthopedic interventions (5).

In the curriculum approved in 2016, it was stated as the use of emergency US under the heading of "emergency imaging methods", and in 2017 and 2019, as the use of bedside emergency US and bedside echocardiography evaluation under the heading "emergency imaging methods" (6,7).

Although it has been used in the emergency departments in our country for a long time, the bedside US Emergency Medicine Education Curriculum is relatively new. In response to this new curriculum, many emergency departments have US, and transportation is getting easier. Accessing and using the US has increased the interest in US training among emergency department personnel and caused learning attempts through various courses or online training. Simultaneously, the ease of access to the US has increased its use for patients, symptoms, or treatment, which increases the perception of competence after a certain use.

This study investigates residents' content of the training and competence of PoCUS in emergency medicine clinics in Turkey.

Materials and Methods

The study is a descriptive study conducted on all emergency medicine residents who were still studying in 2018-2019, and who agreed to participate in the study. After obtaining the approval from the ethics committee, the survey questions about the competence levels and practice details of the participants were created online. During the stage of preparation, the validity of the survey was tested by applying it to 12 emergency medicine residents in different education years. The survey was sent the emergency medical training programs in Turkey in an online environment and were asked to respond.

The questionnaire, which consisted of Likert-type questions, had two parts. The first part includes questions about the demographic data of the participants (institution, age, gender, duration of education), US hardware quality of the program they were educated in, and didactic and practical training content. In the second part, they were asked to evaluate their competencies according to the Likert scale (which includes the options I strongly agree, agree, neutral, disagree, strongly disagree) with the questions prepared based on the comprehensive PoCUS educational objectives suggested by the ACEP;

1) knowledge of its indications and limitations,

2) to be able to define the sonographic anatomy,

3) to be able to evaluate pathology/entrapments,

4) ability to integrate the findings into patient management in the basic areas of PoCUS.

The questions on emergency echocardiographic practices were prepared separately in line with the educational goals, which are also the recommendations of the ACEP (1). In the last part of the survey, it was expected to make evaluation the subject of "integrating US into patient management" in each US intervention.

Statistical Analysis

In the statistical analysis, the "Statistical Package for Social Sciences (SPSS) Statistics 20.0.0 for Windows" (IBM-SPSS, SPSS Inc. Chicagoi Illinois, USA) software was used. While evaluating the results, "strongly agree" and "agree" preferences were considered "positive perception of competence". The perception of "being able to evaluate pathology/entrapments" was compared between the groups with the acceptance that it requires clinical practice experience on basic PoCUS knowledge for competence. The minimum sample size was determined considering a confidence interval of 95%, an alpha of 0.05, and a power of 80%. Categorical data were recorded with the percentage frequency and 95% confidence interval, the data obtained by measurement were recorded with the mean and standard deviation data.

Results

The assessment included the responses of 249 residents after 32 participants who did not complete the entire questionnaire-delivered online between September 2018 and February 2019 were excluded from the study (mean age, 29.2; range, 24-42). US device was available in the clinics of 96% (N=239) of the participants for 7/24, and 176 (N=70.7%) participants stated that they had three different types of probes in their clinics.

Except for in-house bedside procedures, the mean annual practice training time allocated to PoCUS training was 12.5 h [95% confidence interval (CI): 9.6-15.9], and the mean annual didactic training time was 12.1 h (95% CI: 10.2-14.9). Of the participants, 19.3% (N=48, 95% CI: 14.1-24.1) stated that they had ultrasonography (USG) rotations. The mean percentage of monthly PoCUS practice under the supervision of an academic member reported by the participants was 10.1% (range, 0-100). A summary of educational resources and methods is given in Table 1. The most commonly used assessment and evaluation method was multiple choice or standard written exams (43%, 95% CI: 37.3-49). The frequency of other assessment and evaluation methods is given in Table 2.

In the comparison of the groups of education years of 24 months (2 years) or more and less than 24 months (2 years) in our study, positive perception of competence ($p<0.001$ for aortic aneurism and dissection, $p<0,001$ for trauma, $p<0.001$ for gallbladder and cholecystitis, $p<0.001$ for hydronephrosis, kidney stones, mass and bladder volume, $p=0.019$ for DVT, while $p<0.001$ for CIS, $p<0.001$ for thorax, $p=0.003$ for ocular) was significantly different in other headings, while years of education did not make a difference in intestinal ($p=0.09$) and 1st trimester ($p=0.69$) PoCUS procedures, when the ability to "evaluate pathology and entrapments" in the related domain of PoCUS practice, which we positioned on the basic knowledge of indication and sonoanatomy and which requires practical experience, was assessed. The results were similar for the emergency echocardiographic learning goals (for each domain) ($p<0.001$).

Of the participants with ≥2 years of residency training, 46.7% (N=63, 95% CI: 37.8-55.6) had a "positive perception of competence" for the question "I know US physics and relevant definitions (frequency, resolution, Doppler, etc.)". This rate was 61.5% (N=83, 95% CI: 53.3-69.6) for "using the equipment properly", 56.3% for "recognizing common US artifacts" (N=76, 95% 47.4-64.4), and 40.5% for "ability to document US findings understandably and appropriately (N=64, 95% CI: 39.3-55.6).

The responses given by the participants according to the positive competence perception for PoCUS domains are given in Table

Table 1. Data on participants' training resources and methods

Method	Percentage (N, 95% CI)
"Learning by yourself" by applying	77.9 (194, 72.7-82.7)
"Learning by watching"	69.9 (174, 63.9-75.5)
Outside courses	66.3 (165, 59.8-71.9)
In-house seminars and theoretical courses	64.7 (161, 58.2-70.7)
Internet-based learning	35.3 (88, 29.3-41.4)
In-house courses	26.1 (65, 20.5-31.3)
In-house simulation training	18.9 (47, 14.5-23.7)
Supervised practice	13.7 (34, 9.6-18.1)

CI: Confidence interval

Table 2. Data on the measurement and evaluation methods of the participants

Method	Percent (N, 95% CI)
Multiple choice or standard written exams	43 (107, 37.3-49)
Real-time clinical evaluation with supervision	32.5 (81, 26.5-38.6)
Observational Assessment of Skill (DOPS)	32.1 (80, 26.1-37.8)
Objective Formal Clinical Exam (OSCE)	9.6 (24, 6.4-13.3)
Assessment with simulation	6.8 (17, 4-10)
Weekly image evaluation, question-answer exam, feedback	5.2 (13, 2.4-8.4)

CI: Confidence interval

Table 3. Positive perception of efficacy for aortic, thoracoabdominal trauma, biliary, urinary and first trimester pregnancy

PoCUS field, N (percent) 95% CI										
Question	**Aorta**	**Trauma**	**Biliary**	**Urinary**	**1. trimester**	**Ocular**	**Intestinal**	**Thorax**	**DVT**	**CIS**
I know the indications/limitations	169 (67.9) 61.4-73.5	185 (74.3) 68.7-79.9	164 (65.9) 59.8-71.5	136 (54.6) 48.6-60.6	78 (31.3) 25.7-36.9	81 (32.5) 26.5-38.5	59 (23.7) 18.1-28.9	150 (60.2) 53.8-66.7	161 (64.7) 58.6-70.3	81 (32.5) 26.5-38.6
I can describe his sonographic anatomy	128 (51.4) 44.6-57.8	161 (64.7) 58.2-70.3	134 (53.8) 47.4-60.2	151 (60.6) 54.6-66.7	60 (24.1) 19.3-29.3	81 (32.5) 26.9-38.2	28 (11.2) 7.6-15.3	147 (59.0) 52.6-65.5	117 (47) 41-53	78 (27.3) 22.1-33.3
I can evaluate the pathology/pitfalls	146 (58.6) 52.2-64.3	165 (66.3) 60.6-72.3	156 (62.7) 56.6-68.7	135 (54.2) 47.8-60.2	51 (20.5) 15.3-25.3	64 (25.7) 21.5-31.3	25 (10) 6.4-14.1	132 (53.0) 46.6-59.4	133 (53.4) 47.8-59.8	84 (33.7) 27.7-39.4
I can integrate these findings into my patient management	147 (59.1) 52.6-64.7	184 (73.9) 68.7-79.1	158 (63.5) 57.8-69.5	140 (56.2) 50.2-62.2	58 (23.3) 17.7-28.9	71 (28.5) 22.9-34.1	38 (15.2) 10.8-19.7	117 (47) 40.2-53.4	146 (58.6) 52.6-64.7	77 (30.9) 25.3-36.9

CI: Confidence interval, PoCUS: Point-of-care ultrasound, DVT: Deep vein thrombosis

3 for emergency echocardiographic procedures in Table 4. For the basic US-guided procedures, the rate of positive perception of competence was the highest (83.0%) among the participants in the same group. Of the participants, 60.0% (N=81, 95% CI: 51.1-68.1) had a positive perception of "knowing the indications and limitations of interventional US procedures". This rate was 62.2% (N=84, 95% CI: 54.1-69.6) for "I can integrate the US as a procedural guide into clinical patient management", and there was a significant difference compared the students with education years of <24 months ($p<0.001$).

Discussion

Although we could not get regular information about the content and evaluation of the training as there was no structured US training for graduate students, this study on PoCUS training in emergency medicine clinics in Turkey revealed that clinics were attempting to create a US training program and provide training accordingly, by complying with the guidelines as far as their facilities were sufficient.

ACEP recommends a theoretical and practical introductory course covering 16-24 hours of core competency domain for US training, as well as 4-8 hours of short courses for subjects other than basic domains and acquiring approximately 25-50 recorded images in the basic or other domains (1). In our study, the mean annual didactic training time was 12.1 h, and the clinical training time allocated to US training was 12.5 h. In a study conducted on the emergency department specialty programs in the USA, 15% of the programs had a US rotation for 1-2 weeks, and 47% had a US rotation for 2-4 weeks. It was stated that the mean time allocated to US training was 34 h (8). A study by Counselman et al. (9) on emergency medicine specialty programs found that 48% of the US clinical training hours were between 1 and 10 h per year. The didactic and practice training hours allocated to US training, which we determined in the emergency medicine clinics in our country, do not meet the times recommended providing the competencies in the guidelines. The reasons for this are thought to be due to the lack of competent academic members for USG training and the fact that it has recently been included in the TUK skill guidelines for emergency medicine assistants (6,7). Since there is no regular US training program in many of the emergency medicine clinics where we conducted the study, it could not be determined in which years these training was provided or how much of them was on the basic or advanced US training.

Of the research assistants who participated in the study, 19.3% stated that they had US rotations in their departments. Lewiss et al. (10) stated that the training should be provided with a 4-week longitudinal model as 2 weeks in the first year of postgraduate

Table 4. Positive perception of competence of the participants for emergency echocardiographic applications		
Questions	**N**	**Percent (95% CI)**
We can determine the indications and limitations of Emergency ECHO	128	94.8 (91.1-98.5)
I can do standard ECHO (subcostal, parasternal, Apex, four spaces, long and short axis)	126	93.3 (88.9-97.0)
I can recognize the pericardium, heart chambers, veins, the aorta and inferior vena cava anatomy on ECHO	128	94.8 (91.1-97.8)
I can evaluate left ventricular functions (EF) and central venous pressure estimation	124	91.9 (86.7-96.3)
I can recognize cardiac arrest, tamponade with or without pericardial effusion, aortic root dilatation on ECHO	125	92.6 (88.1-96.3)
I can integrate emergency ECHO findings into individual patients or departments	135	93.3 (88.9-97.0)
EF: Ejection fraction, ECHO: Echocardiographic, CI: Confidence interval		

education of trainee sonographers and 2 weeks in the second year. However, there are also some stating that it should be provided with a 4-week intensive program in the first year. Lack of regular training on this subject in our country and continuing only with courses given by specialist associations made it difficult to give a country-wide rate. Therefore, it does not allow us to compare with other results. When all the results are evaluated, it can be speculated that standard structured US training is not sufficiently structured in the emergency medicine training.

Although it was stated that US training should generally be taught by supervisors, this rate was found to be very low in our study (13.7%), a large proportion of the participants stated that they learned on their own. In many studies, US practice is supported as a learning method accompanied by supervision (for the USA, a 'supervisor' or a 'sonogapher' or 'sonogapher' candidate who has passed the exams at the end of the training is a final year student) (11). Damewood et al. (12) recommended that most of the courses be supervised directly by physicians and EUS members (if available at the institution) for the early development of US techniques. Practices with a supervisor and feedback are important in the acquisition of US skills. ACEP's recommendation on teaching methods is USG turn of duty and weekly case discussions under the supervision of an authorized academic member (1). In our study, the most frequently used method of "self-learning by practicing" does not comply with the standards, but the fact that the most frequently used method is self-learning by practicing raises questions about the US competencies of emergency medicine graduate students. Considering that highly sensitive patients are treated in emergency departments, it is important to create educational environments in safe medical simulation environments with the help of competent academic members for basic knowledge and clinical integration (13). The accuracy of the information obtained is doubtful since no feedback is provided in the training not conducted like this. This is perilous for educating people who decide on the treatment of highly sensitive patients, such as emergency medicine personnel. Since there is no feedback in self-learning by practicing, which is the most common learning method in our study, the accuracy of the learned information is doubtful. This needs to be corrected with certain feedback methods.

In US training, it is recommended to benefit from many training strategies, as well as didactic training. Our study found that they received help from online resources (35.3%) and external courses (66.3%) in addition to didactic US training. Even though it seems that the use of online facilities for education is low to a certain extent, it is thought that this rate will increase with the increasing number of options in the native language and the popularization of the existing ones. In a study conducted in Canada, it was observed that emergency department personnel used online training resources (56%), textbooks (52%) and US courses (52%), in addition to didactic training for education (14). Lewiss et al. (10) reported that that asynchronous emergency US learning could be equal to traditional didactic lectures. The results show that the training is provided in standard ways worldwide and that we are close to these standards.

For US training evaluation, it is recommended to be done repeatedly, at the beginning and at the end of the training using individualized assessment and evaluation methods (1). Considering the evaluation method in studies conducted in the USA, it is stated that almost all programs (99%) use the real clinical evaluation method under supervision to evaluate the US competence (2). Simultaneously, it is recommended to use more than one measurement and evaluation method, since domains such as anatomy, physiology, and clinical integration should be evaluated to determine the US competence (15,16). A study used the OSCE method for abdominal US competence, but it was thought that the evaluation performed in a limited simulated environment could not accurately predict their clinical performance (17). In fact, the best way to evaluate USG competence in emergency medical clinics is through direct observation (18-20). But since a certain standard cannot be achieved in this method, studies have been conducted on US competence in the emergency department using the standardized Direct Observation of Procedural Skills (SGOD) method, and it has been concluded that this method is an appropriate measurement

method as it enables emergency department personnel to recognize their strengths and weaknesses, and is an effective assessment method allowing immediate feedback (21), although our study revealed that multiple-choice or standard written exams were most frequently administered, it was followed by real-time clinical assessment under supervision and skill and observation-based assessment. Although the rate of using this assessment remained below 50%, it was observed that it agreed with the recommended assessment and evaluation methods.

It was noted that the participants had more than 50% positive perceptions of competence in determining the US indications for the aorta, trauma, biliary, urinary, thorax, DVT areas, recognizing the anatomy of the region, recognizing pathologies and entrapment, and integrating them into the clinic. According to the article of Emergency Medicine US milestones by the Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Emergency Medicine in 2012, USG competence is divided into 5 levels (22). According to these level criteria, the level of our participants is 2, that is, the early moderate level. According to this level, US users are expected to be actively capable of performing US, to be able to determine the US area consistent with the clinic and demonstrate it. Participants who are level 2 are even probably level 3 (with a certain number of image recording in addition to their level 2 skills), as there is no system that clearly controls how many times and in which area they acquire images. It is thought that as the US training and competency determination criteria are developed in our country, it will be understood that the emergency medicine personnel are at higher levels.

In their study, Bustam et al. (23) found ECHO competence of emergency medicine interns as 93% for left ventricular estimation, 92.9% for ejection frequency measurement, 98% for pericardial effusion measurement, and 64% for the inferior vena cava evaluation. Similarly, in our study, it was observed that there were more than 90% positive perceptions of competence in the mentioned ECHO areas.

According to their own evaluations, it was observed that the participants felt themselves sufficiently in terms of US physics, US equipment, artifacts and documentation.

In a study by Kim et al. (14), more than half of the participants reported that they used US guidance for foreign body removal, incision and drainage, paracentesis, peripheral venous cannulation and thoracic evaluation, both for diagnostic and interventional purposes, and felt sufficient in this regard. In our study, more than 50% of the participants defined themselves competent for US-guided vascular access (67.1%) and thoracentesis (58.2%). This can be explained by the fact that the residents in many emergency medicine clinics have easy access to the US and they can try US-guided interventions very often, as they work in intensive emergency rooms.

Although US training practice, techniques, hours, evaluation criteria do not meet the standards in our survey, when we asked the residents to evaluate their own competence in recognizing pathologies and entrapment before and after 24 months, which is a key point in emergency medicine training, those with an education year above 24 months stated that they were better at aortic, trauma, gall bladder, renal, DVT, CIS, thoracic and ocular US. The most significant reason for this is that they have improved themselves in these areas by self-training on the US device (96%) and common pathologies frequently encountered in their clinics. A book created by medical educators and educational psychologists mentions that self-assessment in medical education is a vital skill in clinical practice. This includes not only self-assessment but also what they can do about what they will learn (goals), how they learn (methods, strategies), whether they have learned, what they learn (assessment) and using what they have learned (adaptation) (24). It can be speculated that the residents can convert these skills into a habit after a while, even if they do unknowingly do these skills. Self-assessment appears to be a driving force in this educational model. This may be because they manage the learning processes together in the adult learning process and gradually take more responsibility for their own learning. Similarly, in our study, it was observed that the more time they spend practicing US, the more they try to learn, feeling more responsible for recognizing common pathologies and applying them to the clinic.

Study Limitations

The major limitation of our study is that it is a survey study based on instant statements and it has the handicaps of similar survey studies. Moreover, since it is an educational content and situation analysis with only the perspective of research assistants, there may be limitations regarding the data of US training practices in emergency medicine educational institutions in Turkey. Another limitation is that only 66% of the educational institutions responded and no sufficient number could be reached. Not recording the geographical and other physical conditions that may affect the perception of competence due to the number and variety of patients is also a limitation of this study.

Conclusion

The US training provided in emergency medicine clinics in Turkey was below the generally accepted standard training programs. However, the fact that the residents consider themselves competent, especially in their basic subjects, shows that the

emergency medicine clinics are sufficient and well-equipped US and although they have not been developed into a specific program and feedback system, effective training is provided. US training programs in the emergency medicine clinics in our country should be prepared in line with the standards of the guidelines accepted in many world countries and training and crediting should be based on these.

Ethics

Ethics Committee Approval: The study were approved by the Akdeniz University of Local Ethics Committee (protocol number: 70904504/395, date: 03.09.2018).

Informed Consent: Survey study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.S., Concept: F.S., A.Y.Ü., Design: F.S., A.Y.Ü., Data Collection or Processing: F.S., E.G., Analysis or Interpretation: E.G., A.Y.Ü., Y.Ş., Literature Search: F.S., Writing: F.S., A.Y.Ü., Y.Ş.

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Malpractice Allegations in Adult and Pediatric Emergency Departments Resulting in Death

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Abstract

Aim: This study aimed to increase the awareness of physicians working in adult and pediatric emergency departments (ED) about malpractice allegations.

Materials and Methods: A retrospective analysis was conducted of cases with malpractice allegations occurring in ED from the lawsuit files decided by the First Specialization Board of the İstanbul Forensic Medicine Institute between 01/01/2012-31/12/2014.

Results: Evaluation was made of 556 cases, comprising 357 (64.2%) males and 199 (35.8%) females, with a mean age of 38.92±24.8 years (minimum: 0, maximum: 87), with the highest number of cases in the 40-59 years age group (n=157, 28.2%). Two-thirds (n=377, 67.8%) of the cases with alleged medical malpractice occurred in a public hospital. The board decided that 24.4% (n=136) of the cases were medical malpractice. Of 556 cases, 1.102 physicians were accused and 151 physicians (13.7%) were found to be at fault by the board. More than half of the physicians accused of medical malpractice (51.7%) were general practitioners. The most common cause of malpractice in 136 files was diagnostic error (n=79, 58.1%). The most common actions of malpractice were failure to diagnose on time, and misdiagnosis (n=29, 21.3%). The most frequent diagnosis was trauma (n=156, 28.1%).

Conclusion: Most of the malpractice allegations against the physicians working in the ED were unfounded and dismissed by the board. order to avoid diagnostic errors, it can be recommended that novice general practitioners should not be employed alone in ED without the support of more experienced colleagues.

Keywords: Malpractise, emergency department, trauma, diagnostic error, forensic medicine

Introduction

The average physician in the United States (USA) spends approximately 11% (50.7 months) of his or her professional life with unresolved manifest malpractice allegations (1). In emergency departments (ED), physicians must manage patient populations with risky and different diseases with limited time and resources. This makes working in the ED a high risk of malpractice allegations (2). Three-quarters of emergency physicians in the USA must face a malpractice lawsuit at least once in their lifetime (3). Emergency physicians work in a knowledge-poor, high-risk, but technology-rich environment. This makes it very easy for physicians working in the ED to turn to defensive medicine (4). In a study conducted in Spain, 89.8% of emergency physicians performed unnecessary diagnostic tests, and 63% prolonged the patient's stay in the ED (5). Malpractice lawsuits wear away at physicians due to both long duration and high compensation rates (6,7).

Prolonged malpractice lawsuits may affect the decisions of physicians as well as cause serious psychosocial effects in the short- and long term. In a survey by Kayipmaz et al. (8), it was reported that the judicial or administrative investigations of 41.5% of emergency medicine physicians affected their medical decisions. In another study of 1206 primary care physicians, those with malpractice disputes were found to have significantly

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lower overall health and mental health (9). As malpractice allegations have more than one negative effect on physicians, they need to be investigated in depth and understood very well. In the USA, death in the adult ED and urgent care setting was the most common severe injury cited in closed adult malpractice claims. Moreover, 38.5% of all closed malpractice allegations and 42.8% of all compensated allegations resulted in death (10). The relationship between death and malpractice has also been proven in other studies (11-13). Examining cases of alleged malpractice that resulted in death will considerably contribute to a better understanding of these cases.

This study aimed to evaluate adult and pediatric emergency cases that resulted in death where medical malpractice allegations were filed to increase the awareness of physicians working in adult and pediatric ED about cases with alleged medical malpractice.

Materials and Methods

Sampling

Medical malpractice claims alleged cases that occurred in the ED and resulted in death were retrospectively analyzed from among the report archives of the First Board of Specialization of the Council of Forensic Medicine between 01/01/2012 and 31/12/2014.

Diagnostic Methods

The First Specialization Board of the İstanbul Forensic Medicine Institute acts as an expert appraisal in cases filed by the judicial authorities across the country regarding allegations of medical malpractice resulting in death. When a lawsuit file containing an allegation of medical malpractice is sent to the board by the judicial authorities, a rapporteur is first assigned to the file. After the rapporteur examines the entire file, if there is missing information in the file, this information is requested from the judicial authorities. When all the necessary information for the evaluation is completed, the rapporteur prepares a preliminary report in which he records all the information in the file (statements of the accused and witnesses, all medical documents, etc.) and presents this preliminary report to the chairman and members of the board. After the detailed evaluation of the chairman and members, a final report is prepared and report sent with a lawsuit file to the judicial authorities about whether the physician is at fault or not.

Data Collection and Implementation

While the data were being recorded, the following parameters were scrutinized: the gender and age of the cases, the healthcare organization where the incident occurred, the reason for the visit to the hospital, specialties of the physician, the clinical diagnosis and the phase at which confirmed malpractice occurred. Although this study was designed as a retrospective study with no identification data or human/animal subjects, and was therefore beyond the scope of the informed consent doctrine; all procedures in the study were performed after obtaining scientific approval of the Ministry of Justice Council of Forensic Medicine dated 15/12/2015., no. 21589509/1020 and in accordance with the 1964 Helsinki Declaration including its later amendments.

Statistical Analysis

The data obtained in the study were analyzed statistically using the Statistical Package for the Social Sciences 21.0 software (Armonk, NY, USA). Descriptive statistics were presented as mean±standard deviation, minimum (min), and maximum (max) values for continuous variables, and as frequency and percentage for categorical variables.

Results

This study included 556 cases, comprising 357 (64.2%) males and 199 (35.8%) females. The age of 10 cases could not be determined. The mean age of the remaining cases was 38.92±24.8 years (min: 0, max: 87), with the highest number of cases in the 40-59 years age group (n=157, 28.2%). Two-thirds of the cases (n=377, 67.8%) occurred in a public hospital (Table 1).

The board came to a decision on medical malpractice in 136 (24.4%) cases. Of 556 lawsuit files, 1102 physicians were accused

Table 1. Characteristics of medical malpractice claims

	n	%
Gender		
Male	357	64.2
Female	199	35.8
Age group		
0-17 years	134	24.1
18-39 years	133	23.9
40-59 years	157	28.2
≥60 years	122	22
Unknown	10	1.8
Hospital visited		
Public Hospital	377	67.8
Private Hospital	60	10.8
Training and Research Hospital	54	9.7
University Hospital	17	3.1
Military Hospital	4	0.7
More than one hospital	44	7.9
Total	**556**	**100**

and 151 physicians (13.7%) were found to be at fault by the board (Table 2).

More than half of the physicians accused of medical malpractice (51.7%) were general practitioners (Table 2). General practitioners (n=97, 64.2%) constituted the largest group among physicians reported to be at fault. When the top ten most frequently accused medical branches were evaluated, 24.2% of pediatricians (8 /33), 17% of general practitioners (97/570), 14.5% of internal medicine physicians (11/76), 12.3% of general surgeons (8/65), 9.8% of orthopedists (5/51), 8.5% of neurosurgeons (5/51), 8.2% of emergency medicine specialists (5/61), 6.25% of cardiologists (5/51) and 3.2% of neurologists (5/51) were decided to be at fault. No fault was attributed to any anesthesia and reanimation physician.

In 136 files, malpractice was most frequently attributed to diagnostic error (n=79, 58.1%). The most common actions causing the malpractice were failure to diagnose on time, misdiagnosis (n=29, 21.3%), and not requesting necessary examinations and X-rays (n=25, 18.4%) (Table 3).

When the primary diagnoses were evaluated; the most frequent diagnosis was trauma (n=156, 28.1%), followed by infection (n=119, 21.4%) (Table 4). Diagnostic error was the most common error in trauma, infectious diseases, cardiopulmonary system diseases, gastrointestinal system diseases and neuropsychiatric diseases (Table 5). Diagnosis and treatment errors were most frequently seen in trauma patients, and follow-up errors were most frequently observed in cardiopulmonary system diseases (Table 5).

Discussion

ED are a chaotic environment that wears away at physicians, with excessive patient load, long working hours, and limited time for diagnosis. However, despite all the difficulties, physicians must meet the general standard of care in every environment

Table 2. Branch distribution of all physicians and physicians with medical malpractice

	Total physicians		Physicians with medical malpractice	
	n	%	n	%
General practitioner	570	51.7	97	64.2
Internal medicine	70	6.9	11	7.3
General surgery	65	5.9	8	5.3
Emergency medicine	61	5.6	5	3.3
Orthopedics and traumatology	51	4.7	5	3.3
Brain and nerve surgery	47	4.3	4	2.6
Anaesthesiology and reanimation	46	4.2	0	0
Pediatrics	33	3	8	5.3
Cardiology	32	2.9	2	1.3
Neurology	31	2.8	1	0.7
Chest diseases	14	1.4	2	1.3
Infection diseases	14	1.4	1	0.7
Otorhinolaryngology	9	0.8	2	1.3
Cardiovascular surgery	9	0.8	0	0
Radiology	8	0.7	0	0
Urology	7	0.6	0	0
Thorasic surgery	6	0.5	3	2
Family physician	5	0.4	0	0
Obstetrics and gynecology	5	0.4	0	0
Plastic surgery	4	0.3	1	0.7
Pediatric surgery	4	0.3	1	0.7
Psychiatry	4	0.3	0	0
Ophthalmology	1	0.1	0	0
Total	**1.102**	**100**	**151**	**100**

Table 3. Distribution of error types in medical malpractice		
Classification of medical malpractice	**n**	**%**
Diagnostic error		
Not being able to diagnose on time	29	21.3
Not requesting necessary medical tests and imagings	25	18.4
Not requesting consultations	19	14
Lack of examination	6	4.4
Treatment error		
Incomplete treatment	8	5.9
Follow-up error		
Lack of follow up in treatment process	19	14
Not admitting the patients that need to receive inpatient treatment	9	6.6
Referring patients carelessly or not referring	9	6.6
Breach of duty		
Causing negligence/breach of duty by not being present at the hospital	1	0.7
Causing negligence/breach of duty by not attending consultation	6	4.4
Multiple reasons	5	3.7
Total	**136**	**100**

and at any time of the day (14). Additionally, physicians in ED may be prone to malpractice due to the intensity of the emergency condition, poor relationship with patients, failure to follow diagnostic tests, insomnia, failure to complete medical documentation, and a previous history of malpractice (15). In their career, 75% of emergency physicians face malpractice allegations at least once (3).

In studies conducted in Turkey, medical malpractice victims were generally male (16,17). In this study, most cases (64.2%) were male, in line with the literature. The mean age of the cases with malpractice claims in general surgery has been reported to be 39.9±17.82 years, with 61% between the ages of 20-49 years (17), and the mean age of the cases that resulted in death in the claims about general surgery was 7.5±18.78 years (16). Almost half (43.3%) of the claims related to obstetrics and gynecology were between the ages of 31-40 years (18). In this study, the mean age of the cases was 38.92±24.8 years (min: 0, max: 87), and the highest number of cases was found to be in the 40-59 years age group. Generally, malpractice claims are seen more frequently related to patients in the fourth decade of life, and therefore physicians should approach patients in this age group more attentively.

Table 4. Primary illness diagnosis distribution in health organizations		
	n	**%**
Primary disease diagnosis		
Trauma	156	28.1
Infectious diseases	119	21.4
Cardiopulmonary diseases	85	15.2
Neuropsychiatric diseases	56	10.1
Gastrointestinal disorders	39	7
Intoxications	31	5.6
Urinary tract diseases	9	1.6
Undiagnosed	1	0.2
Others*	60	10.8
Total	**556**	**100**

*Others (anaphylaxis, diabetic ketoacidosis, myalgia, hyperglycemia, arthritis, bleeding from the ear, bleeding diathesis, pregnancy, dehydration, non-specific pain, etc.)

Previous studies have reported that the action leading to the malpractice claims were often in public hospitals (16,19,20)

Table 5. Distribution of medical malpractice causes according to the primary diagnosis

		Classification of medical malpractice									
		Diagnostic error		Treatment error		Follow-up error		Breach of duty		Multiple reasons	
		n	%	n	%	n	%	n	%	n	%
Primary disease diagnosis	**Trauma**	24	17.7	3	2.3	8	5.8	1	0.7	4	3
	Infectious diseases	17	12.5	1	0.7	9	6.5	1	0.7	1	0.7
	Cardiopulmonary diseases	11	8.1	-	-	4	3	3	2.3	-	-
	Gastrointestinal disorders	8	5.8	2	1.5	4	3	1	0.7	-	-
	Others	7	5.2	1	0.7	6	4.4	-	-	-	-
	Neuropsychiatric diseases	6	4.4	-	-	2	1.5	1	0.7	-	-
	Intoxications	4	3	1	0.7	3	2.3	-	-	-	-
	Urinary tract diseases	1	0.7	-	-	1	0.7	-	-	-	-
	Undiagnosed	1	0.7	-	-	-	-	-	-	-	-
Total		79	58.1	8	5.9	37	27,2	7	5.1	5	3.7

and there are also studies reported that it occurred in private hospitals (18,21). In this study, two-thirds (n=377, 67.8%) of the medical malpractice allegations occurred in a public hospital. The small number of physicians working in public hospital ED and the high number of patient admissions seems to be closely related to the higher incidence of malpractice allegations.

In the Netherlands, 16% of malpractice allegations related to emergency medicine were upheld (22). According to data from the Physician Insurers Association of America, there were 11,259 emergency medicine-related malpractice allegations between 1985 and 2007, of which 31% resulted in compensation (23). Turkan and Tugcu found that 49.1% of 112 emergency services-related malpractice allegations in Turkey were upheld by the Supreme Health Council (24). In this study, 136 (24.4%) of the lawsuit files were decided by the board to be the fault of the physician. Of 556 files, 1.102 physicians were accused and the board decided that 151 (13.7%) were at fault. In other words, 86.3% of the physicians were unfairly accused and no-fault was attributed to their medical practices. Moreover, 17% (97/570) of general practitioners working in the ED were found to be at fault by the board, while this rate was 8% for emergency medicine specialists and 24.2% for pediatricians.

In the USA, in malpractice allegations that occurred in the ED with cases concluded between 2001 and 2015, emergency physicians were accused most frequently (33.5%), followed by internists (12.4%), family physicians (6.6%), radiologists (7.3%) and general surgeons (7.1%) (10). In the Netherlands, 76% of malpractice claims in the ED were related to emergency physicians, and only 15% were related to other medical branches (22). In this study, more than half of the physicians (57.3%) accused of malpractice were working as emergency physicians (general practitioner/emergency medicine specialists). Apart from emergency physicians (general practitioners and emergency medicine specialists), internists (6.9%) and general surgeons (5.9%) most frequently faced malpractice allegations.

Brown et al. (23) reported that diagnostic error (37%) was the most common malpractice in ED. In the USA, the most common reason for paying compensation due to malpractice in adult emergency services was diagnostic error (36.4%) (10). Studies have shown that in pediatric emergency services, physicians often had to pay compensation due to diagnostic errors (39-41%) (12,25). Morgenstern et al. (26) found that most allegations of emergency medicine malpractice were associated with underdiagnosis, misdiagnosis, and delayed diagnosis. In the Netherlands, the most common malpractice claims (48%) in emergency departments was the failure to make a correct diagnosis (22). In a study of emergency medicine physicians' medical malpractice, diagnostic error was the basis of 58% of the claims (13). In this study, diagnostic errors (n=79, 58.1%) were the most common cause of malpractice, and the most common faulty actions were failure to diagnose on time, misdiagnosis (n=29, 21.3%) and not request the necessary tests/imaging (n=25, 18.4%).

Brown et al. (23) stated that acute myocardial infarction (5%) and fractures (6%) were the health conditions associated with the most complaints in emergency services. Myers et al. (13) reported cardiac arrest, pulmonary embolism and acute myocardial infarction to be the three most common diagnoses for which emergency physicians are most blamed for in malpractice. In a study covering a 15-year period, the most common diagnoses in malpractice claims closed with compensation payments were cardiac and cardiopulmonary arrest (9.1%) and acute myocardial infarction (4%) (10). In Taiwan, the most common causes of malpractice allegations in ED were infectious diseases (27%), central nervous system bleeding (15.9%), and trauma (12.7%) (7). Emergency physicians in Massachusetts are reported to be often accused of malpractice due to trauma-related injuries and fractures (27). Nearly half (49%) of allegations about ED in the Netherlands were related to fractures and dislocations caused by trauma (22). In this study, patients were diagnosed with trauma most frequently (n=156, 28.1%), followed by infection (n=119, 21.4%). The findings obtained in this study prove that sudden post-traumatic deaths increase the risk of physicians being accused of malpractice. Therefore, when patients are admitted due to trauma, good communication with the relatives, performing the necessary examinations and consultations, and keeping and maintaining the medical records, including informed consent, will protect physicians against malpractice claims and will strengthen the physician's legal positions.

The most common diagnostic error and missed diagnosis in ED have been reported to be minor traumas, such as fractures and dislocations (28). In Massachusetts, emergency physicians most frequently paid compensation for undiagnosed myocardial infarction (chest pain) and trauma-related fractures that were overlooked (27). In the United Kingdom, 79.7% of 953 diagnostic errors were determined to be associated with undiagnosed trauma-related fractures (29). Traumatic injuries were the leading allegation associated with diagnostic errors in a study in Japan (11). The condition associated with the highest compensation in ED has been reported to be the missed diagnosis of acute myocardial infarction (15). In this study, a diagnostic error was the most common error in trauma, infectious diseases, cardiopulmonary system diseases, gastrointestinal system diseases and neuropsychiatric diseases. The reasons for making the highest number of diagnostic errors in many diseases are the working of inexperienced practitioners, prolonged shifts, the excessive workload, and the need to diagnose in a short time.

Study Limitations

This study had its strength as well as its weaknesses. The medical malpractice decisions in this study were merely the conclusions of an expert institution and did not reflect the final court judgment. The inability to include the court's final judgment was a critical impediment. As the Forensic Medicine Institute is not an exclusive authority, the board's expert report may be traversable, and the court is not obligated to follow the expert's conclusion. Another constraint was the lack of information regarding the compensation sums that the physicians were required to pay by the litigation. Furthermore, because this study only included cases that resulted in death, it cannot be said to effectively represent the complete sample.

Conclusion

ED are one of the most important sources of malpractice claims. However, the results of this study demonstrated that a great majority of physicians (86.3%) were wrongfully accused of malpractice. General practitioners were blamed most frequently in emergency services and committed the most errors. The most common diagnosis in the health institution was trauma (28.1%), and in this study, diagnostic errors (n=79, 58.1%) were the most common reason for an allagetion of malpractice. Considering that the physicians who were accused and made errors in this study were mostly general practitioners and the most common malpractice was diagnostic error, it can be recommended that newly qualified practitioners should not be employed alone in the ED without the support of experienced colleagues. In a previous study conducted in Turkey, 44.4% of emergency medicine specialists working in ED had adequate knowledge about the current legal regulations regarding malpractice, while this rate was 12.2% for general practitioners, and 63% of physicians had not received in-service training on legal responsibility (30). Therefore, training on malpractice claims and prevention strategies should be given to general practitioners who are just starting their professional life.

Ethics

Ethics Committee Approval: The study were approved by the İstanbul Forensic Medicine Institute (no: 21589509/1020, date: 15.12.2015).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: E.G., İ.Ü., E.H., Design: E.G., İ.Ü., E.H., B.H., Data Collection or Processing: E.G., B.H., Analysis or Interpretation: E.G., İ.Ü., E.H., Literature Search: E.G., İ.Ü., E.H., B.H., Writing: E.G., İ.Ü., E.H.

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Association of Smoking Status with Outcomes in Intensive Care Unit with COVID-19

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Abstract

Aim: The effect of smoking on patients hospitalized in the intensive care unit (ICU) due to Coronavirus disease-2019 (COVID-19) infection is unknown. The study determines the relationship between COVID-19 and smoking status on the development of disease and critical illness.

Materials and Methods: The patient files and hospital information system records of COVID-19 patients over the age of eighteen who were hospitalized in the ICU of our hospital between March 2020 and January 2021 and confirmed by polymerase chain reaction method were retrospectively reviewed.

Results: 1.003 of 226 COVID-19 patients included in the study, 58% were male, and the mean age was 65.38 (±14.99). The patients' smoking status was categorized as non-smokers, ex-smokers, and current daily smokers (74.8%; 23%; 2.2%; respectively). The most common comorbid disease of the patients was hypertension (58%). One hundred seventy-nine patients were given respiratory support with invasive mechanical ventilation (IMV), and 37.2% were discharged. The mean duration of IMV application, hospitalization, and hospitalization in the ICU was 7.11 (±5.51); 14.42 (±10.25), respectively; it was 7.58 (±6.29) days. The average APACHE-II score was 23.87±8.86. Mortality was statistically significantly higher in those who received mechanical ventilator support from patients with no smoker stage and without the comorbid disease (p=0.009).

Conclusion: Although the percentage of current smokers in patients hospitalized in the ICU due to COVID-19 is relatively low, we believe that polygenetic and multiple factors can explain it. It should not be recommended that tobacco products be administered for either preventive or therapeutic purposes in the case of COVID-19 infection.

Keywords: COVID-19, critical care, hospitalization, public health, smoking

Introduction

According to the weekly report of the World Health Organization (WHO) dated February 13, 2021, over 174 million confirmed cases and more than 3.7 million deaths had been reported since the start of the Coronavirus disease-2019 (COVID-19) (1). The first documented COVID-19 in Turkey was reported from İstanbul on March 11, 2020. Since this date, a total of over 9.136.565 cases and more than 80 thousand deaths have been observed (2). From the beginning of the pandemic to the present, the "pandemic management guideline" were updated periodically by the scientific board of the Turkish Ministry of Health for health professionals. The severity and course of the disease are affected depending on the characteristics of the patient, such as advanced age, male gender, underlying conditions such as cancer, chronic renal failure, chronic obstructive pulmonary diseases, coronary artery disease, immunodeficiency status (3,4). To avoid smoking-related diseases, it is advised to quit or not to start if one has never used it or stopped and seek behavioral and pharmacological treatment if necessary (5,6). Unfortunately, the rate of smoking in Turkey is quite high compared to many developed countries such as European countries. According to 2019 Turkish Statistical Institute data, when tobacco users were examined by age groups, the highest rate was 42.8% in the 35-44 age group, while the daily smoker rate among aged 15 and over was 18.4% in the European population (7,8). In fact, in countries such as South

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Africa and India, cigarette sales are prohibited during curfews (6). According to WHO's report on the global tobacco epidemic, 2019: with WHO's MPOWER (**M**onitor tobacco use and prevent on policies, **P**rotect people from tobacco use, **O**ffer help to quit tobacco use, **W**arn about the dangers of tobacco, **E**nforce bans on tobacco advertsing, promotion and sponsorship, **R**aise taxes on tobacco) campaign, which started in 2003 for protecting people from tobacco smoke, between 2007 and 2017, smoking rates decreased from a global average of 22.5% to 19.2%, showing a relative reduction of 15% over ten years (9). Although there are studies on the smoking relationship of COVID-19 infection, there is not enough data on this subject. A review study found that smoking does not carry a risk in terms of disease but takes a chance in serious illness, mechanical ventilation, and death (10). In some studies, it has been shown that there is no significant relationship between active smoking and severe disease in COVID-19 patients (11). Therefore, a definite conclusion could not be formed in the literature.

In this study, we tried showing the relationship between COVID-19 and the smoking status of 226 critically hospitalized patients due to COVID-19 infection in the intensive care unit (ICU). The state of being infected with COVID-19 and its effect on developing critical illness contributed to the literature.

Materials and Methods

Study Design and Patient Characteristics

The ethics committee has approved the study by University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital (file number: 2021/22, date: 11.03.2021). The patient files and hospital information system records of COVID-19 patients over the age of 18 who were hospitalized in the ICU of our hospital between March 2020 and January 2021 and confirmed by polymerase chain reaction (PCR) method were retrospectively reviewed.

Infection of COVID-19 is confirmed using PCR testing from nasal or endotracheal aspirate from patients with typical viral pneumonia (ground-glass opacities, air space consolidation, bronchovascular thickening in the lesion, traction bronchiectasis). Additionally, patients with signs of consolidation or infiltration that are not specific to viral pneumonia have been examined.

It is used to express cigarettes, fabricated and rolled tobacco, or tobacco products such as cigars, hookah, pipes. The patients' smoking status was divided into three categories as non-smokers, ex-smokers, and current daily smokers. Patients who have never smoked in their lives are named non-smokers. Current daily smokers are the ones who consume cigarettes daily and whose cigarettes vary depending on the day. Finally, ex-smokers are the ones who smoked in varying amounts regularly or quit smoking intermittently rather than every day.

In addition to smoking status, demographic pieces of information, other diseases, presence of invasive and non-invasive mechanical ventilation (NIMV), length of stay in an ICU, total hospital stay, outcomes, and estimated mortality risks calculated by APACHE II score (Acute Physiology and Chronic Health Evaluation) (10) of the patients were recorded. APACHE II score system includes a 12-point acute physiology score (including temperature, heart rate, respiratory rate, mean arterial pressure, oxygen partial pressure, Ph, K+, Na+, creatinine, hematocrit, white blood cell counts, and Glasgow coma scale), Age, and chronic health evaluation.

Within the scope of the study, 1.003 COVID-19 patients whose clinical or chest computed tomography findings were hospitalized in the ICU were examined. Two hundred-sixty of these patients whose clinical and chest computed tomography findings were thought to be compatible with COVID-19 were included in the study because to the data were complete. Of these patients, 229 had a positive PCR test, and 31 had a negative PCR test. Three of the patients with positive PCR tests were excluded from the study due to a lack of data. And 226 patients were included in the study. Flowchart of patient selection is as follows (Figure 1):

Selection of Participants:

Inclusion criteria of the study;

- >18 years old.

Patient with respiratory failure in ICU needing NIMV or invasive mechanical ventilator (IMV).

- Patient with a COVID-19 PCR test (+).

Exclusion criteria of the study;

- <18 years old.
- Pregnancy.
- The patient was followed up outside the covid ICU.
- Patient with missing or insufficient hospital data.

Statistical Analysis

The conformity of the numerical variables to the normal distribution was tested with the Shapiro-Wilk test. Student's t-test was used to compare normally distributed variables in the two groups. The Mann-Whitney U test was used to compare non-normally distributed variables in the two groups. Relationships between categorical variables were tested with the chi-square test. The ROC curve was used to determine the cut points for

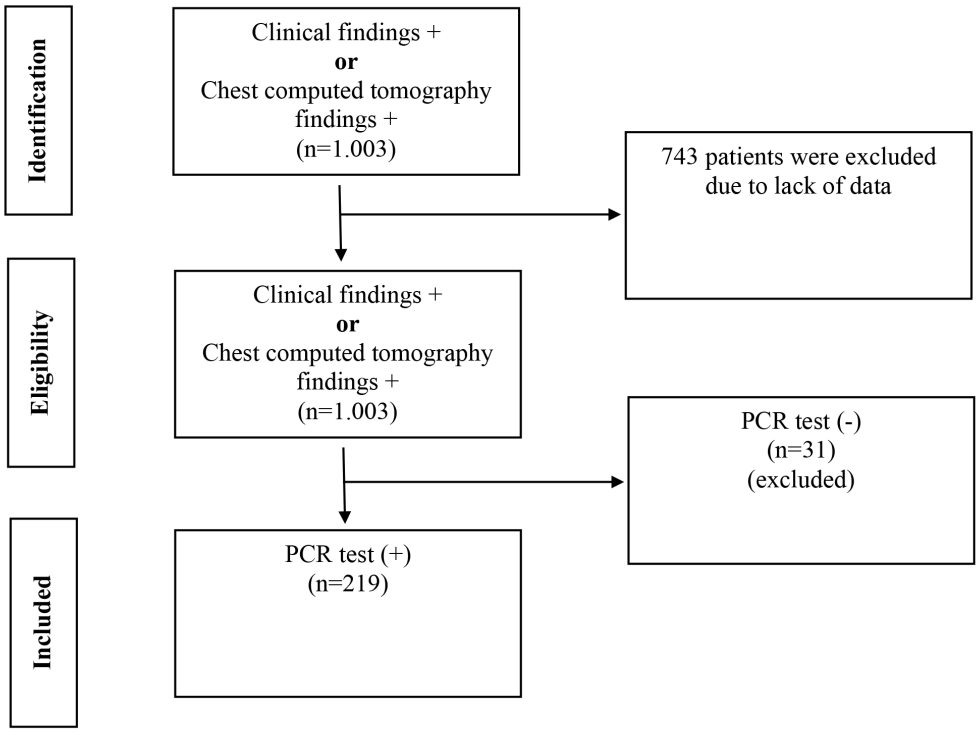

Figure 1. Flow chart of patient selection
PCR: Polymerase chain reaction

the APACHE score. The Statistical Package for the Social Sciences 22.0 Windows version package program was used in the analysis. P<0.05 was considered significant.

Results

Two hundred twenty-six patients were included in the study, 58% of these patients were male, and the mean age was 65.38 (±14.99). 74.8% of them were non-smokers, 23% of them were ex-smokers, and interestingly, at least 2.2% of them were current daily smokers. The most common comorbid disease of the patients was hypertension (58%). One hundred seventy-nine patients were given respiratory support with IMV, and 37.2% were discharged (Table 1).

While the mean duration of IMV application of the patients was 7.11 (±5.51) days, the mean duration of NIMV application was found to be 2.91 (±3.28) days. The mean hospital and ICU length of stay of the patients were 14.42 (±10.25), respectively; it was 7.58 (±6.29). The mean APACHE II score was 23.87±8.86 (Table 2).

The discrimination of the APACHE II score for mortality status was found to be good [AUC=0.870±0.023, (p<0.001)]. If the APACHE II score is above 23, sensitivity is 68.31% [95% confidence

Table 1. Baseline characteristics of patients infected with COVID-19

Baseline characteristics		**n (%)**
Gender	Male	131 (58)
	Female	95 (42)
Smoking status	Daily current smokers	5 (2.2)
	Not-smokers ever	169 (74.8)
	Ex-smokers	52 (23)
Comorbidity		
COPD		34 (15)
HT		131 (58)
DM		78 (34.5)
CHF		59 (26.1)
Malignancy		20 (8.8)
NIMV		79 (35)
IMV		179 (79.2)
Outcome	Survivor	84 (37.2)
	Non-survivor	142 (62.8)

COPD: Chronic obstructive lung disease, HT: Hypertension, DM: Diabetes mellitus, CHF: Chronic heart failure, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation, COVID-19: Coronavirus disease-2019

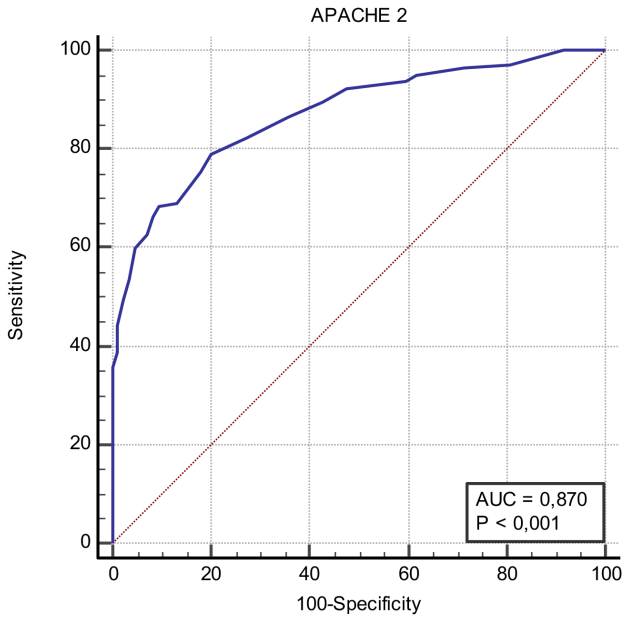

Figure 2. Receiver operating characteristic curves for predicting mortality based on APACHE II score for patients infected with COVID-19

COVID-19: Coronavirus disease-2019

interval (CI)=60.0-75.9], specificity 90.48% (95% CI=82.1-95,8) to distinguish patients with mortality (Figure 2). We found that the mean APACHE II score of the patients who died was significantly higher than the patients who survived.

The mean age of the patients who died (68.86±12.63 years) was significantly higher than those who survived (p=0.001). No significant relationship was found between the gender and smoking status of the patients and mortality (p=0.520, p=0.619; respectively). The mortality rate of patients with chronic disease and hypertension from these diseases was higher than the others, and this rate was statistically significant (p=0.023, p=0.007; respectively).

We observed that patients who underwent IMV were significantly more mortal (p=0.001) (Table 3).

When the relationship between survival and mortality of the patients who underwent mechanical ventilation was evaluated according to comorbidity status, it was determined that all the patients with comorbidities who were not mechanically ventilated survived, and mortality developed in only a patient who had no comorbidity and were not mechanically ventilated (p=0.001; 0.004; respectively) (Table 4).

When the relationship between survival and mortality in mechanically ventilated patients was examined based on smoking and comorbidity status, mortality was significantly higher in those who received mechanical ventilator support from ex-smokers and non-smoker stage patients with comorbidity (p=0.001). While there was no statistically significant difference in mortality between ex-smokers and non-comorbid patients who received mechanical ventilation support versus those who did not (p=0.410), mortality was statistically significantly higher in those who received mechanical ventilation support from patients who were non-smokers and did not have a comorbidity (p=0.009) (Table 5). This table was not subjected to statistical analysis due to the small number of active smokers.

Discussion

In this retrospective study, 226 patients hospitalized in the ICU were examined. Male gender and advanced age (>65) are most frequently associated with mortality and severity of the disease, according to an analysis of a large amount of data obtained at the beginning of the pandemic. The presence of comorbidities (hypertension, diabetes, etc.) in the patient also contributes (5,11,12). In our study, we observed that male gender and advanced age were correlated with the severity of the disease course, following the literature, hypertension was the most common chronic disease among the patients, and this was significantly higher in cases with a mortal approach. Studies suggest that malignancy, a comorbidity, is more susceptible to

Table 2. Descriptive statistics for numeric variables

Descriptive statistics	n	Mean±SD	Median (min-max)
Age	226	65.38±14.99	66 (18-96)
Duration of IMV (days)	164	7.11±5.51	6 (1-30)
Duration of NIMV (days)	79	2.91±3.28	1 (1-18)
Length of stay in the hospital (days)	226	14.42±10.25	12 (1-59)
Length of stay in the ICU (days)	226	7.58±6.29	6 (1-32)
APACHE II score	226	23.87±8.86	22 (5-55)

*A p-value less than 0.05 (typically ≤0.05) is statistically significant, Mann-Whitney U test.
Min-max: Minimum-maximum, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation, ICU: Intensive care unit, SD: Standard deviation

Table 3. Relationship between variables and mortality

Variables		Non-survivor	Survivor	
		n (%)	n (%)	p
Gender	Male	80 (56.7)	51 (60.7)	0.520
	Female	62 (43.7)	33 (39.3)	
Smoking status	Not-smokers ever	104 (73.2)	65 (77.4)	0.619
	Ex-smokers	34 (23.9)	18 (21.4)	
	Daily current smokers	4 (2.8)	1 (1.2)	
Comorbidity	No	24 (16.9)	25 (29.8)	0.023*
	Yes	118 (83.1)	59 (70.2)	
COPD	No	118 (83.1)	74 (88.1)	0.310
	Yes	24 (16.9)	10 (11.9)	
HT	No	50 (35.2)	45 (53.6)	0.007*
	Yes	92 (64.8)	39 (46.4)	
DM	No	89 (62.7)	59 (70.2)	0.248
	Yes	53 (37.3)	25 (29.8)	
CHF	No	99 (69.7)	68 (81)	0.063
	Yes	43 (30.3)	16 (19)	
Malignancy	No	132 (93)	74 (88.1)	0.214
	Yes	10 (7)	10 (11.9)	
NIMV	Not receiving	96 (67.6)	51 (60.7)	0.294
	Receiving	46 (32.4)	33 (39.3)	
IMV	Not receiving	1 (0.7)	46 (54.8)	0.001*
	Receiving	141 (99.3)	38 (45.2)	
Mechanical ventilation	Not receiving	1 (0.7)	39 (46.4)	0.001*
	Receiving	141 (99.3)	45 (53.6)	

*A p-value less than 0.05 is statistically significant, chi-square test.
COPD: Chronic obstructive lung disease, HT: Hypertension, DM: Diabetes mellitus, CHF: Chronic heart failure, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation

Table 4. The relationship of mechanical ventilated patients with survival and mortality by comorbidity status

				Non-survivor	Survivor	
				n (%)	n (%)	p
Comorbidity	Yes	NIMV	Yes	35 (29.9)	21 (35.6)	0.445
			No	82 (70.1)	38 (64.4)	
		IMV	Yes	117 (100)	28 (47.5)	0.001*
			No	0 (0)	31 (52.5)	
		Mechanical ventilation	Received	117 (100)	30 (50.8)	0.001*
			Not received	0 (0)	29 (49.2)	
	No	NIMV	Yes	10 (47.6)	11 (45.8)	0.905
			No	11 (52.4)	13 (54.2)	
		IMV	Yes	20 (95.2)	10 (41.7)	0.001*
			No	1 (4.8)	14 (58.3)	
		Mechanical ventilation	Received	20 (95.2)	14 (58.3)	0.004*
			Not received	1 (4.8)	10 (41.7)	

*A p-value less than 0.05 (typically ≤0.05) is statistically significant, chi-square test.
NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation

Table 5. The relationship of mechanical ventilated patients with survival and mortality by smoking and comorbidity status

						Non-survivor	Survivor	
						n (%)	n (%)	p
Smoking status	Ex-smokers	Comorbidity	Yes	NIMV	Yes	7 (21.2)	6 (40)	0.293
					No	26 (78.8)	9 (60)	
				IMV	Yes	33 (100)	7 (46.7)	0.001*
					No	0 (0)	8 (53.3)	
				Mechanical ventilation	Received	33 (100)	9 (60)	0.001*
					Not received	0 (0)	6 (40)	
			No	NIMV	Yes	0 (0)	1 (33.3)	0.410
					No	1 (100)	2 (66.7)	
				IMV	Yes	1 (100)	2 (66.7)	0.410
					No	0 (0)	1 (33.3)	
				Mechanical ventilation	Received	1 (100)	2 (66.7)	0.410
					Not received	0 (0)	1 (33.3)	
	Not-smokers ever	Comorbidity	Yes	NIMV	Yes	28 (33.3)	15 (34.1)	0.931
					No	56 (66.7)	29 (65.9)	
				IMV	Yes	84 (100)	21 (47.7)	0.001*
					No	0 (0)	23 (52.3)	
				Mechanical ventilation	Received	84 (100)	21 (47.7)	0.001*
					Not received	0 (0)	23 (52.3)	
			No	NIMV	Yes	10 (50)	10 (47.6)	0.879
					No	10 (50)	11 (52.4)	
				IMV	Yes	19 (95)	8 (38.1)	0.001*
					No	1 (5)	13 (61.9)	
				Mechanical ventilation	Received	19 (95)	12 (57.1)	0.009*
					Not received	1 (5)	9 (42.9)	

*Significant at the $p<0.05$ level. Chi-square test.
NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation

severe acute respiratory syndrome infection and complications such as ICU admission, the need for IMV and mortality. In the study of Moiseev et al. (13), it was stated that a relationship between malignancy and COVID-19 was proven to be insufficient compared to the available data. In our study, we found that the mortality rate of patients with malignancy was 50%. Still, we believe that mortality may be affected not only by the malignancy but also by other diseases, the patient's general condition, lung capacity, and cancer stage. In conclusion, malignancy was not a significant factor in COVID-19 infection-related survival in our study.

Although there were many scientific studies during the pandemic, a clear and single parameter is showing the course of the disease could not be obtained. The APACHE II score is frequently used in studies because of its ability to distinguish clinical severity. It can not only predict mortality but also assist the clinician in airway management decisions. In patients treated in the ICU for COVID-19, Cheng et al. (14) found high-flow oxygen inhalation with an APACHE II score of 9.5, NIMV support with a score of 9.5-12, and invasive ventilator support with a score of >12.5 can be considered. If this score was >11.5, the patient would be at a risk of death. Because of the study, it was stated that it is an effective indicator in the estimation of disease severity and mortality. In some studies, the median mean of the APACHE II score in COVID-19 patients hospitalized in the ICU is 17 and differs between patients who died and lived with serious illness (15). As in other studies, the APACHE II score average of patients who died in our study was significantly higher than that of surviving patients. The APACHE II (median mean 22) value is significant in terms of mortality discrimination.

Patients with severe COVID-19 infection generally need mechanical ventilators, and the mortality rate is high in these

patients who are followed up under ICU conditions (16-19). Our study observed that the mortality of patients who did not undergo mechanical ventilation was significantly lower when both comorbidity and smoking status of the patients were considered, which is consistent with the literature.

Smoking is an essential factor in cardiovascular and lung diseases. It shows its effect through nicotinic receptors overexpressed in heart tissue, blood vessels, and lung cells (20,21). Nicotinic receptors activated by this effect of smoking increase protease activation, apoptosis, and inflammatory response. According to studies, the COVID-19 virus exerts its influence through a similar receptor. Of course, the impact of cigarettes depends on the nicotic receptor and shows the effect of many toxins such as carbon monoxide and polycyclic aromatic hydrocarbons. It is thought that smoking affects the outcome of patients infected with COVID-19 for such reasons (22).

A meta-analysis examining the prevalence of smoking in hospitalized COVID-19 patients in China shows that current smoking is not a predisposing factor for hospitalization for COVID-19 (23). In the report of the US CDC consisting of 7.162 COVID-19 cases from the first months of the pandemic, the current smoker rate of patients was reported as 1.3% and the ex-smoker rate as 2.3% (24). In another study conducted in China in 2019, the characteristics of patients with COVID-19 infection were examined. It was determined that 85.4% of the patients and 77.9% of those who had severe illnesses were never smokers (25). In the study of Petrilli et al. (19), it was not determined that tobacco use was associated with an increased risk of hospitalization or critical illness, and it was even observed that it was protective in terms of hospitalization. Ho et al. (26), on the other hand, found that it is not associated with in-hospital mortality due to COVID-19 pneumonia.

Contrary to these studies, other studies show that the severity of COVID-19, in-hospital mortality rate, and the need for mechanical ventilation increase, especially in patients with a smoking history (27-29). According to the study results, the rate of the current daily smokers was 2.2%, and the rate of ex-smokers was 23%. Notably our ICU patients mainly consist of non-smokers, and ex-smokers. Although there was no significant difference in the mortality rate in our study, the development of mortality in 80% of active smokers (4 of five patients) may lead us to investigate the factors that prevent the patient from becoming infected. Still, we can conclude that it can significantly increase mortality after infection.

However, smokers generally have an increased risk of comorbidities, particularly cardiovascular and chronic respiratory diseases. Therefore, it is an expected result that the risk of hospitalization due to COVID-19 is higher in people with smoking-related comorbidity than in healthy smokers. Apart from these effects, we believe that polygenetic factors have an impact. There is still no conclusive evidence for the effect of smoking on the disease and severity of COVID-19.

Study Limitations

- There is a possibility that some patients who describe themselves as ex-smokers have quit smoking because they have the disease or shortly before the illness. Because of this, the duration of smoking cessation in some patients could not be evaluated objectively.

- Due to the low rate of current smokers included in the study, comparison between ex-smokers and non-smokers could not be made sufficiently.

- Only patients hospitalized in the ICU of a city hospital were included in the study population.

- The study was conducted retrospectively. Patient data were obtained from hospital medical data. Therefore, detailed medical records could not be reached.

Conclusion

It is seen that the percentage of current smokers in patients hospitalized in ICU due to COVID-19 during the pandemic period in societies with high smoking rates, such as Turkey and China is relatively low. Although it is impossible to express this situation with a single factor, we think it is possible to explain it due to polygenetic and multifactorial reasons. Because of our study, although the percentage of current smokers is determined to be low, it should not be defended that tobacco products are given neither for protection nor for treatment against COVID-19 infection.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital of Local Ethics Committee (file number: 2021/22, date: 11.03.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.H., Concept: M.S., Design: M.S., Data Collection or Processing: D.H., Analysis, or Interpretation: D.H., M.S., Literature Search: M.S., Writing: D.H., M.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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A COVID-19 Patient Presenting with Acute Hepatitis

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Abstract

A 55-year-old male patient presented to our outpatient clinic with complaints of dark urine and fatigue. The laboratory parameters were as follows: alanine aminotransferase 821 IU/L, aspartate aminotransferase 1042 IU/L, alkaline phosphatase 412 IU/L gamma-glutamyl transferase 268 IU/L and the complete urinalysis revealed hematuria, while other laboratory parameters were normal. The patient's abdominal ultrasonography (USG) and Doppler USG showed no pathological finding. Hepatitis and the other serologies were negative. The patient, who did not exhibit any symptoms of Coronavirus disease-2019 (COVID-19) initially, exhibited bilateral opacities in the middle zones on chest X-ray taken after the development of fever and dyspnea on the third day of hospitalization. The computed tomography scan revealed segmental consolidation across the subpleural regions, mostly in the middle zones, and was evaluated to be consistent with COVID-19. COVID-19 treatment was planned for the patient whose nasopharyngeal swab tested positive for severe acute respiratory syndrome-Coronavirus-2.

Keywords: Acute hepatitis, COVID-19, SARS-CoV-2

Introduction

In December 2019, a novel coronavirus was considered the cause of a group of pneumonia cases in Wuhan, a city in Hubei Province, China. It spread rapidly and resulted in an epidemic across China, followed by a worldwide pandemic with almost 2 million confirmed cases (1). In February 2020, the World Health Organization officially named the disease as "Coronavirus disease-2019 (COVID-19)", which stands for coronavirus disease 2019. The virus that caused COVID-19 was named as Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2). Although severe COVID-19 disease can occur in healthy individuals of all ages, it has been observed to affect predominantly adults with advanced age or underlying diseases (2). By reporting this case, we emphasized that COVID-19 should also be included in the differential diagnosis of patients presenting with acute hepatitis during the pandemic.

Case Report

A 55-year-old male patient presented to our outpatient clinic with complaints of dark urine and fatigue for two days. He did not exhibit dry cough, dyspnea, elevated fever, sore throat, runny nose, headache, myalgia, disrupted sense of smell and taste, and diarrhea, which are the symptoms of COVID-19. Moreover, COVID-19 was not considered in the foreground as the patient did not report a history of traveling out of the city in the last 14 days and contact with anyone diagnosed with COVID-19. The patient's history revealed primary hypertension, diabetes mellitus type-2 and osteoporosis, and the medications used for these conditions as follows: nifedipine, calcium citrate, vitamin D, and metformin. Part of this, it was learned that he did not use any medicine or herbal product within the last week. His physical examination revealed no pathological findings, and his vital signs were as follows: pulse 70 bus, blood pressure 110/75 mmHg and body temperature 36.7 °C. Laboratory results were as follows: hemoglobin 13.5 g/dL (13.5-17.5 g/dL), white blood cell 8100 cells/mcL (3.500-10.500 cells/mcL), platelet count 172,000 mcL (150.000-450.000/mcL), serum creatinine 1.1 mg/dL (0.6-1.2 mg/dL), blood urea nitrogen 19 mg/dL (6-20 m/dL), sodium 135 mmol/L (136-146 mmol/L), potassium 4.3 mmol/L (3.5-5.1 mmol/L), calcium 8.9 mg/dL (8.8-10.6 mg/dL), phosphorus 2.8 mg/dL (2.5-4.5 mg/dL), alanine aminotransferase (ALT) 821

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IU/L (0-50 IU/L), aspartate aminotransferase (AST) 1042 IU/L (0-50 IU/L), alkaline phosphatase (ALP) 412 IU/L (40-150 IU/L), gamma-glutamyl transferase (GGT) 268 IU/L (9-64 IU/L), lactate dehydrogenase 231 IU/L (0-248 IU/L), uric acid 6.0 mg/dL (3.5-7.2 mg/dL), total bilirubin 0.52 mg/dL (0.3-1.2 mg/dL), unconjugated bilirubin 0.49 mg/dL (0.0-0.8 mg/dL), conjugated bilirubin 0.03 mg/dL (0.0-0.2 mg/dL), international normalized ratio (INR) 1.02 (0.8-1.2), albumin 3.0 g/dL (3.5-5.2 g/dL), C-reactive protein (CRP) 7 mg/dL (5-10 mg/dL), glucose 88 mg/dL and hematuria was detected in the complete urinalysis. Hepatitis A, B, C, E, human immunodeficiency virus, Cytomegalovirus, Epstein-Barr virus, *Brucella melitensis*, and *Toxoplasma gondii* serology and blood culture were negative. Autoimmune markers studied to rule out autoimmune diseases of the liver were negative. Abdominal ultrasonography (USG) and Doppler USG showed no pathological findings other than grade-1 hepatosteatosis in the liver. On the third day of hospitalization, the patient developed dyspnea and low saturation (SaO_2 93%) with 38.7 °C fever. The posteroanterior chest X-ray revealed bilateral opacities in the middle zones, whereas the subsequent lung computed tomography revealed a segmental consolidation scattered across the subpleural areas in the middle zones, which was evaluated to be consistent with COVID-19. The nasopharyngeal swab sample tested positive for SARS-CoV-2 because of reverse transcriptase-polymerase chain reaction assay. The patient was administered 200-mg hydroxychloroquine for 5 days in accordance with the treatment protocol applied in Turkey. The post-treatment laboratory results of the patient with good general condition and stable vital signs were as follows: ALT: 117 IU/L, AST: 221 IU/L, ALP: 171 IU/L, GGT: 97 IU/L, total bilirubin: 0.41 mg/dL, INR: 0.9, albumin: 3.7 g/dL, CRP: 3 mg/dL. The patient was discharged upon improved laboratory values and no pathological findings on vital signs and physical examination.

Discussion

The person-to-person transmission was confirmed with the rapid increase in the number of cases following the first reports of COVID-19 along with the emergence of the disease among healthcare workers (3). Although believed to be transmitted by droplets, recent cases have revealed evidence of transmission without any contact with infected individuals. It is considered that asymptomatic individuals may carry the virus in the airways and cause transmission, but transmission mainly occurs via contact with infected individuals. The clinical outcomes of COVID-19 can be mild and severe, with varying degrees or even clinical outcomes lead to death (4). To date, it remains unclear why some patients have developed severe symptoms. Recently, an article reported that COVID-19 affected liver metabolism, but acute hepatitis occurs rarely after COVID-19. Various degrees of liver damage have been observed in COVID-19 patients (5). Recent studies have shown that COVID-19 patients exhibit elevated AST or ALT in case of severe liver damage, whereas the elevation of bilirubin is mild (6). Although the elevation of liver enzymes is mild to moderate in most cases, a case presenting with acute hepatitis before the development of respiratory symptoms was recently published (7). Furthermore, Weber et al. (8) recently presented a case of severe hepatic impairment in a COVID-19 patient with a high model for end-stage liver disease score who had no previous liver disease. However, there is currently insufficient data on cirrhosis and other complications in patients with COVID-19; therefore, there is a need for more research. Although the mechanism of liver damage associated with SARS-CoV-2 remains unclear, the cause of elevated liver enzymes may be the direct effect of the virus on the liver with the angiotensin-converting enzyme 2 (ACE2) receptors (9). Previous studies have shown that ACE2 receptors are expressed in both bile duct and liver cells, but the concentration of ACE2 receptors in hepatocytes is much lower, indicating that liver damage is due to the damage to cholangiocytes (10). However, histopathological liver findings of COVID-19 patients did not exhibit any significant hepatocyte and cholangiocyte damage as cholestatic liver enzymes do not usually increase in COVID-19 patients with liver damage (11). Liver damage in COVID-19 patients may be caused by a hyperactive immune response and cytokine storm or systemic inflammation due to drug hepatotoxicity. Therefore, close patient follow-up and monitoring of liver function are required (12).

Conclusion

In conclusion, our patient's fever and dyspnea improved within a few days without any specific treatment, and the liver function parameters were found to decreased significantly on the fifth day following the diagnosis of COVID-19. Acute hepatitis appears quite rarely, considering that a new symptom and clinical condition are associated with COVID-19 every day. Elevated liver function parameters in individuals without significant COVID-19 symptoms should be regarded as an indicator of COVID-19.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.N.K., Concept: M.N.K., Design: S.F.S., Data Collection or Processing: M.N.K., Analysis or Interpretation: M.N.K., Literature Search: S.F.S., Writing: M.N.K.

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Successful Management of Severe Verapamil Overdose with VA-ECMO

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Abstract

Calcium channel blocker poisonings are the most common agents causing mortality in worldwide and new approaches and updates on antidotal and supportive treatment are still under the investigation. In this case report, the lifesaving effect of veno-arterial-extracorporeal membrane oxygenation support on the sequel-free health of the patients when exposed to cardiovascular system toxicity such as verapamil+trandolapril isosorbid dinitrate for suicidal purposes was discussed, who developed shock not responding to pharmacotherapy and antidote treatments at the 55th hour of drug intake discussed.

Keywords: Verapamil, toxicology, ECMO

Introduction

Calcium channel blocker (CCB) poisonings are the most common agents causing mortality in worldwide and new approaches and updates on antidotal and supportive treatment are still under the investigation. Verapamil is a Class IV antiarrhythmic agent used most commonly for treating supraventricular tachy-arrhythmia and hypertension, and the nondihydropiridine group is a CCB (1,2). The purpose of this case report was to discuss the clinical management of a patient who was stabilized with veno-arterial-extracorporeal membrane oxygenation (VA-ECMO) in the early period of cardiovascular failure, recovered without sequelae in late pharmacotherapy in clinical follow-up after high dose verapamil intake.

Case Report

A 36-year-old man with a history of hypertension and multiple suicide attempts presented to our emergency department (ED) approximately 45 min after ingesting in a suicide attempt, his own 42 tablets of Tarka forte® (verapamil hyrochloride/trandolapril-immediate release) 240/4 mg per tablet, 9 tablets of Zestat® (mirtazapine) 15 mg per tablet, and 14 tablets of Isordil® (isosorbid dinitrate) 5 mg per tablet. He was alert, oriented and cooperative. His initial vital signs were stable (heart rate: 90 beats per minute, blood pressure: 110/80 mmHg) and the electrocardiogram showed normal sinus rhythm with no other abnormalities (Figure 1). In the ED, gastric decontamination was performed using an orogastric lavage tube and activated charcoal and many tablets were aspirated via irrigation. Two hours after arrival, the blood pressure decreased to 80/50 mm high and the heart rate increased to 120 beats/minute. The patient's ejection fraction (EF) and wall motion were deemed normal upon bedside echocardiography (ECHO) performed by the emergency physician (ECHO). The patient's blood pressure improved after intravenous fluid bolus and low-dose norepinephrine infusion (0.05 mcg/kg/minute). Fifty-five hours after the ingestion, the blood pressure decreased to 70/50 mmHg and the heart rate was 62 beats per

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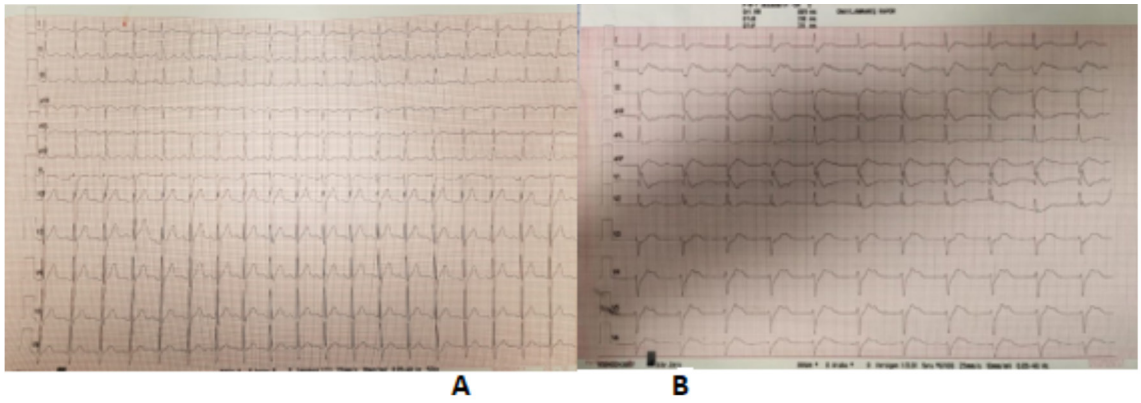

Figure 1. A) ECG during the patient's admission. B) The patient's ECG just before being placed on ECMO after 55 hours
ECG: Electrocardiogram, ECMO: Extracorporeal membrane oxygenation

minute. He was given 3 g of calcium gluconate IV, 1 U/kg bolus of intravenous regular insulin followed by a 1 U/kg/hour insulin infusion and the patient was transferred to the general intensive care unit (ICU). The EF remained normal by bedside ECHO despite the low systolic blood pressure that remained low after increasing the insulin infusion rate to 10 U/kg/h and administering 4-g IV of glucagon. The patient was intubated and mechanically ventilated followed by placement on the ECMO device in the ICU with epinephrine infusion 60-hour post-ingestion. After ECMO, the patient's vital signs improved and need for vasopressors decreased, high dose insulin (HDI) therapy was weaned, urine output increased, and serum lactate decreased. Serial serum lactate levels from the admission to the 3rd day of the ECMO device are shown in Figure 2. In the bedside ultrasound imaging, the thickness of the intestinal wall was measured as 5 millimeters in this region, differential diagnosis was ischemic intestine, ileus, or pharmacobezoars however, no further imaging was obtained because the patient was attached to ECMO device. At the 72 h postingestionafter the patient's clinical condition suddenly worsened and fifteen minutes cardiac arrest period developed, the return of spontaneous circulation occurred after 15 min of cardiopulmonary resuscitation. Diuretic treatment was initiated due to the development of non-cardiogenic pulmonary edema. Vasopressor support was discontinued on the 7th day of post-ingestion. The ECMO catheter was discontinued on the 8th day of hospital admission and the patient was discharged on the 11th day of hospital admission. The blood drug level of the patient was analyzed with LC/MS/MS device in the Forensic Medicine Laboratory. Mirtazapine, trandolapril, and isosorbide dinitrate levels were negative. Serial serum verapamil and lactate levels are shown in Figure 3.

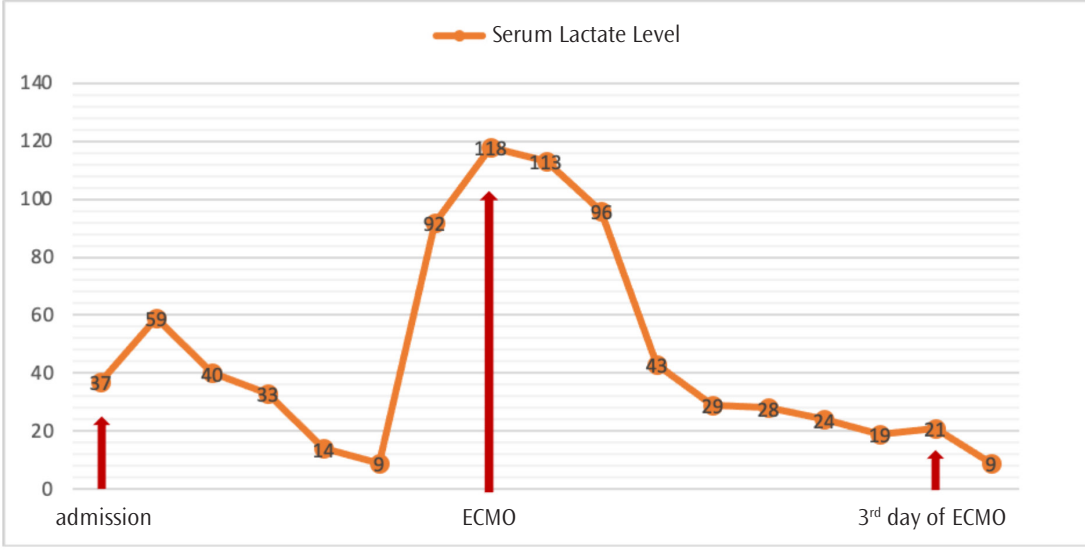

Figure 2. Serum lactate (mg/dL) levels
ECMO: Extracorporeal membrane oxygenation

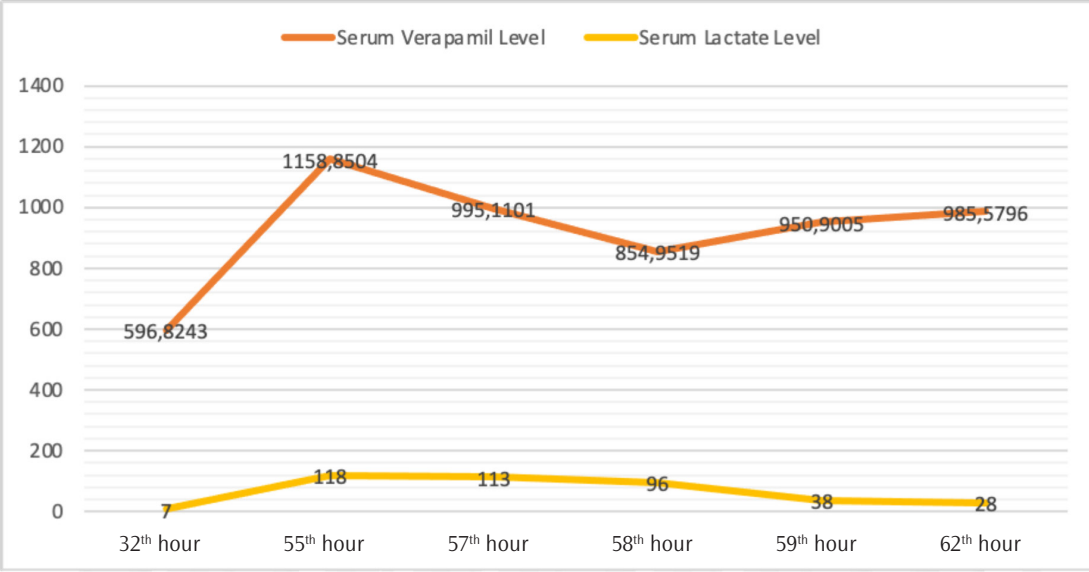

Figure 3. Serum verapamil (ng/mL) and lactate (mg/dL) levels

Discussion

Previous reports of verapamil poisoning where serial serum verapamil levels were measured, have shown that the peak serum level was achieved and then gradually dropped at earlier hours of presentation (3-6). In this case report, serum verapamil levels peaked at 55 h after the ingestion despite being an immediate-release formulation. This can be due to hypotension-induced hypoperfusion of the intestinal tract and secondary slowing of peristalsis. Again, the decrease in peristalsis due to the antimuscarinic effect of mirtazapine, which was another medication ingested by the patient, may have contributed to slowing peristalsis although the ingestion of this drug was not confirmed by LCMS. Also, it was reported in the literature that pharmacobezoars occur in intestinal structures in multidrug overdoses, and that causes delayed serum peaks and deterioration in the patient's clinical manifestation with the dissolution of this bezoars in decreased intestinal motility (7). It is recommended to start HDI early in cases of CCB poisoning in cases of hemodynamic insufficiency with impaired cardiac contractility (8). Although cardiac EF was checked twice, EF did not decrease, and HDI treatment was given due to the patient's non-responsive status to IV fluid, IV vasopressor and IV calcium, but no clinical response was obtained. ECMO should be considered early in cases where the history and initial clinical findings point toward a critical overdose with high risk of death. VA-ECMO in high dose metoprolol and amlodipine intoxication, and VV-ECMO in high dose verapamil intoxication were successful when applied before cardiac arrest (9,10). Here, the early recommendation of VA-ECMO in addition to the advanced therapies administered played a likely role in the favorable outcome of this critical poisoning.

Conclusion

Considering the potential risk of cardiac collapse in severe calcium-channel and betablocker poisonings, it is important to plan for the potential need for advanced therapies like ECMO.

Ethics

Informed Consent: Additional informed consent was obtained from all patients for which identifying information is included in this article.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.Ö., A.O.K., A.E., K.Y.G., H.Ç.K., A.Ş., Concept: V.Ö., A.O.K., A.E., K.Y.G., H.Ç.K., A.Ş., Z.K., Design: V.Ö., A.O.K., A.E., K.Y.G., H.Ç.K., A.Ş., Z.K., Data Collection or Processing: V.Ö., A.O.K., A.E., K.Y.G., H.Ç.K., A.Ş., Analysis or Interpretation: V.Ö., H.Ç.K., A.Ş., Z.K., Literature Search: V.Ö., A.O.K., A.E., K.Y.G., H.Ç.K., A.Ş., Z.K., Writing: V.Ö., A.Ş., Z.K.

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Mesenteric Cyst in a Child with Abdominal Pain: A Perspective from Emergency Department Attendance

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Abstract

Mesenteric cysts are rare benign intra-abdominal pediatric lesions. It has a variable clinical presentation from an asymptomatic mass to an acute abdomen that appears in the omentum or mesentery of the gastrointestinal tract. Abdominal ultrasound and complete surgical resection are the modality of choice for diagnosis and treatment. Here, we present 15 months old boy who presented to the emergency department with constipation and abdominal pain and was found to have a huge mesenteric cyst that was excised surgically.

Keywords: Mesenteric cyst, abdominal pain, acute abdomen, pediatric, abdominal X-ray

Introduction

Mesenteric cysts are rare and benign intra-abdominal lesions (1). The incidence for mesenteric and omental cysts is approximately 1 in 20,000 admissions for pediatric cases (1). Approximately one-third of cases occur in children younger than 15 years, with a mean age of onset of 4.9 years (2). The clinical presentation is diverse and variable and can occur as a spectrum of asymptomatic abdominal lumps and cramps to an acute abdomen or intestinal obstruction (1-3). Diagnosis is based on clinical and radiological findings with abdominal ultrasound (US) to be the modality of choice in the emergency department (ED) (4). Complete excision of the cystic mass is the best modality therapy (1,5). Because of the rarity of this condition and the lack of specific symptoms, a correct diagnosis is difficult and seldom made. Therefore, it is worth reporting this case.

In this paper, a case of 15 months male child who presented with constipation and abdominal pain and underwent surgical resection for a huge mesenteric cyst is reported.

Case Report

Fifteen months old male child presented to our ED with complaints of generalized abdominal pain and constipation for 10 days duration. Symptoms were associated with decreased oral intake in the last two days before presentation to the ED. There was no history of fever, vomiting, or bleeding per rectum. Prenatal, antenatal and postnatal histories were not significant. There was no significant medical, surgical, or family history.

Vital signs recorded on initial assessment were within normal limits, including a temperature of 36.8 °C. Upon examination, the patient was irritable; the abdomen was distended more in the right upper quadrant, firm to palpation with generalized mild tenderness.

As a part of his assessment in the ED, blood tests were performed, which were all within normal limits. In view of his abdominal pain, constipation and abnormal abdominal examination, an abdominal X-ray was ordered to rule-out bowel obstruction, perforation, or abdominal hernia. The X-ray showed a significant soft tissue shadow in the mid-abdomen displacing the bowel loops to the left side (Figure 1).

Therefore, an abdominal US was performed. As shown in (Figure 2), a large midline cystic lesion measuring 10x7.5 cm was seen displacing the bowel with a suggestion of a mesenteric or duplication cyst. An abdominal magnetic resonance imaging (MRI) was then done which showed a large lobulated right-sided

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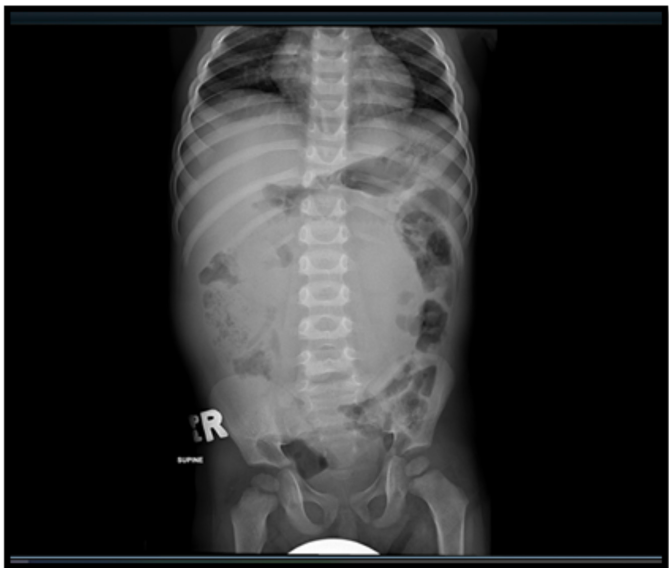

Figure 1. Abdominal X-ray showing large soft tissue shadow in mid abdomen displacing the bowel loops to left side, with no sign of bowel obstruction

and central abdominal cyst, the largest component, had a dumb-bell shape, extended from the superficial central abdomen to the sub-hepatic region and measured 10.5 cm x 14.4 cm x 7 cm. The root of origin of the cyst appeared to be the right iliac fossa, in the ileocaecal region, with the impression of a mesenteric cyst (Figure 3).

The patient underwent surgery, and the cyst was excised entirely. The patient had an uneventful postoperative period. Follow-up was impossible as the patient had traveled out of the country.

Discussion

A mesenteric cyst is defined as any cyst in the mesenterium, which can occur in the mesentery along the gastrointestinal tract anywhere from the duodenum to the rectum (6). The reason behind the occurrence of mesenteric cysts is not identified, yet the most accepted theory for the occurrence of the mesenteric cysts was proposed by Gross, stating that mesenteric cysts results

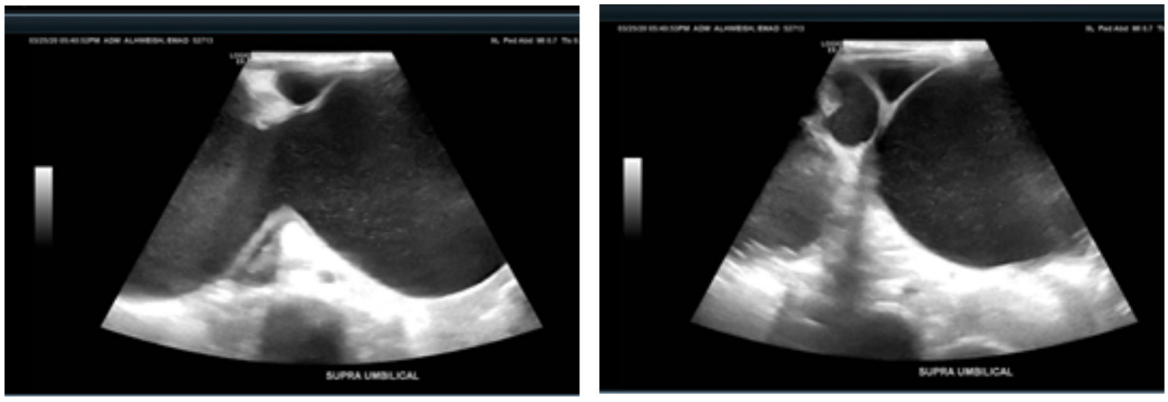

Figure 2. Large midline cystic lesion measuring 10x7.5 cm seen displacing the bowel. No internal septation or solid areas. Fluid contents show internal echoes

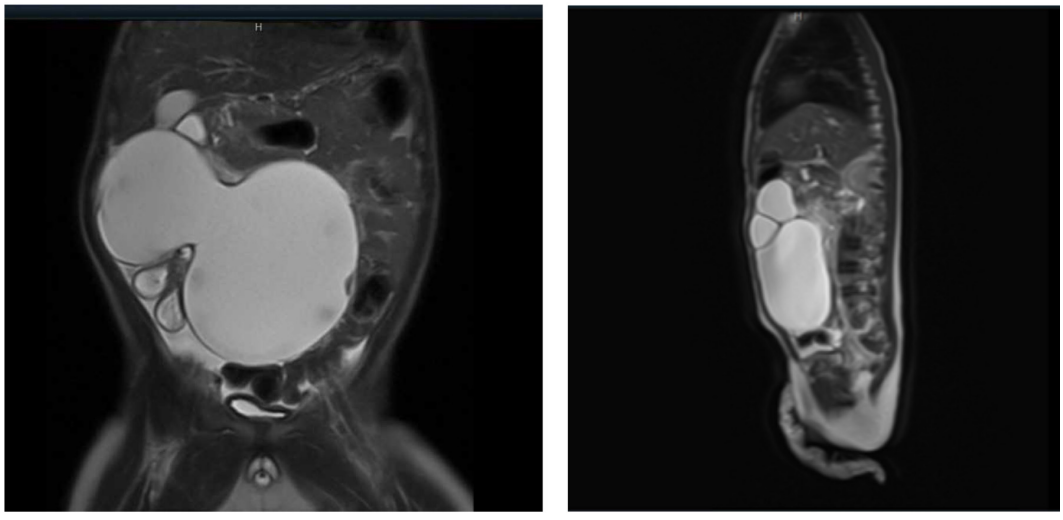

Figure 3. Magnetic resonance imaging showing a large lobulated right-sided and central abdominal cyst, the largest component, had a dumb-bell shape measures 10.5 cm x 14.4 cm x 7 cm

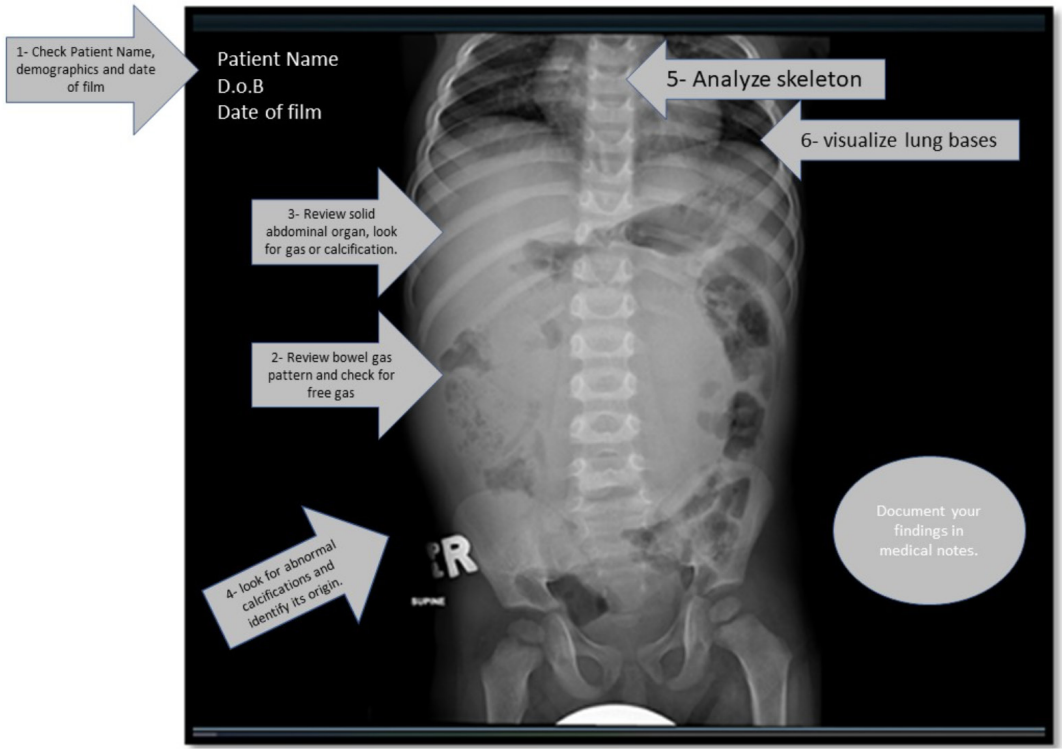

Figure 4. Barry James abdominal-XR interpretation approach [James and Kelly (9)]

from benign proliferation of ectopic lymphatics in the mesentery that lack communication with the remaining of the mesenteric system (1). Mesenteric cysts were first described in 1507 by the pathologist Benivieni during autopsy of an 8 years old child (1,7). Mesenteric cysts may range from a few centimeters to over 10 cm in maximal size length (1). A review of 162 patients mentioned different areas of mesenteric cyst formation with the commonest being in the small-bowel mesentery occurring at a rate of 60% of total described mesenteric cysts, 24% in the large-bowel mesentery, and 14.5% in the retroperitoneum (1).

Patients with mesenteric cyst are usually asymptomatic, but they can also present with vague complaints such as pain from mesenteric cyst, which is the commonest complain (82%), nausea and vomiting (45%), constipation (27%), and diarrhea (6%) while up to 61% of patients had an abdominal mass as a clinical finding (1). Our patient presented with abdominal pain, constipation and reduced oral intake. Such non-specific presenting complaints can be misunderstood as appendicitis, bowel obstruction, or even diverticulitis before surgery.

It is critical to recognize that the red flags of pediatrics' abdominal pain include fever, pain not located in the periumbilical area, nocturnal pain, weight loss, growth disorder, elevated erythrocyte sedimentation rate, and abdominal tenderness. That could increase the likelihood of organic rather than functional pain in pediatrics. Keep differential diagnosis open initially then narrow based on clinical assessment/diagnostic workup (8).

The diagnostic work of vague abdominal pain and constipation usually includes a plain abdominal X-ray. Abdominal X-ray interpretation is an essential skill for the emergency physician. We usually look for signs of constipation, intestinal obstruction, or a foreign body. It's essential to read X-rays in a structural format not to miss such rare pathology when it occurs. James and Kelly (9) suggested an algorithm for a structured abdominal-XR interpretation as outlined in Figure 4.

For the diagnosis of mesenteric cyst, US of the abdomen is the test of choice and in the hand of an expert can provide details of size, location and septation. Computed tomography scan or MRI can add better anatomical orientation of the cyst even though in general adds little findings to the US (1,3,6,10).

The treatment of choice is complete surgical resection, which can be accomplished through either laparoscopic, laparotomy, or laparoscopic assisted techniques (6). Complications from mesenteric cyst if not removed are rare but if they do occur can range from intestinal obstruction (most frequent), intestinal volvulus, hemorrhage, infection, rupture and torsion (1,5). Additionally, there is a possibility of recurrence or malignant transformation of the cyst.

Conclusion

We report a case and a review of literature of a child with a mesenteric cyst who presented with generalized abdominal pain and constipation. He was surgically treated after being diagnosed with a mesenteric cyst based on radiological examination.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.H.L., B.T., Concept: G.H.L., B.T., Design: S.M.B.H., Analysis or Interpretation: S.M.B.H., A.M.A., Literature Search: S.M.B.H., A.H.A., A.M.A., Writing: S.M.B.H., A.H.A.

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Letter to the Editor
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COVID-19 Pandemic-are the Biggest Challenge Yet?

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Keywords: SARS-CoV-2, COVID-19, pandemic

Dear Editor,

The Coronavirus disease-2019 (COVID-19) pandemic is a huge challenge for both the health service and the society struggling with the disease (1,2). However, it is necessary to look at COVID-19 more broadly, not only from the perspective of hospitalization but also with patients after COVID-19 who come to us. To date, chronic symptoms such as fatigue, "brain fog", depression, shortness of breath, cough, and muscle and joint pain have been commonly reported (3). The best known ones were those from the respiratory system, showing long-term damage to the lung tissue. The latest studies also found a 5-fold high risk of Guillain-Barré syndrome and an 11-fold high risk of encephalomyelitis in people having COVID-19, which may lead to further complications in the future (4). COVID-19 also significantly increases the risk of the first heart attack (three to eight times) and the first stroke (three to six times). According to the study, the risk gradually decreased but remained elevated for at least four weeks. Importantly, the study excluded people who had previously had a heart attack or stroke, which may suggest that the risk of another heart attack or stroke is significantly higher (5). Attention should also be paid to the incidence of myocarditis, which is 16 times higher in people with COVID-19, and the incidence of myocarditis in COVID-19 has been estimated at 150 per 100,000 patients. The inflammation of the heart muscle can lead to dysfunction of parts of the heart and increase the risk of heart failure (6). A study involving COVID-19 survivors with symptoms lasting at least 30 days found that around 5% of them experienced at least a 30% decrease in a critical measure of kidney function estimated glomerular filtration rate (eGFR). This study shows that people with long-COVID-19 were 25% more likely to develop a 30% decline in eGFR (7). Currently, LONG-COVID-19 syndrome occurs in 5% of vaccinated patients and 11% of the unvaccinated group (8). Patients after COVID-19 will come to us more often, especially with such a high percentage of virus infection. The only limitation to the incidence of complications is the vaccination. We should pay special attention to the function of the cardiovascular, kidney and respiratory systems, as well as consider creating an algorithm for managing patients with POST-COVID-19 and screening the public in primary care points.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: B.K., M.J., M.P., D.S., L.S.

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Religious Coping in the Parents of Critically Ill Children

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Keywords: Religious coping, parents, children

Dear Editor,

The pediatric intensive care unit (PICU) experience for parents is extremely stressful. Commonly identified parental stressors included the loss of the parenting role, uncertainty over the child's outcome, being separated from the child (1). Religious coping is the use of religious beliefs or practices to reduce the emotional distress caused by loss or change (2). Religion and/or spirituality are important values for many parents of critically ill children (3). Faith helped sustain some parents whose children had died in PICUs and offered comfort in the act of praying for Allah's help and guidance (4). Here, we present religious coping in the parents of critically ill children in the PICU to attract the attention of health caregivers to the parents' spiritual needs.

In PICUs, parents identified six priorities for pediatric end-of-life care including honest and complete information, ready access to staff, communication and care coordination, emotional expression and support by the staff, preservation of the integrity of the parent-child relationship, and faith (4). The main causes of extremely stressful situations for parental stress in a PICU were as follows: the parents' child having breathing difficulty; their child suffering pain; their child being unresponsive; crises in other children in the PICU. Factors least associated with stress included not being alone with baby; and the presence of monitors and equipment. Nearly all parents (99%) felt that prayer was helpful (1). Robinson et al. (5) studied matters of spirituality at the end of life in the PICU. They found that four explicitly spiritual/religious themes emerged prayer, faith, access to and care from clergy, and belief in the transcendent quality of the parent-child relationship that endures beyond death. Parents also identified several implicitly spiritual/religious themes, including insight and wisdom; reliance on values; and virtues such as hope, trust, and love (5). Most parents of children receiving palliative care felt that religion and spirituality were important in helping them deal with tough times, and most parents reported either participation in formal religious communities, or a sense of personal spirituality. Their beliefs and prayers were associated with qualities of their overall outlook on life, questions of goodness and human capacity, or that "everything happens for a reason". From religious participation and practices, parents felt they received support from both their spiritual communities and from Allah, peace and comfort, and moral guidance (6).

We have observed that all parents of children were stressful and psychosocially affected in PICU. Most parents, particularly mothers showed markedly increase in the frequency of supplication, daily religious rituals and charity. The prayed parents have found spiritual relief and inner heart peace because they believe in the following religious teachings: The best, finest, sweetest, most immediate fruit and result of supplication is this, that the person who offers it knows there is someone who listens to his voice, sends a remedy for his ailment, takes pity on him, and whose hand of power reaches everything. He is not alone in this great hostel of the world; there is an all-generous being who looks after him and makes it friendly. Imagining himself in the presence of the One who can bring about all his needs and repulse all his innumerable enemies, he feels a joy and relief; he casts off his load, which is as heavy as the world and exclaims: "All praise be to Allah, the Lord and Sustainer of the Worlds!" (7).

In conclusion, we would like to emphasize that religious coping is important for many parents of critically ill children in PICU in many societies in the world; therefore, we believe that parents in PICU should be supported spiritually by health caregivers.

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Ethics

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