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ORIGINAL ARTICLE

Phnx Med J. December 2024, Volume 6 No 3
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Morphological and Histological Features of Nephrectomy Materials: A Single-Center Experience and Short Review of the Literature

Nefrektomi Materyallerinin Morfolojik ve Histolojik Özellikleri: Tek Merkez Deneyimi ve Literatürün Kısa Gözden Geçirilmesi

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ABSTRACT

Objective: *To determine the demographic characteristics of patients undergoing nephrectomy at a tertiary care hospital and to analyze the spectrum of renal tumors based on histopathological findings of nephrectomy specimens by current literature.*

Material and Method: *The results of nephrectomy materials admitted to the pathology clinic between January 2019 and December 2023 were included in the study. The demographic characteristics of the included patients, presenting complaints, reasons for nephrectomy, surgical method, nephrectomy area, tumor dimension, and histopathological reports were recorded in a standard data form.*

Results: *A total of 325 nephrectomy materials were included in the study. 61.5% of the patients were male. The mean age of the patients was 54.5±20.2 years (min:3 max:91). The most common presenting complaints were flank pain (28.3%). The most commonly observed pathological malignancy was clear cell carcinoma (32%), and it was found to be significantly higher in male patients (38.5%) (p=0.001). The most frequently detected pathological TNM grade of the patients was grade 1, and the histological WHO/ISUP grade was 2. 28.9% of the patients (n:94) received a diagnosis incidentally. Among those incidentally diagnosed patients, 87.2% (n:82) were histopathologically malignant. When benign pathological diagnoses were examined, the most common diagnosis was pyelonephritis, followed by oncocytoma, benign cystic disease, and angiomyolipoma, respectively.*

Conclusion: *According to our study results, malignant tumors are more commonly observed than benign neoplasms. Despite advancements in imaging technologies, the histopathological diagnosis of renal masses cannot be determined preoperatively, and surgical intervention is required for diagnosis.*

ÖZET

Amaç: *Üçüncü basamak bir hastanede nefrektomi yapılan hastaların demografik özelliklerini belirlemek ve güncel literatür doğrultusunda nefrektomi örneklerinin histopatolojik bulgularına dayanarak böbrek tümörleri spektrumunu analiz etmek.*

Gereç ve ve Yöntem: *Çalışmaya Ocak 2019 ile Aralık 2023 tarihleri arasında patoloji kliniğine başvuran nefrektomi materyallerinin sonuçları dahil edildi. Çalışmaya dahil edilen hastaların demografik özellikleri, başvuru şikayetleri, nefrektomi nedenleri, cerrahi yöntem, nefrektomi bölgesi, tümör boyutu ve histopatolojik raporları standart bir veri formuna kaydedildi.*

Bulgular: *Çalışmaya toplam 325 nefrektomi materyali dahil edildi. Hastaların %61,5'i erkekti. Hastaların ortalama yaşı 54,5±20,2 yıl (min:3 max:91) idi. En sık başvuru yakınması yan ağrısı (%28,3) idi. En sık görülen patolojik malignite berrak hücreli karsinom (%32) olup, erkek hastalarda (%38,5) anlamlı olarak daha yüksek olduğu görüldü (p=0,001). Hastaların en sık saptanan patolojik TNM derecesi derece 1, histolojik WHO/ISUP derecesi ise 2 idi. Hastaların %28,9'una (n:94) tesadüfen tanı konuldu. Tesadüfen tanı konulan hastaların %87,2'si (n:82) histopatolojik olarak malign idi. Benign patolojik tanılar incelendiğinde en sık görülen tanı piyelonefrit olup, bunu sırasıyla onkositoma, benign kistik hastalık ve anjiyomiyolipom izlemektedir.*

Sonuç: *Çalışmamızın sonuçlarına göre malign tümörler benign neoplazmlara göre daha sık görülmektedir. Görüntüleme teknolojilerindeki ilerlemelere rağmen böbrek kitlelerinin histopatolojik tanısı ameliyat öncesi net olarak belirlenememekte ve tanı için cerrahi müdahale gerekmektedir.*

Keywords:
Nephrectomy
Tumor
Histopathology
Clear Cell Carcinoma
Oncocytoma
Pyelonephritis

Anahtar Kelimeler:
Nefrektomi
Tümör
Histopatoloji
Berrak Hücreli Karsinom
Onkositoma
Piyelonefrit

INTRODUCTION

Kidney cancer accounts for 5% of malignancies in men and 3% in women. It is the 6th most common cancer in men and the 10th most common cancer in women (1). It is frequently observed in European and North American populations. According to Global Cancer Statistics, the incidence and mortality rate of kidney cancer in 2020 were 431,288 and 179,368, respectively (2). Renal cell carcinoma (RCC) constitutes over 90% of kidney cancers, with a mortality rate of approximately 2% (3). Despite being the most common urogenital malignancy, RCC is often incidentally diagnosed due to the increasing accessibility and utilization of cross-sectional abdominal imaging modalities (4). This rise in incidence is not limited

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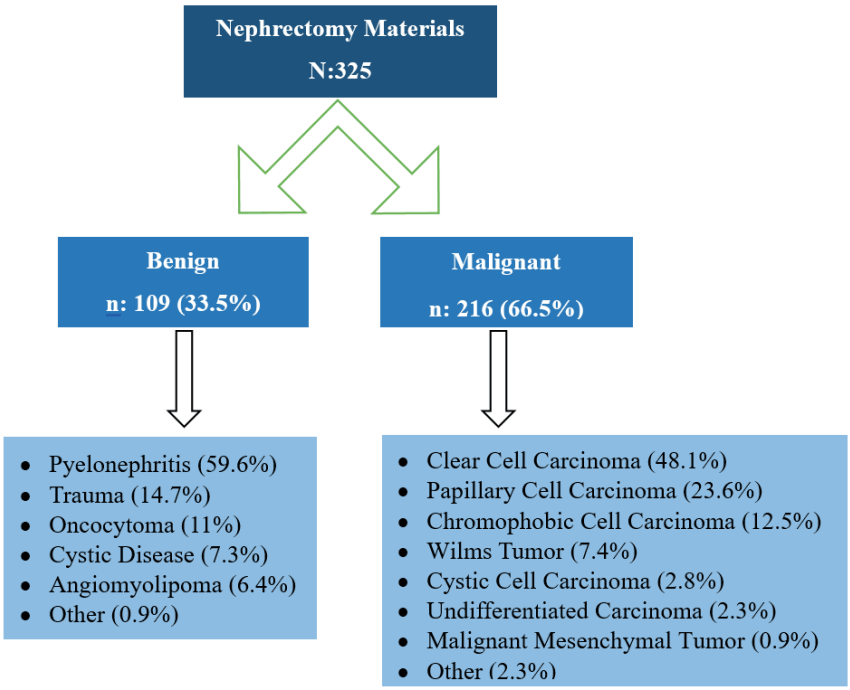

Figure 1: Histopathological Diagnosis Flow Chart of Patients.

to early-stage renal tumors; there has also been an increase in the frequency of advanced-stage tumor diagnoses (5).

Despite all technological advancements, radiological methods remain inadequate in the differential diagnosis of renal masses. The gold standard for treatment in kidney tumors is partial or total nephrectomy. Especially cases such as angiomyolipoma and oncocytoma, which are poor in fat tissue, cannot be distinguished from malignant neoplasms by radiological methods (6,7). In these situations, lesions that do not prove to be benign should be considered malignant and treated accordingly.

Advancements in molecular genetics have led to a better understanding of the molecular biology of kidney tumors, resulting in progress in their classification. The contemporary classification of renal cell carcinoma (RCC), established by the World Health Organization's Kidney Tumor Classification Panel in 2016, incorporates many new entities based on cytological, architectural, immunohistochemical, and cytogenetic features, leading to a decrease in specific RCC types (8).

The spectrum of renal tumors has limited published data and shows geographic variations. This study aims to examine the demographic characteristics of patients undergoing nephrectomy and the histopathological findings of nephrectomy materials, comparing them with the existing literature, and contributing to clinical practice.

MATERIAL AND METHODS

The study was planned as a five-year retrospective observational case series. After obtaining approval from the local ethics committee (Meeting Date: 18.01.2024, Meeting No: 144, Decision No: 3109), the research commenced. The study was conducted under the Helsinki Declaration and good clinical practices.

Patients Selection

The results of nephrectomy materials brought to the pathology clinic of a tertiary care hospital between January 1, 2019, and December 31, 2023, were included in the study. There was no age limit in the study.

Study Design

The demographic characteristics of the patients included in the study, their complaints at presentation, the area of nephrectomy, the sizes of the tumor materials, the surgical method applied, and the histopathological reports were recorded in a standard data form. The primary outcome of the study is to analyze the histopathological examinations of the materials brought to the pathology clinic after nephrectomy.

Statistical Analysis

Continuous data were summarized as mean and standard deviation, while categorical data were summarized as numbers and percentages. Categorical data were compared using the Chi-square test. The Kolmogorov-Smirnov test and assessments with histograms were used to compare the means of the parameters examined. In cases where the variables were normally distributed, the Student's t-test was used for comparisons between two groups; when not normally distributed, the Mann-Whitney U test was employed. The statistical analysis of the data obtained in the study was performed using the SPSS 25 software package (SPSS Inc, Chicago, Illinois, USA). The level of statistical significance was set at $p<0.05$.

RESULTS

The study included 325 cases. The flowchart of the histopathological diagnoses of the patients included in the study is presented in Figure 1.

Among the patients included in the study, 61.5% (n=200) were male, and 38.5% (n=125) were female. The age range of the patients was between 3 and 91 years, with an average age of 54.5±20.2 years. No statistically significant difference was found between age and gender (p=0.935). Incidental diagnoses were found in 28.9% (n=94) of the patients. The average age of patients diagnosed incidentally

Table 1: Distribution of patients' demographic characteristics by gender.

	Total n: 325 (100%)	Male n: 200 (61.5%)	Female n: 125 (38.5%)	p
Mean Age (years) mean±SD (min-max)	54.5±20.2 (3-91)	54.5±19,9 (3-91)	54.7±20.7 (4-98)	0,935
Application Complaint n (%)				
Incidental	94 (28.9%)	60 (30%)	34 (27.2%)	0,447
Flank pain	92 (28.3%)	52 (26%)	40 (32%)	
Haematuria	36 (11.1%)	24 (12%)	12 (9.6%)	
Abdominal Pain	32 (9.8%)	18 (9%)	14 (11.2%)	
Dysuria	26 (8%)	21 (10.5%)	5 (4%)	
Lower back pain	17 (5.2%)	10 (5%)	7 (5.6%)	
Trauma	15 (4.6%)	8 (4%)	7 (5.6%)	
Abdominal Swelling	13 (4%)	7 (3.5%)	6 (4.8%)	
Applied Surgical Method n (%)				
Radical	280 (86.2%)	174 (87%)	106 (84.8%)	0,280
Laparoscopic	133 (40.9%)	90 (45%)	43 (34.4%)	
Open	101 (31.1%)	61 (30.5%)	40 (32%)	
Robotics	46 (14.2%)	23 (11.5%)	23 (18.4%)	
Partial	45 (13.8%)	31 (15.5%)	19 (15.2%)	
Laparoscopic	30 (9.2%)	16 (8%)	14 (11.2%)	
Open	7 (2.2%)	7 (3.5%)	3 (2.4%)	
Robotics	8 (2.5%)	8 (4%)	2 (1.6%)	
Nephrectomy n (%)				
Right	136 (41.8%)	85 (42.5%)	51 (40.8%)	0,762
Left	189 (58.2%)	115 (57.5%)	74 (59.2%)	
Dimension of tumor material n (%)				
<4cm	23 (7.1%)	11 (5.5%)	12 (9.6%)	0,167
4-5cm	50 (15.4%)	32 (16%)	18 (14.4%)	
5-7cm	97 (29.8%)	67 (33.5%)	30 (24%)	
>7cm	155 (47.7%)	90 (45%)	65 (52%)	

(58.5±19.4 years) was statistically significantly higher than that of patients diagnosed after presenting with symptoms (52.9±20.3 years) (p=0.023). Of the patients diagnosed incidentally, 87.2% (n=82) received a histopathological diagnosis of malignancy. Among the malignant patients, 65.9% (n=54) were in pathologic TNM grade 1, while 23.2% (n=19) were in grade 2. A total of 71.1% of the patients were diagnosed after presenting with a complaint. The most common presenting complaints were flank pain (28.3%) and hematuria (11.1%). There was no statistically significant difference between presenting complaints and gender (p=0.447). Radical nephrectomy was performed in 86.2% of the patients while nephron-sparing (partial nephrectomy) surgery was performed in 13.8%. In the patient group, 50.2% (n=163) underwent laparoscopic surgery, 33.2% (n=108) had open surgery, and 16.6% (n=54) received robotic surgery. Of the 58.2% (n=189) were left nephrectomies, and 41.8% (n=136) were right nephrectomies. There was no statistically significant difference between nephrectomy location and gender (p=0.762). When examining the size of the nephrectomy material; it was found that 47.7% were >7 cm, 29.8% were 5-7 cm, 15.4% were 4-5 cm, and 7.1% were <4 cm. There was no statistically significant difference between nephrectomy material size and gender (p=0.167) (Table 1).

7.69% (n:25) of the nephrectomy materials included in the study belonged to patients under the age of 18. 64% of the pediatric patients were male and the average age was 8.28±3.98 years. It was determined that 24% of pediatric patients were diagnosed incidentally. When the histopathology of the nephrectomy materials of this group was examined, 68% were found to be malignant. 64% of pediatric patients had Wilms tumor, 28% had pyelonephritis, 4% had blunt trauma and 4% had undifferentiated carcinoma.

Upon examining the histopathological diagnoses of the nephrectomy materials, it was obtained that 66.5% (n=216) were malignant pathologies, while 33.5% (n=109) were benign pathologies. The most frequently

Table 2: Distribution of patients' histopathological diagnoses by gender.

	Total n: 325 (100%)	Male n: 200 (61.5%)	Female n: 125 (38.5%)	p
Pathology n (%)				
Benign	109 (33.5%)	61 (30.5%)	49 (38.4%)	0,142
Malignant	216 (66.5%)	139 (69.5%)	77 (61.6%)	
Histopathological Benign Diagnoses n (%)				
Pyelonephritis	65 (20%)	37 (18.5%)	28 (22.4%)	0.392
Chronic Pyelonephritis	35 (10.8%)	20 (10%)	15 (12%)	0.635
Nephrolithiasis + Chronic Pyelonephritis	22 (6.8%)	14 (7%)	8 (6.4%)	0.738
Xanthogranulomatous pyelonephritis	8 (2.4%)	3 (1.5%)	5 (4%)	0.236
Trauma	16 (4.9%)	8 (4%)	8 (6.4%)	0.313
Blunt trauma	9 (2.8%)	5 (2.5%)	4 (3.2%)	0.708
Gunshot Wound	7 (2.2%)	3 (1.5%)	4 (3.2%)	0.304
Oncocytoma	12 (3.7%)	8 (4%)	4 (3.2%)	0.710
Benign Cystic Disease	8 (2.5%)	5 (2.5%)	3 (2.4%)	0.955
Angiomyolipoma	7 (2.2%)	2 (1%)	5 (4%)	0.070
Other*	1 (0.3%)	1 (0,5%)	0	0.428
Histopathological Malignant Diagnoses n (%)				
Clear Cell Carcinoma	104 (32%)	77 (38.5%)	27 (21.6%)	0,001
Papillary Cell Carcinoma	51 (15.7%)	35 (17.5%)	16 (12.8%)	0,257
Chromophobic Cell Carcinoma	27 (8.3%)	11 (5.5%)	16 (12.8%)	0.020
Wilms Tumor	16 (4.9%)	9 (4.5%)	7 (5.6%)	0.656
Cystic Cell Carcinoma	6 (1.8%)	5 (2.5%)	1 (0.8%)	0.268
Undifferentiated Carcinoma	5 (1.5%)	1 (0.5%)	4 (3.2%)	0.054
Malignant Mesenchymal Tumor	2 (0.6%)	0	2 (1.6%)	0.073
Other**	5 (1.5%)	1 (0.5%)	4 (3.2%)	0.054

Other: 1 patient each diagnosed with Hyperacute Rejection*
*Other**: 1 patient each diagnosed with B Cell Lymphoma, Well Differentiated Neuroendocrine Tumor, Lipomatous Hemangiopericytoma, Squamous Cell Carcinoma, Malignant Fibrous Histiocytoma*

detected malignant pathology was clear cell carcinoma. Nephrectomy performed due to pyelonephritis was the most commonly diagnosed benign pathology (Table 2).

When examining the diagnoses of benign pathologies, 59.6% were due to pyelonephritis, 14.7% to trauma, 11% to oncocytoma, 7.3% to cystic disease, 6.4% to angiomyolipoma, and 0.9% to other causes (hyperacute rejection in one patient). The average age of patients with benign diseases (45.6±18.4 years) was significantly lower than that of patients with malignant diseases (59.1±19.5 years) ($p<0.001$). Among benign diseases, the lowest average age was observed in trauma patients (34.9±16.3 years), while the highest average age was in patients diagnosed with oncocytoma (60.6±10.9 years).

Patients diagnosed with pyelonephritis most commonly presented with flank pain (52.3%) and dysuria (23.1%). Among patients diagnosed with oncocytoma, 41.7% received an incidental diagnosis. When examining the size of the nephrectomy material, it was found that 70.8% of pyelonephritis patients had a size of >7 cm, while 41.7% of oncocytoma patients had a size of <4 cm. While 96.9% of pyelonephritis patients, 100% of trauma patients, and 87.5% of cystic disease patients underwent radical nephrectomy, nephron-sparing (partial nephrectomy) surgery was performed in 41.7% of oncocytoma patients and 42.9% of angiomyolipoma patients (Table 3).

When examining the diagnoses of malignant pathologies, 48.1% were clear cell carcinoma, 23.6% were papillary cell carcinoma, 12.5% were chromophobe cell carcinoma, 7.4% were Wilms tumor, 2.8% were cystic cell carcinoma, 2.3% were undifferentiated carcinoma, 0.9% were malignant mesenchymal tumor, and 2.3% were other reasons (well-differentiated neuroendocrine tumor, hemangiopericytoma, malignant fibrous histiocytoma, B-cell lymphoma, and squamous cell carcinoma, each one patient). The average age of patients with malignant diseases was 59.1±19.5 years. Among malignant diseases, the lowest average age was observed in patients with Wilms tumor (7.4±2.7 years), while the highest average age was in patients diagnosed with papillary cell carcinoma (66.4±13.3 years). Patients with clear cell carcinoma are most commonly diagnosed incidentally (43.3%). The most common presenting complaints were flank pain (22.1%) and hematuria (13.7%). Among patients with Wilms tumor, 62.5% presented to the hospital due to abdominal swelling. When examining the tumor size in

Table 3: Demographic Characteristics of Benign Pathologies.

	Pyelonephritis	Trauma	Oncocytoma	Cystic Disease	Angiomyolipoma
	n:6 (59.6%)	n:16 (14.7%)	n:12 (11%)	n:8 (7.3%)	n:7 (6.4%)
Mean Age (years) mean±SD	44.6±18.9	34.9±16.3	60.6±10.9	51.4±10.6	45.3±20.9
Application Complaint n (%)					
Incidental	34 (52.3%)	0	3 (25%)	3 (37.5%)	4 (57.1%)
Flank pain	15 (23.1%)	0	1 (8.3%)	1 (12.5%)	0
Haematuria	0	15 (93.8%)	0	0	0
Abdominal Pain	4 (6.2%)	0	5 (41.7%)	2 (25%)	1 (14.3%)
Dysuria	8 (12.3%)	0	1 (8.3%)	0	1 (14.3%)
Lower back pain	2 (3.1%)	1 (6.3%)	1 (8.3%)	0	1 (14.3%)
Trauma	2 (3.1%)	0	1 (8.3%)	1 (12.5%)	0
Abdominal Swelling	0	0	0	1 (12.5%)	0
Dimension of tumor material n (%)					
<4cm			5 (41.7%)	0	1 (14.3%)
4-5cm			1 (8.3%)	1 (12.5%)	1 (14.3%)
5-7cm			2 (16.7%)	2 (25%)	1 (14.3%)
>7cm			4 (33.3%)	5 (62.5%)	4 (57.1%)
Applied Surgical Method n (%)					
Radical	63 (96.9%)	16 (100%)	7 (58.3%)	7 (87.5%)	4 (57.1%)
Laparoscopic	44 (67.7%)	2 (12.5%)	3 (25%)	5 (62.5%)	3 (42.9%)
Open	11 (16.9%)	14 (87.5%)	3 (25%)	1 (12.5%)	0
Robotics	8 (12.3%)	0	1 (8.3%)	1 (12.5%)	1 (14.3%)
Partial	2 (3.1%)	0	5 (41.7%)	1 (12.5%)	3 (42.9%)
Laparoscopic	1 (1.5%)	0	4 (33.3%)	1 (12.5%)	2 (28.6%)
Open	1 (1.5%)	0	0	0	0
Robotics	0	0	1 (8.3%)	0	1 (14.3%)

Other (0.9%): 1 patient diagnosed with hyperacute rejection.

nephrectomy materials, it was found that 34.6% of clear cell carcinoma cases had a size of >7 cm. Among patients with cystic cell carcinoma, 50% had a tumor size of 4-5 cm. Regarding pathologic TNM classification, 64.4% of patients with clear cell carcinoma, 58.8% of patients with papillary cell carcinoma, 48.1% of patients with chromophobe cell carcinoma, and 100% of patients with cystic cell carcinoma were classified as grade 1. Among patients with undifferentiated carcinoma, 60% were in Stage 3. Regarding Histological grade (WHO/ISUP), 43.3% of patients with clear cell carcinoma and 45.1% of patients with papillary cell carcinoma were grade 2. Radical nephrectomy was performed in 79.8% of patients with clear cell carcinoma, 90.2% of patients with papillary cell carcinoma, 81.5% of patients with chromophobe cell carcinoma, and in all patients with Wilms tumor, undifferentiated carcinoma, and malignant mesenchymal tumor, whereas nephron-sparing (partial nephrectomy) surgery was performed in 50% of patients with cystic cell carcinoma (Table 4).

DISCUSSION

In the study, histopathological examination of nephrectomy specimens from cases undergoing nephrectomy was performed. According to the study data, 28.9% of the cases were diagnosed coincidentally and underwent surgical treatment. The most common malignant pathological diagnosis in the study was clear cell carcinoma, while the most frequently detected benign pathologies were pyelonephritis and oncocytoma. In cases with RCC, the female-to-male ratio was approximately 1/2. Additionally, 4.9% of the cases underwent nephrectomy due to trauma.

RCC is a heterogeneous disease with varying clinical features. It accounts for 2-3% of all cancers and is the seventh leading cause of cancer-related deaths according to studies. It is also the most common cause of death among urogenital cancers, accounting for 30-40% of cases (9). The incidence of RCC varies by country but is more common in developed countries. Its incidence is higher in men compared to women. RCC is mostly seen in the 60-70 age group and is less common after the age of 70 (10). Our study included all nephrectomy specimens regardless of age range. Wilms tumors, which are seen in the early age period, were also among the malignant pathological diagnoses we detected. Therefore, the age range of the patients included in the study was 3-91, but the average age was consistent with the literature. Moreover, the female-to-male ratio also paralleled the current literature.

Table 4: Demographic Characteristics of Malignant Pathologies

	Clear Cell Carcinoma	Papillary Cell Carcinoma	Chromophobic Cell Carcinoma	Wilms Tumor	Cystic Cell Carcinoma	Undifferentiated Carcinoma	Malignant Mesenchymal Tumor
	n:104 (48.1%)	n:51 (23.6%)	n:27 (12.5%)	n:16 (7.4%)	n:6 (2.8%)	n: 5 (2.3%)	n: 2 (0.9%)
Mean Age (years) mean±SD	63.2±11.9	66.4±13.3	62.7±12.2	7.4±2.7	45±8.9	55.8±32.2	47±4.2
Application Complaint							
Incidental	45 (43.3%)	14 (27.5%)	14 (51.9%)	5 (31.3%)	2 (33.3%)	0	2 (100%)
Flank pain	23 (22.1%)	15 (29.4%)	5 (18.5%)	0	1 (16.7%)	2 (40%)	0
Haematuria	14 (13.7%)	15 (29.4%)	3 (11.1%)	0	0	0	0
Abdominal Pain	10 (9.6%)	4 (7.8%)	1 (3.7%)	1 (6.3%)	0	2 (40%)	0
Lower back pain	6 (8.8%)	1 (2%)	3 (11.1%)	0	2 (33.3%)	0	0
Abdominal Swelling	1 (1%)	0	0	10 (62.5%)	0	1 (20%)	0
Dysuria	5 (4.8%)	2 (3.9%)	1 (3.7%)	0	1 (16.7%)	0	0
Dimension of tumor material							
<4cm	12 (11.5%)	1 (2%)	1 (3.7%)	0	1 (16.7%)	0	0
4-5cm	23 (22.1%)	9 (17.6%)	6 (22.2%)	1 (6.3%)	3 (50%)	1 (20%)	0
5-7cm	33 (31.7%)	26 (51%)	5 (18.5%)	3 (18.8%)	2 (33.3%)	1 (20%)	0
>7cm	36 (34.6%)	15 (29.4%)	15 (55.6%)	12 (75%)	0	3 (60%)	2 (100%)
TNM Stage							
1	67 (64.4%)	30 (58.8%)	13 (48.1%)		6 (100%)	2 (40%)	0
2	28 (26.9%)	10 (19.6%)	8 (29.6%)		0	0	0
3	9 (8.7%)	6 (11.8%)	6 (22.2%)		0	3 (60%)	0
4	0	5 (9.8%)	0		0	0	2 (100%)
Histologic Grade (WHO / ISUP)							
1	35 (33.7%)	12 (23.5%)	15 (55.6%)		4 (66.7%)	1 (20%)	0
2	45 (43.3%)	23 (45.1%)	7 (25.9%)		2 (33.3%)	0	0
3	22 (21.2%)	13 (25.5%)	4 (14.8%)		0	4 (80%)	0
4	2 (1.9%)	3 (5.9%)	1 (3.7%)		0	0	2 (100%)
Applied Surgical Method							
Radical	83 (79.8%)	46 (90.2%)	22 (81.5%)	16 (100%)	3 (50%)	5 (100%)	2 (100%)
Laparoscopic	38 (36.5%)	20 (39.2%)	8 (29.6%)	3 (18.8%)	2 (33.3%)	2 (40%)	0
Open	28 (26.9%)	17 (33.3)	8 (29.6%)	12 (75%)	1 (16.7%)	1 (20%)	2 (100%)
Robotics	17 (16.3%)	9 (17.6%)	6 (22.2%)	1 (6.3%)	0	2 (40%)	0
Partial	21 (20.2%)	5 (9.8%)	5 (18.5%)	0	3 (50%)	0	0
Laparoscopic	11 (10.6%)	3 (5.9%)	5 (18.5%)	0	3 (50%)	0	0
Open	5 (4.8%)	1 (2%)	0	0	0	0	0
Robotics	5 (4.8%)	1 (2%)	0	0	0	0	0

Other (2.3%): 1 patient each diagnosed with Well-differentiated neuroendocrine tumor, lipomatous hemangiopericytoma, malignant fibrous histiocytoma, B cell lymphoma and Squamous cell carcinoma

In our study, most kidney tumors were detected coincidentally. Subsequently, the most common symptoms were, in order, flank pain, hematuria, and abdominal pain. Over 50% of RCCs are discovered incidentally. Patients with this cancer may present with local or systemic symptoms, but the incidence of kidney masses being detected coincidentally has significantly increased following routine imaging for various medical disorders (11). The widespread use of ultrasonography and cross-sectional imaging is now associated with the incidental detection of many asymptomatic kidney tumors, and some now refer to RCC as the radiologist's tumor (12). In reality, due to the increased detection of incidental kidney masses, there is a decrease in the presentation of concurrent metastatic disease, allowing this cancer to be frequently detected at early stages (13). The most common pathological TNM stage observed in the study was stage 1. According to the WHO/ISUP classification, the most

common histopathological grade was grade 2.

Local symptoms like hematuria, flank pain, or palpable abdominal masses are associated with poorer prognoses. Systemic symptoms, on the other hand, may be largely related to proteins secreted due to paraneoplastic events or metastases. Among these proteins are factors like parathyroid hormone, renin, and erythropoietin, which can lead to conditions such as hypercalcemia, hypertension, and erythrocytosis. Additionally, fever or weight loss can emerge as additional symptoms.

The meticulous and detailed histopathological examination of nephrectomy specimens is essential for the accurate diagnosis, classification, prognosis, and treatment of potential carcinomas (14, 15). In our study, the most common malignant RCC type was Clear Cell Renal Cell Carcinoma (CCRCC), followed by papillary cell carcinoma and chromophobe cell carcinoma, respectively. CCRCC originates from the proximal renal tubular epithelium. The overall prognosis of CCRCC is worse than most other types of RCC (16). These tumors can be sporadic (accounting for 95% of cases) or part of a familial cancer syndrome, such as von Hippel-Lindau disease. This tumor type is characterized by the loss of genetic material on chromosome 3p, either through the loss of the entire chromosome or through the loss of function via hypermethylation (17). Papillary RCC (PRCC) is also derived from the renal tubular epithelium and is the second most common morphotype encountered in RCC. It has traditionally been divided into two types. Type 1 PRCC appears to be a distinct and compact histomolecular entity and possesses a unique immunoprofile positive for CK7, CD10, and racemase. The most common cytogenetic abnormalities are trisomy 7 and 17 and loss of Y in sporadic cases in male patients, while in familial forms, trisomy 7 is the most frequent. Type 2 tumors appear to be a contentious entity consisting of a group of tumors sharing papillary/tubulopapillary structures but having distinct molecular and genetic characteristics. RCCs with fumarate hydratase deficiency, which are high-grade PRCCs previously categorized as “type 2” PRCC, have been reclassified from type 2 PRCC thanks to recent molecular and genetic studies. This reclassification reflects the ongoing evolution in the understanding of RCC subtypes, highlighting the importance of molecular and genetic profiles in accurately diagnosing and treating renal cancers. Type 2 tumors appear to be a controversial entity consisting of a group of tumors with different molecular and genetic characteristics but sharing a papillary/tubulopapillary structure. High-grade PRCCs previously categorized as “Type 2” PRCC, which are RCCs with fumarate hydratase deficiency, have been reclassified within Type 2 PRCC based on recent molecular and genetic studies. The “third” subtype of PRCC, oncocytic papillary RCC, is a papillary RCC consisting of oncocytic neoplastic cells with variable copy number variation patterns (17, 18). Chromophobe Renal Cell Carcinoma (ChRCC) constitutes 5-7% of all renal cell carcinomas. ChRCCs are well-defined and encapsulated tumors with a homogeneous light tan to brown color and central scar tissue. Microscopic examination reveals solid growth with nests, layers, or trabeculae composed of two types of cells. Type 1 ChRCC exhibits voluminous reticular cytoplasm, plant-like cell membranes, and large pale cells. Type 2 ChRCC, on the other hand, presents smaller cells with fine granular eosinophilic cytoplasm in its eosinophilic variant. These tumors demonstrate distinctive irregular wrinkled, coarse chromatin, raisin-like nuclei, and a characteristic perinuclear halo due to the accumulation of cytoplasmic micro-particles. Immunohistochemically, these tumors are positive for CD117 and CK7 while negative for vimentin and CD10, distinguishing them from PRCC (19).

In this study, the second most common pathological diagnosis in cases who underwent nephrectomy was pyelonephritis. Pyelonephritis is the inflammation of the renal parenchyma and can be acute or chronic. Acute pyelonephritis is characterized by fever, costovertebral angle pain, and nausea-vomiting triad. Chronic pyelonephritis (CPN) progresses with recurrent acute attacks and sometimes can be identified as a cause of end-stage renal disease (ESRD) (20). CPN has variants such as xanthogranulomatous pyelonephritis, emphysematous pyelonephritis, and unspecified variants (21). CPN has been reported as the cause in approximately 4-6% of patients requiring dialysis due to ESRD (20). CPN is the most common cause of renal biopsies and nephrectomies. In studies, this rate varies between 29% and 63% (22-26). Although malignant tumors of the kidney are more common than benign pathologies, the frequency of benign lesions has been increasing recently (27). Kidney benign lesions include renal adenoma, metanephric adenoma, renal oncocytoma, nephrogenic adenofibroma, mesoblastic nephroma, capsuloma, juxtaglomerular cell tumor, medullary fibroma, cystic nephroma, cystic hamartoma, angiomyolipoma (AML), leiomyoma, hemangioma, lipoma, xanthogranulomatous pyelonephritis, malakoplakia, renal cysts, and fibroepithelial polyps (28). Studies have shown that the incidence of benign lesions in the kidney varies approximately between 15-20% (27, 29-31). In this study, the rate of nephrectomy performed due to benign lesions was 33.5%. The most common ones were oncocytoma, benign cystic disease, and AML, respectively.

Oncocytoma and AML are the most common benign renal pathologies (32). Renal oncocytoma is the most common benign pathology of the kidney and is often seen in adults (33). It constitutes roughly 5% of renal masses. It is usually asymptomatic and detected incidentally. Currently used imaging methods cannot make a clear distinction between oncocytoma and malignant lesions, so a definitive diagnosis is only made through biopsy or resection. Paying attention to pathological characteristics and using immunostains together can help distinguish oncocytoma, characterized by granular, eosinophilic cytoplasm, from other kidney tumors, especially chromophobe renal cell carcinoma (34).

Most kidney cysts are benign and asymptomatic, having no impact on kidney function. These “simple” cysts are typically managed conservatively. However, some kidney cysts may be symptomatic or have atypical radiological findings, leading to suspicion of malignancy; in such

cases, surgical evaluation may be indicated. Other cystic kidney diseases are genetic or acquired later in life, often associated with malformation syndromes, and can impair kidney function. In such cases, a nephrectomy may be necessary (35).

Angiomyolipoma is a benign mesenchymal tumor belonging to the perivascular epithelioid cell tumor family. Most of these pathological kidney lesions are found incidentally, similar to other renal masses. The prevalence varies between 0.2% and 0.6% and is most commonly seen in females (36). While 80% of cases are sporadic, the remaining 20% develop in association with tuberous sclerosis complex or pulmonary lymphangioleiomyomatosis (37). Inherited lesions typically manifest at a younger age and tend to be larger, bilateral, and more aggressive (38).

In this study, 41.8% of cases underwent right nephrectomy, while 58.2% underwent left nephrectomy. Although this ratio shows similarity to some previous studies (39,40), it has been observed differently in other studies (41).

In our study, malignant tumors had a tumor size >7 cm. There are several studies indicating no correlation between tumor size and malignancy in kidney tumors, with a particular focus on RCC. Tumor sizes in studies conducted in Pakistan, Saudi Arabia, and India were similar to our study (39, 42-44). However, tumor sizes have been reported smaller in studies conducted particularly in the West (45-47).

In this study, the most commonly encountered grades in malignant tumors were grade 2 CCRCC and grade 2 PRCC. Different studies have reported different grades (39, 41, 48, 49). These discrepancies may be related to the tumor size, which can vary depending on whether cases present early or late.

In the past, radical nephrectomy was the standard treatment option for kidney masses. However, with advancements in surgical techniques and considering the high prevalence of benign lesions in small-sized tumors, nephron-sparing surgery is now more commonly used. Nephron-sparing surgery is as successful as radical nephrectomy in tumor control, as demonstrated by several studies (50). In this study, the rate of nephron-sparing surgery was around 14%. The reason for this difference may be related to the fact that the majority of the masses detected in the cases included in the study were >7 cm, the large number of malignant masses, and the surgeon's perioperative decisions.

LIMITATION

The absence of survival, follow-up, and comorbid conditions in the study could be a limitation. However, including them might have extended the study duration. Larger, multicenter, and long-term follow-up studies are necessary to determine the prognostic value of histological types and other tumor characteristics in kidney tumors.

CONCLUSION

According to the study findings, malignant tumors are more common than benign pathologies in patients undergoing nephrectomy in our region. The most common malignant tumor type is clear cell renal cell carcinoma (CCRCC). Malignant tumors are typically larger in size and have a higher nuclear grade. Despite advancements in imaging technologies, the histopathological diagnosis of kidney masses cannot be determined preoperatively, and surgical intervention is required for diagnosis.

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ORIGINAL ARTICLE

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Evaluation of *In Vitro* Biofilm Formation of *Helicobacter pylori* in Different Culture Media

Helicobacter Pylori Farklı Kültür Ortamlarında *İn Vitro* Biyofilm Oluşumunun Değerlendirilmesi

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ABSTRACT

Objective: *Biofilms are surface-attached cell communities that play a role in the survival of bacteria. Helicobacter pylori, a gram-negative pathogen that colonizes the human gastric mucosa, forms biofilms, causing treatment failure and the risk of developing peptic ulcers, gastritis and gastric cancer in infected individuals. The aim of the study is to evaluate the biofilm formation abilities of H. pylori ATCC 26695 and three clinical strains in different culture media.*

Material and Method: *Biofilm formation characteristics of H. pylori strains using different culture media were evaluated, and the crystal violet (CV) staining method (measured at OD 595) was used. Various media were used for incubating H. pylori strains: Brucella broth (BB), TSB with 10% FBS, BHI with 10% FBS, BB with 10% FBS, BB with 10% FBS + 0.25% glucose, and BB with 10% FBS + 1% glucose (incubated for 3 days). Additionally, BB with 1% FBS, BB with 10% FBS, and BB with 5% inactivated human serum were incubated for 2 and 4 days at 37°C under microaerophilic conditions.*

Results: *It was observed that 5% inactived human serum was more effective in biofilm formation of H. pylori ATCC 26695 and three clinical strains. However, there was no biofilm production in the strains cultured with Brucella broth alone and that the strains cultured with TSB + 10% FBS could not form a strong biofilm compared to other media.*

Conclusion: *Different culture media used for H. pylori ATCC 26695 and three clinical strains affect biofilm formation. It is thought that in vitro experiments to prevent biofilm formation may provide a solution to the prevention of H. pylori infection.*

ÖZET

Amaç: B*iyofilmler, bakterilerin hayatta kalmasında rol oynayan yüzeye bağlı hücre topluluklarıdır. İnsan mide mukozasını kolonize eden gram negatif bir patojen olan Helicobacter pylori, biyofilm oluşturarak tedavi başarısızlığına ve enfekte bireylerde peptik ülser, gastrit ve mide kanseri gelişme riskine neden olur. H. pylori ATCC 26695 ve üç klinik suşun farklı kültür ortamlarında biyofilm oluşturma yeteneklerinin değerlendirilmesi amaçlanmıştır.*

Gereç ve Yöntem: *H. pylori suşlarının biyofilm oluşturma özellikleri farklı kültür ortamları kullanılarak biyofilm oluşturmaları Kristal viyole (CV) yöntemi ile spektrofotometrede (OD595) değerlendirildi. Kullanılan ortamlar; Brucella broth (BB) besiyeri, TSB + %10 FBS, BHI + %10 FBS, BB + %10 FBS, BB + %10 FBS + %0.25 glukoz ve BB + %10 FBS + %1 glukoz-(3 gün inkübasyon) ve BB + %1 FBS, BB + %10 FBS, BB + %5 inaktive insan serumu 2 ve 4 gün 37°C de mikroaerofilik koşullarda inkübasyon gerçekleştirildi.*

Bulgular: *H. pylori ATCC 26695 ve üç klinik suşun biyofilm oluşumunda %5 inaktive edilmiş insan serumunun daha etkili olduğu görüldü. Sadece Brucella besiyeri ile biyofilm üretiminin olmadığı TSB + %10 FBS ile suşların diğer ortamlara göre güçlü bir biyofilm oluşturmadığı gözlendi.*

Sonuç: *H. pylori ATCC 26695 ve üç klinik suş için kullanılan farklı kültür ortamları biyofilm oluşumunu etkilemektedir. Biyofilm gelişiminin önlenmesine yönelik in vitro deneylerin yapılmasının H. pylori enfeksiyonlarının önlenmesinde çözümler sağlayabileceği düşünülmektedir.*

Keywords:
ATCC 26695
Biofilm
Crystal violet
Helicobacter pylori
Infection

Anahtar Kelimeler:
ATCC 26695
Biyofilm
Kristal Viyole
Helicobacter pylori
Enfeksiyon

INTRODUCTION

Helicobacter pylori is a spiral-shaped, gram-negative, microaerophilic bacterium that colonizes the human stomach (1). It has been observed that in developing countries, the prevalence of *H. pylori* can reach 90% of the population and the infection can last a lifetime. The study group of the World Health Organization's International Agency for Research on Cancer concluded in 1994 that *H. pylori* is classified as a group I carcinogen in humans. *H. pylori* is associated with several gastric disorders, including peptic ulcer disease, which is a major cause of both duodenal ulcers and gastric ulcers. Additionally, it is linked to chronic active gastritis, Mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma. Long-term infection with *H. pylori* increases the risk of developing gastric cancer

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(2). Most people infected with *H. pylori* are asymptomatic However, infected people are at high risk of developing related diseases. *H. pylori* exhibits 2 morphological forms. One appears as a spiral form, while the other is a coccoid form that cannot be cultured but is viable the spiral shape is the most common form in colonization of the human stomach. This microorganism has ability to change its spiral shape in to a coccoid form in order to survive when the environmental conditions deteriorate (3). Most bacteria can adapt to life under environmentally restrictive conditions by developing different mechanisms.

Bacteria form surface-attached communities defined as "bacterial biofilms" to protect themselves from adverse environmental conditions. Biofilms are ubiquitous in natural, industrial and clinical environments and have a critical role in the establishing persistent infection (4). Biofilms are composed of dead and living microbial cells and extracellular polymeric substances (EPS), which are proteins, nucleic acids and polysaccharides synthesized and secreted by these microbial cells (5). The EPS matrix constitutes approximately 90% of the biofilm biomass. The first binding phase is formed by specific bacterial surface molecules as well as hydrophobic or electrostatic interactions. The next stage is the proliferation of bacteria. In the third stage (maturation stage), as the number of bacteria increases, the biofilm forms a thick tower-like structure. The expanding biofilm releases planktonic bacterial cells to dissolve and spread to other sites (6,7). Stark et al. conducted the first research on biofilm formation for *H. pylori*. First demonstration of the ability of *H. pylori* to form biofilms *in vitro*, the presence of a water-insoluble polysaccharide at the liquid–air interface was reported that *H. pylori* strain NCTC 11637 was grown continually in a glass fermentor (8). Later, in the study with clinic isolate laboratory strains of *H. pylori*, Cole and colleagues reported that biofilms formed over glass surfaces only in the air-liquid interface, which was an indicator of microaerobicity (9). Several studies have mentioned in ability of *H. pylori* to form biofilms when grown upon a glass surface, observing a biofilm whose content is polysaccharide in the air-liquid interface (10,11). Biofilm formation is also critical for bacteria to survive and establish a successful infection. Biofilms exhibit the ability to survive exposure to antibacterial agents. Bacteria within biofilms are able to become 10-1000 times resistant to the effects of antimicrobial agents. This is because EPS is a diffusion barrier that prevents substances that inhibit bacterial growth from entering the biofilm. Even if some antibacterial agents can penetrate freely, protection will be provided by EPS blocking the diffusion reaction of the antibacterial agent, bringing it to a sublethal concentration before it reaches all bacterial cells in the biofilm. Thus, bacteria are found deep within the biofilm, creating an opportunity for them to develop resistance to the drug (12). *H. pylori*, uses biofilm production as a strategy to evade the host's immune system and protect itself from the harsh environment and antimicrobial agents found in the stomach (13,14). The aim of this study is to investigate the effectiveness of the biofilm-forming ability of *H. pylori* clinical strains, which is the reason for treatment failure, in different culture environments.

MATERIAL AND METHOD

This study was carried out by Dokuz Eylül University Faculty of Medicine Ethics Committee with the decision dated 20.02.2019/20.07.2022 and numbered 2019/4-35;2022/04-16 at Dokuz Eylül University Faculty of Medicine, Department of Medical Microbiology.

Bacterial strains and culture conditions

ATCC 26695 and three clinical isolates were used in the study. *H. pylori* ATCC 26695 was obtained from the American Type Culture Collection (Rockville, MD, USA) and was later used in this study. Clinical isolates were retrospectively obtained from previously studies including the patients antrum and corpus gastric biopcies Rapid urease test (RUT) and histopathology were also performed. Three clinical isolates in stock culture medium stored in aliquots in BHI medium containing 20% glycerol at -80°C, were brought to room temperature and cultured on Columbia Blood agar (Oxoid) medium containing 7% Defibrined Horse Blood with *H. pylori* Selective Supplement (DENT, Oxoid) for three to five days at 37°C in microaerophilic condition using the GasPak Campy Container System (Becton Dickinson and Company) in an anaerobic jar (Oxoid). Subcultures were made from the colonies that grew as a result of incubation.

Biofilm formation and its quantification

Bacteria growing over Columbia Blood agar (Oxoid) medium containing 7% Defibrinated Horse Blood, and *H. pylori* Selective Supplement (DENT, Oxoid) were collected in 1 mL Brucella broth (BB; Biolife, Italiana). Bacterial suspensions with a standard turbidity of 3.0 McFarland (~6x108 CFU/ml) were obtained using the Densimat device (Biomerieux SA, France). 20 µl of *H. pylori* bacterial suspension and 180 µl BB supplemented with 1% FBS were added to each well of a sterile flat-bottom 96-well polystyrene microtiter plate (Greiner bio-one Austria); 20 µl of *H. pylori* bacterial suspension and 180 µl BB supplemented with 10% FBS were added to the second plate; 20 µl of *H. pylori* bacterial suspension and 180 µl BB supplemented with 5% inactivated human serum were added to the third plate; The environmental and time-dependent biofilm formation were evaluated by incubation in an anaerobic jar in a microaerophilic environment for 2 days and 4 days in an anaerobic jar in a microaerophilic environment at 37°C using the GasPak Campy Container System (Becton Dickinson and Company). Each plate was run on consecutive days and the experiments were repeated 3 times.

In the other study; Biofilm formation of the strains were evaluated using different culture media and contents. Culture media used; alone Brucella Broth (BB), Tryptic Soy Broth (TSB) (LAB M, UK) supplemented with 10% Fetal bovine serum (FBS), Brain Heart Infusion broth (BHI) (Oxoid Ltd., England) supplemented with 10% FBS, BB supplemented with 10% FBS, BB supplemented with 10% FBS and 0.25% glucose (AppliChem, Germany), and BB supplemented with 10% FBS and 1% glucose (15).

Using six separate plate for each culture medium from a sterile flat-bottomed 96-well polystyrene microtiter plate (Greiner bio-one Austria), 180 µL of the culture medium and 20 µl of *H. pylori* suspension were added to each well. The microplates were incubated for 3 days in an anaerobic

jar in a microaerophilic environment at 37°C using the GasPak Campy Container System (Becton Dickinson and Company). Each plate was run on consecutive days and the experiments were repeated 3 times.

The planktonic cell suspension was removed by washing the microplate three times with sterile phosphate-buffered saline (PBS, pH 7.3). The microplate was air dried for 1 hour. The cells adhering to the microplate were fixed by adding 200 µl methanol (Merck, Germany) to each well and waiting for 15 minutes. The wells were emptied and left at room temperature for 1 hour to dry. Then, each well was stained with 200 µl 1% (w/v) crystal violet (CV) (Merck, Germany) on account of 5 minutes, and the wells were emptied. Washed 2 times with PBS. It was air dried for 15 minutes. Then, 200 µl of ethanol-acetic acid (ethanol: acetic acid = 95:5) (Merck, Germany) was added to the wells stained with crystal violet and waited for 1 minute. The quantity of biofilm was obtained from absorbance measurements with a spectrophotometer (BioTech Synergy HT, USA) at a wavelength of 595 nm. The experiments were performed in triplicate. In this study, absorbance measurement of the well containing bacteria-free medium was used as a negative control.

Biofilm formation was evaluated in 3 classes: a negative biofilm-former ODT < control ODC, a weak biofilm-former ODT ≥ the control ODC, and a strong biofilm-former ODT ≥ 2 times of the control ODC (16).

RESULTS

Effect of cell growth on biofilm formation

Two different concentrations of FBS (1%, 10%) and 5% inactivated human serum were added to the BB medium of *H. pylori* ATCC 26695 standard strain and 3 clinical strains, and 2-day and 4-day biofilm formations were compared.

Total biomass of biofilm formation (time and %FBS) under different settings was evaluated among three clinical strains and *H. pylori* ATCC 26695 standard strain. At the end of the study, a significant increase in growth was observed in all the strains on day four BB supplemented with 5% inactivated human serum. This was chosen as the ideal condition because of the development due to the biofilm model of *H. pylori* strains (Figure 1,2).

The ability of *H. pylori* strains to model biofilms was

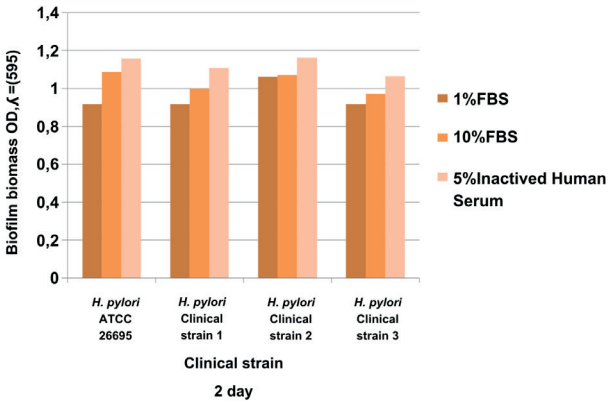


Figure 1: Two-day biofilm evaluation of *H. pylori* in culture medium with 1% FBS, 10% FBS, and 5% inactivated human serum.

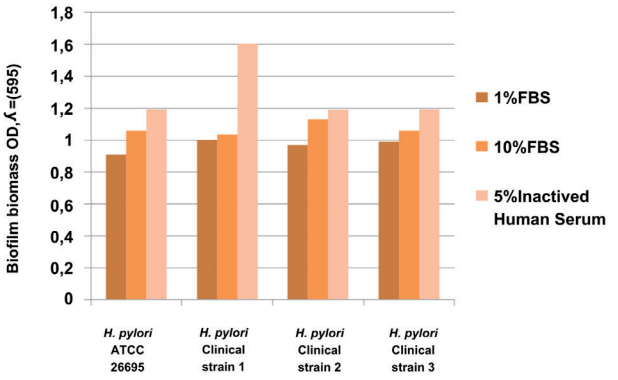


Figure 2: Four-day biofilm evaluation of *H. pylori* in culture medium with 1% FBS, 10% FBS, and 5% inactivated human serum.

determined by a microplate-based assay using flat-bottom polystyrene microtiter plates (Greiner bio-one Austria) with CV (w/v) staining. The results were evaluated by spectrophotometric measurement (OD595). An ıncrease in biofilm biomass of strains was observed between the 1% FBS, 10% FBS and 5% inactivated human serum used (Table 1,2).

Biofilm formation capacity due to *H. pylori* strains in six varied culture media was determined by a microplate-

Table 1: Average ODT of *H. pylori* two-day biofilm formation.

	*ODT of BB+1%FBS (2 day)	ODT of BB+10%FBS (2 day)	ODT of BB+5% inactivated human serum (2 day)
**ODC	0.919	0.900	0.978
***H. pylori* ATCC 266695**	0.917	1.087	1.157
***H. pylori* clinical strain 1**	0.916	0.999	1.107
***H. pylori* clinical strain 2**	1.062	1.071	1.162
***H. pylori* clinical strain 3**	0.917	0.971	1.064

**ODT = Optical Density of the isolates*

***ODC = Optical Density of the controls (BB+1%FBS, BB+10%FBS, BB + 5% inactivated human serum)*

Table 2: Average ODT of *H. pylori* four-day biofilm formation.

	*ODT of BB+1%FBS (4 day)	ODT of BB+10%FBS (4 day)	ODT of BB+5% inactivated human serum (4 day)
****ODC**	1.015	1.093	1.246
***H. pylori* ATCC 266695**	1.014	1.240	1.212
***H. pylori* clinical strain 1**	0.959	1.024	1.263
***H. pylori* clinical strain 2**	0.979	0.971	1.256
***H. pylori* clinical strain 3**	1.052	1.139	1.340

**ODT = Optical Density of the isolates*
***ODC = Optical Density of the controls (BB+1%FBS, BB+10%FBS, BB + 5% inactivated human serum)*

based assay using flat-bottom polystyrene microtiter plates (Greiner bio-one Austria) with CV (w/v) staining. The results were evaluated by spectrophotometric measurement (OD595) (Table 3,4) .

In all experiments, three *H. pylori* clinical strains and one *H. pylori* ATCC 26695 standard strain (n = 4) were used. The results obtained from the experiments were as follows: BB was 100% (n=4) non biofilm, TSB + 10% FBS produced 75% (n = 3) weak biofilm and 25% (n=1) non biofilm, BHI + 10% FBS 75% (n = 3) strong biofilm and 25% (n=1) weak biofilm BB + 10%FBS 75% (n = 3) strong biofilm and 25% (n=1) weak biofilm, BB + 10%FBS + 0.25% glucose It was observed that three was 75% (n=3) strong biofilm and 25% (n=1) weak biofilm, and BB+10% FBS+1% glucose was 50% (n=2) strong biofilm and 50% (n=2) weak biofilm producers (Figure 3,4).

DISCUSSION

Bacterial biofilms are a serious global health problem due to their ability to evade host defence systems, antibiotics, and other external stresses, thereby contributing to persistent chronic infections (17). Several studies have reported that *H. pylori* is able to form biofilms on abiotic surfaces *in vitro* and on the surface of human gastric

Table 3: H. pylori Biofilm Formation on BB, TSB + 10 % FBS, BHI + 10 % FBS, BB + 10 % FBS, BB + 10 % FBS + 0,25 % glucose and BB + 10 % FBS + 1 % glucose culture media.

***Helicobacter pylori* strains**	**BB**	**TSB+ 10%FBS**	**BHI+ 10%FBS**	**BB+1 0%FBS**	**BB+10%FBS +0,25%glucose**	**BB+10%FBS +1%glucose**
ATCC 26695	non	weak	strong	strong	strong	strong
Clinical strain 1	non	non	weak	weak	weak	weak
Clinical strain 2	non	weak	strong	strong	strong	weak
Clinical strain 3	non	weak	strong	strong	strong	strong
Number (n) and % for Biofilm Formation on Culture Media	non-biofilm (n=4) (100%)	non-biofilm (n=1) (25%) weak (n=3) (75%)	weak-biofilm (n=1) (25%) strong (n=3) (75%)	weak-biofilm (n=1) (25%) strong (n=3) (75%)	weak-biofilm (n=1) (25%) strong (n=3) (75%)	weak-biofilm (n=2) (50%) strong (n=2) (50%)

Table 4: Average ODT of *H. pylori* Biofilm Formation on BB, TSB + 10 % FBS, BHI + 10 % FBS, BB + 10 % FBS, BB + 10 % FBS + 0,25 % glucose and BB + 10 % FBS + 1 % glucose culture media.

***Helicobacter pylori* strains**	***ODT of BB**	***ODT of TSB+ 10%FBS**	***ODT of BHI+ 10%FBS**	***ODT of BB+10%FBS**	***ODT of BB+ 10%FBS +0,25%glucose**	***ODT of BB+ 10%FBS+ 1%glucose**
****ODC**	0,126	0,132	0,124	0,142	0,145	0,148
ATCC 266695	0,110	0,158	0,403	0,353	0,420	0,426
Clinical strain 1	0,123	0,130	0,172	0,182	0,169	0,196
Clinical strain 2	0,116	0,146	0,248	0,320	0,342	0,215
Clinical strain 3	0,108	0,136	0,362	0,332	0,326	0,384

**ODT = Optical Density of the isolates*
***ODC = Optical Density of the controls (BB, TSB+10%FBS, BHI+10%FBS, BB+10%FBS, BB+10%FBS+0,25%glucose, BB+10%FBS+1%glucose)*

Figure 3: *H. pylori* Biofilm Formation Percentages on BB, TSB + 10 % FBS, BHI + 10 % FBS, BB + 10 % FBS, BB + 10 % FBS + 0,25 % glucose and BB + 10 % FBS + 1 % glucose culture media.

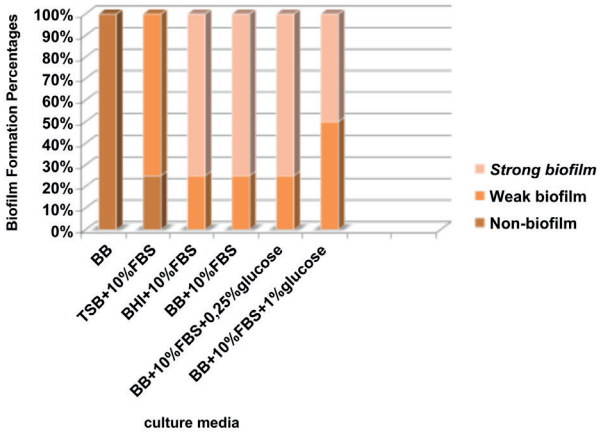
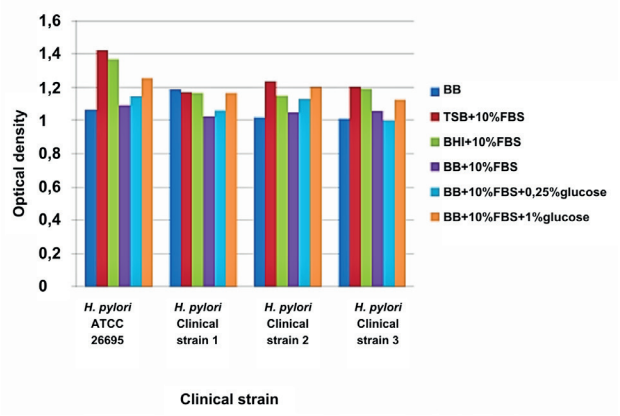


Figure 4: *H. pylori* ODT of H. pylori Biofilm Formation on BB, TSB + 10 % FBS, BHI + 10 % FBS, BB + 10 % FBS, BB + 10 % FBS + 0,25 % glucose and BB + 10 % FBS + 1 % glucose culture media.



mucosal (18,19). Studies have shown that some bacterial biofilms consist of two processes: (i) initial adhesion to the surface via adhesins; (ii) formation of multilayered cell clusters by spontaneous production of extracellular matrix by cell growth (20,21). Our results showed that *H. pylori* biofilm formation proceeds in the same way. The results showed that for 1% FBS, the number of viable bacteria in the biofilm matrix was low despite the time-related increase. However, 5% inactivated human serum was found to be more effective as the most suitable environmental condition for *H. pylori* viability and growth. It resulted in the highest amount of biofilm biomass among the conditions tested. Accordance with the habitat due to *H. pylori* with consideration of the media used due to standard culture, some of the most common rich growth media were used for biofilm formation (22). Despite the differences in *H. pylori* medium compositions, it formed biofilms at similar levels in each medium. The data obtained indicating that slight changes in rich growth media did not significantly influence *H. pylori* biofilm formation and that our determination of biofilm formation was not an creation of medium selection. Pinho et al., in their study with 1% FBS, 5% FBS and 10% FBS, found that the decrease in FBS supplementation (normal 10% versus 5% FBS) resulted in higher biofilm biomass production.They showed that under 10% FBS supplementation, bacteria did not have a defense strategy as in biofilm formation (23). In the study conducted by Cole et al., the effect of mucin on biofilm formation was investigated and it was shown that it significantly increased the number of planktonic *H. pylori* in the mucus-rich stomach environment, but did not affect biofilm formation (24). Many published studies have demonstrated the amino acid requirement of *H. pylori* and have shown that amino acids are used instead of sugar as a carbon source. In his study, Mends et al. showed that *H. pylori* was able to survive by using amino acids as its main nutrient, converting arginine, asparagine, aspartate, glutamine, and serine, which are used as substrates, into the metabolic products acetate, succinate, and lactate (25). In the study of Reynolds et al., it was found that the addition of alanine in the presence of glucose in the environment induces growth using it as a nitrogen or carbon source (26). In another study designed by Abdollahi et al., it was found that *H. pylori* isolates showed positive chemotaxis and negative chemotaxis (repellency) towards the tested sugars and amino acids phenylalanine, aspartic acid, glutamic acid, isoleucine and leucine, and tyrosine, since the ability to move for biofilm plays an important role in *H. pylori* pathogenicity (27). Commonly used in tissue culture media, Ham's F-12 has been shown to promote the growth of *H. pylori* in the absence of serum or protein (28). Although F-12 promotes *H. pylori* growth, the addition of fetal bovine serum (FBS) to the medium has been shown to significantly increase growth; This showed that further optimization or supplementation with identified nutrients was required (29).

Another environmental situation that affected biofilm creation was the surface on which the biofilm formed. Initiating biofilm formation necessity bacterial cells attached to a surface and shape microcolonies. These microcolonies turn into a grown biofilm structure. In biofilm formation, bacterial cells adhere to a surface or interface. This duration conditional on provided that the bacteria come into direct touch with the surface and on appropriate cell-surface interactions to overcome the repellent forces generated between the two surfaces. Windham et al. in their study, they showed that although various enriched growth media did not significantly affect biofilm formation, surface selection had a significant effect on biofilm mass (15). There is evidence to suggest that the microorganism can sense contact with a superficies and in answer change gene expression to promote stable cell-surface interactivity. However, the exact molecular mechanisms are still unknown. For this reason, uncertainties about biofilm development remain on the agenda (30,31).

H. pylori has the capacity to form biofilms in the environment, on abiotic surfaces, and in the human stomach. *H. pylori* can be found embedded in drinking water biofilms in water distribution systems in countries (32,33). Various studies have shown that understanding *H. pylori* biofilm formation is important for in the

prevention and control of *H. pylori* infection (34,35). The emergence of drug resistance in *H. pylori* has become a serious clinical problem. Biofilm formation is considered an important factor contributing to antibiotic resistance in humans. Therefore, it is essential to develop anti-biofilm agents with strong antagonistic effects against bacterial biofilms. These agents can enhance *H. pylori* eradication by reducing drug resistance, and offering a promising approach to combat a key challenge related to antibiotic resistance.

CONCLUSION

Assessment of the biofilm formation ability of *H. pylori* plays an significant role in controlling and biofilm preventing the formation of antibiotic resistance. Therefore, it is thought that investigating *H. pylori* biofilm creation may be efficient in understanding the infection and colonization of this microorganism. There are differences in how biofilm is carried out. Although studies have been conducted to examine factors related to *H. pylori* biofilm formation, it is not yet resolved where it may vary depending on conditions. It is thought that awareness of *H. pylori*, an overlooked bacterium, is also important in the protection of public health and multidisciplinary studies are needed to understand the complexity of biofilm formation.

Conflict of Interest: No conflict of interest was declared by the authors.
Ethics: This study was conducted after approval by the Ethics Committee of the Faculty of Medicine of Dokuz Eylül University (Decision No: 2019/4-35;2022/04-16, Date 20.02.2019;20.07.2022).
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ORIGINAL ARTICLE

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Examination of Cases who Admitted to the Emergency Department of a Mental Health Hospital in 2020

Bir Ruh Sağlığı Hastanesinin Acil Servisine 2020 Yılında Başvuran Olguların İncelenmesi

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ABSTRACT

Objective: *The emergency department of mental health and diseases hospitals (MHDH) is a primary entry point into the network of mental health services for people who need urgent psychiatric help. Examining the emergency department admissions of MHDHs will pave the way for possible interventions to be carried out more appropriately. This study aimed to retrospectively examine the sociodemographic and clinical characteristics of cases who admitted to the emergency department of a MHDH in 2020.*

Material and Methods: *Cases who admitted to the emergency department of Elazığ MHDH between 01.01.2020 and 31.12.2020 were included. Sociodemographic and clinical data of the cases were accessed through the patient record system.*

Results: *The total number of admissions to the Elazığ MHDH emergency department between the specified dates was 7071 [5262 (74.4%) male and 1809 (25.6%) female].Sixty-four percent of the cases admitted through the Social Security Institution and 28% through the Ministry of Justice. Seven thousand fifty-five cases (99.7%) were the Republic of Turkey citizens. Three thousand two hundred fifty-four (46.0%) of the cases were evaluated within the scope of medical examination, 1599 (22.6%) were injection, 156 (2.2%) were involuntary hospitalization, and 1887 (26.7%) were judicial illegal drug screening. While 5877 (83.1%) of the cases left the emergency department after examination, 1194 (16.9%) were hospitalized at Elazığ MHDH. Two thousand one hundred forty-six (30.3%) of the cases were diagnosed with general psychiatric examination, 866 (12.2%) were anxiety spectrum disorders, 1464 (20.7%) were schizophrenia spectrum disorders, and 1658 (23.4%) were bipolar spectrum disorders. A statistically significant difference was found between male and female cases in terms of health insurance ($p<0.001$), reason for admission ($p<0.001$), month of admission ($p=0.005$), place of residence ($p<0.001$), and diagnosis ($p<0.001$).*

Conclusion: *This study reveals that the male gender is the majority in the admissions made to an MHDH emergency department, the rate of illegal drug screenings in emergency department admissions is high, and the diagnoses of schizophrenia and bipolar spectrum disorder have an important place in hospitalizations following the emergency department admission.*

ÖZET

Amaç: *Ruh sağlığı ve hastalıkları hastanelerinin (RSHH) acil servisi, acil psikiyatrik yardıma ihtiyaç duyan kişiler için ruh sağlığı hizmetleri ağına birincil giriş noktasıdır. RSHH'lerin acil servis başvurularının incelenmesi olası müdahalelerin daha uygun şekilde gerçekleştirilmesinin önünü açacaktır. Bu çalışmada, bir RSHH acil servisine 2020 yılında başvuran olguların sosyodemografik ve klinik özelliklerinin geriye dönük olarak incelenmesi amaçlanmıştır.*

Gereç ve Yöntemler: *Elazığ RSHH'nin acil servisine 01.01.2020-31.12.2020 tarihleri arasında başvurmuş olgular dâhil edilmiştir. Olgulara ait sosyodemografik ve klinik verilere hasta kayıt sistemi aracılığıyla ulaşılmıştır.*

Bulgular: *Belirtilen tarihler arasında Elazığ RSHH acil servisine toplam başvuru sayısı 7071 [5262 (%74,4) erkek, 1809 (%25,6) kadın] idi. Vakaların %64'ü Sosyal Güvenlik Kurumu, %28'i ise Adalet Bakanlığı aracılığıyla başvurdu. Vakaların 7055'i (%99,7) Türkiye Cumhuriyeti vatandaşıydı. Vakaların 3254'ü (%46,0) muayene, 1599'u (%22,6) enjeksiyon, 156'sı (%2,2) istem dışı yatış, 1887'si (%26,7) yasa dışı madde taraması kapsamında değerlendirildi. Olguların 5877'si (%83,1) muayene sonrası acil servisten ayrılırken, 1194'ü (%16,9) Elazığ RSHH'ye yatırıldı. Olguların 2046'sına (%30,3) genel psikiyatrik muayene, 866'sına (%12,2) anksiyete spektrum bozukluğu, 1464'üne (%20,7) şizofreni spektrum bozukluğu, 1658'ine (%23,4) bipolar spektrum bozukluğu tanısı konuldu. Erkek ve kadın olgular arasında sağlık güvencesi ($p<0,001$), başvuru nedeni ($p<0,001$), başvuru ayı ($p=0,005$), ikamet yeri ($p<0,001$) ve tanı ($p<0,001$) açısından anlamlı farklılık saptandı.*

Sonuç: *Bu çalışma bir RSHH acil servisine yapılan başvurularda erkek cinsiyetin çoğunlukta olduğunu, yasadışı madde taramalarının acil servis başvuruları içerisindeki oranının yüksek olduğunu, acil servis başvurusunu takiben hastaneye yatışlarda şizofreni ve bipolar spektrum bozukluğu tanılarının önemli bir yeri olduğunu göstermektedir.*

Keywords:
Psychiatric emergency
Old age
Emergency
Hospitalization
Drug detection

Anahtar Kelimeler:
Psikiyatrik acil
Yaşlılık
Acil
Yatış
Madde taraması

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INTRODUCTION

Psychiatric emergencies can be defined as clinical conditions in which symptoms occurring in one or more of the areas of thought, emotion, and behaviour pose a threat to the patient or other people and require urgent psychiatric intervention. In addition to psychiatrists, physicians working in emergency departments frequently encounter psychiatric emergencies (1). Cases under physical or emotional stress who admit to the emergency department are vulnerable (2). These patients may have various expectations that are far from reality, and this affects their response to treatment and communication with healthcare personnel. Psychiatric emergencies can be caused by many chronic mental disorders, psychosocial stressors, and adverse life events. Drug poisoning and use, suicide, psychotic and manic exacerbations, medication side effects, and drug-drug interactions may lead to emergency psychiatric admissions (3). Psychiatric emergency departments ensure that patients and their relatives are saved from the material and moral burdens of the disease with minimal loss by directing patients quickly and accurately with effective measures in a short time. Psychiatric intervention in emergency services is also important for preventive psychiatry. Since successful first aid can prevent a second emergency, it can also facilitate the patient's compliance with subsequent treatments (4).

It is reported that anxiety, panic, conversion, and suicide-related situations are more common in admissions to the emergency departments of general hospitals (3,5). In addition to the conditions listed above, it has been reported that psychotic and manic exacerbations, criminal cases, alcohol and drug-related conditions are observed in admissions to the emergency departments of Mental Health and Diseases Hospitals (MHDH). Agitation, suicidal and homicidal behaviour can cause harm to people and the people around them. In our country, these patients are mostly hospitalized in MHDHs with closed ward facilities. Some of the admissions for hospitalization are made to the emergency departments of MHDHs (2). It is thought that the characteristics of admissions to the emergency departments of MHDHs may also change over time. As a matter of fact, past studies have shown that the reasons for admission, especially drug use characteristics and criminal cases, change over time. This study aimed to examine the cases who admitted to the Elazığ MHDH emergency department within a one-year period in terms of sociodemographic and clinical variables.

MATERIALS AND METHODS

This study addresses all cases who admitted to the emergency psychiatric unit of Elazığ MHDH between 01.01.2020 and 31.12.2020. Elazığ MHDH is one of the largest psychiatric branch hospitals in Turkey, providing mental health services to 18 different provinces in the Eastern Anatolia, Black Sea and South-eastern Anatolia regions.

This study also includes cases referred to Elazığ MHDH within the scope of Turkish Civil Code 432 (TCC 432) decision. In Turkey, TCC 432 decision can be obtained directly by the Civil Courts of Peace or indirectly through hospitals. All TCC 432 cases included in this study were referred by the Civil Courts of Peace. In these cases, all patients are hospitalized and discharged as soon as it is determined that they are suitable for discharge.

All information presented in the study was obtained retrospectively from the hospital registry system. The psychiatric diagnoses included in the study were written according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (6). Ethics committee approval was received from Fırat University (Date: 22/04/2021; No: 2021/06-18).

SPSS version 26.0 was used in statistical analysis. Descriptive statistics and continuous variables are given as mean±standard deviation, and categorical variables are given as frequency and percentage. Chi-Square test was used to compare categorical data, and independent samples T-test was used to compare numerical data. The statistical significance level was determined as $p<0.05$.

RESULTS

The total number of admissions to the Elazığ MHDH emergency department between January 1, 2020 and December 31, 2020 was 7071. The mean age of the cases was 36.98±13.94 years (minimum 6 years, maximum 100 years, and median 34 years). Of the cases included in our study, 5262 (74.4%) were male and 1809 (25.6%) were female. While the mean age was 35.07±12.70 years in male cases, it was 42.55±15.80 years in female cases ($p<0.001$).

There was no missing data in the study, except that the health insurance of three cases was unknown. The cases were examined in terms of health insurance. Four thousand five hundred twenty-three (64.0%) of the cases admitted through "Social Security Institution", 236 (3.3%) through "Bağkur", 93 (1.3%) through "Ministry of Justice", 133 (1.9%) through "SHÇEK Persons Under State Protection by Law No. 2828", 4 (0.1%) through "Refugees", 2046 (28.9%) through "Forensic Cases", 10 (0.1%) through "Foreign Provision Activation Health System (YUPASS)", and 5 (0.1%) through the "Union of Chambers and Commodity Exchanges of Turkey Members' Retirement and Assistance Fund Foundation". There were 18 (0.3%) cases without health insurance. Seven thousand fifty-five cases (99.7%) were from the Republic of Turkey, 8 (0.1%) were from Syria, 7 (0.1%) were from Afghanistan, and 1 (0.1%) was from Germany.

Three thousand two hundred fifty-four (46.0%) of the cases were evaluated within the scope of examination, 1599 (22.6%) were injection, 156 (2.2%) were TCC 432, 1887 (26.7%) were judicial illegal drug screening, 175 were (2.5%) were referral from another institution. While 5877 (83.1%) of the cases left the emergency department after examination, 1194 (16.9%) were hospitalized at Elazığ MHDH.

The months in which the cases (n=7071) admitted were examined: 650 (9.2%) in January, 615 (8.7%) in February, 658 (9.3%) in March, 433 (6.1%) in April, 531 (7.5%) in May, 795 (11.2%) in June, 647 (9.2%) in July, 547 (7.7%) in August, 592 (8.4%) in September, 605 (8.6%) in October, 505 (7.1%) in November, and 493 (7.0%) in December. Five thousand one hundred twenty-six (72.5%) of the admissions resided in Elazığ, and 1945 (27.5%) resided outside Elazığ.

The cases were examined for diagnosis. Two thousand one

hundred forty-six (30.3%) of the cases were examined by general psychiatric examination, 866 (12.2%) were anxiety spectrum disorders, 1464 (20.7%) were schizophrenia spectrum disorders, 1658 (23.4%) were bipolar spectrum disorders, and 26 (0.4%) were Alzheimer's disease.

Comparisons were made between genders in terms of various variables. A statistically significant difference was found between male and female cases in terms of health insurance ($p<0.001$), reason for admission ($p<0.001$), month of admission ($p=0.005$), place of residence ($p<0.001$), and diagnosis ($p<0.001$). No statistically significant difference was found between male and female cases in terms of hospitalization after emergency admission ($p<0.001$) and nationality ($p=0.778$) (Table).

Various variables were compared in terms of health insurance. A significant difference was found between health insurances in terms of the reason for admission ($p<0.001$), hospitalization status after examination ($p<0.001$), month of admission ($p<0.001$), residence ($p<0.001$), and diagnosis ($p<0.001$). Almost all of those with Social Security Institution and Bağkur health insurance admitted to be examined or to have an injection. Those who admitted for TCC 432 cases and illegal drug screening in urine were entered through the Ministry of Justice. Fifty-seven percent of the detained/convicted cases were brought from outside the province.

None of those who admitted for illegal drug screening and injection were hospitalized. All of the admissions were hospitalized with the TCC 432 decision. 83.4% of the cases referred from another institution were hospitalized. 27.4% of the admissions for examination were hospitalized. 95.5% of TCC 432 cases and 91.4% of referrals were brought from outside the Elazığ.

99.4% of those who admitted for illegal drug screening were diagnosed by general psychiatric examination. Of the patients who received injections, 39.0% were diagnosed with bipolar spectrum disorder and 46.0% were diagnosed with schizophrenia spectrum disorder. 43.6% of TCC 432 cases were diagnosed with general psychiatric examination, 11.5% with bipolar spectrum disorder, 19.9% with schizophrenia spectrum disorder, 9.6% with personality disorder, and 8.3% with alcohol/drug use disorder. Of the cases referred from another institution, 40.6% were diagnosed with bipolar spectrum disorder and 33.7% were diagnosed with schizophrenia spectrum disorder.

The post-examination hospitalization rate for those residing outside Elazığ was 69.6%, and the post-examination hospitalization rate for those residing in Elazığ was 19.0% ($p<0.001$). Of the 1194 hospitalized cases, 488 (40.9%) were diagnosed with bipolar spectrum disorder, 410 (34.3%) with schizophrenia spectrum disorder, 66 (5.5%) with personality disorder, and 48 (4.0%) with alcohol/drug use disorder.

DISCUSSION

This study deals with cases admitted to the emergency

Table: Comparison of Male (n=5262) and Female (n=1809) Cases

Variable		Males n (%)	Females n (%)	p
Health Insurance	Social Security Institution	2994 (56.9)	1529 (84.6)	<0.001*
	Ministry of Justice	1958 (37.2)	88 (4.9)	
	Bagkur	121 (2.3)	115 (6.4)	
	Other	189 (3.6)	181 (4.1)	
Reason of Admission	Examination/Visit	2044 (38.8)	1210 (66.9)	<0.001*
	İnjection	1135 (21.6)	464 (25.6)	
	TCC 432/Involuntary Hospitalization	139 (2.6)	17 (0.9)	
	Screening for Illegal Drugs in Urine	1816 (34.5)	71 (3.9)	
	Referral from Another Institution	128 (2.4)	47 (2.6)	
Examination Result	Discharge from the Emergency Department	4353 (82.7)	1524 (84.2)	0.137
	Hospitalization	909 (17.3)	285 (15.8)	
Residence	Elazığ	3745 (71.2)	1381 (76.3)	<0.001*
	Outside Elazığ	1517 (28.8)	728 (23.7)	
Nationality	Turkiye	5249 (99.7)	1806 (99.8)	0.778
	Syria	7 (0.1)	1 (0.1)	
	Afghanistan	5 (0.1)	2 (0.1)	
	Germany	1 (0.1)	0 (0.0)	
Diagnosis	General Psychiatric Examination	2019 (38.4)	127 (7.0)	<0.001*
	Bipolar Spectrum Disorders	1029 (19.6)	629 (34.8)	
	Schizophrenia Spectrum Disorders	1174 (22.3)	290 (16.0)	
	Anxiety Spectrum Disorders	396 (7.5)	470 (26.0)	
	Other	644 (12.2)	293 (16.2)	

**p<0.05, Chi-square analysis was used in statistical analysis. Abbreviations: TCC=Turkish Civil Code*

department of an MHDH in Turkey. The findings shows that the majority of cases admitting to the Elazığ MHDH emergency department are males, that the mean age was lower in males, that the health insurance of the majority of cases is the Social Security Institution, that the majority of the cases are citizens of the Republic of Turkey, that the majority of cases admitted for examination and illegal drug screening, and that the majority of the cases hospitalized after examination have bipolar and schizophrenia spectrum disorders. This study shows that the rate of non-emergency conditions among MHDH emergency service admissions is high.

When the literature is examined, it is seen that gender ratios vary between studies. Küçükali et al. (2) examined the cases admitted to the Bakırköy MHDH emergency psychiatric department in August 2011 and reported that 54% of the cases were females. Muştucu et al. (7) reported that 53.1% of the cases were females in their study, which included 748 patients who admitted to the emergency department of Uludağ University Hospital and were consulted by psychiatry between 11 March 2019 - 1 September 2019 and 11 March 2020 - 1 September 2020. Cincioğlu et al. (5) in their study, which included patients who admitted to the emergency department of a training and research hospital and were diagnosed with psychiatric disorders within a one-year period covering 2017, it was reported that 69.50% of the cases were females. In this study, the female rate was found to be 25.6%. It was observed that there were significant differences between studies in terms of gender. The characteristics of the hospitals (such as university hospital, training and research hospital, MHDH) and the time when the study was conducted affect the findings. In the study conducted by Montemagni et al. (8), it was reported that male who admitted to the psychiatric emergency department with a diagnosis of acute psychosis were younger than female, the rate of drug abuse was higher, and anxiety complaints were higher in female. In the study of Sáenz-Herrero et al. (9), female gender was found to be overrepresented in anxiety and stress-related disorders, mood disorders, and personality disorders. In contrast, males accounted for 70% of all psychoactive drug use disorders. Our findings are consistent with the literature.

In previous studies examining psychiatric emergency cases, the health insurance, reasons for admission, and nationality of the cases were not examined. In this study, it was reported that the majority of the cases were admitted for examination, injection and urine screening for illegal drugs. Cases admitted for examination refer to cases admitted to the hospital individually. It is known that the majority of these cases reside within the Elazığ province. Noncompliance with treatment is a common situation in patients with psychotic features. Problems in compliance with treatment lead to increased involuntary hospitalizations, longer hospital stays, longer recovery times for psychotic symptoms, poor prognosis, and suicides. Treatment compliance problems may be greater in rural areas where there is not enough social support (10). Long-acting antipsychotic injections provide significant benefits in this group of patients whose medication cannot be monitored. These long-acting antipsychotic injections need to be administered intramuscularly at certain intervals (once every two weeks, once a month, once every three months, etc.) (11). These injection admissions can be performed in family health centres and emergency departments. These long-acting antipsychotic injections are frequently performed in the Elazığ MHDH emergency department. Admission for injection access in this study refer to long-acting antipsychotic injection admissions. Determination of whether individuals captured by security forces are using illegal drugs is carried out only by Elazığ MHDH in Elazığ province. This is the reason why the number of admissions for illegal drug screening in urine was found to be high among the emergency admissions in this study. In our country, restrictions on freedom for protection purposes and their conditions are regulated in Article 432 of the TCC. Involuntary hospitalization orders are issued through the Civil Courts of Peace for patients who are incompatible with treatment and have the potential to harm themselves and the environment. With the decision of TCC 432, hospitalizations are carried out in MHDHs in our country (12). Elazığ MHDH is a hospital where TCC 432 cases in 18 provinces are hospitalized. The findings of this presented study provide the opportunity to interpret the characteristics of TCC 432 cases.

When the diagnostic distributions of psychiatric emergency admissions were examined, it was determined that there were various differences and similarities between the studies. In a study by Küçükali et al. (2) examining the cases admitted to the emergency department of an MHDH, it was reported that the most common diagnosis was mood disorder with 36% and psychotic disorder with 22%. In a study by Muştucu et al. (7) examining psychiatric cases admitted to the emergency department of a university hospital, it was shown that 40.6% of the cases were diagnosed with depression and related disorders, 20.7% with schizophrenia and other psychotic disorders, and 19.6% with bipolar and related disorders. In a study by Cincioğlu et al. (5) examining psychiatric cases admitted to the emergency department of a training and research hospital, it was shown that 84.04% of the cases were evaluated with a diagnosis of anxiety spectrum disorder. In this study, it was shown that the most common diagnosis was general psychiatric examination. Bipolar and schizophrenia spectrum disorder diagnoses appear to be the most common diagnoses after the general psychiatric examination diagnosis. It was concluded that these differences between the studies were related to institutional characteristics and changes in security practices in the country. Cases with psychotic features and mood symptoms are mostly hospitalized in MHDHs with closed ward facilities. In addition, all TCC 432 cases are hospitalized in MHDHs and the majority of these cases are diagnosed with schizophrenia and bipolar spectrum disorder. On the other hand, anxiety and depression spectrum disorders are admitted to universities and training and research hospitals. In recent years, an increasing number of cases of illegal drug use have been caught by security forces (13). Illegal drug use panels for these cases are generally carried out by MHDHs. Since these cases

were diagnosed with a general psychiatric examination, the rate of general psychiatric examination diagnosis was found to be high in our study. Since illicit drug use is more common in men, the proportion of men with a general psychiatric examination diagnosis was higher. When the findings were examined in terms of hospitalization after the examination, it was determined that the most frequently hospitalized cases were those diagnosed with bipolar spectrum disorder and schizophrenia spectrum disorder. This finding is also compatible with studies in the literature.

One of the most important limitations of this study is that it is retrospective. Another limitation is that the sociodemographic data of the cases, such as marital status, employment status, and educational status, are not known. Detailed clinical features of the psychiatric disorders of the cases could not be obtained. Details of situations related to suicide, one of the most important psychiatric emergencies, could not be accessed through records. It is assumed that these possible suicide cases were admitted under other diagnoses such as depression, bipolar, and schizophrenia spectrum disorders. Cross-sectional and longitudinal studies are needed to obtain data related to suicide. It is also unknown whether the cases arrive accompanied by an ambulance or law enforcement and whether they wish to be hospitalized or not. Additionally, this study was based on the records of the cases in the system. In other words, it is not known whether there were diagnoses entered into the system accidentally or hastily due to urgent conditions. It is seen that there are cases where people are taken to the emergency psychiatric department even though it is not an emergency. These entries, in the form of illegal drug screening, are carried out through the emergency psychiatric department as per the procedure due to official processes. Further studies in which the important limitations mentioned here are reduced will be guiding. The strength of the study is that it deals with recent admissions to the emergency department of an MHDH and that there is no recent study with similar features.

CONCLUSION

This study considers all cases admitted to the emergency department of a MHDH and shows that general psychiatric examination, schizophrenia spectrum disorder, and bipolar spectrum disorder are the most common diagnoses. It is seen that the most common diagnoses in cases hospitalized after admission are schizophrenia and bipolar spectrum disorders. Although it is a psychiatric emergency study, it includes a significant number of non-urgent cases. This situation suggests that there are some obstacles to the appropriate use of psychiatric emergency services. These non-urgent admissions, such as illegal drug screening, also occur during the interpretation process of the findings and cause the male gender to be more dominant. Investigating the findings obtained from the research in future studies in the light of the information presented here will facilitate the discussion of the findings.

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ORIGINAL ARTICLE

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Epidemiology, Clinical Features and Predictors of Mortality in Patients with Candidemia in a Tertiary Care Hospital in Turkiye: A Single-Center Retrospective Study

Türkiye'de Üçüncü Basamak Bir Hastanede Kandidemili Hastalarda Epidemiyoloji, Klinik Özellikler ve Mortalite Belirteçleri: Tek Merkezli Retrospektif Bir Çalişma

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ABSTRACT

Objective: *We aimed to evaluate the epidemiology of candidemia among hospitalized patients and identify risk factors associated with mortality.*

Materials and methods: *The medical data of 81 adult patients with candidemia who were hospitalized between May 1, 2015 and May 1, 2016 constituted the study. We recorded vital signs, clinical characteristics, ward or intensive care unit (ICU) interventions, comorbidities, and biochemistry findings. To identify factors independently associated with 30-day mortality, a forward conditional inclusion model was used in multivariable logistic regression.*

Results: *The annual incidence of candidemia was 23 cases per 10000 individuals (0.23%). The three most frequently detected species were C. albicans (46.91%), C. parapsilosis (29.63%) and C. glabrata (8.64%). The 30-day mortality rate was 59.26% (n=48). Multivariable logistic regression showed that older age (OR: 1.037, 95% CI: 1.006 - 1.070, p=0.018), ICU admission (OR: 3.325, 95% CI: 1.132 - 9.766, p=0.029) and acute renal failure (OR: 3.383, 95% CI: 1.024 - 11.173, p=0.046) were independently associated with mortality.*

Conclusion: *We revealed an annual candidemia incidence of 0.23% and a notably high 30-day mortality rate at our center. Older patients, individuals admitted to the ICU, and those with renal dysfunction may face an elevated risk of mortality, underscoring the importance of close monitoring in these populations.*

ÖZET

Amaç: *Bu çalışmada hastanede yatan hastalarda kandidemi epidemiyolojisini değerlendirmeyi ve mortalite ile ilişkili risk faktörlerini belirlemeyi amaçladık.*

Gereç ve yöntem: *Bu çalışmada 1 Mayıs 2015 ile 1 Mayıs 2016 tarihleri arasında hastaneye yatırılan kandidemili 81 yetişkin hastanın tıbbi verileri kullanıldı. Vital bulguları, klinik özellikleri, servis veya yoğun bakım ünitesi (YBÜ) yatışı, komorbiditeleri ve biyokimya bulgularını kaydettik. 30 günlük mortaliteyle bağımsız olarak ilişkili faktörleri tanımlamak için çok değişkenli lojistik regresyonda ileri koşullu dahil etme modeli kullanıldı.*

Bulgular: *Yıllık kandidemi insidansı 10.000 kişi başına 23 vakaydı (%0.23). En sık tespit edilen üç tür ise C. albicans (%46,91), C. parapsilosis (%29,63) ve C. glabrata (%8,64) oldu. 30 günlük mortalite oranı %59,26 (n=48) olarak bulundu. Çok değişkenli lojistik regresyon ile, ileri yaşın (OR: 1.037, 95% CI: 1.006 - 1.070, p=0.018), yoğun bakım ünitesine yatışın (OR: 3.325, 95% CI: 1.132 - 9.766, p=0.029) ve akut böbrek yetmezliğinin (OR: 3.383, 95% CI: 1.024 - 11.173, p=0.046) bağımsız olarak mortaliteyle ilişkili olduğu gösterildi.*

Sonuç: *Merkezimizde yıllık kandidemi insidansının %0,23 olduğunu ve 30 günlük mortalite oranının oldukça yüksek olduğunu ortaya çıkardık. Yaşlı hastalar, yoğun bakım ünitesine kabul edilen kişiler ve böbrek fonksiyon bozukluğu olan kişiler artmış mortalite riskiyle karşı karşıya kalabilir; bu popülasyonlarda yakından izlem önemlidir.*

Keywords:
Candidemia mortality
Candidemia epidemiology
Candidemia clinical feature

Anahtar Kelimeler:
Kandidemi mortalite
Kandidemi epidemiyoloji
Kandidemi klinik bulgu

INTRODUCTION

Invasive candida infection is the most common fungal infection that is detected among hospitalized patients (1), and according to the international EPIC II study (Extended Prevalence of Infection in Intensive Care) candida infections rank third among all agents (2) –with *Candida albicans* being the most common type (3). The burden of candida is well known, but major studies have shown a decreasing trend in the frequency of *C. albicans* from 57.4% 25 years ago to 46.4% in the last 5 years (4). This shift is important since non-albicans candida strains may be less susceptible to azoles (5).

Prior studies have established a number of risk factors associated with candida infection among in-patients, including catheter use, heart disease, occurrence of systemic life-threatening events, renal dysfunction, and exposure to substances (aminoglycoside, nitroimidazole, glycopeptide) (6,7). The gold standard diagnostic approach is culture obtained from blood, peritoneal fluid and pleural fluid. Therefore, molecular diagnostic tests

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that circumvent the need for culture can potentially reduce morbidity and mortality (8).

Resistant fungal infections, including infections caused by Candida spp. (9), are becoming more common (3) and these data illustrate the need for risk stratification in order to create meaningful treatment strategies against resistant fungal infections (10). In a study comparing the COVID-19 pre-pandemic and pandemic period, a slight increase in candidemia periods was detected (11).

Despite advances in management and therapeutics, candidemia can still cause mortality rates as high as 40–60% (6,10). In order to reduce the morbidity and mortality associated with candidemia, a better understanding of candida epidemiology and risk factors is necessary. As such, we aimed to retrospectively examine candidemia cases arising in hospitalized adults during a one-year period and to evaluate risk factors associated with 30-day mortality.

MATERIALS AND METHODS

In this study, cases in which candida species were isolated in blood culture were accepted as candidemia (12). The dataset for this study comprised medical records from 81 patients aged 18 years and above, all diagnosed with candidemia and treated as inpatients at Trakya University Medical Faculty Hospital during the period from May 1, 2015, to May 1, 2016. Throughout this timeframe, a total of 35066 patients had undergone inpatient care for various medical conditions at our hospital.

All patients with candidemia were evaluated for vital signs, clinical characteristics, ward or intensive care unit (ICU) interventions, comorbidities, complete blood counts, biochemistry findings including liver and kidney function tests, inflammation-related parameters, and specific parameters associated with candidemia, such as hospitalization duration, therapy duration, therapeutic agents administered before and after antibiograms, and diagnosis (based on site of infection). In the mortality evaluation, the 30-day period beginning at positive blood culture signal was evaluated. Any treatment that was administered to patients was continued for at least 14 days after the first negative blood culture result (9); however, evidently, treatment duration was cut short in some patients who died before normal termination of therapy.

Sample Collection, Isolation and Identification of Microorganisms

Samples were collected utilizing aseptic procedures and subjected to analysis employing an automated blood culture system (Bactallert 460, bioMérieux, France). Cultures with a positive signal in this automated system underwent Gram staining. Subsequently, dilution sowing was performed (blood agar medium) and incubated at 37°C for 24-48 hours. Specimens with pure growth were verified and these underwent the germ tube test. Yeast isolates demonstrating germ tube formation were identified as *C. albicans*. Those lacking germ tube formation were designated as non-albicans candida, and typing procedures were initiated. Typing methodologies included the conventional, Cornmeal Agar, and the Analytical Profile Index (API) 20 C System (bioMérieux). Yeast isolates were cultured on various media including Sabouraud dextrose agar Antibiograms were performed on most of the samples with VITEK-2 Compact (bioMérieux, France), except for 15 isolates. Antibiograms for fluconazole, micafungin, and voriconazole were assessed, and minimum inhibitory concentration (MIC) values were computed. The procedures outlined by the manufacturer's standard operating protocols were strictly adhered to. The obtained results were appraised in accordance with the recommendations set forth by the Clinical and Laboratory Standards Institute (CLSI).

Candida Score

In determining the Candida score, an objective scoring system devised by Leon et al. was employed to assess the risk of candidemia in critically-ill patients. The scoring system assigned points for a history of major surgical intervention (1 point), severe sepsis (2 points), multiple colonization (1 point), and the use of total parenteral nutrition (1 point). This scoring methodology allowed for the prediction of the risk of invasive candidiasis based on the cumulative score derived from these clinical factors (13).

Statistical Analysis

Two-tailed p-values less than 0.05 were considered statistically significant. All analyses were conducted using IBM SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). The normal distribution of variables was assessed using the Shapiro-Wilk test. Descriptive statistics included presentation of mean ± standard deviation for normally distributed continuous variables or median (25th percentile - 75th percentile) for non-normally distributed continuous variables. We used frequency (n) and relative frequency (%) to describe categorical data distributions and analyzed these via chi-square tests with specific use of Spearman chi-square, Yates's correction, Fisher's exact test, or Fisher-Freeman-Halton test. For normally distributed continuous variables, the independent samples t-test was applied. For non-normally distributed continuous variables, the Mann-Whitney U test was employed. To identify factors independently associated with 30-day mortality, a forward conditional inclusion model was used in multivariable logistic regression.

RESULTS

Among the 81 patients included in the analysis, 30 were females, 51 were males and the median age (Minimum-Maximum) was 65 (18-92) years. During the one-year period in which the data were evaluated, the incidence of candidemia among hospitalized patients was calculated as 23 cases per 10000 individuals (0.23%). The three most frequently detected candida species were *C. albicans* (46.91%), *Candida parapsilosis* (29.63%) and *Candida glabrata* (8.64%). The 30-day mortality rate was 59.26% (n=48). The most common comorbidity was hypertension (38.27%) (Table 1).

The most common candida risk factors detected in the study group were previous antibiotic use (95.06%), gastric acid suppression (93.83%) and urethral catheter (85.19%). Fluconazole resistance was found in 8.47%, Amphotericin B resistance in 4.62%, Voriconazole resistance in 3.39%, while no resistance was found to Micafungin. Patients with 30-day mortality had a higher median age (p=0.005), a higher frequency of ICU stay (p=0.008), and a higher frequency of intubation (p=0.028). The mortality group

Table 1: Comorbidities, laboratory tests and the other variables with regard to mortality

		30-days mortality		
	Total (n=81)	**No (n=33)**	**Yes (n=48)**	**p**
Age	65 (54 - 75)	57 (37 - 70)	68 (58 - 80)	0.005
Sex				
Female	30 (37.04%)	10 (30.30%)	20 (41.67%)	0.420
Male	51 (62.96%)	23 (69.70%)	28 (58.33%)	
Comorbidities				
Diabetes mellitus	14 (17.28%)	5 (15.15%)	9 (18.75%)	0.903
Hypertension	31 (38.27%)	12 (36.36%)	19 (39.58%)	0.952
Chronic renal failure	7 (8.64%)	4 (12.12%)	3 (6.25%)	0.435
Malignancy	30 (37.04%)	8 (24.24%)	22 (45.83%)	0.081
Immunodeficiency	6 (7.41%)	3 (9.09%)	3 (6.25%)	0.683
Cerebrovascular disease	22 (27.16%)	11 (33.33%)	11 (22.92%)	0.435
Stay in intensive care unit	54 (66.67%)	16 (48.48%)	38 (79.17%)	0.008
Intubation	45 (55.56%)	13 (39.39%)	32 (66.67%)	0.028
Body temperature	38.2 (37.5 - 38.3)	38.2 (37 - 38.4)	38.2 (38 - 38.3)	0.658
Heart rate	88 (77 - 110)	84 (75 - 92)	95 (84 - 110)	0.010
Systolic blood pressure	110 (100 - 120)	110 (100 - 120)	107.5 (90 - 122.5)	0.195
Diastolic blood pressure	65 (56 - 70)	70 (60 - 70)	60 (52.5 - 70)	0.184
Systemic inflammatory response syndrome	51 (62.96%)	17 (51.52%)	34 (70.83%)	0.125
WBC (x103)	11.72 ± 6.20	12.40 ± 5.88	11.26 ± 6.43	0.420
Hemoglobin	10.11 ± 1.92	10.28 ± 2.35	9.99 ± 1.58	0.512
Platelet (x103)	188 (94 - 307)	203 (124 - 313)	159 (81.5 - 269.5)	0.374
CRP	139 (65 - 195)	113 (58 - 179)	153 (67 - 198)	0.254
Urea	77 (43 - 105)	50 (32 - 96)	83.5 (62 - 119.5)	0.012
Creatinine	0.87 (0.69 - 1.40)	0.76 (0.60 - 1.20)	0.90 (0.70 - 1.56)	0.216
AST	32 (22 - 50)	30 (22 - 41)	35.5 (25 - 63)	0.123
ALT	23 (14 - 39)	24 (16 - 37)	22 (14 - 47)	0.823
Blood culture signal duration				
One day	52 (64.20%)	22 (66.67%)	30 (62.50%)	
Two days	23 (28.40%)	9 (27.27%)	14 (29.17%)	1.000
Three days or above	6 (7.41%)	2 (6.06%)	4 (8.33%)	
Type of Candida, blood culture				
C. albicans	38 (46.91%)	15 (45.45%)	23 (47.92%)	
C. parapsilosis	24 (29.63%)	12 (36.36%)	12 (25.00%)	
C. glabrata	7 (8.64%)	2 (6.06%)	5 (10.42%)	
C. tropicalis	4 (4.94%)	2 (6.06%)	2 (4.17%)	
C. lusitaniae	4 (4.94%)	1 (3.03%)	3 (6.25%)	0.859
C. krusei	1 (1.23%)	0 (0.00%)	1 (2.08%)	
C. dubliniensis	1 (1.23%)	0 (0.00%)	1 (2.08%)	
C. norvegensis	1 (1.23%)	0 (0.00%)	1 (2.08%)	
C. famata	1 (1.23%)	1 (3.03%)	0 (0.00%)	
Fluconazole susceptibility				
Susceptible	53 (89.83%)	24 (92.31%)	29 (87.88%)	
Intermediate	1 (1.69%)	0 (0.00%)	1 (3.03%)	1.000
Resistant	5 (8.47%)	2 (7.69%)	3 (9.09%)	

Continuation of Table 1: Comorbidities, laboratory tests and the other variables with regard to mortality

Amphotericin B susceptibility				
Susceptible	56 (86.15%)	21 (77.78%)	35 (92.11%)	
Intermediate	6 (9.23%)	4 (14.81%)	2 (5.26%)	0.238
Resistant	3 (4.62%)	2 (7.41%)	1 (2.63%)	
Micafungin susceptibility				
Susceptible	65 (98.48%)	27 (100.00%)	38 (97.44%)	
Intermediate	1 (1.52%)	0 (0.00%)	1 (2.56%)	1.000
Resistant	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Voriconazole susceptibility				
Susceptible	56 (94.92%)	25 (96.15%)	31 (93.94%)	
Intermediate	1 (1.69%)	1 (3.85%)	0 (0.00%)	0.331
Resistant	2 (3.39%)	0 (0.00%)	2 (6.06%)	
Other candida positive cultures				
Urine	41 (50.62%)	17 (51.52%)	24 (50.00%)	1.000
Sputum	8 (9.88%)	3 (9.09%)	5 (10.42%)	1.000
Tracheal aspirate	3 (3.70%)	0 (0.00%)	3 (6.25%)	0.267

Descriptive statistics were presented by using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.

again demonstrated higher urea levels (p=0.012), higher frequency of acute renal failure (p=0.003), and higher frequency of severe sepsis (p=0.025). Deceased patients also had higher candida score (p=0.015), shorter treatment duration (p<0.001), and lower frequencies of negative blood culture (p<0.001) (Table 2). Mortality was unassociated with sex, comorbidities, blood pressure, systemic inflammatory response syndrome, CRP (p=0.254), WBC (p=0.420), candida type (p=0.859) and empirical treatment (p=1.000). It was found that the heart rate level was significantly higher in the patients who died within 30 days (p=0.010),

According to multivariable logistic regression, high age (OR: 1.037, 95% CI: 1.006 - 1.070, p=0.018), stay in ICU (OR: 3.325, 95% CI: 1.132 - 9.766, p=0.029) and acute renal failure (OR: 3.383, 95% CI: 1.024 - 11.173, p=0.046) were independently associated with mortality. Other variables included in the analysis, intubation (p=0.797), heart rate (p=0.164), urea (p=0.203), candida score (p=0.146) and severe sepsis (p=0.637) were found to be non-significant (Table 3).

DISCUSSION

Yeast-associated infections are a clinical challenge due to the inherent complexities in antifungal management. Fungal infections extend hospital stays, elevate morbidity and mortality rates, and increase treatment cost. The epidemiology is characterized by dynamic shifts in species distribution and different resistance patterns (14,15). In this retrospective study, we analyzed the epidemiology of candidemia and risk factors for mortality in hospitalized patients. The most frequently identified candidemia risk factor was previous antibiotic use and the most frequently identified candida species was *C. albicans*. The 30-day mortality rate was 59.26% and the three factors that independently increased mortality were advanced age, ICU stay and acute renal failure.

C. albicans, *C. glabrata*, *C. parapsilosis*, *Candida tropicalis* and *Candida krusei* account for more than 90% of all diagnosed candida cases, but relative frequency varies greatly from study to study (16). In a study conducted by Barchiesi et al in Italy, it was reported that although *C. albicans* remained the most frequently isolated species from 2010 to 2014, its frequency decreased from 68% to 48% (17). This proportional decrease may indicate an increase in other species when taken together with the fact that the annual incidence of candidemia has exhibited an upward trend (from 2.96 to 4.20 cases per 100,000). Noteworthy alterations in the prevalence of Candida species were reported in the aforementioned study which examined a period of 15 years, with a significant decrease in *C. albicans* (despite still being the most common with 58%) and notable frequencies for other types: *C. glabrata* (21%), *C. tropicalis* (5%), and *C. parapsilosis* (5%) (18). The frequency of candida infections shows unpredictable variations even in the same center, as evidenced by a study describing a sharp increase in 2016-2018 compared to 2006-2015 and 2006-2008. This variation could be partially explained by the data showing that *C. albicans* was responsible for 62.8% of cases in the 2006-2008 period and 51.2% in the 2016-2018 period (19), again suggesting that there was a surge in non-albicans cases. Other investigations, for instance by Hii et al., support such conclusions by showing an overall increase in candidemia incidence over time accompanied by a decline in the proportion of *C. albicans* (64.8% to 43.6%) and a 20-fold increase in *C. glabrata* prevalence (1.1% to 21.6%) (20). Similarly, retrospective analyses in Helsinki and Uusimaa hospital districts from 2007 to 2016 depicted *C. albicans* as the predominant cause of candidemia (60.4%), followed by *C. glabrata* (21.5%), *C. parapsilosis* (5.2%), and *Candida dubliniensis* (5.2%) (21).

In a meta-analysis evaluating the epidemiology of

Table 2. Risk factors, diagnosis and the other variables with regard to mortality

		30-days mortality		
	Total (n=81)	**No (n=33)**	**Yes (n=48)**	**p**
Candida risk factors				
Acute renal failure	29 (35.80%)	5 (15.15%)	24 (50.00%)	0.003
Urethral catheter	69 (85.19%)	25 (75.76%)	44 (91.67%)	0.061
Inotropic agent use	28 (34.57%)	7 (21.21%)	21 (43.75%)	0.063
Gastric acid suppression	76 (93.83%)	29 (87.88%)	47 (97.92%)	0.153
Previous antifungal use	11 (13.58%)	3 (9.09%)	8 (16.67%)	0.511
Previous antibiotics use	77 (95.06%)	31 (93.94%)	46 (95.83%)	1.000
Intubation history	51 (62.96%)	17 (51.52%)	34 (70.83%)	0.125
IV catheter history	65 (80.25%)	25 (75.76%)	40 (83.33%)	0.577
Transfusion history	61 (75.31%)	24 (72.73%)	37 (77.08%)	0.854
Candida score	2 (2 - 3)	2 (2 - 3)	2.5 (2 - 4)	0.015
>2.5	32 (40.51%)	9 (27.27%)	23 (50.00%)	0.072
Severe sepsis	44 (55.70%)	13 (39.39%)	31 (67.39%)	0.025
Total parenteral nutrition	51 (64.56%)	19 (57.58%)	32 (69.57%)	0.390
Initial surgery	36 (45.57%)	16 (48.48%)	20 (43.48%)	0.832
Multifocal candida colonization	8 (10.13%)	2 (6.06%)	6 (13.04%)	0.457
Empiric therapy	75 (92.59%)	32 (96.97%)	43 (89.58%)	0.393
Fluconazole	65 (86.67%)	29 (90.63%)	36 (83.72%)	
Amphotericin B	1 (1.33%)	0 (0.00%)	1 (2.33%)	
Caspofungin	0 (0.00%)	0 (0.00%)	0 (0.00%)	1.000
Anidulafungin	8 (10.67%)	3 (9.38%)	5 (11.63%)	
Voriconazole	1 (1.33%)	0 (0.00%)	1 (2.33%)	
Length of stay at therapy onset, days	15 (10 - 24)	13 (8 - 21)	18 (12 - 27)	0.069
Duration of therapy, days	15 (5 - 19)	18 (16 - 23)	7 (3 - 15)	<0.001
Negative blood culture	51 (62.96%)	29 (87.88%)	22 (45.83%)	<0.001
Diagnosis				
Catheter infection	44 (54.32%)	18 (54.55%)	26 (54.17%)	
Intra-abdominal infection	2 (2.47%)	1 (3.03%)	1 (2.08%)	
Lung infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.889
Urinary tract infection	1 (1.23%)	0 (0.00%)	1 (2.08%)	
Endocarditis	1 (1.23%)	1 (3.03%)	0 (0.00%)	
Unknown	33 (40.74%)	13 (39.39%)	20 (41.67%)	
Length of stay in hospital, days	35 (25 - 50)	39 (27 - 60)	34.5 (20 - 48)	0.093

Descriptive statistics were presented by using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.

candidemia in Europe with population-based studies, it was reported that the overall pooled incidence rate between 2000 and 2019 was 3.88 per 100,000 people (22). Meyahnwi et al. documented the cumulative incidence of candidemia at 5.9 cases per 100,000 in a US population, from 2017 to 2020. Notably, the predominant Candida species identified in their study were *C. glabrata* (38.0%) and *C. albicans* (33.2%), diverging from the trends observed in other investigations (23). Conversely, a study conducted in China reported an annual candidemia incidence ranging between 0.71 and 0.85 per 1000 people from 2009 to 2011, with *C. tropicalis* (28.6%), *C. albicans* (23.3%), and *C. parapsilosis* (19.5%) being the most prevalent Candida species (24). In Brazil, the prevalence of Candida species also demonstrated distinct proportions, with *C. albicans* accounting for 34.3%, followed by *C. parapsilosis* (24.1%), *C. tropicalis* (15.3%), and *C. glabrata* (10.2%) (25). For Turkiye, a prospective observational study assessing data from 2009 and 2010 reported that the incidence of candidemia was 0.94 per 1000 persons, with *C. albicans* isolated in 52.1% of cases, followed by *C. parapsilosis* and *C. tropicalis* (26). In agreement with international literature, Ulu Kılıç et al reported a noteworthy increase in the annual incidence of candidemia in Turkiye, rising from 0.10 to 0.30 cases per 1000 patient days from 2010 to 2016. The predominant

Table 3: Significant factors independently associated with 30-day mortality, multivariable logistic regression analysis

	β coefficient	Standard error	p	Exp(β)	95% CI for Exp(β)
Age	0.037	0.016	0.018	1.037	1.006 1.070
Stay in intensive care unit	1.202	0.550	0.029	3.325	1.132 9.766
Acute renal failure	1.219	0.610	0.046	3.383	1.024 11.173
Constant	-3.029	1.065	0.004	0.048	

CI: Confidence interval, Nagelkerke R2=0.322

candida species in this study were *C. albicans* (48.1%), *C. parapsilosis* (25.1%), and *C. glabrata* (11.7%) (27). In the present study from Turkiye, we found the incidence of candidemia to be 23 per 10000 individuals (0.23%).

In a retrospective analysis of candidemia cases, Aydın et al. reported prevalent risk factors observed between 2013 and 2019. The commonly identified contributors to candidemia included antibiotic use (71.3%), urinary catheterization (56.3%), placement of central venous catheters (50.3%), total parenteral nutrition (47.9%), the presence of solid organ malignancy (46%), surgical procedures (48.6%), chemotherapy (37%), and steroid treatment (25.5%) (15). These results were largely similar to other reports from Turkiye. For instance, Mirza et al found the risk factors for candidemia in their cohort were antibiotic use (94.4%), recent (within the prior month) hospitalization (93%), ICU admission (74.6%), and the utilization of central venous catheters (70.4%) (26). Ulu Kılıç et al. reported that the presence of central venous catheters was a risk factor for non-albicans candidemia, highlighting an interesting relationship (27). In the present study, the most common risk factors for candidemia were antibiotic use (95.06%), gastric acid suppression (93.83%) and urethral catheter use (85.19%). It was thought that revision of infection control policies in the prevention and follow-up of infections in hospitalized patients and the use of current guidelines in the application of antibiotherapy may reduce candida infections.

Epidemiological surveillance studies play a pivotal role in monitoring antifungal resistance profiles and informing updates to guidelines for antifungal therapy (18). Better therapeutic management and creation of new guidelines are needed to reduce anti-fungal resistance, especially in countries with a concerning growth in resistance that may be a result of incautious use of therapeutics (28).

In the study conducted by Koehler et al. spanning from 2000 to 2019, the estimated incidence of candidemia in Europe was approximately 79 cases per day. Among these cases, 29 were projected to result in fatalities within 30 days, yielding a 30-day mortality rate estimated at 37% (22), which is consistent with real-world data showing a death rate of 30.7% in a 10-year period (21). Nonetheless, better management and close follow-up of at-risk individuals appears to result in improved outcomes. For instance, a study evaluating cases between 2014 and 2018 at Nice University Hospital and Antoine Lacassagne Oncology Center found that the 30-day mortality rate decreased to less than half from 2014 (46%) to 2018 (18%) (29). In Schroeder et al.'s retrospective analysis of candidemia cases over a decade in a single center, the reported mortality rate after 28 days was 47% (14). Despite reports of high resistance, a study collecting data from tertiary healthcare institutions during a 3-year period (2009-2010) in China reported a 30-day mortality rate of 26.0% (24). In Italy, the 30-day mortality rate in candidemia cases between 2010 and 2014 was reported as 35% (17). These data demonstrate the extreme variability in candida-attributed mortality, but it is necessary to conduct detailed analysis of studies to understand potential pitfalls and biases in the results. In the present study, 30-day mortality rate (59.26%) is considerably higher compared to the majority of research. This is likely due to differences in the study populations and specific patient characteristics, such as the fact that 66.67% of the patients included in our study had been admitted to the ICU and the study was conducted in a tertiary care institution receiving referral of relatively severe patients.

The elevated mortality observed in patients with candidemia is linked to specific risk factors, including advanced age, high APACHE score, immunosuppression, renal failure, and prior exposure to triazoles. Conversely, initiating antifungal therapy promptly and effectively managing the source of infection early on may serve to mitigate mortality in patients afflicted with candidemia (9). In the present study, factors that independently predicted improved 30-day morale were higher age, ICU stay and having acute renal failure. Our result is consistent with the results of other studies reporting that the risk of mortality increases with age (14,17,21,23,28,30), ICU stay (17,23) and acute renal failure (6, 17). In the study of Medeiros et al., it was reported that older age was associated with a higher risk of mortality (28). Such results concerning age-related risks have been circulated widely in the literature (17,21,30). Many other risk factors reported in prior literature are also worthy of mention. In the current study, contrary to what has been reported in other studies, we did not find a relationship between mortality and a number of these risk factors, including central venous catheter use (19,24), sepsis (6,14,17,28), candida score (14), mechanical ventilation (28,30), intubation (30), and parenteral nutrition (20). According to previous studies, the fact that catheter use was not one of the factors affecting mortality may be related to improved aseptic approaches and catheter care practices. In hospitalized patients, candidemia cases with characteristics such as advanced age, ICU stay and acute renal injury should be treated with broader spectrum antifungals and closely monitored to prevent mortality. The fact that infectious diseases consultation leads to reduced mortality and higher compliance with the guidelines in patients with

candidemia (19) should be taken into consideration and it would be useful to seek the opinion of infectious disease specialists in the follow-up of infection in candidemia cases followed in every unit of the hospital.

One of the limitations of the study is that we may have missed useful information regarding the management of patients with candidemia as a result of some uncontrollable variables that may not have been included in this retrospective data collection approach. Another limitation is that antibiogram testing could not be performed on 15 of the isolates. Despite these, this study has important implications for characterizing the epidemiology of candidemia which may be utilized to create new guidelines and practices.

In conclusion, the findings of this study revealed that *C. albicans* was the predominant causative agent in hospitalized candidemia cases, and that 30-day mortality rate was 59.26% –likely due to the high proportion of patients admitted to the ICU. Notably, advanced age, ICU stay, and acute renal injury emerged as independent factors associated with an increased risk of mortality. It is evident from the data and the limitations of this study that extensive population-based studies are necessary to better understand the local characteristics of candidemia and make recommendations for improved management, thereby enabling more effective preventive and therapeutic interventions.

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ORIGINAL ARTICLE

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The Effects of an Eight-Hour Six-Step Point-of-Care Ultrasound Training Program: A Pilot Study

Sekiz Saatlik Altı Adımlı Bakım Noktası Ultrasonu Eğitim Programının Etkileri: Pilot Bir Çalışma

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ABSTRACT

Objective: *The use of ultrasonography in emergency departments is becoming widespread all over the world. However, the recommendations of the guidelines that form the framework of training may not be suitable for all regions. In this study, we investigated the effect of a targeted eight-hour Point-of-Care Ultrasound (PoCUS) course planned in an emergency medicine clinic with limited facilities on the practical skills of emergency physicians.*

Materials and Methods: *A six-step ultrasonography course was planned for twenty-six emergency physicians. Four hours of theoretical course followed by four hours of practical training was given. Participants were administered a practical exam a week before and a week after the training. Whether sufficient images were provided in the practical exam depended on certain criteria. The time to achieve adequate images by fulfilling all criteria was recorded in seconds.*

Results: *After the training, the success rates of cardiac ultrasound (US), extended focused assessment with sonography in trauma (E-FAST), and the adequacy of hepatobiliary and aortic imaging increased statistically significantly ($p<0.05$).*

Conclusion: *Targeted eight-hour theoretical and practical ultrasonography training, which was provided in line with the demands of emergency physicians, has a significant contribution to the successful imaging time of participating emergency physicians.*

ÖZET

Amaç: *Acil servislerde ultrasonografi kullanımı tüm dünyada yaygınlaşmaktadır. Ancak, eğitimin çerçevesini oluşturan kılavuzların önerileri tüm bölgeler için uygun olmayabilir. Bu çalışmada, kısıtlı imkanlara sahip bir acil tıp kliniğinde planlanan hedefe yönelik sekiz saatlik Point-of-Care Ultrasound (PoCUS) kursunun acil hekimlerinin pratik becerileri üzerindeki etkisini araştırdık.*

Gereç ve Yöntem: *Yirmi altı acil tıp hekimi için altı aşamalı bir ultrasonografi kursu planlandı. Dört saatlik teorik dersin ardından dört saatlik pratik eğitim verildi. Katılımcılara eğitimden bir hafta önce ve bir hafta sonra pratik sınav uygulandı. Pratik sınavda yeterli görüntü sağlanıp sağlanmadığı belirli kriterlere bağlıydı. Tüm kriterleri yerine getirerek yeterli görüntü elde etme süresi saniye cinsinden kaydedildi.*

Sonuçlar: *Eğitim sonrasında kardiyak ultrasonografi (US), travmada sonografi ile genişletilmiş odaklı değerlendirme (E-FAST) ve hepatobiliyer ve aort görüntülemenin yeterliliği başarı oranları istatistiksel olarak anlamlı şekilde arttı ($p<0.05$).*

Sonuç: *Acil hekimlerinin talepleri doğrultusunda verilen hedefe yönelik sekiz saatlik teorik ve pratik ultrasonografi eğitiminin, katılımcı acil hekimlerinin başarılı görüntüleme sürelerine önemli bir katkısı vardır.*

Keywords:
Ultrasonography
Point-of-care systems
Education

Anahtar Kelimeler:
Ultrasonografi
Yatakbaşı teknolojisi
Eğitim

INTRODUCTION

Many terms are used by emergency physicians for bedside ultrasonography. These include emergency, bedside, focused, and others. However, the most widely accepted term is point-of-care ultrasound (PoCUS). PoCUS is gaining importance in emergency practice. Its use as a diagnostic tool in emergency departments is increasing with its bedside, rapid, non-invasive, and radiation-free features. With the increasing use of emergency ultrasonography, training curricula are also developing every year. In many countries, ultrasonography training has even started to be provided for medical faculty students (1, 2). In these trainings, medical faculty students have benefited from the trainings and their skills in the use of ultrasonography have improved (3).

Ultrasonography can be used in many fields in the emergency medicine practice. In emergency medicine, ultrasonography is used to guide diagnosis, treatment, follow-up, and the resuscitative and procedural procedures. According to the content of ultrasonography training renewed by the American College of Emergency Physicians (ACEP) in 2023, it is recommended to complete a total of 80 hours of training during the speciality training period after a 2-week rotation in the first year (4). However,

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studies have shown that ultrasonography training varies and there are serious differences in qualification assessment methods (5,6). When the emergency point-of-care ultrasound training guideline of the South African Society of Emergency Medicine (SAMJ) is examined, we see that a comprehensive, systematic, and continuous training program similar to the ACEP guideline is recommended (7).

It has been revealed that the biggest problem preventing the widespread use of ultrasound especially in developing countries and the rural areas of developed countries is training (8,9). In Turkey, ultrasonography training of emergency medicine speciality students may vary depending on the region and hospital. Local emergency medicine associations across the country provide paid emergency ultrasonography trainings. In our country, the most common learning methods are learning on one's own or by watching the procedure. These results show that emergency ultrasonography training in our country is not at an adequate level and does not have a certain standardization.

In this study, we planned a targeted basic ultrasonography training in line with the needs of emergency physicians. We investigated the effect of this 8-hour didactic and practical training on emergency physicians.

MATERIAL AND METHOD

We conducted the study at an Emergency Department (ED) with an annual volume of 600,000 patients, which hosts a four-year Emergency Medicine (EM) residency program. The residency provides training for 35 residents. Residents who did not complete 6 months of residency were excluded. The 26 resident doctors who agreed to participate in the study had not received systematic or certified PoCUS training before. In our study, the path followed in the planning of PoCUS training was the basic 6-step approach suggested by Kern, modified according to local needs (10). The steps of this 6-step approach are given on Table 1.

Assessment of General Needs and Training Needs

An observational assessment of the overall need for PoCUS showed that the biggest preventing factor for residents to use ultrasound in their daily practice was training. Residents who did not receive adequate training were hesitant to include US in their daily practice.

Table 1: A basic 6-step approach modified according to local needs

1	Identification of the problem and a general needs assessment
2	Targeted local needs assessment in prospective PoCUS trainees
3	Setting of goals and objectives for the local curriculum
4	Selection of educational strategies that match with the resources available and match with the length of longitudinal training opportunities
5	Implementation of the program
6	Development of concepts for evaluating the effectiveness of the curriculum again adhering to available resources and ability to measure outcomes to predetermined mastery standards

To organize the training content, 26 emergency medicine physicians who agreed to participate in the study were asked to choose four of the PoCUS contents they wanted to receive training. The options consisted of ultrasonography courses defined for diagnostic procedures. These options were as follows: Aorta Ultrasound, Bowel, Cardiac, Haemodynamic Assessment, Deep Vein Thrombosis, Hepatobiliary System, Musculoskeletal Ultrasound, Ocular, Pregnancy, Skin and Soft Tissue Ultrasound, Testicular Ultrasound, Trauma, and Urinary Tract ultrasound. Among the options presented, the most preferred four were planned.

Identifying Learning Objectives for Training

When planning the training content, guidelines of national EM organisations with sections focusing on clinical ultrasound education such as ACEP, EuSEM, and SAMJ were reviewed. A 4-hour didactic training followed by a 4-hour practical training on the same day was planned. In the course planning, targets in cardiac US, E-FAST, hepatobiliary, and aortic imaging were determined. In the first part of the training, a short training was planned about the functions and features of the device in our emergency department. The learning objectives and the allocated time for our 8-hour training course are given on Table 2 below.

Determination of training strategy with local resources

When the guidelines of national EM organisations with departments focusing on ultrasound education were reviewed, it was found that the ACEP and SAMJ guidelines clearly stated the course criteria. Considering the resources of our clinic, we tried to determine the best implementation strategy. Firstly, since we have one M5 Model US device (Mindray, NJ, USA) in our clinic, the practical trainings were performed at a single station. The trainees were divided into small groups in a large room. The trainings were provided by two Associate Professor Doctor of Emergency Medicine and a Specialist Doctor of Emergency Medicine, who were experienced and competent in the ultrasonography field. However, the ratio of 5 trainees to 1 instructor recommended by both guidelines could not be achieved. The following are the course criteria of the ACEP and SAMJ guidelines that we were able to fulfil and the criteria that we could not fulfil due to our local resources (Table 3).

Implementation of the Training Program and Evaluation of the Training

Trainings on cardiac US, extended focused assessment with sonography in trauma (E-FAST), hepatobiliary, and aortic US, which were selected according to the requests of emergency medicine residents, were performed within the given periods. One week before and one week after the trainings, image acquisition success and image acquisition times were measured. While imaging was performed before and after the training, the observer and a single participant were taken into the room, and after the imaging process was completed, the other participants were taken into the room in turn. Imaging studies exceeding 180 seconds were considered unsuccessful. The pre-training and post-training evaluations were performed with the same US device and the same healthy simulated patient.

Table 2: Learning objectives and duration of the training

Course	Course content and learning goals	Course duration
Theoretical Lessons		
Course 1.1	**Basic features of USG device, Basic information on probes**	
	1. Describe the features of the control panel 2. To be able to define the function of gains 3. To be able to define the function of depth 4. To be able to define the function of zooming 5. To be able to locate the freeze button on the control panel 6. To be able to define measurement and calculation functions 7. To be able to recognize linear, sector, and convex probe and understand their functions	15 min.
Course 1.2	**Cardiac US**	
	1. To be able to define clinical indications 2. To provide Probe-Display orientation 3. To be able to identify anatomical regions in the parasternal long axis image 4. To be able to define anatomical regions according to the parasternal short axis and levels 5. To be able to identify anatomical regions in apical 4-chamber view 6. To be able to define the anatomical regions in the subxiphoid window 7. To be able to recognize the appearance of pericardial tamponade 8. To be able to recognize pulmonary embolism findings on Cardiac US	90 min.
Course 1.3	**E-FAST**	
	1. To be able to define clinical indications 2. To be able to define the anatomical regions in the perihepatic area 3. To be able to describe the anatomical regions in the splenorenal area 4. To be able to describe the anatomical regions in the suprapubic area 5. To be able to describe the anatomical regions in the subxiphoid area 6. To be able to describe the anatomical regions in the anterior thoracic window 7. To be able to understand the pitfalls in E-FAST 8. To be able to interpret pathological images in E-FAST	60 min.
Course 1.4	**Hepatobiliary System**	
	1. To be able to define clinical indications 2. To be able to describe the anatomical images of the hepatobiliary system in short and long axis 3. To be able to recognize the common bile duct, portal vein, and hepatic artery 4. To be able to list the ultrasonographic findings of acute cholecystitis 5. To be able to interpret pathological images	45 min.
Course 1.4	**Aorta Ultrasound**	
	1. To be able to recognize the abdominal aorta, to define the anatomical structures 2. To be able to describe the anatomical images of the celiac trunk, mesenteric artery, and renal arteries 3. To be able to state the normal value of the diameter of the abdominal aorta 4. To be able to recognize the pathological appearance of aortic aneurysm and aortic dissection	30 min.

Table 2: Learning objectives and duration of the training (Continue)

Practical Applications		
Course 2.1	**Cardiac US**	
	1. Parasternal Long Axis image acquisition 2. To be able to visualize the LV, LA, RV, MV, AV and Aorta in the parasternal long axis image and identify the structures 3. Parasternal Short Axis image acquisition 4. To be able to visualize and identify the apical level, papillary muscles, MV and AV in the parasternal short axis image 5. Apical 4 chamber image acquisition 6. To be able to see and identify LV, RV, LA, RA, RA, MV, TV structures in apical 4-chamber image 7. To be able to show pericardial borders in the subxiphoid window 8. To understand how to optimize images	75 min.
Course 2.2	**E-FAST**	
	1. Visualize and describe the structures in the perihepatic area 2. Visualize and describe the structures in the splenorenal area 3. Visualize and describe the structures in the suprapubic area 4. Visualize and describe the structures in the subxiphoid area 5. Visualize and identify structures in the anterior thoracic window	75 min.
Course 2.3	**Hepatobiliary System**	
	1. Visualize and scan the hepatic parenchymal tissue 2. Visualize the gallbladder and measure the wall thickness 3. Visualize and recognize the common bile duct, portal vein, and hepatic artery	45 min.
Course 2.4	**Aorta Ultrasound**	
	1. Visualize the abdominal aorta and measure the aortic diameter at appropriate points 2. Visualize the celiac trunk, mesenteric artery and renal arteries and describe the structures	45 min.

Table 3: The fulfillment of the course criteria for PoCUS guidelines in our training

Stretcher at every station (Successful)
Large/multiple rooms (Successful)
Maximum ratio of one instructor to five students (Unsuccessful)
Ultrasound gel and paper towels (Successful)
Simulated patient with normal anatomy (Successful)
Simulated patient with pathological appearance (Unsuccessful)
Informed consent of the simulated patient (Successful)
Post-course feedback questionnaire (Unsuccessful)

The criteria for successful imaging are given on Table 4 below.

In summary, on the first day, the needs of emergency medicine residents were determined by a questionnaire. Within 7 days, the learning objectives were created. After 3 days, an exam was applied to the participants. One week later, the training was applied. Finally, the same exam was performed again after the training. The timeline of our study is shown in Figure 1 below.

Ethical Committee Approval

This study was approved by the Local Ethics Committee (Date: 06.06.2022, decision no: 139/36). The study was conducted in line with the creiteria of the Helsinki Declaration throughout the research process. A written informed was obtained consent form for each participant.

Statistical analysis

The data were analysed with SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, Illinois, USA) 25.0 software package. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used. The normality of the distribution of the data was checked by Shapiro-Wilk test. The distribution of continuous data was tested by Kolmogorov-Smirnov test. The success rates of the participants in the theoretical and practical exams were evaluated separately for each person. Mann-Whitney U test was used to compare two groups with respect to non-normally distributed data. The significance test of the difference of two matched groups was performed with Wilcoxon test.

RESULTS

In our study, 26 emergency medicine residency students working in Training and Research Hospital were included. The votes for the PoCUS courses cast by the 26 emergency

Table 4: Criteria for successful visualization

	Imaging areas			
	Cardiac US	**E-FAST**	**Hepatobiliary System**	**Aorta Ultrasound**
Criteria	PLAX view LV, RV, MV, AV structures	Demonstration of the perihepatic space	To be able to show the gallbladder and scan the entire gallbladder	To be able to show the abdominal aorta
	PSAX view papillary muscle, MV, AV visualization	Demonstration of the splenorenal space	To be able to show the common bile duct, portal vein and hepatic artery	To be able to show celiac trunk, mesenteric artery and renal arteries
	Apical 4 chambers LV, RV, LA, RA, MV, TV visualization	Demonstration of the suprapupic space		
	Visualization of pericardial borders in subxiphoid view	Visualization of pericardial borders in subxiphoid view		
		Demonstration of pleural movement in the anterior thoracic window		

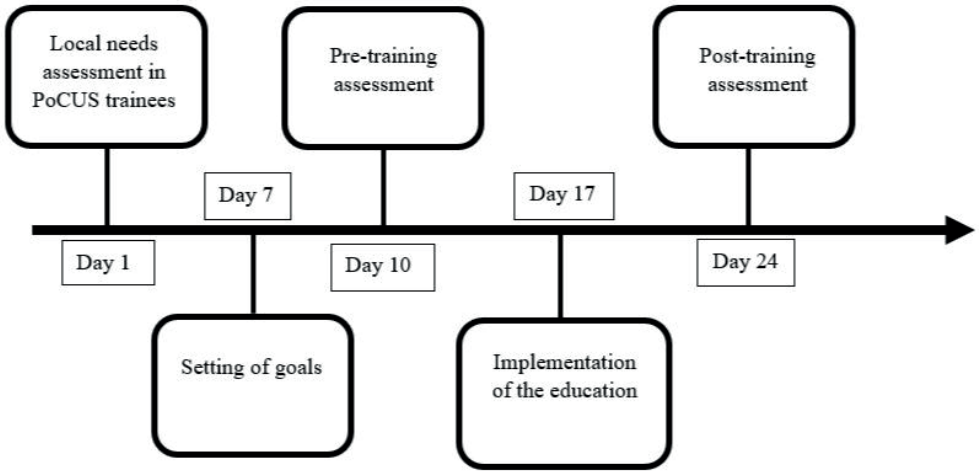

Figure 1: The timeline of our study

medicine residency students, who agreed to participate in the study in line with their needs, are shown in Figure 2.

Before the training, the minimum cardiac US imaging time was 29 seconds, maximum 60 seconds, and 42.33±9.20 seconds on average. It was found that the pre-training cardiac US imaging time was normally distributed ($p>\alpha=0.05$). Aortic imaging time before the training was minimum 17 seconds maximum 40 seconds, with a mean duration of 25.00±7.50 seconds. Aortic imaging time before the training was found to be normally distributed ($p>\alpha=0.05$). Hepatobiliary imaging time before training was minimum 23 seconds, maximum 65 seconds, and 41.00±12.49 seconds on average. Hepatobiliary imaging time before the training was found to be normally distributed ($p>\alpha=0.05$). E-FAST imaging time before the training was minimum 45 seconds, maximum 63 seconds, and 54.00±5.19 seconds on average. It was found that the pre-training E-FAST imaging time was normally distributed ($p>\alpha=0.05$).

After the training, it was found that cardiac US imaging time was normally distributed ($p>\alpha=0.05$). Aortic imaging time after the training was minimum 11 seconds, maximum 30 seconds, and 18.67±5.78 seconds on average. After the training, it was found that the aortic imaging time was normally distributed ($p>\alpha=0.05$). After the training, hepatobiliary imaging time was minimum 21 seconds, maximum 52 seconds, and 33.33±9.49 seconds on average. Hepatobiliary imaging time after the training was found to be normally distributed ($p>\alpha=0.05$). After the training, E-FAST imaging time was minimum 11 seconds, maximum 34 seconds, and 22.67±6.64 seconds on average.

The participants included in the study worked in the Emergency Medicine clinic for a minimum of 6 months and a maximum of 48 months. The average duration of Emergency Medicine practice was 23.1 months. The number of residents who successfully performed Cardiac imaging, Aortic imaging, Hepatobiliary imaging, E-FAST before the training was less than half of all participants. After the training, the number of participants

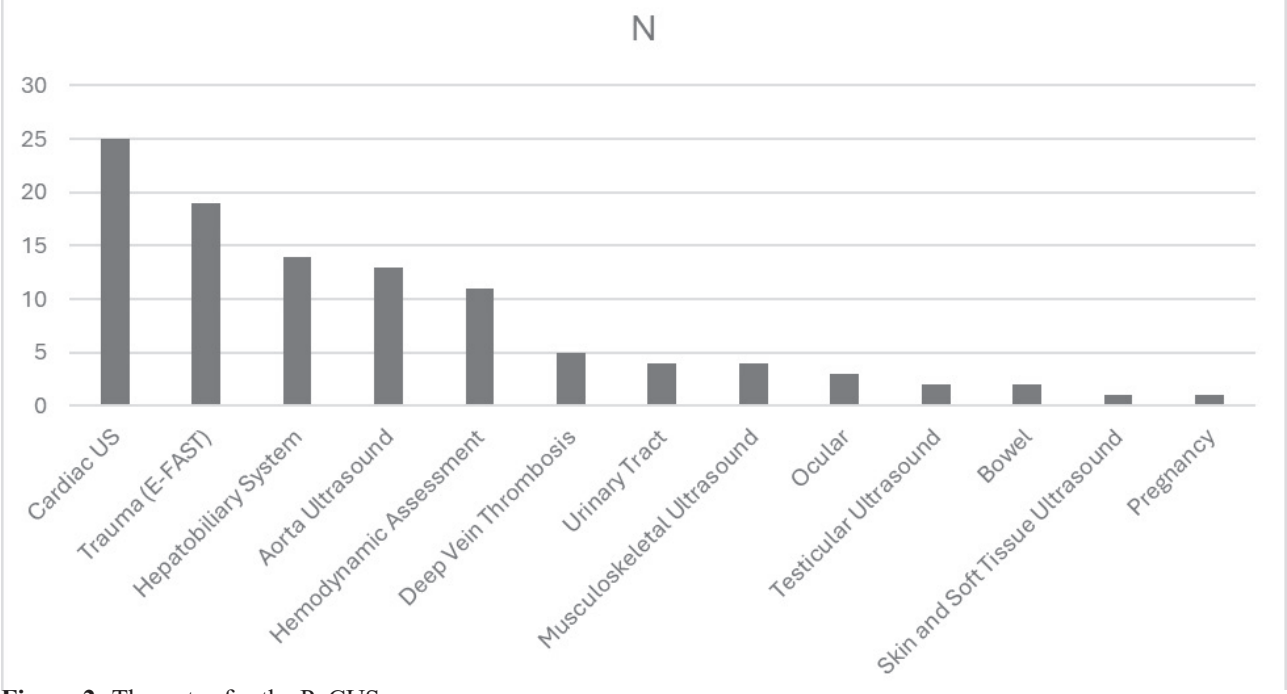

Figure 2: The votes for the PoCUS courses

who provided adequate images in all imaging studies increased. Descriptive statistics and distribution tests of the measurements are given on Table 5.

There was no correlation between the duration of working in emergency medicine clinic and pre-training and post-training imaging times, except for a single imaging. There is a highly significant negative correlation (r: -0.783) between the duration of working in the emergency medicine clinic and pre-training E-FAST imaging time.

After the training, created in line with the needs of emergency medicine resident physicians, was completed, the time to provide successful images in all imaging methods (Cardiac imaging, Aortic imaging, Hepatobiliary imaging, E-FAST) significantly decreased. The comparison of the measurements before and after the training is shown on table 6.

DISCUSSION

In this study, we applied the PoCUS course curriculum, which was created in line with the needs of emergency medicine residents, in eight hours, and investigated whether it increased the rate of adequate image acquisition and reduced the time of adequate image acquisition. As our results showed, the rate of adequate image acquisition increased, and the time of adequate image acquisition was reduced significantly. Training is important when considering barriers to PoCUS use, and PoCUS course curricula vary (11). With this study, we think that we have shown that certain emergency medicine ultrasound trainings such as the present emergency medicine ultrasound application, which is targeted and provides important information to physicians in a short time can be provided in a period as short as eight hours. The most important point that distinguishes our course curriculum from many other course programs is its six-step training planning. In this planning, determining the needs and shaping the planning with regional facilities constitute the most important steps. This shows that the program can be shaped according to hospital facilities in other regions. With this study, we think that the PoCUS curriculum can be shaped in a region-specific manner rather than a universal structure, which may increase the success of emergency medicine residentsin ultrasound use.

Table 5: Descriptive Statistics and Distribution Tests of Measurements

Variables	N	Min.	Max.	Mean ± SD	Normality Test / p
Emergency department residency period (Months)	26	6	50	23.12±13,53	0.812/0.144*
Pre-training Cardiac imaging (sec)	6	29	60	42.33±9.20	0.945/0.546*
Pre-training Aortic imaging (sec)	11	17	40	25.00±7.50	0.783/0,073*
Pre-training Hepatobiliary imaging (sec)	8	23	65	41.00±12.49	0.942/0.537*
Pre-training E-FAST (sec)	11	45	63	54.00±5.19	1.000/1.000*
Post-training Cardiac imaging (sec)	19	10	31	21.33±6.11	0.981/0.739*
Post-training Aortic imaging (sec)	22	11	30	18.67±5.78	0.900/0.384*
Post-training Hepatobiliary imaging (sec)	20	21	52	33.33±9.49	0.889/0.350*
Post-training E-FAST (sec)	26	11	34	22.67±6.64	0.999/0.952*

**Shapiro-Wilk Normality Test **p>α=0.05 statistical significance*

Table 6: Comparisons of Measurements Before and After Training

	Variables	Mean ± Standard Deviation	T Test	p
Pre - Post training Cardiac US time	Pre-training Cardiac	52.83±18.19	4.404	0.007*
	Post-training Cardiac	20.83±7.75		
Pre- Post training Aorta time	Pre-training Aortic	66.18±43.13	3.603	0.005*
	Post-training Aortic	38.64±26.51		
Pre- Post training Hepatobiliary time	Pre-training Hepatobiliary	64.50±33.44	2.649	0.033*
	Post-training Hepatobiliary	37.50±14.53		
Pre- Post training E-FAST time	Pre-training E-FAST	91.82±40.54	5.522	0.000*
	Post-training E-FAST	22.18±8.30		

**Paired Sample T Test, **Wilcoxon T Test, p<α=0.05 statistical significance*

The unique aspect of our training curriculum is that it is formed in six steps and the first of these steps is shaped in line with the needs of the participants within the capabilities of our clinic. Similarly, there are studies in the literature showing the difficulty of a standardized training in different regions and suggesting the creation of a region-specific training curriculum (12).

In the survey study conducted to determine the PoCUS needs of the participants, the four most requested PoCUS studies were Cardiac US, E-FAST, Hepatobiliary imaging and Aorta US. The three most preferred PoCUS applications in the studies were like the survey results in our study (13,14). This may be due to the rapid and significant contribution of cardiac US, E- FAST, and Aorta US to emergency medicine practice. The three PoCUS applications, which are needed for situations where urgent decisions need to be made for a given patient, were among the most preferred studies by the participants in our study and formed the basis of our training curriculum. When the literature was reviewed, obstetric US was the most performed PoCUS application after cardiac US and E-FAST (15). However, since our hospital does not have an obstetrics clinic, obstetric emergencies may not have been among the first four PoCUS studies since those emergencies are not frequently admitted.

Following the widespread application of emergency ultrasound, emergency ultrasound training has become a necessity. Most emergency medicine residents want to receive training on emergency ultrasound (14). The prevalence of the demand for training among emergency physicians may indicate a lack of knowledge on the subject. At the same time, although ultrasound training curricula are already in place, it is evident that there is no common training system between clinics (16). In our study, imaging success rates of the participants for echocardiography, hepatobiliary, aortic, and E-FAST were lower than 50% before the emergency ultrasound training. The fact that only 23.1% of the participating emergency physicians were able to provide adequate images in cardiac US may explain the inadequacy of the training programs and the demand by emergency physicians for more training on emergency ultrasound. Similar to our study, in a study conducted in Haiti, the success rate increased after a training program on cardiac US compared to the pre-treatment period (17).

There are also data in the literature that contradict our results. In a study conducted in Guyana, the pre-training ultrasound success of emergency medicine physicians was significantly higher than the participants in our study (18). We attribute these different results to achievement assessment scales differing from country to country. There are several structured assessment criteria for the evaluation of ultrasound training (19-22). These guiding evaluation criteria are not widely used.

There was a highly significant negative correlation (r: -0.783) between the duration of working in the emergency department and E-FAST imaging time before training. We think that the routine use of E-FAST in our clinical practice, especially in trauma patients, is influential in this correlation. In the literature, , short-term E-FAST training in students was found beneficial in providing successful images even in pre-clinical medical students (23). It can also be considered that the routine use of E-FAST in our clinic contributes to peer training (24).

In this study, we found that a targeted eight-hour basic ultrasonography training in line with the demands of emergency residents had a positive contribution on the practical examinations performed by emergency physicians. Only after an eight-hour training, the times to successfully acquire an image in emergency echocardiography, aortic imaging, hepatobiliary, and E-FAST imaging were significantly shorter than those recorded before the training. In a study by Mandavia et al., 16 hours of training contributed to the success of the participants (25). Another recent study found that a 9-hour introductory training course improved the participants' skills in using ultrasound and increased the physicians' confidence in using ultrasound (26). In our study, we observed that interest in ultrasound increased with pre- and post-training exams and eight hours of training, and physicians included ultrasound more in their daily practice.

Training curricula on the use of emergency ultrasound are not fully and uniformly implemented in our country. There is still no consensus on the evaluation scales of trainings in the world (27). However, even this eight-hour training we applied in our clinic increased the participants' ability to acquire adequate images in certain PoCUS applications

and shortened the time to provide adequate images. We think that a basic PoCUS training with a systematic approach in 6 steps may be effectively improve the ultrasound utilization skills of emergency physicians.

Limitations

Our study has some limitations. In our study, while providing practical training to emergency physicians and applying practical exams, studies were conducted on healthy volunteers. Despite obtaining successful images, physiological images were taken as the basis. No aim was made to detect and interpret pathological images in the practical exams. This is a limitation of our study, but the pathological images were used in the theoretical exams and the participants were asked to interpret them.

In our study, the practical exam was planned by ensuring that each participant was alone with the volunteer mannequin and the proctor. However, we could not determine whether the hyperemic area remaining on the body of the volunteer mannequin after the trainee used ultrasound was used by the next participant as a guiding point.

CONCLUSION

More than half of emergency medicine trainees are unable to acquire images in PoCUS. Cardiac US, E-FAST, Hepatobiliary imaging, and Aorta US are the most demanded PoCUS applications. The eight-hour PoCUS training curriculum, created in six steps and shaped by participant needs and clinical resources, increases the image acquisition success of the participants and shortens the image capture time.

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

Ethics: The study was approved by the Local Ethics Committee for Dışkapı Dışkapı Yıldırım Beyazit Training and Research Hospital (Date: 06.06.2022, decision no: 139/36)

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CASE REPORT

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Pelvic Traumas and Hybrid Emergency Medicine System: Literature Review Based on Two Cases

Pelvik Travmalar ve Hibrit Acil Tıp Sistemi: İki Olguya Dayalı Literatür Taraması

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ABSTRACT

Objective: *Bleeding, the most common life-threatening complication of pelvic trauma occurs due to injuries of pelvic arterial and venous structures and bone fractures. The outcomes of patients can be improved by a timely performed angioembolisation (AE). Hybrid Emergency Service System (HERS) has been recently introduced a novel approach which provides trauma resuscitation room equipped with computerized tomography, fluoroscopy, and an operating room, thus effects the outcomes of trauma patients.*

Cases: *We presented two pelvic traumas and in both cases with the most common life-threatening complication was bleeding. In both cases, whole-body computed tomography (WBCT), endovascular procedures (Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA), transcatheter arterial embolization (TAE)), and injury control surgery can be simultaneously performed without the need to transport a patient to an operating room which is called HERS resuscitation. Both patients were discharged and remained free of any medical problem at long-term (12 months) follow-up.*

Conclusion: *Considering the recently introduced HERS system in patient management and integrating it into emergency services will be extremely useful in the management of trauma and trauma-induced bleeding.*

ÖZET

Amaç: *Pelvik travmanın en sık görülen, yaşamı tehdit eden komplikasyonu olan kanama, pelvik arteriyel ve venöz yapıların yaralanması ve kemik kırıklarına bağlı olarak ortaya çıkar. Zamanında yapılan anjiyoembolizasyon (AE) ile hastaların sonuçları iyileştirilebilir. Hibrit Acil Servis Sistemi (HERS), bilgisayarlı tomografi, floroskopi ve ameliyathane ile donatılmış travma resüsitasyon odasını sağlayan ve böylece travma hastalarının sonuçlarını etkileyen yeni bir yaklaşımla yakın zamanda tanıtılmıştır.*

Olgular: *Pelvik travması olan iki hasta sunduk ve her iki olguda da en sık görülen yaşamı tehdit eden komplikasyon kanamaydı. Her iki durumda da tüm vücut bilgisayarlı tomografi (BT) taraması, endovasküler işlemler (Aortun Resüsitatif Endovasküler Balon Oklüzyonu (REBOA), Transkateter Arteriyel Embolizasyon (TAE)) ve yaralanma sonrası kontrol cerrahi, hastanın ameliyathaneye nakledilmesine gerek kalmadan, HERS resüsitasyonu adı verilen sistemde eş zamanlı olarak gerçekleştirilebilmektedir. Her iki hasta da sağlıklı olarak taburcu edildi ve* ***uzun dönem (12 ay) takiplerinde herhangi bir tıbbi sorun yaşanmadı.***

Sonuç: *Son dönemde kullanıma sunulan HERS sisteminin hasta yönetiminde dikkate alınması ve acil servislere entegre edilmesi travma ve travmaya bağlı kanamaların yönetiminde son derece faydalı olacaktır.*

Keywords:
Pelvic trauma
Bleeding
HERS

Anahtar Kelimeler:
Pelvik travma
Kanama
HERS

INTRODUCTION

Bleeding, the most common life-threatening complication of pelvic trauma occurs due to injuries of pelvic arterial and venous structures and bone fractures. Although it most commonly occurs secondary to venous injury, arterial bleeding is associated with a higher mortality rate (1). Current treatment approaches for pelvic bleeding include pelvic binder, external fixator, Pelvic C-Clamp, Pelvic Angiography, and Pelvic packing techniques (2). Although pelvic stabilization is sufficient to treat a considerable number of venous injuries, arterial bleeding causing hemodynamic instability primarily requires intervention via transcatheter arterial embolization (TAE) (3).

The outcomes of patients with bleeding caused by pelvic fractures can be improved by a timely performed angioembolisation (AE). In addition, a correlation has been found between delayed AE and increased mortality (4). One of the approaches that have recently been put forward in this regard is the Hybrid Emergency Service System (HERS) which is used to describe a novel trauma resuscitation room equipped with computerized tomography, fluoroscopy, and an operating room. In

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this way, HERS resuscitation and WBCT, endovascular procedures (Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA), transcatheter arterial embolization (TAE)), and injury control surgery can be simultaneously performed without the need to transport a patient to an operating room (5). In this case series, we aimed to stress the importance of HERS for the management of pelvic trauma-associated bleeding.

CASE 1

A 59-year-old man was brought to our emergency department (ED) by the ambulance service with a provisional diagnosis of blunt abdominal and pelvic trauma within approximately 40 minutes after a motor vehicle accident. On admission, the patient has a poor overall status, but he was conscious and oriented and showed full cooperation. He had a Glasgow Coma Scale (GCS) score of 15 (E4V5M6), and his vital signs were as follows: Blood pressure (BP): 105/68 mmHg, heart rate (HR): 107bpm, respiratory rate (RR): 22/min, SaO2: 94%. His physical examination (PE) was otherwise normal except diffuse abdominal and both pubic arms tenderness. WBCT was ordered, which revealed liver laceration as well as sacral and bilateral pubic arm fractures (Figure 1). His laboratory tests showed a hemoglobin level of 14.7 g/dL and a WBC of 19.1 mm3. Blood gas analysis showed the following: pH 7.304, BE -5.8 mmoI/L, lactate level 5.2 mmoI/L. The patient had a liver injury (AAST II. Stage hematoma), multiple non-displaced rib fractures, pelvic lateral compression fracture, and urethral injury. He had an Injury Severity Score (ISS) of 30, Revised Trauma Score (RTS) of 7.8408 and, according to the Trauma Injury Severity Score (TRISS), a survival likelihood of 83.77%. The shock index was calculated at 1.0. Erythrocyte suspension (ES) replacement was planned. The patient's hemodynamic instability was attributed to a vascular injury resulting from a pelvic injury, as evidenced by a significant and uncontrollable decrease in hemoglobin levels. Since pelvic computed tomography (CT) angiography showed active contrast material extravasation in the left pelvic region, the patient was urgently taken to Digital Subtraction Angiography (DSA).

The pelvic angiograms showed no active extravasation. However, there was a filling pattern that may have been due to a vessel stump in the mid-portion of the posterior trunk of the left internal iliac artery, or to a pseudoaneurysm of the internal pudendal artery. Considering the possibility of transient blockage of extravasation by the compressive effect of a large hematoma, embolization of the described vessel stump was planned. Urgent TAE was performed and hemostasis was achieved. No postoperative complication occurred, and hemoglobin drop was effectively stopped. The patient gradually got hemodynamic stability during his ED follow-up and treatment process. A consultation was obtained from the department of orthopedics, which recommended conservative care. A consultation was also obtained from the department of urology due to urethral injury detected by a retrograde cystography, for which a cystofix was placed (Figure 2). The patient was then transferred to the intensive care unit (ICU). After close follow-up by various surgical branches for three days, he was transferred to the regular ward. He experienced no other problem during his follow-up and was discharged with a cystofix 5 days later. He was free of any medical problem at long-term (12 months) follow-up.

Figure 1: Left superior pubic ramus comminuted fracture seen in coronal plane on abdominal CT

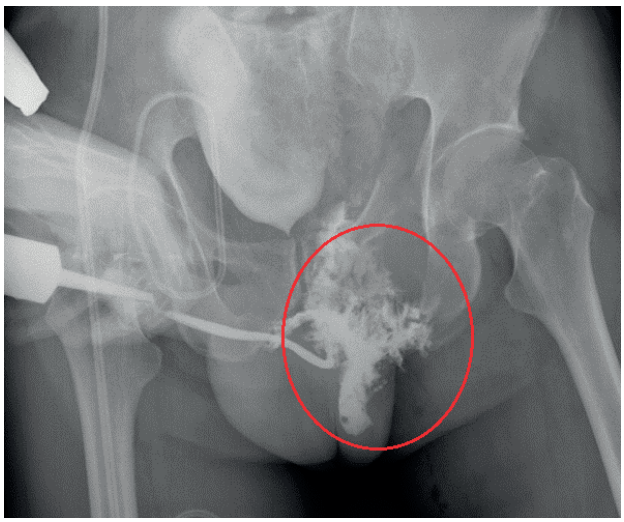

Figure 2: Urethral injury image on retrograde cystography

CASE 2

A 53-year-old woman was brought to our ED by the ambulance service with the provisional diagnoses of pelvic and head trauma 30 minutes after an out-of-vehicle traffic accident. On admission, she has altered mental status (GCS score of 13, E3V4M6) with restricted cooperation. Her vital signs were as follows: BP: 90/67 mmHg, HR: 115 bpm, RR: 24/min, SaO2: 92%. PE revealed ecchymosis on neck and head and abdominal tenderness. Targeted bedside ultrasonography revealed no intraabdominal bleeding. She had a WBC of 19.16 mm3 and a Hb level of 13.5 g/dL. A head CT performed to check head trauma showed a linear non-depressed fracture in the occipital region, cerebral contusion, and minimal subarachnoid bleeding in the frontal region. A plain radiogram showed fractures in the sacrum and both pubic arms (Figure 3). The patient had an ISS of 32, a RTS of 7.108, and a shock index of 1.5. It was considered that hemodynamic instability may have been due to pelvic vascular injury secondary trauma. Since a pelvic CT angiogram showed no contrast extravasation, a DSA was performed, which showed a

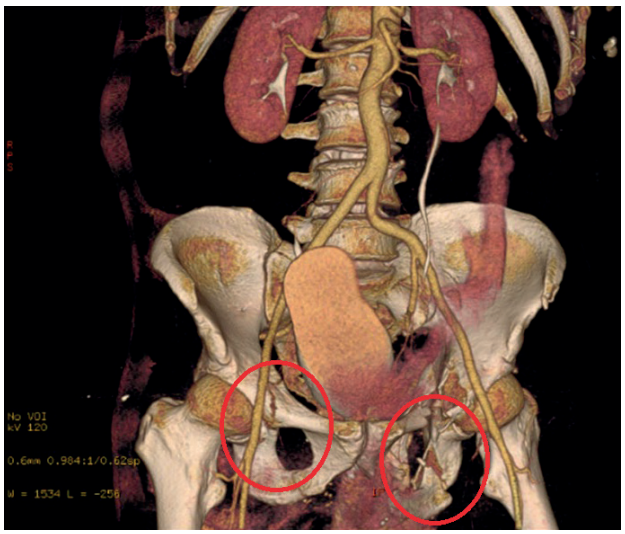

Figure 3: Bilateral pubic arm fracture CT Angiography 3D view (contrast material accumulated in the bladder due to concomitant urethral injury)

bleeding focus in the distal part of the pudendal branch of the left internal iliac artery. Urgent TAE procedure was performed and the bleeding focus was blocked with the help of a coil. The subsequent angiograms showed that the pathological staining disappeared. The patient gradually got hemodynamic stability during her ED follow-up and treatment. A consultation was obtained from the department of orthopedics, and the patient was admitted to the ICU. The patient was free of any complications during her follow-up and was discharged on the fourth day. She also remained free of any medical problem at long-term (12 months) follow-up (Figure 4).

DISCUSSION

Since fractures involving the pelvis, a highly vascular region, are associated with excessive mortality, prompt diagnosis and rapid management of a bleeding source in that region are of critical importance in terms of survival

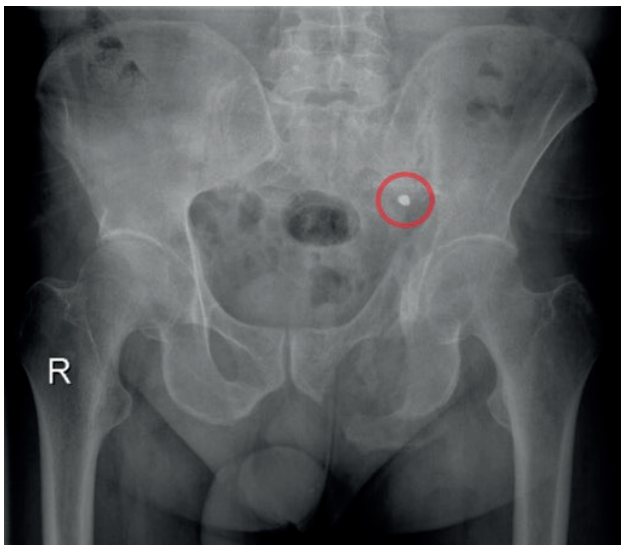

Figure 4: Embolizing coil in the black circle that can be seen on the radiograph of the patient who came to the outpatient clinic.

(1,6). As demonstrated by our cases, iliolumbar, sacral, superior-inferior gluteal, obturator, internal pudendal, or inferior epigastric artery can be injured, depending on the fracture site (7).

Pelvic vascular injuries due to fractures are diagnosed by demonstrating contrast material extravasation in pelvic CT angiography; however, the absence of contrast material extravasation does not necessarily imply the absence of bleeding because contrast material extravasation is not observed in 25% of patients, and it is also the most effective technique for controlling ongoing arterial bleeding (4,8). However, DSA is indicated to rule out potential sources of intermittent bleeding in hypotensive patients who show no sign of active extravasation but have a large pelvic hematoma, and in patients having signs of arterial bleeding on CT angiography (1). A timely performed AE may improve patient outcomes in bleeding secondary to pelvic fracture; hence, a relationship has been demonstrated between delayed AE and increased mortality (4). One of the approaches that have come up recently in this regard is the HERS, which was first reported in Japan in 2012 as a novel management flow protocol for patients with severe blunt trauma and named as “Hybrid Emergency Room (Hybrid ER)” since it is based on a combination of “examination “and “treatment”. This system was updated by a study dated 2018 that enrolled 336 patients with blunt trauma, and subsequently named Hybrid Emergency Service System (9). This term is used to describe a novel type of trauma resuscitation room equipped with computerized tomography, fluoroscopy, and an operating room. HERS resuscitation enables physicians to simultaneously perform WBCT, endovascular procedures (REBOA/TAE), and injury control surgery without needing an operating room (5). Although the introduction of multidetector CT has largely shortened the time to perform a CT scan, prolongation of the time to perform urgent surgery due to patient transfer to a room equipped with CT in the traditional technique continues to be unacceptable for patients with hemodynamic instability (9); hence, HERS resuscitation has gradually gained importance. In HERS, airway and respiratory tract abnormalities are evaluated first; a CT examination can be performed within 10 minutes after ED admission under continuous monitoring, which allows rapid recognition of life-threatening injuries even in patients having shock.

If a patient’s vital signs remain extremely unstable despite a rapidly performed CT scan, more aggressive resuscitation including resuscitative thoracotomy and REBOA can be pursued (9).

Although life-threatening hemorrhagic events are traditionally managed surgically, non-surgical management of trauma by interventional radiology (IR) procedures in trauma care systems equipped with the latest technology have become an important focus of interest even for the care of hemodynamically unstable patients; however, the unavailability of interventional radiologists (IRs) at times negatively affects the timing of the treatment (10). In HERS, on the other hand, a well-trained multidisciplinary team consisting of highly specialized professionals such as surgeons, emergency medicine specialists, IRs, and technicians/nurses always

stays ready to intervene in accordance with the concept of trauma resuscitation in a single room; patients with a lower chance of survival according to TRISS can survive in HERS (4). This particularly improves the AE timing of patients with pelvic fracture and fatal bleeding, thereby allowing early bleeding control and improved survival (11).

As can be seen in the two cases that we intervened with the conventional method in our hospital, critical patients were first transferred to the tomography room and then to the operating room or DSA. In addition to the extra burden of gathering the team for DSA for emergency medicine specialists, patient intervention is very challenging for intensive emergency services with a limited number of personnel, since serious patients must be accompanied by a professional healthcare worker during transport. One of the obstacles to the spread of HERS is sufficient capital investments not only for the installation of the CT angiography machine but also for the rebuilding of the ED and maintenance of the equipment. Although this system is thought to be effective in the management of patients with life-threatening hemorrhagic trauma, it is still unclear if these investments would worth their cost (12). Further studies are needed to aid healthcare decision-makers to decide if it is worth investing in equipment to improve the survival of target populations.

Conflict of Interest: No conflict of interest was declared by the authors.
Ethics: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images, and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.
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CASE REPORT

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Surprising Result in A Patient Presenting with Agitation: Neurobrucellosis

Ajitasyon ile Başvuran Hastada Şaşırtıcı Sonuç: Nörobruselloz

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ABSTRACT

Brucellosis is one of the most common zoonotic diseases worldwide. Neurobrucellosis develops within approximately 12 months after the diagnosis of brucellosis. Since the classical triad of meningitis (fever, nuchal rigidity, confusion) is rare in cases of meningitis due to brucellosis, brucellosis should be considered in the differential diagnosis of patients with unexplained neurological findings in endemic areas. In our case, a 31-year-old male patient with no history of chronic disease in his medical history was admitted to the emergency department with agitation, confusion, meaningless movements, unsteadiness in walking and blurred vision which started on the same day. In his anamnesis, it was learned that he had been treated for brucella 8 months ago in an external centre, but he did not continue his treatment regularly and did not attend the follow-up visits. LP revealed microprotein 255 mg/dL and albumin 114 mg/dL. CSF brucella agglutination was positive at a titre of 1/40. The patient was transferred to the intensive care unit with a diagnosis of neurobrucellosis. In this case report, we aimed to ensure that neurobrucellosis should be considered as a differential diagnosis in patients presenting with neurological and psychiatric symptoms, especially in regions where animal husbandry is practised. We believe that with this case report, we will contribute to a subject that does not have many examples in the literature and that we will be able to create different perspectives on patients with atypical symptoms.

ÖZET

Bruselloz dünya çapında görülen en yaygın zoonotik hastalıklardandır. Nörobruselloz, brusella tanısı alındıktan sonra yaklaşık 12 ay içerisinde ortaya çıkar. Bruselloza bağlı menenjit olgularında, menenjitin klasik triadı (ateş, ense sertliği, bilinç bulanıklığı) nadir görüldüğünden, endemik bölgelerde açıklanmayan nörolojik bulguları olan hastaların ayırıcı tanısında bruselloz mutlaka düşünülmelidir. Olgumuzda; tıbbi geçmişinde kronik hastalık öyküsü bulunmayan 31 yaşında bir erkek hasta, aynı gün başlayan ajitasyon, bilinç bulanıklığı, anlamsız hareketler, yürümede dengesizlik, görmede bulanıklık ile acil servise müracaat etti. Anamnezinde 8 ay önce dış merkezde brucella tedavisi gördüğü ancak tedavisine düzenli devam etmediği ve takiplerine gitmediği öğrenildi. LP sonucunda mikroprotein 255 mg/dL ve albümin 114 mg/dL saptandı. BOS brucella aglütinasyonu 1/40 titrede pozitif geldi. Hasta nörobruselloz tanısı ile yoğun bakım ünitesine devredildi. Bu olgu sunumunda özellikle hayvancılıkla uğraşılan bölgelerde nörolojik ve psikiyatrik semptomlarla gelen hastalarda nörobrusellozun ayırıcı tanı olarak düşünülmesini sağlamayı amaçladık. Bu olgu sunumu ile literatürde çok fazla örneği olmayan bir konuya katkı sağlayacağımızı ve atipik semptomlar barındıran hastalarda farklı bakış açıları oluşturabileceğimizi düşünmekteyiz.

Keywords:
Neurobrucellosis
Agitation
Encephalitis

Anahtar Kelimeler:
Nörobruselloz
Ajitasyon
Ensefalit

INTRODUCTION

Brucellosis is one of the most common zoonotic diseases seen worldwide (1). The most common route of transmission is direct contact with infected animals and consumption of dairy products such as fresh milk, butter and cheese (2). Brucella is a Gram (-), intracellular, aerobic bacterium and Brucella abortus, B. melitensis, B. suis and B. canis cause brucella infection in humans (2). Brucellosis is an infection that may involve multiple systems including spleen, liver, central nervous system, musculoskeletal system, lymphatic system and gastrointestinal system and requires a multiple approach (2). Although rare, nervous system involvement due to Brucella infection can be observed in endemic regions (1). The definition of neurobrucellosis is the name given to neurological involvement of brucella infection and is observed in approximately 5% of patients with brucella infection (3). Neurobrucellosis occurs within approximately 12 months after the diagnosis of brucella (2). Clinically, it presents with different neurological presentations and may be seen as myelitis, encephalitis, abscess, meningitis, demyelination, cranial neuropathy, intracranial hypertension, meningovascular syndrome and psychiatric symptoms (2,3). The fact that neurorucellosis is not a common diagnosis in clinical practice led us to

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prepare a case report on this subject. With this case report, we aimed to establish an additional preliminary diagnosis, along with other possible causes, in patients presenting to the emergency department with neurological symptoms, especially in endemic regions.

CASE REPORT

A 31-year-old male patient with no history of chronic disease was brought to the emergency department with agitation, confusion, meaningless movements, unsteadiness in walking and blurred vision which started on the same day. In his anamnesis, it was learned that he had been treated for brucella 8 months ago in an external centre, but he did not continue his treatment regularly and did not attend the follow-up visits. On physical examination, pulse rate was 106/min and temperature was 36.6 °C. Neurological examination revealed no acute pathological findings except nuchal rigidity and other system examinations revealed no pathological findings. ECG was in normal sinus rhythm. Blood parameters were WBC:13.72 10^3/µL, NE: 11.7 10^3/µL, CRP: 0.4 mg/L, procalcitonin: 0.06 µg/L. No ethanol was detected in the blood. The patient was sedated with benzodiazepine for imaging. Brain CT (Computed Tomography) revealed a hypodense lobulated lesion (cyst?) adjacent to the 3rd ventricle. Diffusion MRI (Magnetic Resonance Imaging) revealed no pathology. Lumbar puncture was planned. Microprotein 255 mg/dL and albumin 114 mg/dL were found in LP (Lumbar Puncture). CSF (Cerebrospinal Fluid) brucella agglutination was positive at a titre of 1/40. (Table I) Pleocytosis with lymphocyte dominance was present. During the emergency department follow-up, 2 grams of 3rd generation cephalosporin was administered intravenously. The patient was consulted with the infectious diseases department with a preliminary diagnosis of neurobrucellosis. Considering his current findings, he was transferred to the intensive care unit for follow-up and treatment. Doxycycline, rifampicin and ceftriaxone combined treatment was started. During intensive care unit follow-up, the patient described low back and hip pain and was evaluated with thoracolumbar and sacroiliac MRI and the results were significant for brucella sacroiliitis. On the 16th day of follow-up, the patient with no active complaints and neurological symptoms was discharged with oral doxycycline and rifampicin prescription.

Table 1: Blood and CSF results

Parameters	Results
Blood results	
WBC	13.72 10^3/µL
NEU	11.7 10^3/µL
CRP	0.4 mg/L
Procalcitonin	0.06 µg/L
Ethanol	(-)
CSF results	
Microprotein	255 mg/dL
Albumin	114 mg/dL

DISCUSSION

In this case report, lumbar puncture was performed in a patient who presented with altered consciousness and microprotein was found to be high in CSF tests. There was also pleocytosis with a predominance of lymphocytes. It is a current case report that supports the existing literature by obtaining similar results to the findings in the literature. Nervous system involvement is a rare complication of brucellosis, occurring in 3-10% of patients with brucellosis. Despite this, neurobrucellosis is reported to be relatively common in countries where brucellosis is endemic. It is estimated that neurobrucellosis constitutes 0.5% of all episodes of community-acquired central nervous system infections (1). Neurobrucellosis is most commonly diagnosed 2-12 months after the onset of symptoms. Our case, similarly, symptoms appeared approximately 8 months after diagnosis. Since neurological complications may develop chronically, they are frequently confused with other infections such as tuberculosis (2). Variable neurological pictures may include meningitis, encephalitis, myelitis-radiculoneuritis, brain abscess, epidural abscess, granuloma and demyelination. While subacute or chronic meningitis is most common in neurobrucellosis, classical meningitis findings may not be seen. In patients with unexplained neurological findings, especially in endemic areas, the possibility of brucellosis should not be ruled out and should be included in the differential diagnosis. Neurological examination of patients frequently reveals partial loss of strength, nuchal rigidity, cranial neuropathy and confusion (3). Psychiatric pictures including depression, amnesia, psychosis, agitation, personality change and euphoria may be observed in the course of neurobrucellosis (4). In CSF examinations of neurobrucellosis patients, lymphocytic cell dominance and moderate protein increase are observed (3). In the CSF examinations of our patient, findings compatible with the literature were found. Antibiotic selection, dosage and duration of antibacterial treatment for neurobrucellosis are still controversial and a combination of three or four antibiotics is usually used until clinical symptoms improve and cerebrospinal fluid normalises. Currently, the treatment plan is usually based on the use of rifampicin, ceftriaxone or quinolone in combination with doxycycline and one of the aminoglycosides. Doxycycline, rifampicin and ceftriaxone were administered to our patient during follow-up. In a study published by Zhuang et al. on 21 patients, minocycline (100 mg, twice a day) was added to the treatment, unlike our case, but similar results were obtained (5). The average duration of treatment in the literature is 6 months. However, it varies between 3 and 9 months depending on clinical symptoms (4). Due to the possibility of recurrence, it is recommended to follow up the patients every 3 months. Brucellosis should be considered as a potential cause of cervical epidural abscess, especially in endemic areas. Timely detection and effective management of this condition are crucial in order to minimize the associated morbidity and mortality. For patients with detectable brucellar cervical epidural abscess, we recommend decompression and fusion surgery (6). The prognosis of neurobrucellosis varies according to clinical symptoms. It has been concluded that patients presenting with meningitis generally have a good prognosis, whereas patients involving the brain

parenchyma and spinal cord often have severe sequelae (7). It is thought that the elevation of free oxygen radicals and a decrease in antioxidant capacity may have an importance in the pathogenesis of brucellosis. In a study by Caylak E, the therapeutic power of antibiotic combinations used in patients was determined by the oxidant and antioxidant agents measured before and after treatment in patients, and the addition of antioxidants to effective treatment protocols for brucella will make an extra contribution (8). Optogenetics is a technology that combines genetic and optical methods to regulate cellular processes with light signals. Cell behavior is affected by the change in shape of genetically encoded proteins in the presence of light. This method is a candidate for use in the treatment of neurobrucellosis in the near future. In a study by G Li et al., melatonin (5 mg/kg), which plays a critical role in mammalian immune regulation, was injected intravenously into three adult sheep with brucellosis. Blood samples were collected at 0, 1, 3 and 6 h after injection for cytokine analysis. IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α levels were evaluated (9). Melatonin is recognized for its ability to mitigate the harmful consequences of free radicals through the activation of antioxidant enzymes. Melatonin demonstrates diverse antioxidant properties, including the neutralization of free radicals, suppression of free radical generation in neurons, astrocytes, and microglia, and regulation of antioxidant enzymes (10). In this study, the proinflammatory cytokines IFN-γ, IL-2 and IL-6 levels of sheep with brucellosis were significantly decreased at different times after exogenous melatonin treatment, suggesting that melatonin alleviates inflammation caused by brucellosis infection to some extent. The level of IL-4, an anti-inflammatory cytokine, was significantly up-regulated 1 h after melatonin treatment, indicating that melatonin plays an important role in anti-inflammatory activity. Various studies have shown anti-inflammatory effects of melatonin treatment in both animals and patients. It can be predicted that melatonin treatment may alleviate brucellosis by modulating inflammatory cytokine responses. The use of melatonin as a therapeutic or adjuvant treatment for brucellosis in both animals and humans may find a place in the future (9).

CONCLUSION

In patients presenting to the emergency department with similar symptoms, neurobrucellosis, which is one of the central nervous system infections, should be considered in the differential diagnosis after central pathologies are excluded and toxic substance and ethanol intake is excluded. It should definitely be considered in the differential diagnosis in patients presenting with such symptoms, especially in endemic regions, as in our country.

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LETTER TO EDITOR

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A New Hope in the Treatment of Rett Syndrome: Trofinetide

Rett Sendromu Tedavisinde Yeni Bir Umut: Trofinetid

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Dear Editor;

Rett syndrome (RTT) is a rare neurodevelopmental disorder that almost exclusively affects women. Andreas Rett first described the syndrome in the German medical literature in 1966. The disorder is characterized by a period of normal development during infancy, followed by a period of regression that leads to severe cognitive and motor skill impairments. Patients diagnosed with classic Rett Syndrome usually exhibit developmental stagnation and regression, acquired loss of speech and purposeful hand use, development of stereotypic hand movements, and may also develop microcephaly, seizures and autistic features between the ages of 6 and 18 months (1). Rett syndrome can present significant challenges for affected individuals and their families. Therefore, it is crucial to increase awareness of the disease and enhance treatment options. Researchers are actively working to gain a better understanding of the disease's causes and effects and to develop more effective treatments.

In March 2023, the United States approved Trofinetide for the treatment of Rett syndrome in adults and pediatric patients aged 2 years and older. Trofinetide, an oral, small molecule, synthetic analogue, is derived from the N-terminal tripeptide of insulin-like growth factor-1 (IGF-1). The phase 3 study showed a significant improvement in communication and social cognition with trofinetide treatment compared to placebo (2). Another study published in Nature Medicine reported significant enhancements in the Rett Syndrome Behaviour Questionnaire (RSBQ) and Clinical Global Impression-Improvement (CGI-I) scores with trofinetide treatment. Systematic review and meta-analysis further supported the efficacy of trofinetide, particularly at the 200 mg dosage, in improving RSBQ and CGI-I scores (3). Clinical trials have underscored Trofinetide's effectiveness in enhancing Rett syndrome behavioral scores, suggesting a notable advancement in syndrome treatment, potentially through its impact on neuronal morphology and synaptic functioning (4). Noteworthy, trofinetide demonstrated efficacy in treating the core symptoms of Rett syndrome in Phase 3 studies. Common side effects observed during treatment included mostly mild to moderate diarrhea, along with vomiting, fever, seizure, anxiety, and fatigue. Trofinetide is not recommended for patients with moderate or severe renal impairment. The FDA's approval of trofinetide marks the first authorized treatment for Rett syndrome, a condition that has lacked effective treatment options for over five decades (5).

The approval of Trofinetide by the FDA represents a significant advance in the management of rare and difficult-to-treat diseases such as Rett syndrome. This approval is a promising step for both patients and their families because it could potentially have a major impact on managing symptoms. However, it should be noted that Trofinetide does not treat the disease and aims to manage symptoms. In this context, it is important to consider the potential role of future research in the development of innovative approaches, such as a true cure for diseases such as Rett syndrome or perhaps even genetic correction therapies. In particular, the approval of Trofinetide could further motivate the scientific and clinical community to better understand the complex mechanisms underlying such disorders and develop more effective treatments. In this process, it is also important to consider measures such as raising awareness in the community and improving opportunities for early diagnosis, which could significantly improve the quality of life of patients and their families.

The FDA's approval of Trofinetide can be considered a promising step towards the treatment of rare and difficult-to-treat diseases such as Rett Syndrome. Trofinetide is designed to manage symptoms, not to treat Rett Syndrome. However, this drug could be of great value if it can provide a noticeable increase in patients' quality of life. It is of paramount importance to conduct further research in order to enhance the improvement offered by Trofinetide and to identify a genuine cure for Rett Syndrome.

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LETTER TO EDITOR

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Unmasking the Unspoken: The Epidemic of Suicide among Healthcare Professionals in India

Konuşulmayanların Maskesini Ortaya Çıkarmak: Hindistan'da Sağlık Çalışanları Arasında İntihar Salgını

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Dear Editor;

In the bustling corridors of hospitals and the serene confines of clinics, healthcare professionals (HCPs) stand as pillars of strength and compassion, dedicated to healing others. Yet, behind the façade of white coats and stethoscopes lies a silent crisis that demands urgent attention the alarming prevalence of suicide among healthcare workers (1). A recent study sheds light on this sobering reality, revealing that the suicide mortality rate among HCPs in India is a staggering 2.5 times higher than the global average. Academic stress, mental illness, and workplace harassment emerge as predominant factors driving individuals in this noble profession to the brink of despair. The COVID-19 pandemic has only exacerbated these challenges, thrusting healthcare workers onto the frontline of an unprecedented health crisis while subjecting them to heightened levels of stress, anxiety, and burnout (2). The relentless demands of battling the pandemic, coupled with the fear of infection and the trauma of witnessing countless lives lost, have taken a toll on the mental health of HCPs. Despite the gravity of the situation, there remains a glaring lack of comprehensive research and clinical studies in this field, particularly in the Indian context. It is imperative that we bridge this knowledge gap and develop evidence-based strategies tailored to the unique needs of different subgroups within the healthcare workforce. Moreover, proactive interventions are urgently needed to address this crisis. Routine mental health screenings, stress management workshops, and telehealth services are essential components of a multifaceted approach to safeguarding the well-being of healthcare professionals (3). Destigmatizing mental illness and fostering a supportive environment within healthcare institutions are also critical in encouraging individuals to seek help without fear of judgment or reprisal (4).

Firstly, Addressing the silent crisis of suicide among healthcare professionals in India requires comprehensive research initiatives as a foundational step. Longitudinal studies and qualitative research can offer invaluable insights into the unique stressors faced by medical students, resident doctors, nursing staff, and senior consultants. Such research endeavours will pave the way for tailored interventions that address the specific needs of each subgroup, promoting mental well-being and resilience. Secondly, institutional reforms are essential to cultivate a supportive work environment within healthcare institutions. This entails implementing policies that reduce workplace stressors, foster a culture of psychological safety, and promote work-life balance. By prioritizing the mental health of employees and providing access to confidential support services, institutions can mitigate the risk factors associated with suicide and create a healthier workplace culture. Lastly, leveraging technology-driven solutions and advocating for awareness and collaboration are critical components of suicide prevention efforts. Telepsychiatry platforms, mobile applications for self-care, and online support groups offer accessible avenues for healthcare professionals to seek help and support. Advocacy campaigns can challenge stigma, raise awareness, and promote open dialogue about mental health within the healthcare community. Through these concerted efforts, we can strive towards creating a safer and more supportive environment for those who dedicate their lives to caring for others.

In conclusion, the plight of healthcare professionals grappling with mental health issues and suicidal thoughts demands immediate attention and concerted action. By unveiling the silent crisis behind the scenes of healthcare settings, we can begin to dismantle the stigma surrounding mental health and ensure that those dedicated to saving lives receive the care and support they so desperately need. Only through collective efforts and unwavering commitment can we hope to stem the tide of this silent epidemic and protect the mental well-being of our healthcare heroes.

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LETTER TO EDITOR

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An Approach whose Importance is More Understood in Natural Disasters Experienced in Turkey: Telerehabilitation

Türkiye'de Yaşanan Doğal Afetlerde Önemi Daha Çok Anlaşılan Bir Yaklaşım: Telerehabilitasyon

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Dear Editor,

Disaster refers to a significant disruption of the routine functioning of a society by causing widespread human, material, economic, or environmental losses that exceed the limits of that society's ability to utilize its resources (1). Increasing disasters in recent years have necessitated changes in countries' health services and policies. With the strategic goals established, activities to improve disaster management have gained momentum. It has become a priority to prepare for possible disasters with a proactive approach by learning from past natural disasters. It is emphasized that necessary medical rehabilitation initiatives should be a part of disaster management to minimize the devastating effects of possible natural disasters that may occur in the future (2).

The coronavirus disease (COVID-19) that has affected the world and the Kahramanmaraş (Pazarcık and Elbistan) earthquakes that have had devastating effects on many cities in Turkey have left deep traces in the lives of millions of people. These natural disasters have negatively affected not only the financial, psychological, and social lives of many people with various chronic diseases but also the management of their illnesses (3). These natural disasters have made it necessary to change the daily functioning of health systems. Because both the isolation process and the process caused by the destruction have disrupted patients' routine hospital visits. The difficulties experienced in providing health services have made it necessary to implement alternative strategies. Digital health technologies are one of these strategies and have potential contributions to the effective management of health systems in many parameters such as access, efficiency, cost, and transfer of patient information in health services (4).

After disasters, it is essential to make the rehabilitation of previously disabled individuals as well as individuals with new disabilities due to disaster sustainable (5). In such cases, telerehabilitation, which is evaluated within the scope of telehealth strategies, can be used as an effective way of applying medical resources. The benefits of telerehabilitation in this regard have been proven, but the studies on this subject are still minimal (6-8).

During disasters, it can be very difficult for disabled individuals with limited resources to access health services, especially in rural areas. These limited opportunities can further increase the illness and disability of individuals with disasters. It is known that disasters increase the rates of disability before the disaster and cause an increase in the demand for rehabilitation. In the context of meeting and managing this demand, the limited opportunities caused by the disaster can be managed more easily within the scope of telerehabilitation and can provide an opportunity for better health outcomes (9). In these cases that limit access to the hospital, early sustainable rehabilitative approaches can be implemented without delay with telerehabilitation. The benefits of this early rehabilitation include (a) fewer acute and long-term complications, (b) reduced length of hospital stay in the acute phase, (c) better functional outcomes, and (d) better integration of individuals participating in rehabilitative interventions into society (10). These benefits aimed at early rehabilitation can be achieved by addressing individuals from a physical, psychological, and social perspective.

It is possible to evaluate the physical, psychological, and social effects of both the individuals who became disabled after the disaster and the individuals who were disabled before, in a holistic manner with the biopsychosocial model (Figure 1) (11). Individuals who need post-disaster rehabilitation experience restrictions in activity and participation due to their physical effects during this process. Reducing these problems can be achieved by implementing the necessary rehabilitative interventions at an early stage by considering individual and environmental factors together (12). Online consultation,

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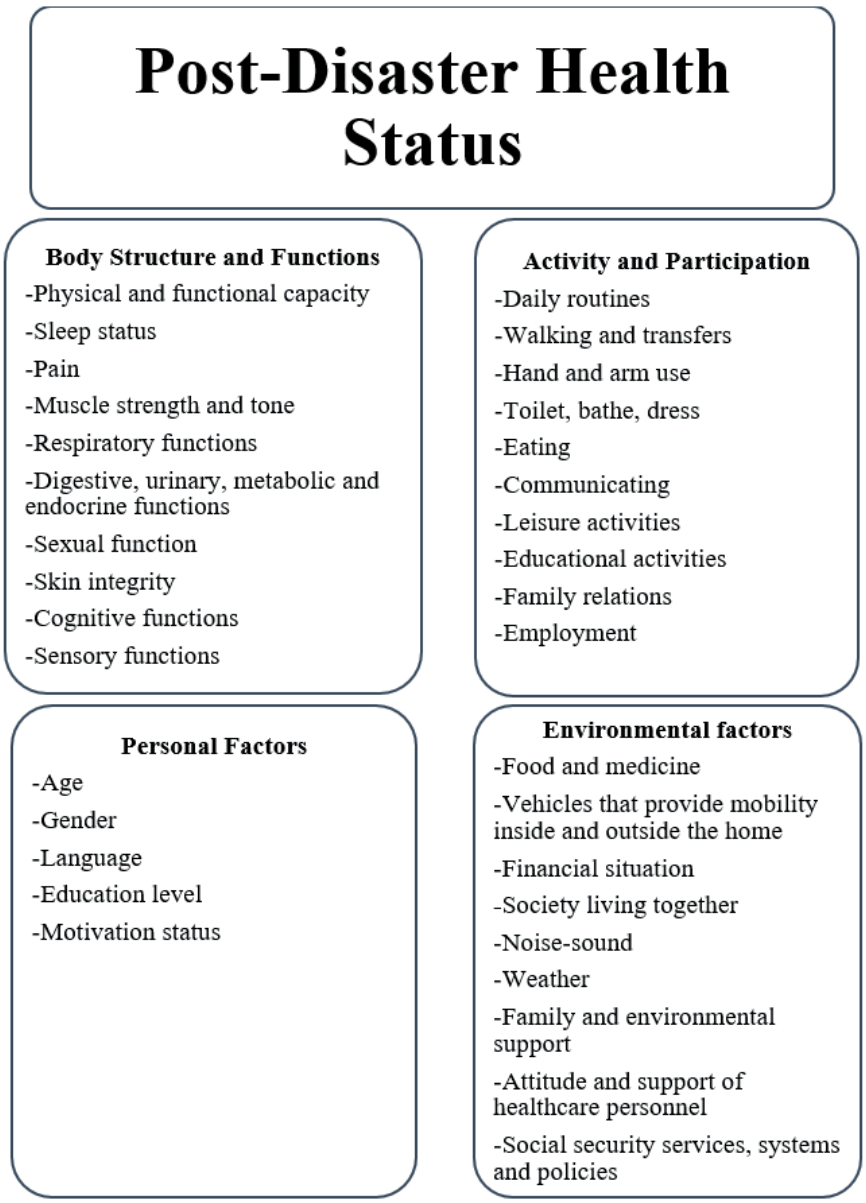
evaluation, treatment, rehabilitation approaches, and 24-hour monitoring can be managed with telerehabilitation, coordinated by the multidisciplinary team (13). However, when the limitations caused by the disaster are reduced, necessary hospital-based rehabilitation interventions should be continued. Because the limitations of the telerehabilitation approach, which cannot provide objective results as much as face-to-face evaluation, can be overcome in this way.



Figüre 1: Assessment of Post-Disaster Health Status in the Context of the International Classification of Functioning, Disability and Health (ICF) (11)

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