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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
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ORIGINAL RESEARCH

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Evaluation of Patients Hospitalized from the Emergency Department with Pyelonephritis

Sibel Bakırçivi[1], Mustafa Burak Sayhan[2], Ömer Salt[3], Aykut Yucal[2]

[1]*Çerkezköy State Hospital, Clinic of Emergency Medicine, Tekirdağ, Türkiye*
[2]*Trakya University Faculty of Medicine, Department of Emergency Medicine, Edirne, Türkiye*
[3]*Kayseri State Hospital, Clinic of Emergency Medicine, Kayseri, Türkiye*

Abstract

Objective: We aimed to evaluate the demographic, etiologic, and clinical characteristics, complicating factors, laboratory and radiodiagnostic evaluations, treatment practices, and follow-up processes of hospitalized patients diagnosed with acute pyelonephritis (APN).

Materials and Methods: The files of 241 patients diagnosed with APN in the emergency department and admitted to clinics in our center between May 1, 2012, and May 1, 2016, were accessed through the automation information system of our hospital. Demographic characteristics, seasonal distribution, complaints, clinical findings, laboratory tests and imaging results, treatment, follow-up, and outcome status of the patients were retrospectively scanned and evaluated.

Results: The mean age of the patients was 66.00±19.61 years. 54.4% were women. The most common presenting complaints were fever and flank pain; physical examination finding was suprapubic tenderness; predisposing factor was urinary catheterization; and comorbid diseases were chronic renal failure and DM. The most common causative agent was *Escherichia coli* The most common imaging findings were hydronephrosis and urolithiasis. The duration of hospitalization was 10.81±7.09 days; 1.2% of patients died.

Conclusion: The most common predisposing factors for the development of APN were recent antibiotic use, particularly in the last two weeks, history of hospitalization in the last two weeks, chronic renal failure, and diabetes mellitus. APN may present as a spectrum ranging from mild to urosepsis.

Keywords: Pyelonephritis, urinary tract infection, predisposing factor, diagnosis

Introduction

Acute pyelonephritis (APN) is a progressive infection of the parenchymal tissue of the kidney that can result in high mortality and morbidity [1-5]. The main symptoms are flank pain, fever, low back pain, and burning sensations during urination. It is more common in women than men, and it can be observed at any age [3-7]. Gram (-) enteric bacteria are frequently seen as causative agents. Pyelonephritis can be divided into two categories: complicated pyelonephritis associated with complicating factors, such as urinary system anomalies, urinary system stones, diabetes, pregnancy, catheter use, and similar foreign bodies, and uncomplicated pyelonephritis, which is a disease without complicating factors. The determination of these factors is important for diagnosis and treatment. Treatment should be started as soon as possible in such patients. In untreated patients, it may progress to the loss of renal parenchyma, followed by sepsis and death [1,7-9]. The diagnosis of APN is made using the rational use of clinical findings, laboratory tests, and imaging methods [5,10].

In this study, we aimed to evaluate the demographic, etiologic, and clinical characteristics, complicating factors, laboratory and radiodiagnostic evaluations, treatment practices, and follow-up processes of hospitalized patients with APN.

Address for Correspondence: Mustafa Burak Sayhan, Trakya University Faculty of Medicine, Department of Emergency Medicine, Edirne, Türkiye
E-mail: mustafaburak@yahoo.com **ORCID-ID:** orcid.org/0000-0001-9335-9001
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Materials and Methods

Ethics Statement

The study was conducted according to the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the Trakya University Faculty of Medicine Scientific Research Ethics Committee (decision number: 1707, date: 12.10.2016) of our university before starting the study.

Study Design and Data Collection

The files of 241 patients diagnosed with APN in the emergency department and admitted to the clinics in our center between May 1, 2012, and May 1, 2016, were accessed through the automation information system of our hospital. The data were retrospectively scanned and recorded on the study forms.

Demographic characteristics, seasonal distribution, complaints, clinical findings, laboratory tests and imaging results, treatment, follow-up, and outcome status of the patients were retrospectively scanned and evaluated.

Statistical Analysis

SPSS 20.0 for Windows® statistical software (IBM Inc. Chicago, IL, USA) was used. Minimum-maximum values and arithmetic mean±standard deviation were calculated as descriptive statistics, and numbers (n) and percentages (%) were calculated for qualitative data.

Results

Descriptive Characteristics of the Patients

We included 241 patients in the study. It was determined that 7.5% of the patients (n=18) had previously visited another clinic and were referred to our center for further examination and treatment. Furthermore, 54.4% of the patients were female, and the mean age was 66.00±19.61 years. The mean age of male participants was higher than that of female participants. When the patients' presenting complaints were questioned; 47.1% (n=114) had dysuria, 75.9% (n=183) had fever, 45.6% (n=110) had chills, 50.2% (n=121) had flank pain, 36.5% (n=88) had nausea, and 33.6% (n=81) had vomiting (Table 1).

Table 1. Descriptive characteristics of the patients

Gender n (%)	**Male**	**Female**	**Total**
	110 (45.6)	131 (54.4)	241 (100)
Age (year) (mean±SD)	74.00±14.06 (26-95)	58.00±20.68 (20-89)	66.00±19.61 (20-95)
Complaints at admission n (%)	Irrative voiding symptoms	Dysuria	114 (47.1)
	Pollakiuria	19 (7.9)	
	Polyuria	8 (202)	
	Urgency	39 (16.3)	
	Haematuria	18 (7.5)	
	Fever		183 (75.9)
	Flank pain		121 (50.2)
	Shaking chills		110 (45.6)
	Nause		88 (36.5)
	Vomiting		81 (33.6)
	Diarrhea		15 (6.2)
Physical examination findings n (%)	Vital parameters (mean±SD)	Respiratory rate (/min.)	15±2.21
		Pulse rate (/min.)	90±15.57
		Systolic blood pressure (mmHg)	110±19.10
		Diastolic blood pressure (mmHg)	70±11.79
		Body temperature (°C)	38±1.02
	Fever		62 (25.7)
	Unconsciousness		91 (37.7)
	Hypotension		67 (27.8)
	Tachycardia		45 (18.6)
	Tachypnea		22 (9.1)
	Dehydratation		95 (39.6)
	Costovertebral angle tenderness		138 (57.3)
	Suprapubic tenderness		147 (60.9)

SD: Standard deviation, Min.: Minimum, Mean: Average

Complaints at Admission and Physical Examination Findings

When the vital parameters of the patients were evaluated; mean respiratory rate was 15±2.21/min., mean systolic blood pressure was 110±19.10 mmHg, mean diastolic blood pressure was 70±11.798 mmHg, mean axillary body temperature was 38±1.02 °C and mean pulse rate was 90±15.576 beats/min. According to the physical examination findings, 60.9% (n=147) had suprapubic tenderness, 57.3% (n=138) had costovertebral angle tenderness, 39.6% (n=95) had dehydration, and 37.7% (n=91) had impaired consciousness (Table 1).

Predisposing Factors

Predisposing factors were evaluated under the main headings of urinary system-derived factors, medical factors, and comorbid diseases. When the patients were questioned in terms of predisposing factors, the most common urinary tract-derived factors were foley catheter use (17.4%) and urolithiasis (17.0%); the most common medical factor was inappropriate and unindicated use of antibiotics (34.9%); and the most common comorbid diseases were diabetes mellitus (23.2%) and chronic renal failure (27.0%) (Table 2).

Laboratory Results

The mean urea value was 53.29±40.52 mg/dL, mean creatinine value was 1.36±1.03 mg/dL, mean C-reactive protein (CRP) value was 15.68±13.90 and mean sedimentation value was 65.58±30.61/h. In addition, a left shift (increased polymorphic leukocytes) was detected in the peripheral smears of 91.3% of patients. Complete urine analysis revealed bacteriuria (80.1%), leukocyte cilia, microscopic hematuria (55.2%), and sterile pyuria (14.1%). When the urine culture results of the patients were analyzed, it was found that 61.8% had single microorganism and 22.8% had poly microorganism. Among these microorganisms, *Escherichia coli (E. coli)* (71.0%) is the most common (Table 3).

Imaging Findings

In the emergency department, 39.6% of patients underwent direct urinary tract radiography (DUSG), 85.5% underwent urinary tract ultrasonography, and 27.9% underwent urinary tract computed tomography (CT). When the patients who underwent imaging examinations were analyzed, the examination was normal in 65.8% (n=61) of those who underwent DUSG, 35.4% (n=73) of those who underwent Ultrasonography (USG), and 14.9% (n=10) of those who underwent CT. Stone-compatible radiopacity was observed in 25.8% (n=23) of patients who underwent DUSG. Heterogeneity in the renal parenchyma was found in 19.4% (n=40), hydronephrosis in 35% (n=72), renal calculi in 16.8% (n=33), and ureteral calculi in 15.2% (n=11) of patients who underwent urinary system USG. In patients who underwent CT scan, 32.8% (n=22) had renal calculi, 43.3% (n=29) had hydronephrosis, and 47.8% (n=32) had hydronephrosis (Table 3).

Table 2. Predisposing factors

		n (%)*
Urinary system related factors	Foley catheter use	42 (17.4)
	History of pyelonephritis/recurrent urinary tract infection	32 (13.3)
	Benign prostatic hypertrophy	31 (12.9)
	Nephrolithiasis/urolithiasis	41 (17.0)
	Genitourinary anomaly	13 (5.4)
	History of urological operations	
	Enterovesical-fistula	3 (1.2)
	Renal transplantation	4 (1.7)
	Nephrectomy	12 (5.0)
Medical factors	Inappropriate and unindicated use of antibiotics	84 (34.9)
	Use of nonsteroidal anti-inflammatory drugs	33 (13.7)
	Immunosuppressive treatment	16 (6.6)
Comorbid diseases and other factors	Pregnancy	5 (2.1)
	Diabetes mellitus	56 (23.2)
	Chronic renal failure	65 (27.0)
	History of tuberculosis	3 (1.2)
	History of malignancy	30 (12.4)
	History of immune system disease	9 (3.7)
	History of hospitalization within the last two weeks	79 (32.8)

*: A patient may have multiple factors

Treatment, Prognosis, and Outcome

When the treatments applied to the patients in the emergency department and hospitalized ward were analyzed, 64.7% of the patients were started on a single antibiotic, whereas 35.3% were started on multiple antibiotics. When the clinics where the patients were hospitalized were examined; 88.8% (n=214) of the patients were hospitalized in the infectious diseases clinic and 8.3% (n=20) in the urology clinic. In addition, 14.5% of patients had surgical indication (Table 4).

Table 3. Laboratory and imaging findings

Laboratory results		
Biochemical blood tests (mean±SD)	Urea (mg/dL)	53.29±40.519
	Creatinine (mg/dL)	1.36±1.028
	C-reactive protein level (mg/L)	15.68±13.898
	Sedimentation rate (mm/h)	65.58±30.610
	Left shift in peripheral smears	220 (91.3)
Urinalysis n (%)*	Bacteriuria	193 (80.1)
	Sterile pyuria	34 (14.1)
	Proteinuria	68 (28.2)
	Leukocyte cast	233 (96.7)
	Microscopic hematuria	133 (55.2)
Urine culture n (%)*	Single microorganism	149 (61.8)
	Polymicroorganism	55 (22.8)
	Bacteria type	
	Escherichia coli	171 (71.0)
	Proteus	4 (1.7)
	Enterobacter	18 (7.5)
	Klebsiella	13 (5.4)
	Pseudomonas	13 (5.4)
	Others	40 (16.6)
Imaging findings n (%)*		
Direct urinary tract radiography 89 (36.9)	Stone-compatible radiopacity	23 (25.8)
Ultrasonography of the urinary tract 206 (85.5)	Kidney stone	33 (16.8)
	Ureter or bladder stone	11 (15.2)
	Hydronephrosis	72 (35.0)
	Congenital urinary tract anomalies	26 (12.6)
	Emphysematous pyelonephritis	1 (0.5)
	Increased kidney size	9 (4.4)
	Pararenal abcess	12 (5.8)
	Heterogeneity of the renal parenchyma	40 (19.4)
Computerized tomography 67 (27.9)	Kidney stone	22 (32.8)
	Increased kidney size	8 (11.9)
	Emphysema	2 (3.0)
	Congenital urinary tract anomalies	17 (25.4)
	Hydronephrosis	29 (43.3)
	Renal parenchymal damage	32 (47.8)

*: A patient may have multiple factors,
SD: Standard deviation, Mean: Average

The mean length of stay in the emergency department was 1.10±0.32 days, while the mean length of stay in the hospitalized clinics was 10.81±7.09 days. While 6.2% of the treated patients were transferred to another center, 1.2% of them had an exitus (Table 4).

Discussion

Pyelonephritis is more common in women and causes hospitalization five times more frequently than in men [6]. Karakeçili et al. [2] similarly reported that 39.5% of the patients were male and the mean age was 55.5 years. Işıkgöz Taşbakan et al. [1] found that 38% of the patients were male, and the mean age was 48.8±18.7 years. In our study, although the male sex ratio was similar to that reported in the literature, the mean age of our patients was higher.

The symptoms of APN are very variable. In a study in which 190 cases were evaluated, fever was reported in 84.7%, dysuria in 33.1%, nausea in 29.4%, and flank pain in 42.6% [1,2]. In a study evaluating APN cases in elderly patients, fever was found in 53%, dysuria in 35%, and nausea/vomiting in 18% [1,4]. In our study, the most common symptoms were fever, flank pain, dysuria, chills and chills, respectively, and our findings are consistent with the literature. In our study and other studies, fever was the most common symptom of pyelonephritis. This is followed by flank pain, irrative voiding symptoms, nausea, and vomiting. These findings suggest that patients with pyelonephritis may not always present with urinary system-specific complaints.

APN may present clinically on a spectrum ranging from a mild presentation to urosepsis. Altered consciousness, delirium, and agitation may indicate severe urinary tract infection [7,8]. Doyuk Kartal et al. [3] reported that 23% of their patients presented with urosepsis. In our study, 26.1% of patients developed urosepsis. The development of urosepsis increases the mortality rate of the disease, and early recognition is critical for diagnosis and treatment.

In our study, when the vital signs detected at the time of initial presentation were evaluated, the most common findings were fever and hypotension, and when the physical examination was performed, the most common findings were costovertebral angle tenderness, dehydration, and unconsciousness, respectively. However, tachycardia and tachypnea may not always be observed in elderly patients because of the failure of these mechanisms to reach their desired levels. A similar situation was found in the data. It should be noted that although urinary tract infection can progress to a very serious condition, such as sepsis, systemic inflammatory response syndrome symptoms are not always present, especially in elderly individuals.

Urinary catheters are frequently used for urinary retention, incontinence control, wound management, and patient comfort. Catheter-associated urinary tract infections are very common. This is associated with an increased risk of complications and morbidity. Long-term catheter use should be preferred only in patients with valid medical indications. The term complicated urinary tract infection is generally used to refer to infections in patients with structural or functional abnormalities that prevent urinary flow or cause changes in the defense system of the individual [3,11]. The presence of predisposing factors in patients with APN must be evaluated because they are the most important factors for guiding diagnosis and treatment. There are many predisposing factors for the development of complicated urinary tract infection. The most common of these are conditions that cause obstruction in the urinary tract. As a result of obstruction of the urinary tract and stasis of urine flow, the entry and attachment of pathogenic microorganisms into the urinary system becomes easier, and a focus that cannot be easily treated with antibiotics is formed and causes disruption of the local defense system [1,3,10,11]. Işıkgöz Taşbakan et al. [1] reported obstructive uropathy as the most common complicating factor and urinary catheterization as the second most common complicating factor in their study of 133 patients diagnosed with APN.

Table 4. Treatment, prognosis, and outcome

Clinics	n (%)	Infectious diseases	214 (88.8)
		Nephrology	7 (2.9)
		Urology	20 (8.3)
Medical treatment (antibiotics)		Monomicrobial agent	85 (35.3)
		Polymicrobial agents	156 (64.7)
Surgical treatment			35 (14.5)
Urosepsis		63 (26.1)	
Mortality		3 (1.2)	
Hospitalization duration (mean±SD) (days)		10.81±7.09	

SD: Standard deviation, Mean: Average

The essential elements of successful patient treatment and management are effective history taking and detailed identification of risk factors. Awareness by emergency physicians of these factors will contribute positively to the prognosis of the disease. When other studies conducted in our country were examined, it was reported that the most common complicating factor was diabetes mellitus (27-41%). Similarly, diabetes mellitus was reported as the most common complicating factor, with a rate of 26%, in a study by Tanyel et al. [4], in which urinary tract infections in the geriatric age group were evaluated. Other complicating factors include diabetes mellitus, recent history of antibiotic use, congenital anomalies of the urinary system, urological interventions, immunosuppression, renal insufficiency (azotemia), renal transplantation, and neurogenic factors [1-5,7,11-13]. In our study, a history of not indicated and inappropriate antimicrobial use and hospitalization within the last 2 weeks were the two most common factors, followed by obstructive uropathy and urinary tract catheterization. Diabetes mellitus was present in about a quarter of our cases. Differences in the prevalence of other predisposing factors may vary according to the center where the study was conducted and the facilities of these centers. When our findings are evaluated; the high average age and number of comorbid diseases in our patients may explain the high rate of recent hospitalization history. In addition, since our hospital is a regional hospital, many patients with obstructive complication factors are referred to our hospital for surgical procedure evaluation. Another important point that we found in our study and that we think should be emphasized is that inappropriate antimicrobial use is quite common. Jansåker et al. [14] reported that appropriate antibiotic treatment decreased admissions and hospitalizations associated with pyelonephritis. In addition, Doyuk Kartal et al. [3] reported that not indicated and inappropriate antimicrobial use is an important factor that increases the risk of urinary tract infection in all age groups. In our study, approximately one-third of the patients had a history of not indicated and inappropriate antibiotic use (without paying attention to dose and posology). Based on these findings, we believe that this is a common facilitating disease factor. Recently, many meetings have been held both in our home country and abroad about rational drug use and unnecessary antibiotic use, and the importance of the dangers awaiting patients in the future has been emphasized. Physicians play a great role in raising public awareness regarding this issue.

When the laboratory tests of the patients at the time of first presentation were examined, it was found that 77% of the patients had leukocytosis, 71% had elevated sedimentation, and all patients who were examined for CRP had elevated CRP levels in the study by Işıkgöz Taşbakan et al. [1] In our study, we found elevated mean CRP and sedimentation values in the tests performed at the time of first presentation. In peripheral smear examination, 91.3% of patients exhibited a left shift. APN, an infective event, was associated with leukocytosis secondary to increased neutrophil counts and increased sedimentation due to increased complement, along with increased CRP levels, which is known as an acute phase reactant.

In our study, no pathologic finding was detected on urinary system USG performed in 1/3 of the patients, whereas the most frequently detected pathologies were hydronephrosis, obstructive uropathy due to calculi, and pyelonephritis at a rate of 19.4%, respectively. In a study by Karakeçili et al. [2], USG was found to be normal in 62.7% of patients; stones were found in 20.3%, hydronephrosis in 18.7%, and benign prostatic hyperplasia in 7.8%. Işıkgöz Taşbakan et al. [1] found that urinary system USG was normal in 50% of the patients, stones were found in 14%, and hydronephrosis was found in 9% of the patients with pathologic findings. The studies showed partial similarity with the literature and with each other in terms of urinary system USG. Despite these data, there is not enough data in the literature to compare DUSG and CT.

Urine culture is one of the important tests that should be performed for treatment planning of APN. When the urine culture results of APN patients in the study by Karakeçili et al. [2] were analyzed, *E. coli* was found to be the most common organism at a rate of 62.6%, and *Klebsiella* was the second most common organism at a rate of 12.7%. In a study conducted by Işıkgöz Taşbakan et al. [1], *E. coli* was the most frequent pathogen (in 77% of the patients and *Klebsiella* was the second most frequent growth in 10% of the patients. In the study by Doyuk Kartal et al. [3], *E. coli* was the most common causative agent at a rate of 63%, and in the study by Tanyel et al. [4], *E. coli* was the causative agent with a rate of 55%. In our study, *E. coli* was the most common causative agent in 71% of the urine cultures of the patients and enterococcus was the second most common pathogen with a rate of 7.5%. Our study was consistent with the literature regarding the most frequent detection of *E. coli* in urine cultures.

In our study, the most frequently hospitalized service was infectious diseases 88.8% bacteremia was observed in 30.7% of patients, and 1.2% had a mortal course. In the study by van Nieuwkoop et al. [15], the bacteremia rate was 27% and the mortality rate was 5%. In a study by Karakeçili et al [2], the mortality rate was 4.7%. The lower mortality rate in our study compared with the studies in the literature was attributed to the fact that the mortality data of patients referred to external centers could not be accessed and therefore could not be recorded.

Study Limitations

Our study has several limitations. First, this study was conducted at a single center with a small sample size. Some results may

differ among different populations. The results should be confirmed in future multicenter studies with large sample sizes. In our study, data about the operations performed by patients who underwent surgical operations.

Conclusion

In our study, the most common predisposing factors for the development of APN were not indicated and inappropriate antibiotic use, history of hospitalization within the last two weeks, chronic renal failure, and diabetes mellitus. APN may present as a spectrum ranging from a mild picture to urosepsis. The essential components of successful patient treatment and management are effective history taking and detailed identification of complicating factors. Awareness of these factors by emergency physicians can contribute positively to disease prognosis.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Trakya University Faculty of Medicine Scientific Research Ethics Committee (decision number: 1707, date: 12.10.2016) of our university before starting the study.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.B., M.B.S., Design: Ö.S., A.Y., Data Collection or Processing: S.B., Analysis or Interpretation: M.B.S., Ö.S., A.Y., Literature Search: S.B., Ö.S., Writing: S.B., M.B.S., A.Y.

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ORIGINAL RESEARCH

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Retrospective Analysis of Poisoning Cases Presenting to the Emergency Department After Drug Intake: Demographic Characteristics and Necessity of Antidote Use

Evren Dal, Suna Eraybar

University of Health Sciences Türkiye Bursa Faculty of Medicine, Bursa City Hospital, Department of Emergency Medicine, Bursa, Türkiye

Abstract

Objective: The primary objective of this epidemiological study was to systematically examine the demographic attributes of patients accessing the emergency department due to drug overdose. The study further aims to evaluate the imperative for hospitalization or intensive care and to meticulously scrutinize disparities in the clinical trajectory, specifically distinguishing between inadvertent and intentional substance ingestion.

Materials and Methods: Patients admitted to the emergency department because of drug intake were retrospectively evaluated. The analysis encompassed the evaluation of presenting symptoms and emergency department interventions. Parameters such as the duration of emergency department stay, blood tests conducted during the initial assessment, requested consultations, necessity for clinic or intensive care unit hospitalization, and administration of a specific antidote in the emergency setting were systematically examined. Additionally, the impact of antidote use on patient outcomes, as well as the correlation between antidote administration, hospitalization requirements, and subsequent follow-up for referred patients, were subjected to comparative analysis.

Results: Among the examined patient cohort, a predominant 156 individuals (89.7%) manifested a deliberate suicidal intent, while 34 patients (20.6%) had a documented history of psychiatric illness. It is noteworthy that a mere 3 patients (1.8%) were referred to our institution, and conspicuously, none of these cases warranted the administration of antidotes. In totality, the imperative for antidote utilization was identified in 15 patients (8.7%). A statistically significant differentiation emerged between admissions characterized as suicidal and accidental, particularly with regard to 28-day mortality (p=0.001), The mortality rate in cases of accidental admissions stood at 17.6%, exhibiting statistical significance. However, no statistically significant relationships were discerned between polypharmacy, antidote utilization, and 28-day mortality (p=0.164, p=0.246).

Conclusion: Identification of critically ill patients, consideration of specific antidote treatments, strategic determination of treatment options from the point of initial presentation, foresight into potential additional pathologies during follow-up, and recognition of the potential need for a multidisciplinary approach within the scope of third-tier health services collectively constitute integral facets of an effective and comprehensive treatment paradigm for cases involving drug overdose. These measures are essential for ensuring a nuanced and thorough approach to address the evolving clinical needs of affected individuals.

Keywords: Intoxication, drug-related intoxication, antidote use, emergency department

Introduction

Poisoning is a clinical picture that occurs as a result of substance intake intentionally or accidentally into the body. In acute poisoning, the fundamental objective of medical management, which often occurs in emergency departments, is to recognize the conditions that disrupt clinical stability, provide the necessary supportive treatment, and eliminate these toxic effects with specialized treatments when necessary. In our country, poisoning cases constitute approximately 0.5-2.1% of emergency room admissions, and therapeutic drugs (tricyclic antidepressants, analgesics, and antihypertensive drugs), and pesticides constitute the most common exposure groups [1,2].

Address for Correspondence: Evren Dal, University of Health Sciences Türkiye Bursa Faculty of Medicine, Bursa City Hospital, Department of Emergency Medicine, Bursa, Türkiye
E-mail: evrendal2000@yahoo.com **ORCID-ID:** orcid.org/0009-0003-7755-3703
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Poisoning cases may vary from region to region in terms of demographic characteristics, poisoning agents, frequency, and social characteristics. For instance, the rate of insecticide poisoning is 3.22% in the United States and 10% in Türkiye. Accordingly, various poisoning profiles should be determined for each country or region, and measures should be taken [3,4].

Mistakes in the hospital environment and unconscious drug use are among the causes of poisoning. In particular, overdose and unwanted intake of narcotics and recreational substances can cause poisoning. Suicidal drug use is when people take unwanted or toxic doses of drugs with the intention of ending their lives. Such suicide attempts represent a serious public health problem and have become a major health concern worldwide. Suicide is a complex situation resulting from a combination of psychosocial, emotional, economic, and environmental factors. Drugs are easily accessible for suicidal use, and they are therefore among the most preferred methods for suicide attempts.

Early recognition and treatment of poisoning are vital. When poisoning cases admitted to the emergency department in our country were analyzed, differences in the number of cases were observed. Because they are widely used and easily accessible, drugs are among the most common agents causing poisoning today. In order to shed light on the future planning and health policies of hospitals and especially emergency medicine clinics, information about demographic characteristics, active substances, and prognosis of poisoning cases is of great importance. Although poison counseling centers have been established in Türkiye to address the situation, data on drug poisoning are limited.

The clinical condition and symptoms of a patient presenting to a health center with a complaint of poisoning may vary due to several factors, including the dose of the agent, duration of intake, mode of intake, sex, age, body mass index, existing diseases, and first intervention before hospital admission. The necessity of antidote use is often questioned during the initial evaluation, and patients are referred if access to antidote is not available. This increases patient care costs, hospital occupancy rates, and the risk of hospital-acquired complications. Familiarization with the frequency of antidote use and active substances can improve the quality of patient care and prevent inappropriate referrals.

This regional epidemiological study aimed to examine the demographic data of patients presenting to the emergency department because of drug overdose, the need for hospitalization, or intensive care, and to review the differences in the clinical course of accidental or intentional drug intake. Simultaneously, the use of antidotes in the management of common poisonings is evaluated, and the frequency and diversity of antidote use in the general approach to poisonings is investigated. Within this scope, we aimed to define poisonings in the region, investigate the underlying causes, reveal their effects on mortality and morbidity, and contribute to the literature on the prevention of poisonings based on the information obtained in this direction.

Materials and Methods

Patients evaluated in the emergency department of our hospital between January 01, 2022 and March 31, 2023 for drug intake were retrospectively screened. In total, 22,000 patient files were accessed by examining forensic case registries within the specified period. Among these patients, the data of all patients recorded as “suicide by drug” and “poisoning by drug” were analyzed through the hospital automation system. In the patient diagnosis grouping by scanning forensic reports, 21655 patients were recorded for reasons other than suicide, such as vehicular traffic accidents, falling from height, and assault. In the specified time interval, 345 patients were evaluated because of drug-mediated suicidal attempts. 56 patients were excluded from the study because they could not be accessed, 114 patients were excluded because they were over 18 years of age, and 2 for being pregnant. A total of 173 patients were included in the study (Figure 1).

Ethics committee approval was obtained from Bursa City Hospital Clinical Research Ethics Committee during the planning phase of the study (decision number: 2023-9/6, date: 24.05.2023). Because the study was conducted retrospectively, patient data were obtained from the files on the hospital automation system, and no informed consent form was provided. The patient data were examined only by the responsible investigators, who took into account patient privacy. Age, gender, time of presentation to the emergency department, mode of presentation, accidental or intentional drug intake, and which drug was taken were recorded retrospectively. The presenting symptoms, blood test results ordered during the initial evaluation in the emergency department, and emergency department treatment were evaluated. The length of stay in the emergency department, the number of consultations requested, clinic or intensive care unit (ICU) hospitalization requirements, and the use of a specific antidote in the emergency department were further evaluated. The effects of antidote use on patient outcomes and the need for hospitalization and follow-up in patients evaluated as a result of referrals were compared. Patients younger than 18 years, pregnant women, and those for whom study data were not available were excluded.

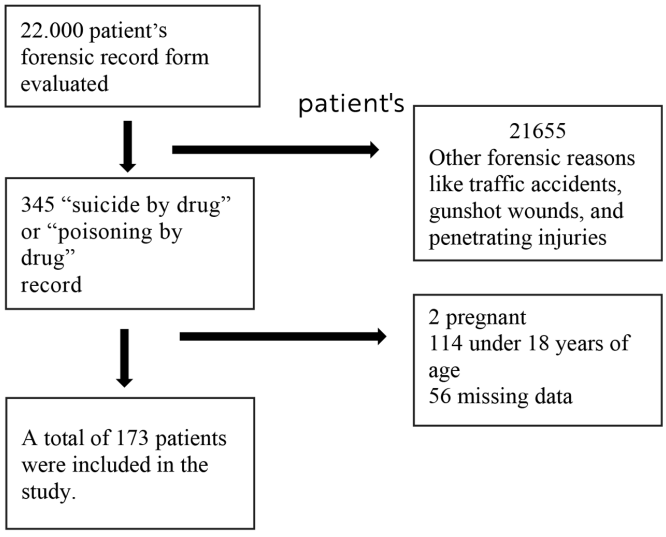

Figure 1. Flow chart of study

Statistical Analysis

The statistical analyses of the study were performed using the SPSS 29.0 package. Descriptive statistics of quantitative variables are presented as mean, standard deviation, median, minimum, and maximum values, whereas qualitative variables are presented as frequency and percentage. Conformity of quantitative variables to normal distribution was tested using the Shapiro-Wilk test. The Fisher chi-square and Fisher-Freeman-Halton chi-square tests were used to compare qualitative variables between independent groups. The relationships between quantitative variables were analyzed using the Mann-Whitney U test. In all statistical comparisons in the study, a p-value 0.05 was considered statistically significant.

Results

The mean age of the 173 patients included in the study was 32.44 min: 18-max: 73, and 108 (62.1%) patients were female. It was observed that 40.8% of the admissions occurred in winter months and 53.9% of the admissions occurred between 16:00-00:00. While 156 (89.7%) of the patients had suicidal intent, whereas 34 (20.6%) had a history of psychiatric illness. In 32 (96.9%) patients with a history of psychiatric illness, the intake was suicidal.

Only 3 (1.8%) patients were referred to our hospital, and none of these patients had any indication for antidote therapy. Six patients were administered acetyl cysteine for paracetamol poisoning, 3 patients were administered calcium for calcium channel blocker, 3 patients were administered ethanol for methanol poisoning, and 3 patients were administered flumazenil for benzodiazepine poisoning. In total, the need for antidote use was present in 15 patients (8.7%). The demographic characteristics of the patients and their presentation to the emergency department are summarized in Table 1.

When the presenting symptoms of the patients were analyzed, the most common symptoms were found to be nausea and vomiting (8.6%), confusion (8.6%), dizziness (4.6%), and agitation (3.4%). In the analysis performed to evaluate the variation of admission symptoms in terms of whether the intake was accidental or suicidal, the rate of dizziness was 33.3% in accidental intakes but 1.3% in suicidal intakes, which was statistically significant ($p<0.001^a$). Similarly, statistically significant differences were found in the incidence of headache, agitation, and confusion ($p=0.001^a$), ($p=0.015^a$) ($p<0.001^a$) (Table 2).

Accidental or suicidal drug intake history, need for antidote or hemodialysis, outcome of treatment in the emergency department, and 28-day mortality were analyzed. There was a statistically significant difference in terms of sex between those who reasoned for intake was suicidal and those who took it accidentally ($p=0.017^a$). The rate of suicidal admission was significantly higher in women than in men. There was a statistically significant difference between suicidal and accidental admissions in terms of 28-day mortality ($p=0.001^a$). The mortality rate was 17.6% in accidental admissions, which was higher than that for suicidal use, which was statistically significant (Table 3).

When laboratory values were analyzed in terms of suicidal or accidental intake, Aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), and potassium values were significantly lower, whereas creatinine and calcium ($p=0.019^a$) values were significantly higher in those with suicidal intake ($p=0.005^a$) ($p=0.020^a$) ($p=0.005^a$) ($p=0.019^a$).

In the comparison of blood gas analysis, base deficit, lactate, and anion gap levels were found to be higher in accidental intake, and this difference was statistically significant ($p\leq0.001^a$) ($p=0.003^a$) ($p=0.031^a$). Table 4 summarizes the laboratory values of the patients and their relationship with the mode of intake.

When the types of drugs causing intoxication in patients were analyzed, antidepressant drugs were the most common cause of intoxication in 53 patients (30.5%), whereas 84 (48.6%) of the patients were found to have polypharmacy (Table 5).

There was no statistically significant relationship between polypharmacy, antidote use, and 28-day mortality ($p=0.164^a$) ($p=0.246^a$) (Table 5).

While 30 (17.3%) patients were followed up in the ICU (17%) and 71 (41.6%) patients were followed up in internal medicine clinics, mortality was seen in 3 patients (1.73%) within the first 28 days during ICU follow-up.

Table 1. Demographic data of the patients and time of presentation to the emergency department			
		n	%
Season	Winter (December - January - February)	71	40.8
	Spring (March - April - May)	31	17.8
	Summer (June - July - August)	32	18.4
	Autumn (September - October - November)	40	23.0
Time of presentation	08-16	30	18.2
	16-00	89	53.9
	00-08	46	27.9
Referral	Yes	3	1.8
	No	162	98.2
Reason for intake	Suicidal	156	89.7
	Accidental	18	10.3
Gender	Male	66	37.9
	Female	108	62.1
Additional disease	No	122	70.1
	Yes	52	29.9
Psychiatric history	Yes	34	20.6
	No	131	79.4
Antidote	No	158	91.3
	Yes	15	8.7

Table 2. Reasons for drug intake and symptomatology				
		Suicidal	**Accidental**	**p**
Nausea/Vomiting	**No**	145 (92.9%)	14 (77.8%)	0.053[a]
	Yes	11 (7.1%)	4 (22.2%)	
Abdominal pain	**No**	155 (99.4%)	18 (100%)	1.000[a]
	Yes	1 (0.6%)	0 (0%)	
Dizziness	**No**	154 (98.7%)	12 (66.7%)	**<0.001[a]**
	Yes	2 (1.3%)	6 (33.3%)	
Headache	**No**	156 (100%)	15 (83.3%)	**0.001[a]**
	Yes	0 (0%)	3 (16.7%)	
Hallucination	**No**	155 (100%)	17 (94.4%)	0.104[a]
	Yes	0 (0%)	1 (5.6%)	
Agitation	**No**	153 (98.1%)	15 (83.3%)	**0.015[a]**
	Yes	3 (1.9%)	3 (16.7%)	
Confusion	**No**	149 (95.5%)	10 (55.6%)	**<0.001[a]**
	Yes	7 (4.5%)	8 (44.4%)	

[a]Fisher chi-square test

Discussion

Acute poisoning is one of the most serious medical emergencies worldwide, resulting in high morbidity and mortality rates, especially in developing countries. It is important because poisoning is mostly observed in young people, its frequency is increasing, it is life-threatening, causes permanent damage, and requires urgent intervention.

The approach to poisoning is similar in all emergency departments. The profiles of patients presenting to emergency departments may vary due to regional conditions, age range, and place of the individual in society.

In many studies, it has been reported that among patients presenting to emergency and ICUs, the female population is higher in both accidental and intentional poisoning cases, and this rate varies between 53 and 77%. In our study, similarly, the

Table 3. Relationship between drug intake patterns and treatment and outcome in the emergency department

		Suicidal	Accidental	p
Gender	Male	54 (34.6%)	12 (66.7%)	**0.017[a]**
	Female	102 (65.4%)	6 (33.3%)	
Hemodialysis	No	156 (100%)	8 (44.4%)	**<0.001[b]**
	Yes	0 (0%)	2 (11.1%)	
	Continuous hemodialysis	0 (0%)	8 (44.4%)	
Outcome	Discharged	11 (7.1%)	2 (11.8%)	N/A
	Clinical hospitalization	67 (42.9%)	4 (23.5%)	
	IC hospitalization	20 (12.8%)	2 (11.8%)	
	General IC hospitalization	2 (1.3%)	6 (35.3%)	
	Treatment refusal	49 (31.4%)	3 (17.6%)	
	Referral	5 (3.2%)	0 (0%)	
	Other	2 (1.3%)	0 (0%)	
	Yes	1 (1.4%)	0 (0%)	
Antidote	No	143 (91.7%)	15 (88.2%)	0.645[c]
	Yes	13 (8.3%)	2 (11.8%)	
28-day mortality	No	156 (100%)	14 (82.4%)	**0.001[c]**
	Yes	0 (0%)	3 (17.6%)	

[a]Yates chi--square test; [b]Pearson chi-square test; [c]Fisher chi-square test,
IC: Internal medicine

rate of female patients was 62.1%. We believe that reasons such as the socio-cultural structure in which women live, their close environment, and family pressure that may occur on females may trigger the tendency to attempt suicide with drugs and similar substances that can be easily accessed at home [5-8].

In a study conducted by Ödemiş et al. [9] on the distribution of drug intoxication cases according to the month of presentation, the highest presentation was observed in January (11.6%), with two peaks in January and September, and presentation to the emergency department was observed between 20.00 and 24.00. The general opinion in the literature is that suicide risk is higher in winter when air temperature and sunlight are low. This finding supports the fact that suicide attempts increase in winter months by pointing out that the increase in air temperature and sunlight intensity are negatively correlated with suicidality, whereas cloudy weather and high pressure are positively correlated. In our study, the most frequent admission was found in winter months, thereby reflected similar results. On the contrary, in another study conducted in our country, poisoning cases showed seasonal characteristics, most admissions were observed in the summer months (28.9%), and more than half of the admissions (55.2%) occurred between 20:00 and 08:00 [10].

In a large series of studies, it has been reported that although there is a history of accidental drug intake in the pediatric age group, the majority of adult patients have a history of suicidal drug intake. Studies conducted in our country also support these data and 82.4% of the cases having a history of drug intake due to suicide attempts [11]. In our study, the rate of suicidal drug intake was 89.7%, which supports the literature.

In our study, the most common drug group causing poisoning was antidepressants (30.5%). The antidepressant group (34.7%) also had a high rate in the study by Özdemir et al. [12]. In similar studies, the rates varied between 22.7% and 35.3% [12-14]. We believe that this high rate of poisoning cases is due to the fact that analgesic and anti-inflammatory agents and antidepressants are more easily accessible in our country as a result of their widespread use without prescription. In addition, we believe that the use of antipsychotic or antidepressant drugs due to the psychiatric problems of patients makes it possible for them to use these drugs for suicide attempts. Our rate of patients with a psychiatric history was 20.6%, which was reported to be 34.1%-35.3% in similar studies [13,14].

In the analysis of Akgün et al. [15], the most common complaints in cases of acute poisoning were central nervous system symptoms, such as confusion, tendency to sleep, convulsions, and dizziness (75.7%), while gastrointestinal symptoms, such as nausea and vomiting, ranked second with 24.3%. Similarly, neurologic and gastrointestinal symptoms, such as nausea and vomiting, were at the forefront of our study. When we evaluated the relationship between symptoms and the reasons for drug intake, dizziness, headache, agitation, and confusion were higher in accidental intake.

Table 4. Relationship between patients' laboratory values and mode of intake

	Suicidal	Accidental	p
Blood sugar	107.59±36.35 98 (60-419)	131.44±67.08 109 (60-315)	0.290[a]
BUN	10.46 ± 3.57 9.70 (107.59±36.35)	10.53±4.85 10.65 (4.20-21.60)	0.934[a]
Creatinine	1.31±7.07 0.72 (0.46-89)	0.97±0.37 0.93 (0.49-1.71)	**0.019[a]**
AST	19.38±7.00 18 (9-45)	39.60±37.91 25 (0.70-143.5)	**0.005[a]**
ALT	18.47±12.44 14.5 (6-81)	35.53±36.89 24 (7-159)	**0.020[a]**
Na	138.14±11.29 139 (0.1-143)	133.65±19.89 138 (57-142)	0.276[a]
Potassium	4.03±0.34 4 (3.2-4.9)	4.48±0.98 4.40 (2.6-6.9)	**0.005[a]**
Calcium	9.52±0.44 9.5 (8-11.20)	9.11±0.67 9.30 (8.10-10.30)	**0.019[a]**
pH	7.38±0.04 7.38 (7.22-7.50)	7.20±0.26 7.30 (6.62-7.47)	**0.002[a]**
Base deficit	1.26±3.11 1.20 (-10-10.5)	13.45±11.36 6.50 (3-32.60)	**<0.00[a]**
Lactate	1.66±1.07 1.30 (0.5-7.20)	3.55±2.69 2.70 (0.7-9.80)	**0.003[a]**
Anion Gap	9.75±3.68 9.15 (3.20-23.60)	20.21±13.51 18.90 (5.70-47.80)	**0.031[a]**
Blood gas bicarbonate	26.35±3.19 26.10 (17.40-39.70)	18.58±11.29 22.20 (2.70-31.40)	0.084[a]

[a]Mann-Whitney U test, *Mean±standard deviation/median (min.-max.),

BUN: Blood urea nitrogen, AST: Aspartat aminotransferaz, ALT: Alanin aminotransferaz, Na: Sodium, min.-max.: Minimum-maximum

Table 5. Relationship between drug type and mortality

		n		%
Drug types	**Analgesic/antipyretic**	48		27.6
	Antidepressant	53		30.5
	Antibiotics	15		8.6
	Antiepileptics	3		1.7
	Anxiolytics	10		5.7
	Antihypertensive	13		7.5
	Antiarrhythmics	2		1.1
	Other	29		16.7
Drug intake	**Single**	89		51.4
	Multiple	84		48.6
		Drug intake		
		Single	**Multiple**	
Antidote	**No**	78 (89.7%)	79 (96.3%)	0.164[a]
	Yes	9 (10.3%)	3 (3.7%)	
28-day mortality	**No**	86 (96.6%)	84 (100%)	0.246[a]
	Yes	3 (3.4%)	0 (0%)	

[a]Yates chi-square test

We believe that this difference may be a result of increased anxiety about accidental or intentional intake or a result of ignoring affective disorders and complaints about suicidal intake.

Routine biochemical parameters used during the evaluation of patients in the emergency department and blood gas analysis, which are particularly useful in guiding the decision on severity, are often used effectively in treatment follow-up, not in the diagnostic process. In our analysis, AST, ALT, and potassium values among biochemical parameters were found to be high in accidental intake. Accidental intake may be associated with an increase in the amount of intake or prolonged admission time, contrary to planned interventions. In blood gas analysis, parameters such as lactate and base deficit, which indicate impaired tissue perfusion, were also found to be elevated in accidental intake. This difference reflected the fact that most of our study patients presented with more serious clinical symptoms as a result of accidental intake, as we encountered in our three patients who died. The reflection of metabolic changes in biochemical and blood gas parameters as a result of intoxication may be an important indicator of impaired tissue perfusion. Increased liver function tests and elevated potassium levels after accidental ingestion may reflect, in particular, renal and hepatic tissue involvement. In cases of suicidal intake, a higher drug dose or earlier presentation may reflect the treatment administered.

The primary and first goal of treatment for acute poisoning is to eliminate threats related to vital signs, correct the symptoms and pathological conditions of the patient, and reduce the complaints, which constitute the basis of supportive treatment. Activated charcoal, gastric lavage, and the use of active drugs containing known antidotes are the first steps of treatment. In addition to supportive treatment, specific antidote treatment was administered to 28% of patients. N acetyl cysteine (NAC) was the most commonly used antidote in 59.1% of patients receiving antidote treatment. Atropine, PAM, vitamin K, fresh frozen plasma, and desferoxamine have also been reported as antidotes [16]. In our study, the rate of antidote use was 6.35% (n=11) and the most commonly used antidotes were NAC and calcium. The data of our study showed that antidote treatment in the emergency management of patients with poisoning is important only for specific agents, and the majority of these cases can be managed with supportive treatment.

In our study, 17.4% of patients were followed up in the ICU, and the mortality rate was 1.73%. Suicidal intake may be the result of underlying psychological stress and completion of the attempt with more easily accessible drugs or earlier presentation. In the literature, there are data showing that 5.5-12.8% of drug intoxication presenting to the emergency department are followed up in ICU [17,18]. In our country, this rate can go up to 37% [19]. Although in-hospital mortality is around 33% in certain patient groups in ICU patients, this rate is only 2.1% in those with drug intoxication [17,20,21].

In most of the drug intoxications presenting to the ICU for various reasons, no treatment (such as mechanical ventilation, hemodialysis, or vasopressor therapy) is applied to support vital functions, and patients are hospitalized only for observation [17,18]. Despite the low mortality rates, relatively high rates of ICU hospitalization may be considered logical in terms of patient safety due to the concern that patients may develop severe symptoms in the following hours; however, this is not acceptable both economically and in terms of unnecessary intensive care bed occupation. Although most patients had no significant symptoms, ICU admission was requested for observation given the concern that life-threatening complications might occur later. Appropriate emergency department follow-up for the management of poisoning patients, prediction of serious poisonings specific to active substances, early recognition of patients requiring antidotes, and referral to appropriate treatment may prevent unnecessary hospitalization indications.

Study Limitations

The first limitation of our study was that it was conducted retrospectively and in a single center. For this reason, patient data may be lost at the point of access. Second, data loss due to missing demographic data in the patient files may not reflect the actual number of patients. Additionally, we considered the subgroup of drugs that direct the patient's clinic to multiple drug intake as pimer, so we could not obtain any data on drug interactions.

Conclusion

Supportive treatment is essential for the evaluation of poisoning cases in emergency departments. It is important to ensure appropriate stabilization of patients and to decide on the necessary follow-up and treatment periods. Recognizing the critical patient and evaluating the need for specific antidote treatments, determining the appropriate treatment options from the moment of presentation at this point, predicting additional pathologies that may develop during follow-up, and determining the need for a multidisciplinary approach within the scope of 3rd step health services, if necessary, constitute effective treatment steps. In this way, patients can be ensured to receive effective treatment at appropriate healthcare institutions while preventing inappropriate referral requests.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Bursa City Hospital Clinical Research Ethics

Committee of our hospital (decision number: 2023-9/6, date: 24.05.2023) during the study planning phase.

Informed Consent: The study was conducted retrospectively, patient data were obtained from the files on the hospital automation system, and no informed consent form was provided.

Footnotes

Authorship Contributions

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

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ORIGINAL RESEARCH

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The Role of Local Anesthesia Methods on the Development of Wound Infection at Upper Extremity Lacerations

Oğuzhan Demir[1], Serhad Ömercikoğlu[1], Erhan Altunbaş[2], Eren Onur Karavin[1], Mustafa Altun[1], Haldun Akoğlu[2], Özge Onur[2], Arzu Denizbaşı Altınok[2]

[1]*Marmara University Pendik Training and Research Hospital, Department of Emergency Medicine, İstanbul, Türkiye*
[2]*Marmara University Faculty of Medicine, Department of Emergency Medicine, İstanbul, Türkiye*

Abstract

Objective: This study was designed to identify whether the application method of a local anesthetic agent before suturing affects the development of wound infection.

Materials and Methods: Adult patients with upper extremity lacerations were randomized into two groups if they required wound repair with simple sutures. Direct infiltration of a local anesthetic was performed in patients in Group 1, whereas parallel margin infiltration was performed in patients in Group 2. After 1 week, patients were evaluated clinically by different physicians who were blinded to the patients' wound infection.

Results: A total of 164 patients were enrolled in the study, but 144 were available for data analysis. 4 patients [1 patient was in group 1 (1/73, 1.4%), 3 patients were in group 2 (3/71, 4.2%)] were found to have an infection during the follow-up visit.

Conclusion: The application method of the local anesthetic agent before suturing does not affect the development of wound infection. There were no statistically significant differences related to the development of infection between the two methods.

Keywords: Local anesthesia, wound infection, suturation, laceration

Introduction

In our country, there are over 100 million visits to emergency departments (EDs) annually, and most of these are for traumas [1]. Lacerations and open wounds are the third most common cause of ED admissions in the United States, with an average of 6 million visits annually. Most of these injuries, which are on head or extremities, caused by blunt traumas. The rest are caused by sharp objects in the form of metal, glass, and wood [2,3]. Traumatic lacerations typically occur at the face, hairy skin, and hands, and generally, in young adult males. Wounds seen in children differ from adults. Lacerations in pediatric patients are usually linear lesions found at the head. Additionally, blunt traumas and dirty wounds are less common in pediatric patients [4].

The purpose of laceration management is to prevent wound infections and to provide functional and esthetically satisfactory wound healing. Risk factors of wound infections are separated into the following groups:

1) Factors related to the wound: mechanism of injury, type, and degree of contamination, time from injury to treatment, presence of the foreign body, deep lesions causing soft tissue trauma, and lacerations caused by ice or glass;

2) Factors related to the patient: diabetes mellitus, obesity, peripheral arterial diseases, malnutrition, chronic renal disease, immunosuppressor use, predisposition to keloid formation, and connective tissue disorders [5]. The effects of time on wound suturation, choice of suturing material, and use of irrigants and cleaning solutions are still unclear. The standard

Address for Correspondence: Oğuzhan Demir, Marmara University Pendik Training and Research Hospital, Department of Emergency Medicine, İstanbul, Türkiye
E-mail: droguzhandemir@gmail.com **ORCID-ID:** orcid.org/0000-0002-9854-0050
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management of wounds includes wound cleaning, irrigation and appropriate dressing [6]. Although controversial, routine prophylactic antibiotic use is not recommended [7].

Although there are different methods, such as tissue adhesives, skin staples, and secondary healing for laceration repair, most lacerations require primary suturing, which is still the most commonly used method to cover was designed [4]. The duration of wound healing after primary suturing changes from patient to patient. According to previous reports, the possible factors affecting wound healing time are age, sex, presence of immunosuppression, sight of the foreign body, antibiotic use, and location and depth of the wound [4,8].

Many *in vivo* and *in vitro* studies have shown that local anesthetics can also prevent surgical site infections. Noda et al. [9] showed in a recent study that local anesthetics had bactericidal activity at standard clinical concentrations. Aydin et al. [10] investigated the antimicrobial activity of local anesthetics ropivacaine, bupivacaine, lidocaine, and prilocaine on various pathogens and showed that lidocaine and prilocaine had stronger antimicrobial effects than the other two local anesthetics. However, as we know, no study has investigated whether different methods of applying local anesthetics have an effect on the development of infection at the surgical site [9-11]. This study was designed to determine the effect of a local anesthetic application method on the development of wound infection.

Materials and Methods

This is a single-center, prospective, 1:1 randomized clinical trial with parallel groups. The study was approved by the institutional Marmara University Faculty of Medicine Clinical Research Ethics Committee (decision number: 09.2017.419, date: 02.06.2017). An informed written consent form was obtained from all participants. Our ED is a large medical center with approximately 350,000 visits per year. The sample of this study was enrolled from 03.06.2017 to 10.09.2018.

Patients who presented to the ED with upper extremity lacerations and met the following criteria were included in the study:

1) >18 years old

2) No allergic reaction to local anesthetics

3) No tendon or nerve laceration requiring intervention by hand surgeons

4) No antibiotic use for the last week

5) Non-human or animal bite wounds

6) No diabetes mellitus or other immunosuppressed situations

Patients who did not meet the above criteria were not included in the study. If there was a participant who did not come to follow-up or revoked his consent for participation in the study, he was excluded. Because the proportion of patients with devitalized tissue was low, subgroup analysis could not be performed because statistically significant results could not be obtained.

Study Protocol

This study was conducted by a single researcher. Patients who administered on researchers duty hours and met the inclusion criteria for upper extremity laceration were examined by ED physicians and were decided for primary suturing in the study. Every patient was evaluated for a foreign body using X-ray. The patients' wounds were recorded as either contaminated or non-contaminated. Every wound was cleansed with 200 cc normal saline, and materials such as soil and clotted blood were removed from the wound as much as possible. Devitalized tissues were debrided, and foreign bodies were removed if necessary. Topical anesthesia was not administered to the patients. After randomization, a local infiltration method was applied to the patients whose groups were determined. Prilocaine was used as the local anesthetic in all patients.

For Group 1 (direct infiltration into the wound), the injector was inserted into the superficial fascia (subcutaneous fat) from the open wound to the dermis, and a small bolus anesthetic solution was injected. The needle was removed, and another bolus was injected into an area immediately adjacent to the edge of the anesthesia of the previous injection. This procedure was repeated until all edges and corners of the wound were anesthetized.

For Group 2 (parallel margin infiltration), the injector, starting from the end of the laceration, was inserted into the intact skin of the wound and pushed forward parallel to the junction of the dermis and superficial fascia. After aspiration, the needle was pulled from the tissue plane to the entrance site, and slow anesthesia injections were performed. The needle was then re-inserted at the end of the first port at which the anesthetic effect had begun, and the procedure was repeated. This re-intervention and injections were continued on all sides of the wound until complete pain control was achieved.

After the administration of local anesthesia, simple interrupted sutures were applied to each patient. The suture material was non-absorbable polypropylene. After suturation, topical antibiotic containing mupirocin was applied to the wound, and the wound was closed with a sterile gauze bandage. Each patient was told that the wound should remain closed for at least 48 hours, and after that, it should remain dry. They were told that they had to dress wound 3 times a day with the same topical antibiotic containing mupirocin until they came to

control. No oral or parenteral antibiotics were prescribed to the patients. Tetanus prophylaxis was performed if necessary. Each patient was given a detailed form to follow up on wound care and was called for follow-up after 7 days. Each patient confirmed that they followed the wound care instructions during follow-up, and those who did not comply were excluded from the study. Regarding signs of infection, check-in patients were evaluated by emergency specialists who were blinded to the groups of patients.

Outcome Measures

The primary outcome of the study was the presence of infection in patients coming for control and the outcome measure was the difference in the rates of infection. The presence of any of the following criteria, which were created by Dire et al. [12] and used in another study, was considered sufficient for evidence of infection: fever and heat increase, erythema, edema, induration, sensitivity at the wound site, discharge, adenopathy, or development of lymphangitis. As secondary outcome measures, the presence of contamination, laceration length, depth, number, location, gender, age, and non-follow-up rates were compared between the assigned groups.

Statistical Analysis

In this study, we collected all cases that administered on researchers duty hours. Randomization was performed by a non-researcher lecturer who was interested in statistics and planning clinical trials via Research Randomizer software (http://www.researchrandomizer.org) and used 1:1 allocation. A randomization order list was prepared, and a consecutive plan was created with each number in an envelope. The group to which each patient would be assigned the next envelope extraction was determined during the patient's examination. Patient data were collected by ED physicians.

The suitability of continuous variables for normal distribution was evaluated using the Shapiro-Wilk test. Accordingly, in our study, since there were no continuous variables that fit the normal distribution, all were reported as median and interquartile range (IQR). Categorical variables were expressed by frequency and number. Mann-Whitney U test was used to compare continuous variables between different groups. The chi-square test was used to compare categorical variables between different groups. In addition to the analysis in which patients who were dropped from follow-up for the primary outcome were excluded, a secondary analysis (intent-to-treat) was also performed in which these patients were evaluated in the randomized group, and all those who were lost were considered infected. The Medcalc v19 statistical package program (Medcalc bvba, Belgium) was used for statistical analysis, and the Jamovi v0.9 package was used for graphics.

Results

A total of 164 patients were included and randomized in the study. After randomization, the study included 81 patients in Group 1 and 83 patients in Group 2. In Group 1, 8 subjects did not come to control on the specified date, 1 subject in Group 2 revoked consent during the transaction; and 11 subjects in Group 2 did not come to control on the specified date. All of these subjects could not be included in the primary analysis. After excluding subjects, there were 144 patients, 73 patients in Group 1 and 71 in Group 2, for primary analysis and 163 patients, 81 patients in Group 1 and 82 in Group 2, for secondary analysis (intent-to-treat analysis) in the study. Detailed information can be found in the patient flow chart (Figure 1).

Demographical Characteristics

A total of 163 patients were included in the study [median age: 35.0 years (IQR: 26.0-48.0)]. The median age was 35.0 years (IQR: 23.0-47.0) for 81 subjects in Group 1 and 35.0 years (IQR: 28.0-50.0) for 82 subjects in Group 2. There were no statistically significant differences between the median ages of the groups (p=0.4609). The number of male patients was 132 (81.0%) in total, 63 (77.8%) in Group 1, and 69 (84.1%) in Group 2. There were no statistically significant differences between the groups in terms of gender distribution (p=0.3017). The main characteristics of the enrolled patients were itemized in Table 1.

Wound Characteristics

The median number of lacerations requiring suturing in the upper extremities among the 163 patients included in the study was 1 (IQR: 1-1). The median number of lacerations in Groups 1 and 2 was 1 (IQR: 1-1). There was no statistically significant difference between the groups in the number of laceration (p=0.6365). Twenty-two of the 163 patients (13.5%) had lacerations requiring multiple sutures. Multiple lacerations occurred in 10 patients (12.3%) in Group 1 and 12 patients (14.6%) in Group 2. No statistically significant intergroup difference was observed regarding the rates of multiple laceration rates (p=0.6699).

The total number of patients who had only skin laceration and no subcutaneous tissue damage was 91 (55.8%). Forty four patients (54.3%) in Group 1 and 47 patients (57.3%) patients in Group 2 had only skin lacerations. There were no statistically significant differences between the groups in terms of superficial and deep laceration rates when grouped by laceration depth (p=0.7010).

The median length of lacerations in the 163 patients included in the study was 2.80 cm (IQR: 2.00-3.40). The median length of the lacerations of the patients in Group 1 was 3.00 cm (IQR: 2.00-4.05), and the median length of the lacerations of

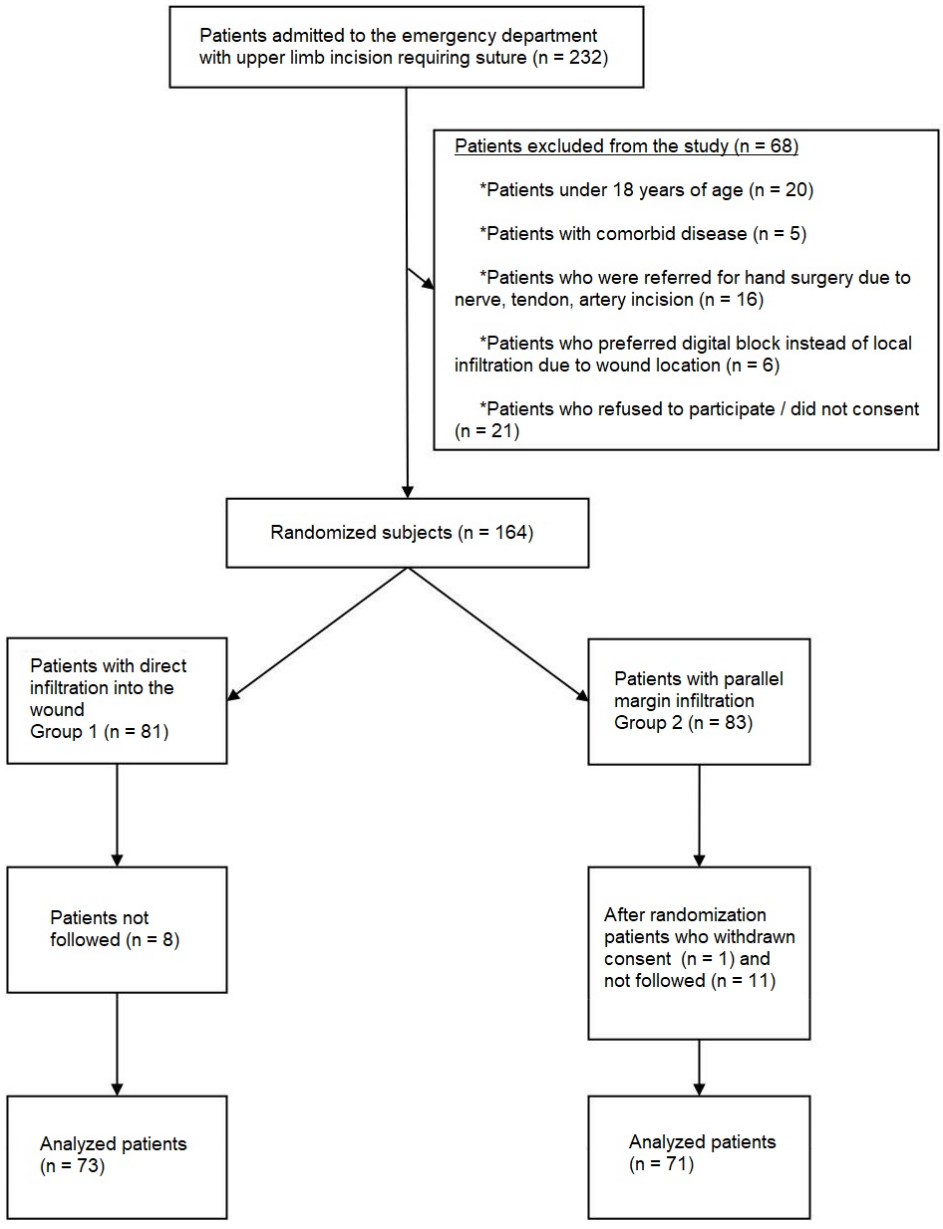

Figure 1. Patient flow chart

the patients in Group 2 was 2.50 cm (IQR: 2.00-3.20). There were no significant differences between the groups in terms of laceration length (p=0.1429).

Incisions were made in the finger in 83 (50.9%) of 163 patients, in the hand in 44 (27.0%), in the wrist in 15 (9.2%), in the forearm in 20 (12.3%), and in the arm in 1 (0.6%). The distribution of lacerations according to anatomical locations is presented in Table 1. There was no statistically significant difference between the groups in terms of the region in which accuracy was found (p=0.6894).

According to wound evaluation at admission, the wounds of 31 patients (19.0%) were contaminated. Fifteen (18.5%) of the patients in Group 1 and 16 (19.5%) of the patients in Group 2 had contaminated wounds. No statistically significant differences were found between the groups in terms of contamination rates (p=0.8720).

Outcomes

Nineteen (11.7%) of the 163 patients included in the study did not attend the control examination. In Group 1, the number of patients who did not come to control was 8 (9.9%), whereas, in Group 2, 11 patients (13.4%) were not present. There were no statistically significant differences between the groups in terms of non-control patients (p=0.4829).

Infection findings were detected in 4 (2.8%) of 144 patients who visited the control center and underwent primary analysis. Infection findings were detected in 1 patient (1.4%) in Group 1

Table 1. The main characteristics of the enrolled patients

Variable		Total (n=163)	Group 1 (n=81)	Group 2 (n=82)	p
Age (years)		35.0 (26.0-48.0)	35.0 (23.0-47.0)	35.0 (28.0-50.0)	0.4609*
Male gender, n (%)		132 (81.0)	63 (77.8)	69 (84.1)	0.3017**
Number of lacerations		1 (1-1)	1 (1-1)	1 (1-1)	0.6365**
Rate of patients with multiple wounds, n (%)		22 (13.5)	10 (12.3)	12 (14.6)	0.6699**
Rate of patients with only skin laceration, n (%)		91 (55.8)	44 (54.3)	47 (57.3)	0.7010**
Length of (cm)		2.80 (2.00-3.40)	3.00 (2.00-4.05)	2.50 (2.00-3.20)	0.1429*
Location of wound	Finger, n (%)	83 (50.9)	39 (47.0)	44 (53.0)	0.6894**
	Hand, n (%)	44 (27.0)	23 (52.3)	21 (47.7)	
	Wrist, n (%)	15 (9.2)	7 (46.7)	8 (53.3)	
	Forearm, n (%)	20 (12.3)	12 (60.0)	8 (40.0)	
	Arm, n (%)	1 (0.6)	0 (0.0)	1 (100.0)	
Contaminated wounds, n (%)		31 (19.0)	15 (18.5)	16 (19.5)	0.8720**
Uncontrolled patients, n (%)		19 (11.7)	8 (9.9)	11 (13.4)	0.4829**
Primary Analysis		**Total (n=144)**	**Group 1 (n=73)**	**Group 2 (n=71)**	**p**
Presence of infection, n (%)		4 (2.8)	1 (1.4)	3 (4.2)	0.2989**
Secondary Analysis		**Total (n=163)**	**Group 1 (n=81)**	**Group 2 (n=82)**	**p**
Presence of infection, n (%) (intent-to-treat analysis)		23 (14.1)	9 (11.1)	14 (17.1)	0.2758**

Data are presented as median (IQR) or n (%), Medians and IQRs; IQR: Interquartile range,
*Mann-Whitney U test; **Chi-square test

and 3 patients (4.2%) in Group 2, but no statistically significant difference was found between the groups in terms of infection rate (p=0.2989).

Data of 19 patients who were randomized to the groups but did not come to the control group were evaluated for bias risk by secondary analysis. Accordingly, it was determined that the infection rates between the groups were not statistically significant (11.1%-17.1%, p=0.2758) even if all patients who did not come to the control were infected. The outcome characteristics of the study are summarized in Table 1.

Discussion

Traumatic extremity lacerations are among the most common admissions to the ED. Although there are different methods for incision repair, primary suturation remains the most commonly used method. Local anesthetics are usually used to reduce pain before the primary suturing [11,13]. The results of numerous previous *in vitro* and *in vivo* studies have also proven that local anesthetics play an important role in the potential prevention and treatment of surgical site infections. However, as we know, there has been no study on whether different methods of applying local anesthetics have an effect on the development of infection at the surgical site. Therefore, this study aimed to compare the two most commonly used local anesthetic administration methods, whether there was a difference between them in terms of infection development. As a result of the study, no significant difference was found between local anesthesia methods in terms of wound infection development.

Aydin et al. [10] investigated the antimicrobial activity of local anesthetics ropivacaine, bupivacaine, lidocaine, and prilocaine against various pathogens such as *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Candida albicans*. Of the four drugs tested, lidocaine and prilocaine had the strongest antimicrobial activity; both inhibited the growth of all pathogens tested at anesthetic concentrations of 2%; prilocaine at a concentration of 1% inhibited the growth of *E. coli, S. aureus,* and *P. aeruginosa*, whereas 1% lidocaine inhibited only *P. aeruginosa*.

Although there are many studies about the development of infection after wound management and laceration repair in the ED, we have not encountered a previous study that compared two local anesthesia methods in terms of infection development [9,10,12,14,15]. Most of the studies are old, and due to the limited number of patients, strong results could not be obtained. To appropriately evaluate the development

of wound infection correctly, it would be appropriate to work in larger groups. The importance of our study, which has the largest working group among these studies, emerges at this point.

In many studies, the relationship between prophylactic antibiotic use and wound infection has been investigated, and no statistically significant difference was observed in the development of infection between patients receiving prophylactic antibiotics and placebo or prophylactic antibiotics. In the majority of studies, similar results were found for infection rates (2.8%). In general, the rate of wound infection was 1-5% in the literature [14,16]. In some studies, patients with diabetes mellitus were not excluded from the study, and these patients were among those who developed wound infection [14,16]. Although there are similar results, our study found a relatively lower infection rate compared with other studies [14]. This may have been due to the exclusion of patients with diabetes from our study. However, in one study, the infection rate was 9.9% in all patients, and the difference between the two groups receiving prophylaxis and the placebo group (infection rates: 5.5%, 4.5%, 12.1%, respectively) was statistically significant (p=0.0018). In this study, not only upper extremity incisions but also other body injuries were performed, and no topical antibiotics were administered to the patients. These may be some of the reasons for the higher rates of wound infection compared to our study [12].

In the study of Roodsari et al. [14] the median age was 28 years; 24.7 years in the study of Hood et al. [15]; 17.1-19.9 years of the range of 4 different groups in the study of Dire et al. [12]; and 40 years in the study of Berwald et al. [16] In the present study, only patients aged over 18 years were included, and the median age was 35.0 (IQR: 26.0-48.0) years. In the first three studies, the median age was found to be lower than that of our study because patients under 18 years were also included in these studies. According to the study design, age groups vary significantly, but patients with laceration are a relatively young population. In the abovementioned studies, male sex ratios were 64%, 46%, 70%, and 71%, respectively. In our study, we found that the male proportion was 81%. In all studies, it is seen that the male sex ratio is higher. The median wound lengths in the groups were 2-2.5 cm; 2.5-3.5 cm; 2.4-2.7 cm; and 1.5-2 cm, respectively. In our study, the median wound length was 2.80 cm (IQR: 2.00-3.40) and was consistent with other studies [12,14,16]. In the study of Hood et al. [15]. The incidence of superficial incisions was found to be 53% among all patients, and it was found to be 55% in our study. The results of both studies were consistent regarding the depth of the incision.

Study Limitations

Our study was conducted at a single center in a tertiary referral hospital. The analysis of the study was performed by a single researcher to avoid bias among the researchers. Different results may be obtained in a multicenter study with more than one physician and more patients. As for the design of the study, it is not possible for the physician conducting the study to be blind to the patients. This can create bias. During the follow-up period after wound repair, although some patients follow the instructions for wound care, not all patients can maintain the same hygiene and dryness of the wound site. The physicians who evaluated the patients when they came for control were residents and specialist physicians, and all their knowledge and skills were accepted at the same level. The criteria for determining the presence of infection were ascertained before the study began. However, there may be differences in infection decision-making because the physicians-evaluating patients are different people. This is another limitation of our study.

Conclusion

In this study, we sought to answer the question of whether local anesthetics are associated with the development of wound infection according to the method of administration. Although there have been many studies on wound care, we could not find any studies on this topic in the literature. In our study, we found no statistical differences related to the development of infection between the two different methods, and the total infection rates obtained as a result of our study were similar to those of previous studies.

Ethics

Ethics Committee Approval: The study was approved by the institutional Marmara University Faculty of Medicine Clinical Research Ethics Committee (protocol number: 09.2017.419, date: 02.06.2017).

Informed Consent: An informed written consent form was obtained from all participants.

Footnotes

Authorship Contributions

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

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

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ORIGINAL RESEARCH

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Effect of Biomarkers on Predicting Mortality in COVID-19 Pneumonias: A Retrospective Clinical Study

Tamer Durdu, Habibe Selmin Özensoy, Hakan Oğuztürk

University of Health Sciences Türkiye, Ankara City Hospital, Clinic of Emergency Medicine, Ankara, Türkiye

Abstract

Objective: Coronavirus disease-2019 (COVID-19) remains a significant challenge in emergency services worldwide. This study investigated the relationship between hematocrit (Htc), hemoglobin (Hb), amylase, lactate, and interleukin 6 (IL-6) levels and hospitalization and mortality in patients diagnosed with COVID-19.

Materials and Methods: Htc, Hb, amylase, lipase, lactate, and Interleukin 6 (IL-6) levels of patients with a positive COVID-19 polymerase chain reaction (PCR) test (Bio-speedy® Severe acute respiratory syndrome-Coronavirus-2 Triple Gene Reverse transcription quantitative PCR, Türkiye) who presented to the emergency department were analyzed. Hospitalizations and short-term (28 days) mortality were retrospectively examined. The data were analyzed using SPSS for Windows 20.0. Normality analysis of continuous data was conducted using the Shapiro-Wilk test. Multiple logistic regression analysis was performed to analyze predictors of mortality and discharge.

Results: Data from 6,627 emergency department patients were examined. The gender ($p<0.001$), age ($p<0.001$), Hb ($p<0.001$), lactate ($p<0.001$), and lipase ($p<0.001$) levels of the hospitalized patients. Increasing age was associated with mortality ($p<0.001$). In the analysis of biomarkers, a decrease in Hb and Htc ($p<0.001$; $p=0.038$) and an increase in lactate, lipase, amylase, and IL-6 ($p<0.001$; $p<0.001$; $p=0.022$; $p<0.001$) were determined to be associated with mortality. The area under the receiver operating characteristic curve for the mortality model was calculated as 0.724, with specificity and sensitivity determined as 91.8% and 97.5%, respectively.

Conclusion: Age, amylase, lipase, serum lactate, and interleukin-6 levels, when calculated together, are important predictors of both mortality and hospitalization in COVID-19 pneumonia.

Keywords: Biomarkers, COVID-19, emergency department, pneumonia

Introduction

Coronavirus disease-2019 (COVID-19) is an infectious disease caused by the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) virus [1]. Despite a decline in the potency of the SARS-CoV-2 virus, it continues to be a global health crisis [2,3]. As of January 2024, the WHO reported over 774 million confirmed cases and more than seven million deaths worldwide, with a concurrent increase in hospitalizations [4].

The clinical presentation of patients seeking care in emergency departments with a COVID-19 diagnosis varies widely, ranging from mild upper respiratory tract infections to severe pneumonia, acute respiratory distress syndrome, and multiple organ failure, leading to fatalities [3,5].

Certain biomarkers, including hematocrit (Htc), hemoglobin (Hb), amylase, lipase, lactate, and interleukin 6 (IL-6), are used in clinics and intensive care units (ICUs) for diagnosis, effective treatment, and prognosis assessment of patients with COVID-19. Proper interpretation of these parameters is essential for accurate clinical decision-making and successful treatment [6,7]. A meta-analysis revealed associations between low Hb,

Address for Correspondence: Habibe Selmin Özensoy, University of Health Sciences Türkiye, Ankara City Hospital, Clinic of Emergency Medicine, Ankara, Türkiye
E-mail: habibeozensoy@gmail.com **ORCID-ID:** orcid.org/0000-0001-9261-2669
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lymphocyte, platelet, and albumin levels and COVID-19 mortality [8]. Another study explored the prognostic properties of IL-6, C-reactive protein, and procalcitonin in COVID-19 pneumonia and highlighted IL-6 as a prognostic factor [9]. IL-6, produced in response to infections and tissue damage, acts as a pleiotropic cytokine that participates in inflammatory responses [10]. The overproduction of IL-6 can lead to a cytokine storm, causing severe systemic inflammation, vascular hyperpermeability, multiple organ failure, and death [11].

Emergency departments remain the primary point of contact for individuals with symptoms of COVID-19 pneumonia. Evaluating the prognosis of these patients is vital for managing the emergency department workload and planning examinations and treatments appropriately.

This study aimed to investigate the correlation between Htc, Hb, amylase, lipase, lactate, and IL-6 levels and the severity of COVID-19 in patients. Notably, there is a gap in the existing literature because previous studies did not collectively examine these biomarkers. Establishing the efficacy of these parameters and advocating for their widespread use in emergency departments can significantly enhance patient assessment and treatment. Additionally, our findings aim to contribute valuable insights into the scientific literature on COVID-19, serving as a foundation for future research.

Materials and Methods

Data Source

Patients diagnosed with COVID-19 pneumonia who presented to the emergency department of one of the largest hospitals in Türkiye between May 01, 2021 and October 30, 2021, were retrospectively examined. The data were retrieved by the researchers from the hospital information system and physician orders.

Patients older than 18 years and those whose data could be accessed were included in the study. Among patients with pneumonia according to the ICD code, those whose polymerase chain reaction (PCR) test result was positive for COVID-19 were included in the study.

Patients whose data could not be accessed, patients <18 years of age, pregnant women, and those who applied to the emergency department due to trauma were not included in the study.

The article was prepared using the STROBE checklist.

Data Collection

Htc, Hb, amylase, lipase, lactate, and IL-6 values of patients with positive COVID-19 PCR (Bio-speedy® SARS CoV-2 Triple Gene RT-qPCR, Türkiye) in nasopharyngeal swab samples who presented to the emergency department with COVID-19 symptoms were scanned. Whether the patients were discharged from the emergency department, were hospitalized (service and ICU), or had short-term (28-day) mortality was recorded.

Statistical Analysis

The analyses of the study were performed using SPSS for Windows 20.0. Normality analysis of continuous data was performed using the Shapiro-Wilk test. Median comparisons of data that did not show normal distribution were made using the Mann-Whitney U test. Ratio comparisons of categorical variables were made using the Pearson's chi-square test. Multiple logistic regression analysis was performed to identify predictors of mortality and discharge. The regression model was created by excluding factors related to multicollinearity analysis. In addition, receiver operating characteristics (ROC) analysis was performed for diagnostic accuracy, and the area under the curve is presented. The $p<0.05$ level was used for statistical significance.

Ethics Statement

This study was approved by the Ankara City Hospital No. 2 Clinical Research Ethics Committee (decision number: E2-21-987, date: 10.11.2021) and was conducted in accordance with the Declaration of Helsinki. Because this was an observational study using an anonymized dataset, the requirement to obtain informed consent from the participants was waived.

Results

Demographic Data of Patients

A total of 6.975 patients were identified by examining the hospital's electronic information system and physician orders. Among them, 334 (4.8%) were excluded from the study because they were younger than 18 years. Of the remaining 6.641 (95.2%) patients, 14 were excluded because of a lack of data. Consequently, analyses were conducted on the remaining 6.627 patients.

Table 1 presents the descriptive information and the results of the biomarkers of the patients. The median age of the patients is 58 (range between 18-105 years). Patients were most frequently male, 50.1% (n=3322). It was determined that 638 (9.6%) of the 6.627 patients died and 4.058 (61.2%) were alive. The mean±standard deviation, median, and minimum-maximum values of the biomarkers are presented in Table 1.

Clinic Outcomes

Table 2 presents data on the age, sex, and biomarker levels of patients with mortality. Increased age was associated with mortality ($p<0.001$). When analyzing the biomarkers, decreases in Hb and Htc ($p<0.001$; $p=0.038$); Increase in lactate, lipase, amylase, IL-6 ($p<0.001$; $p<0.001$; $p=0.022$; $p<0.001$) were determined to be associated with mortality.

Table 3 shows the gender ($p<0.001$), age ($p<0.001$), Hb ($p<0.001$), Htc ($p<0.001$), lactate ($p<0.001$), and lipase ($p<0.001$) levels of the hospitalized patients. and was

Table 1. Demographic, outcome, and biomarker analyses

Variables		n (%)	Mean±SD	Median (25-75%)	Min.-Max.
Total		6627 (100.00)			
Gender	Male	3322 (50.10)			
	Female	3305 (49.90)			
Age (year)			57.80±18.60	58 (44-72)	18-105
Mortality	Survival	5989 (90.40)			
	Mortal	638 (9.60)			
Discharge	Discharge	4058 (61.20)			
	Hospitalization	2569 (38.80)			
Blood analysis	Hb		12.70±2.10	12.80 (11.40-14.10)	3.50-19.40
	Htc		38.50±6.10	38.80 (34.70-42.50)	2.20-60.90
	Lactate		2.20±1.40	1.84 (1.40-2.53)	0.07-17.88
	Lipase		57.20±98.10	40.00 (28.10-58.25)	9.0-2332.0
	Amylase		78.90±85.20	61.00 (44-87)	5-2032
	IL-6		93.30±377.00	20.60 (8.35-56.4)	2.70-7153.20

Hb: Hemoglobin, Htc: Hematocrit, IL-6: Interleukin-6, Min.-Max.: Minimum, Maximum

Table 2. Groups in terms of mortality

Variables		Mortality				p
		Survival		Non-survivor		
		n (%)	Median (25-75%)	n (%)	Median (25-75%)	
Gender	Male	2979 (89.7)		343 (10.3)		0.054*
	Female	3010 (91.1)		295 (8.9)		
Age (year)			57.0 (43.0-71.0)		73.0 (61.0-83.0)	<0.001**
Hb			12.8 (11.40-14.20)		12.4 (10.60-13.90)	<0.001**
Htc			38.9 (34.90-42.50)		38.3 (33.20-42.90)	0.038**
Lactate			1.77 (1.37-2.40)		2.22 (1.60-3.10)	<0.001**
Lipase			40.7 (29.0-58.35)		35.55 (23.65-58.05)	<0.001**
Amylase			61.0 (44.0-86.0)		64.0 (42.0-108.0)	0.022**
IL-6			17.3 (7.40-44.70)		54.6 (23.40-167.60)	<0.001**

Hb: Hemoglobin, Htc: Hematocrit, IL-6: Interleukin-6,
*Pearson's chi-square test, **Mann Whitney-U test

Table 3. Comparison of patients' hospitalization/discharge status and age, gender and laboratory data

Variables		Hospitalization/discharge				p
		Discharge		Hospitalization		
		n (%)	Median (25-75%)	n (%)	Median (25-75%)	
Gender	Male	1933 (58.20)		1389 (41.80)		<0.001*
	Female	2125 (64.30)		1180 (35.70)		
Age (year)			55.0 (40.0-68.0)		65.0 (51.0-77.0)	<0.001**
Hb			12.90 (11.60-14.20)		12.5 (10.90-14.0)	<0.001**
Htc			39.10 (35.30-42.60)		38.3 (33.90-42.40)	<0.001**
Lactate			1.740 (1.36-2.36)		1.94 (1.44-2.70)	<0.001**
Lipase			41.00 (30.15-58.75)		38.0 (26.0-58.0)	<0.001**
Amylase			62.0 (45.0-86.0)		60.0 (42.0-90.0)	0.680**
IL-6			15.0 (6.8-34.2)		29.40 (10.9-81.55)	<0.001**

Hb: Hemoglobin, Htc: Hematocrit, IL-6: Interleukin-6,
*PPearson's chi-square test, **Mann Whitney-U test

discharged without being hospitalized (p=0.001), there was a significant relationship with IL-6 (p<0.001) levels. No significant relationship was detected with amylase (p=0.680).

Logistic regression analysis for mortality is presented in Table 4. Gender and Hb levels were not found to be significant predictors of mortality. A relationship was found between increased age, lactate, amylase, and IL-6 levels, and mortality (p<0.001; p<0.001; p=0.008; p<0.001).

As a result of logistic regression analysis, age, lactate, amylase, and IL-6 levels were found to be independent predictors of mortality. Although the area under the ROC curve of the model regarding mortality was calculated as 0.724, its specificity was determined as 91.8% and its sensitivity was determined as 97.5%. The ROC curve of the model is presented in Figure 1.

Table 5 presents the logistic regression analysis for hospitalization/discharge status. It was determined that age, lactate, amylase, IL-6 increase, and discharge were significantly related. There were no significant relationships between the patients' hospitalization/discharge status, gender, and Hb value.

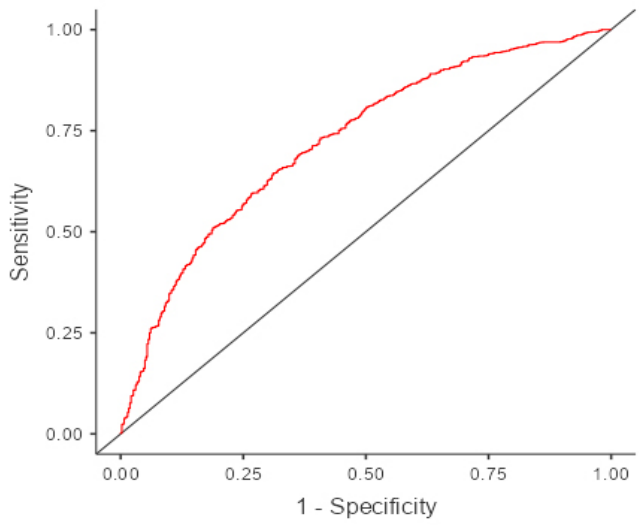

Figure 1. ROC curve for mortality: Although the area under the ROC curve of the model regarding mortality was calculated as 0.724, its specificity was determined as 91.8% and its sensitivity was determined as 97.5%

ROC: Receiver operating characteristics

Table 4. Logistic regression analysis: model coefficients and mortality

				95% Confidence interval	
Predictor	**Estimate**	**p**	**Odds ratio**	**Lower**	**Upper**
Intercept	-4.76376	<0.001	0.008	0.003	0.024
Gender	0.099	0.418	1.104	0.868	1.404
Age	0.036	<0.001	1.037	1.029	1.045
Hb	0.021	0.443	1.021	0.967	1.077
Lactate	0.215	<0.001	1.240	1.128	1.364
Amylase	0.002	0.008	1.002	1.000	1.003
IL-6	0.001	<0.001	1.001	1.001	1.002

Hb: Hemoglobin, IL-6: Interleukin-6,
Estimates represent the log odds of "Mortality = Mortal" vs, "Mortality = Survival"

Table 5. Logistic regression analysis-model coefficients-discharge

				95% Confidence Interval	
Predictor	**Estimate**	**p**	**Odds ratio**	**Lower**	**Upper**
Intercept	-0.458	0.314	0.632	0.259	1.540
Gender	-0.187	0.077	0.829	0.674	1.020
Age	0.014	<0.001	1.014	1.008	1.020
Hb	-0.040	0.098	0.961	0.916	1.010
Lactate	0.352	<0.001	1.423	1.262	1.610
Amylase	0.002	0.036	1.002	1.000	1.002
IL-6	0.001	0.001	1.001	1.001	1.001

Hb: Hemoglobin, IL-6: Interleukin-6,
Estimates represent the log odds of "Discharge = Admitted" vs. "Discharge = Discharge"

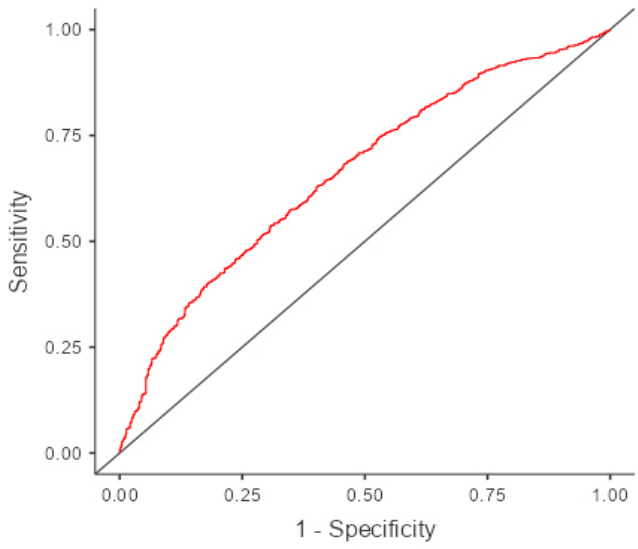

Figure 2. ROC curve for discharge: The area under the ROC curve of the discharge model was calculated as 0.650, its specificity was determined as 14.2% and its sensitivity was 93.5%

ROC: Receiver operating characteristics

In the logistic regression analysis, age, lactate, amylase, and IL-6 level were found to be independent predictors of discharge. Although the area under the discharge model's ROC curve was calculated as 0.650, its specificity was 14.2%, and its sensitivity was 93.5%. The model's ROC curve is presented in Figure 2.

Discussion

The inflammatory response to the COVID-19 virus is implicated in developing COVID-19-related complications. An unbalanced proinflammatory immune response indicates that the disease can have life-threatening consequences. Accordingly, studies have reported that high levels of circulating cytokines and acute phase reactants are associated with poor outcomes in COVID-19 patients [12].

The most important aspect of our study is the high sample size. Data from 6.627 patients were examined. Since the hospital where the study data is provided is one of the largest central hospitals in Türkiye, has a high patient capacity, and is a reference hospital in surrounding cities, it includes patients of all characteristics (age, gender, chronic diseases, etc.). Although there was no relationship between patient sex and a decrease in Hb level and hospitalization/discharge or mortality, increasing age and an increase in lactate, amylase, lipase, and IL-6 levels were associated with mortality and hospitalization. When these biomarkers were examined together, the specificity for hospitalization was determined as 14.2% the sensitivity as 93.5%, and the specificity for mortality was determined as 91.8% and the sensitivity was 97.5%. These results are highly significant for patient outcomes.

Some studies have found the same findings as our study and did not detect a relationship between gender and mortality [13]. In our study, no relationship was found between sex and mortality or hospitalization in patients with COVID-19 pneumonia.

Some studies have shown the opposite, finding that males have a higher risk of getting COVID-19 [14,15]. In our study, patient age was associated with mortality and hospitalization. The median age of patients who died was 73, which was a statistically significant result. In a study examining the prognostic features of age, sex, and comorbid diseases in patients with COVID-19 pneumonia, patients aged ≥65 years were more mortal than patients aged <65 years, and men were more likely to die than women [16].

The decreases in Hb and Htc levels were significant for mortality and hospitalization/discharge in our study. Likewise, Asghar et al. [17] conducted their study in 2020. In a retrospective study in which 364 cases were examined, Hb decrease was found to be associated with mortality. In their study published in 2023, Alizad et al. [18] examined disease severity using hematological parameters and found that low Hb levels were associated with both mortality and disease severity.

In a study examining amylase and lipase values of 176 COVID-19-positive patients and 103 COVID-19-negative patients, the relationship between amylase and lipase increase and the severity of COVID-19 pneumonia was determined, but its relationship with mortality was not examined [14]. In our study, increased amylase and lipase levels were found to be associated with mortality. However, although lipase elevation made a significant difference in admission/discharge, amylase elevation did not make a significant difference.

There are not many studies in the literature examining the relationship between COVID-19 pneumonia and serum lactate levels. In one of these studies, the lactate content and mortality of COVID-19 pneumonia patients hospitalized in the ICU were examined. The relationship between the increase in lactate value and mortality was determined [13]. Our study found that the increase in serum lactate levels were significantly associated with mortality and hospitalization/discharge status.

Gür Vural et al. [9] found that IL-6 was 53.8% effective in predicting mortality in patients with COVID-19 pneumonia, and its specificity was 84.1%. In another study, IL-6, PRC, and neutrophil-to-lymphocyte ratios were found to be prognostic for mortality in patients with COVID-19 (sensitivity specificity; 94.9%-93.2%; 76.3%-79.5%; 71.7%-80.3%, respectively) [12]. In a systematic review of 16 articles, a correlation was detected between elevated IL-6 levels and prolonged COVID-19 [19]. Our study found that when age, lactate, amylase, and IL-6 were

considered together, we achieved a specificity of 91.8% and sensitivity of 97.5%. Combining age, lactate, amylase, and IL-6 levels appeared to be more predictive of both mortality and hospitalization/discharge.

Study Limitations

Although our study provides valuable information, it is important to acknowledge its limitations. The major limitation of this study is its retrospective, single-center design. Limited to a single center may limit the generalizability of our findings to larger populations. Additionally, notable limitations include the lack of a graded severity classification for COVID-19 pneumonia and the exclusion of other potential biomarkers.

Conclusion

In conclusion, calculating age, serum lactate, amylase, lipase, and IL-6 levels together constitute an important criterion for both mortality and hospitalization in terms of COVID-19 pneumonia. It is informative for studies in which more comprehensive biochemical parameters are examined.

Ethics

Ethics Committee Approval: This study was approved by the Ankara City Hospital No. 2 Clinical Research Ethics Committee (decision number: E2-21-987, date: 10.11.2021).

Informed Consent: The requirement to obtain informed consent from the participants was waived.

Footnotes

Authorship Contributions

Concept: T.D., H.O., Design: T.D., H.O., Data Collection or Processing: T.D., H.S.Ö., Analysis or Interpretation: H.S.Ö., H.O., Literature Search: H.S.Ö., H.O., Writing: T.D., H.S.Ö., H.O.

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

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ORIGINAL RESEARCH

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Evaluation of Sleep Quality in Patients with Migraine Attacks Presenting to the Emergency Department

Sümeyye Çakmak[1], Ruken Şimşekoğlu[2]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Emergency Medicine, İstanbul, Türkiye
[2]Istanbul Medeniyet University Faculty of Medicine, Göztepe City Hospital, Department of Neurology, İstanbul, Türkiye

Abstract

Objective: To investigate the sleep quality of adult patients presenting to the emergency department (ED) with migraine attacks and explore the correlations with age, gender, and education period. The aim of this study was to compare the sleepiness scores and sleep quality of migraine patients presenting to the ED with severe migraine attacks with those of healthy controls.

Materials and Methods: This cross-sectional prospective study, adult migraine patients seeking care at the ED of a tertiary hospital over a 1-month period. Fifty-seven migraine patients and 25 age- and sex-matched healthy controls were enrolled in the study. A single medical professional utilized the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) to assess each patient's headache-related disability.

Results: Patients with migraine attacks had significantly higher PSQI scores than the healthy control group (6.75±4.57 vs. 4.08±2.12; p=0.020). No substantial differences were observed in the PSQI between patient groups using the ESS. In patients with migraine attacks, ESS was significantly positive and strongly correlated with education level (rho=0.294, p=0.007) but not age.

Conclusion: This study highlighted a significant independent association between poor sleep quality and an increased risk of migraine attacks. Strengthening the assessment of sleep quality using the PSQI is valuable for the early prevention and treatment of migraine patients.

Keywords: Migraine, sleep quality, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale

Introduction

Headache is a prevalent medical concern affecting a substantial proportion of the global adult population, with estimates indicating its prevalence in 50%-75% of adults, as reported by the World Health Organization [1]. Among primary headache disorders, migraine stands as a notably impactful condition characterized by heightened morbidity and disability. The current global prevalence of migraine ranges from 10% to 18% [2,3]. Sleep, an essential aspect of daily life, is a pivotal clinical consideration, with sleep disorders posing significant challenges in healthcare. The intricate relationship between headache, especially migraine, and sleep is well established. Inadequate sleep and various sleep disorders have been identified as factors that elevate the risk of developing headaches while simultaneously reducing pain thresholds [4-7]. The relationship between headache disorders and sleep disturbances is complicated and multidimensional, often exhibiting bidirectional influences. Establishing causal relationships in patients concurrently experiencing sleep and headache disorders poses significant challenges. The coexistence of these syndromes often leads to chronicity, worsening the burden on individuals by diminishing their quality of life, increasing the frequency of complications, and reducing the effectiveness of treatment [8]. Migraine and sleep disorders are prevalent in a substantial proportion of the population, often leading to prolonged disability in affected individuals [9]. The Epworth Sleepiness Scale (ESS), an eight-item scale, is a valuable tool for assessing excessive daytime sleepiness [10]. Another commonly employed measure, the Pittsburgh Sleep Quality Index (PSQI),

Address for Correspondence: Sümeyye Çakmak, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Emergency Medicine, İstanbul, Türkiye
E-mail: sumeyyetumturk@gmail.com **ORCID-ID:** orcid.org/0000-0001-9573-8611
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is a self-reported questionnaire designed to evaluate sleep quality over the preceding month. Numerous studies have utilized the PSQI to identify poor sleep quality in migraine patients [11]. Given the evident connection between sleep quality and migraine attack, PSQI and ESS scores have the potential to serve as predictive indicators of migraine attacks. Despite this, few studies have systematically explored the predictive value of PSQI scores in the context of migraine.

The current study aimed to provide an objective evaluation of sleep quality among patients presenting to the ED with migraine attacks. Additionally, previous studies have evaluated the predictive efficacy of PSQI and ESS scores in the context of migraine, offering novel insights for the early prevention and screening of migraine attacks.

Materials and Methods

Ethical clearance for the present study was granted by the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital (approval number: 155-2023, date: 16.10.2023). The research adhered to the ethical principles outlined in the 1989 Declaration of Helsinki.

Patient Population

This prospective cross-sectional study enrolled a total of 57 consecutive adult patients who sought medical attention at the ED. Additionally, a healthy control group consisting of 25 age- and sex-matched healthy volunteers was included. After the measurement of vital functions, patients were observed in an isolated area within the ED, and either they or their authorized representatives provided written informed consent. The healthy participants were briefed on the study protocol and provided signed informed consent prior to participation. Migraine diagnoses were based on the third edition criteria of the International Classification of Headache Disorder [12].

Data Collection

Patient data, including age, sex, symptoms, and years of education, were systematically recorded. Subsequently, a separate cross-sectional analysis was conducted on 57 migraine patients to explore the associations between sleep quality and education years. All participants underwent a professional diagnostic assessment using standardized questionnaires administered by an emergency medicine specialist. Voluntarily and with signed informed consent, participants actively engaged in the study.

Pittsburgh Sleep Quality Index

The sleep quality of the participants was evaluated using the PSQI, a widely utilized self-rated questionnaire consisting of 19 items across seven components. These elements comprise subjective assessment of sleep quality, time to fall asleep (sleep latency), length of sleep, regularity in achieving restful sleep, disruptions during sleep, use of sleep medications, and daytime impairment. A PSQI score exceeding 5 indicated poor sleep quality, with a diagnostic sensitivity and specificity of 98.7 and 84.4, respectively [13].

Epworth Sleepiness Scale

The excessive daytime sleepiness was assessed using the ESS, an eight-item self-reported instrument widely adapted to various languages. ESS was used to measure the propensity for daytime sleepiness [14].

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 for Windows. Descriptive statistics included numbers, percentages, means, standard deviations, minimum and maximum values, and medians. Student's t-test or the Mann-Whitney U test were employed to compare numerical variables between two independent groups based on normal distribution conditions. The chi-square test was used for rate comparisons among independent groups. Spearman's correlation analysis explored relationships between numerical variables due to non-parametric conditions. Linear regression analysis was used to investigate the determinant effects on numerical variables, and the significance level was set at $p<0.05$

Results

The mean age of the 57 participants in this study was 37.7±10.8 years, ranging from 18 to 67 years and the cohort was predominantly composed of females, with 51 individuals (89.5%). No significant difference in age was observed between the patient and control groups. However, female gender and PSQI scores were significantly higher in the patient group. A detailed comparison of demographics, education years, PSQI, and ESS scores between the patient and control groups is presented in Table 1. A statistically significant association was identified between education level and ESS, as outlined in Table 2. Exploring the collective impact of group assignment, gender, age, and education level on PSQI levels revealed that the group effect was the most significant factor (Table 3). No significant difference was observed between the PSQI and ESS scores ($p=0.603$). Upon jointly examining the group effect, gender, age, and education level impact on the ESS level, age and education level were identified as the most statistically significant factors (Table 4).

Discussion

This study aimed to examine the sleep quality and sleepiness scores of patients presenting to the emergency department (ED) with migraine attacks. The main findings were as follows: 1) Low sleep quality was significantly higher among patients who suffered from migraine than in the control group. 2) There

was a significant stastitical relationship between education level and sleepiness score. 3) No substantial differences were observed in the PSQI when comparing patient groups using the ESS. An examination of 1283 patients at a tertiary headache center revealed that more than half of the patients experienced occasional challenges with falling asleep and staying asleep, while over one-third reported experiencing these difficulties frequently [15]. In a meta-analysis of primary headaches that included 27.000 people, it was determined that the most common factor triggering migraine was sleep disturbance [16]. Shortening of sleep duration in migraine patients is inversely proportional to headache severity [17].

Table 1. Demographic and clinical characteristic features of participitans

Characteristics		Patients	Controls	p
Age mean±SD min.-max. (median)		37.7±10.8 18-67 (38)	33.4±12.9 18-60 (33)	0.121
Gender n (%)	Male	6 (10.5)	10 (40.0)	0.005
	Female	51 (89.5)	15 (60.0)	
Education level mean±SD min.-max. (median)		12.7±4.8 5-22 (12)	11.1±3.8 4-16 (12)	0.091
PSQI mean±SD min.-max. (median)		6.75±4.57 0-17 (6)	4.08±2.12 1-9 (3)	0.020
ESS mean±SD min.-max. (median)		4.35±4.83 0-22 (4)	3.24±3.73 0-13 (2)	0.465

Data are expressed as numbers (n), percentage (%), mean standard deviation (SD). Intergroup comparisons (control versus patients) were conducted using the chi-squared test, independent samples t-test, and Mann-Whitney U test, as appropriate,

PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, Min.: Minimum, Max.: Maximum

Table 2. Correlations of PSQI and ESS with age and education level

	PSQI[1]		ESS[2]	
	r	p	r	p
ESS	0.058	0.603		
Age	0.104	0.352	0.114	0.310
Education level	0.001	0.993	0.294	0.007

[1]PSQI: Pittsburgh Sleep Quality Index, [2]ESS: Epworth Sleepiness Scale

Table 3. Multivariate linear regression analysis

	B	Beta	p
Stable	8.43		
Age	0.027	0.074	0.547
Gender	0.161	0.015	0.899
Educaiton level	-0.017	-0.019	0.875
Group	-2.636	-0.293	0.017

Dependent Variable: Pittsburgh Sleep Quality Index

Table 4. Multivariate regression analysis

	B	Beta	p
Stable	-3.259		
Age	0.102	0.259	0.034
Gender	-0.248	-0.022	0.856
Educaiton level	0.324	0.328	0.007
Group	-0.068	-0.007	0.953

Dependent Variable: Epworth Sleepiness Scale

Similarly, in our study, PSQI scores were significantly higher in the patient group than in the control group. In another study examining primary headaches and sleep disorders, the ESS score was not significant in the patient and control groups, which is consistent with the present study, with no significant difference in the ESS score between the patient and healthy control groups (p=0,465) [18]. The latest edition of the ICSD third edition encompasses sleep disorders classified into seven major diagnostic categories: insomnia, sleep-related breathing disorders, sleep-related movement disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnia, and other sleep disorders [19]. Existing evidence suggests a bidirectional relationship between migraine and insomnia, which is not independent of anxiety and depression. Insomnia is a risk factor for migraine onset and exacerbation, leading to increased migraine impact, pain intensity, and chronification. Conversely, individuals with migraine are at higher risk of developing insomnia. However, this association may not be specific to migraine, as insomnia is broadly linked to headache [20]. Population-based studies have shown that the prevalence of obstructive sleep apnea syndrome (OSAS) is comparable between individuals with migraine and those without migraine [21]. Treatment of OSAS with continuous positive airway pressure has been linked improved sleep quality and migraine outcomes, including reductions in the frequency and intensity of attacks, duration of pain, days of incapacity to work, and intake of acute medication [22]. Results from a rural-based population study in Italy among adults showed a distinct correlation between migraine and restless legs syndrome (RLS), indicating a higher prevalence of migraine among individuals with RLS compared to those without (12.6% vs. 8.0%). A strong bidirectional relationship between migraine and RLS appears evident; however, the exact strength and direction of this association with narcolepsy remain uncertain due to insufficient available evidence. Although evidence supports an association between migraine and sleepwalking, determining the precise strength and nature of the association between migraine and parasomnia in adults remains challenging due to limited research [23]. The limited number of available studies and heterogeneity in the methodology used to define circadian rhythm sleep-wake disorders hinder reaching definitive conclusions regarding their relationship with migraine [20].

Study Limitations

This study has some limitations. Future research with a larger sample size is recommended. Additionally, although the PSQI and ESS tests provide subjective evaluations of sleep, the inclusion of polysomnography is suggested for the objective assessment of sleep disorders in diagnosed patients. Third, the sample of migraine patients presenting to the ED who may have suffered from severe pain may not adequately reflect the general migraine population.

Conclusion

The findings of this study highlight a substantial, standalone link between low sleep quality and a high likelihood of migraine attacks. Enhancing the evaluation of sleep quality by implementing the PSQI demonstrates its efficacy in the early prevention and treatment of migraine. Diagnosis and management of concurrent sleep disorders should be integrated into the treatment approach for migraine, as improvements in sleep quality are anticipated to lead to reductions in both the frequency and severity of headache.

Ethics

Ethics Committee Approval: Ethical clearance for the present study was granted by the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital (approval number: 155-2023, date: 16.10.2023). The research adhered to the ethical principles outlined in the 1989 Declaration of Helsinki.

Informed Consent: The healthy participants were briefed on the study protocol and provided signed informed consent prior to participation.

Footnotes

Authorship Contributions

Concept: S.Ç., R.Ş., Design: S.Ç., R.Ş., Data Collection or Processing: S.Ç., R.Ş., Analysis or Interpretation: S.Ç., R.Ş., Literature Search: S.Ç., R.Ş., Writing: S.Ç., R.Ş.

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Assessing the Performance of ChatGPT in Medical Toxicology Through Simulated Case Scenarios

İbrahim Altundağ[1], Semih Korkut[2], Ramazan Güven[2], Aynur Şahin[2]

[1]University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Emergency Medicine, İstanbul, Türkiye

Abstract

Objective: The insufficient number of medical toxicologists and poison information centers worldwide limits the accessibility of adequate medical recommendations for the management of poisoned patients. This study aimed to assess the effectiveness of Chat Generative Pretrained Transformers (GPTs) medical recommendations in medical toxicology and evaluate its accuracy as a valuable resource when accessing medical toxicologists or poison information centers is limited.

Materials and Methods: A toxicologist created 10 different toxicology-simulated case scenarios based on the possible presentations of poisoned patients in an emergency department setting. The categories of general approach and stabilization, diagnostic activities, and medical treatments and follow-up were used to measure case assessment and ChatGPT's medical recommendation capacity.

Results: ChatGPT-4o achieved an average success rate of 90.88% across the simulated case scenarios. ChatGPT-4o received a passing grade in 9 cases (90%) and received "improvable" in only 1 case (10%). ChatGPT-4o's average success rate in all categories and across all cases increased from 90.88% to 97.22% with the secondary test.

Conclusion: Our study indicates that it is possible to improve the success rate of ChatGPT in providing medical toxicology recommendations. The ability to query current medical toxicology information through ChatGPT-4o demonstrates the potential of ChatGPT to serve as a next-generation poison information center.

Keywords: Artificial intelligence (AI), ChatGPT-4o, clinical decision support systems, generative pretrained transformer, poison control center, toxicology

Introduction

The significant mortality and illness rates resulting from poisonings, particularly in developing countries, have made poisoning an escalating public health issue requiring specialized attention and care. The establishment of medical toxicology as a subspecialty, along with the increasing prevalence of toxicologists and poison information centers, can facilitate a decrease in mortality and morbidity rates among poisoned patients [1]. This approach can also help reduce unnecessary hospital admissions and shorten hospitalization periods. However, the insufficient numbers of medical toxicologists and poison information centers worldwide limit the access of poisoned patients to adequate medical support.

One of the main objectives of developing technology and computer systems is to eliminating dependence on human labor and create autonomous systems. Natural language processing (NLP) enables computers to comprehend texts and spoken words in a manner similar to humans [2]. NLP technology has made a noteworthy contribution to the advancement of clinical decision support (CDS) systems. CDS systems are designed to ensure complete, timely, efficient, and accurate data presentation in the healthcare industry, with

Address for Correspondence: İbrahim Altundağ, University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Türkiye
E-mail: dr.ibrahimaltundag@gmail.com **ORCID-ID:** orcid.org/0000-0002-0880-7218
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the aim of supporting healthcare professionals in making the most accurate decisions [3]. Currently, although not usable for CDS, a notable example of an NLP model is the Generative Pretrained Transformer (GPT) model [4]. The popularity of artificial intelligence (AI) has increased recently in mainstream media and literature, with the emergence of GPT-3, a language model capable of producing human-like text [5]. The latest version of this system, ChatGPT-4o, was made available for free use on May 13, 2024.

Although the existence of numerous sources of information related to medicine and healthcare is an indication of advanced medical literature, it complicates accessing accurate information. Despite the widespread use of the internet, there can still be challenges in obtaining specific and accurate information. This is particularly vital for clinicians operating in chaotic settings, such as emergency departments, where swift access to accurate information is of significant importance.

The aim of this study was to test the feasibility of AI applications (ChatGPT-4o) in the field of medical toxicology using simulated case scenarios. Our study is significant because it is the first to assess the utility of AI in the analysis and management of toxicology in patients encountered in daily clinical practice. In contrast to previous AI studies, our investigation employed realistic case scenarios involving patients who might present to the emergency department. The effectiveness of ChatGPT's medical recommendation in medical toxicology has been evaluated to assess its accuracy as a resource when accessing a medical toxicologist and poison information centers are limited.

Materials and Methods

This study was conducted at University of Health Sciences Türkiye, Çam and Sakura City Hospital, Clinic of Emergency Medicine, Medical Toxicology Intensive Care Unit. Since the study involved the use of simulated case scenarios (the data of any animals, patient or patient group was not used), Ethics Committee approval and individual consent were not required.

Study Design

This study was designed to test the usability of AI applications (ChatGPT) in medical toxicology. The latest version of ChatGPT available for free use is ChatGPT-4o. Due to its ease of accessibility worldwide without cost, the ChatGPT-4o version was used. To measure ChatGPT-4o's level of knowledge about current patient approaches and practices in medical toxicology, we asked open-ended question-answer pairs based on case scenarios that specifically focused on commonly encountered important types of poisoning. ChatGPT-4o underwent testing in two stages, each consisting of 10 different simulated case scenarios tailored for individual common poisoning types, which encompassed questions related to frequently encountered poisoning types.

In the first stage, the interpretation of the case and the success of recommendations from ChatGPT-3.5 were tested using open-ended questions. In the second stage, the questions that were not successfully answered in the first test were converted into knowledge-based questions and presented to ChatGPT-4o for a second attempt, with the answers then scored. This enabled ChatGPT-4o to directly assess the level of medical toxicology knowledge, independent of NLP and CDS features (without the need for case analysis). The success of ChatGPT-4o for the posed questions and received answers was evaluated by an experienced, blinded medical toxicologist with at least 5 years of experience in medical toxicology. The accuracy rates of ChatGPT-4o were evaluated both at the case level and under three categories: general approach and stabilization, diagnostic activities, and medical treatments and follow-up.

Simulated Case Scenarios

A total of 10 different toxicology simulated case scenarios were designed by experienced toxicologists based on the possible presentation of poisoned patients in an emergency department setting. The case scenarios included overdose of acetaminophen, tricyclic antidepressant (TCA) overdose, methanol toxicity, organophosphate toxicity, digoxin poisoning, sympathomimetic toxidrome, lithium overdose, carbon monoxide (CO) poisoning, calcium channel blocker (CCB) overdose, and snake bite. An example of a simulated case scenario is shown in Figure 1. The simulated case scenarios are available in Supplemental Material-1.

Assessment and Statistical Analysis

ChatGPT's knowledge of poisoning was assessed using questions addressing the differential diagnosis, stabilization, diagnosis, treatment, and follow-up of simulated case scenarios. Examples of questions that assess the evaluation and recommendation capacity of ChatGPT-4o in simulated case scenarios are shown in Figure 2.

Each simulated case scenario was evaluated in three different categories. The categories of "general approach and stabilization," "diagnostic activities," and "medical treatments and follow-up" were used to measure the case assessment and ChatGPT-4o's medical recommendation capacity. A medical toxicologist evaluated each category of each simulated case scenario, awarding a maximum score of 100 points. Additionally, the medical toxicologist identified the key recommendations and points, assigning scores based on the importance of each answer. The simulation case scenarios and scoring table (scoring that shows only high-rated, key points) are shown in Table 1. The remaining points for parameters outside the key points were distributed equally. The scoring of the simulated case scenarios and the results was uploaded as Supplemental Material-2. Each of the three categories within a case was assessed independently to evaluate the accuracy

Case 4: Organophosphate Toxicity

42-year-old male patient weighing 70kg and measuring 175cm. No known medical conditions or medication use. He was working as a farmer and entered the field three hours ago. His friend became concerned when he didn't see him for a long time and found him lying on the ground when he entered the field. He noticed that this patient had vomited and there was foaming in his mouth, and his skin was sweaty. He was immediately transported to the hospital by ambulance. The other friend who entered the field also experienced headache, nausea/vomiting, and sweating, but recovered shortly after. This patient was intubated when his Glasgow Coma Scale (GCS) dropped from 12 in the ambulance to 8 in the emergency room. Significant secretion was observed from the mouth and tube. His overall condition was fair to poor. Vital signs revealed blood pressure of 90/50 mmHg, pulse rate of 40/min, respiratory rate of 15/min, oxygen saturation of 87%, and blood sugar level of 88 mg/dl. Bilateral rales were heard in lung sounds. Pupils were bilaterally myotic. His skin was diaphoretic. No pathology was observed in other system examinations.

Blood gas analysis showed pH of 7.34, bicarbonate of 22 mEq/L, lactate of 2.4 mmol/L, and BE of -4. Other laboratory parameters were normal. EKG showed sinus bradicardia of 42/min, QRS duration of 75ms, and QTc duration of 430ms. No pathology was observed in the brain tomography. Bilateral ground-glass opacities were present in thorax tomography.

Figure 1. A case presentation of a simulated case scenario example prepared in accordance with the poisoning table

1. What pathologies should be considered in the differential diagnosis?
2. What is the most likely diagnosis for this patient?
3. How should the treatment approach be in this patient? List the general principles of approach and what needs to be done?
4. Should decontamination methods (skin decontamination, gastric lavage, activated charcoal) be used for this patient?
5. What diagnostic tests should be ordered? Explain the reason for each diagnostic test.
6. Is there a specific diagnostic tool? When should it be used? How does it contribute to the treatment process?
7. How should I treat this patient? What treatment steps should be used?
8. Is there an antidote that can be used to treat this patient? If so, what is it and how is it administered? What's the dose of antidote?
9. Is there an indication for the use of elimination-enhancing methods (repeated dose of activated charcoal, urine alkalization, extracorporeal treatment)?

Figure 2. Example question list designed to assess the evaluation and recommendation capacity of ChatGPT in simulated case scenarios in medical toxicology

of ChatGPT-4o responses. Responses were scored according to a predefined scale to obtain category scores. The questions that were answered incorrectly in the first part were repeated in the second part. Here, the questions were presented as direct knowledge questions rather than case scenarios. Thus, ChatGPT-4o's knowledge level was directly assessed rather than its analytical thinking skills. The evaluation results for the second part (questions answered incorrectly in the first part) have been uploaded as Supplemental Material 3.

Table 1. The scoring system for key points used in the evaluation of simulated case scenarios

Simulated cases	General evaluation and stabilization		Diagnostic acitivies		Medical treatments and follow-up	
	Points and parameters		Points and parameters		Points and parameters	
1. Acetaminophen overdose	50	Recognition of APAP overdose	25	Serum acetaminophen level	25	Antidote=NAC
					25	Dose of NAC
			25	Request for serum APAP at 4 h	25	Serum ALT-AST-INR levels
2. TCA overdose	50	Recognition of TCA overdose	25	ECG	25	Antidote=bicarbonate
			25	Recognition of Na channel blockade	25	Dose of sodium bicarbonate
3. Methanol toxicity	50	Recognition of toxic alcohol ingestion	25	Serum ethanol level	25	Antidote = fomepizole antidote = ethanol
			25	Blood gas	25	Elimination using ECTR
4. Organophosphate toxicity	50	Recognition of OF poisoning	x	N/A	25	Antidote= atropine antidote=pralidoxime
					25	Atropinization
5. Digoxin poisoning	50	Recognition of digoxin poisoning	25	Serum digoxin level	25	Digifab / digibind
			25	ECG		
6. Sympathomimetic toxidrome	50	Recognition of sympathomimetic toxidrome	25	Serum CK level	25	IV fluid benzodiazepine
				UDS	25	Cooling methods
7. Lithium overdose	25	Ineffectivity of activated charcoal	25	Serum lithium level	25	Elimination using ECTR
	25	WBI	25	ECG	25	Indication for ECTR
8. CO poisoning	50	Recognition of CO poisoning	50	Blood gas	25	Non-rebreathing mask
					25	HBOT
9. CCB overdose	25	Decontamination	25	Echocardiography	15	Vasopressors
					15	IV calcium
			25	ECG	15	HDI
					15	ECMO
10. Snake bite	50	Snake bite grading	25	CBC, routine biochemistry	25	Antidote=anti-venom
	25	Supportive treatment of extremity edema	25	Serum CK level	25	Dose of anti-venom

ALT: Alanine aminotransferase, APAP: Acetaminophen (n-acetyl-p-aminophenol), CBC: Complete blood count, AST: Aspartate aminotransferase, CCB: Calcium channel blocker, CK: Creatinine kinase, CO: Carbon monoxide, ECG: Electrocardiography, ECMO: Extracorporeal membrane oxygenation, ECTR: Extracorporeal treatment, HBOT: Hyperbaric oxygen therapy, HDI: High-dose insulin treatment, INR: International normalized ratio, IV: Intravenous, NAC: N-acetylcysteine, OF: Organophosphate, TCA: Tricyclic anti-depressant, UDS: Urine drug screen, WBI: Whole bowel irrigation

The average case score was determined by computing the mean of the three category scores for each case. The mean score of cases was employed as an indicator of ChatGPT-4 performance on a case-by-case basis. Subsequently, the overall performance of ChatGPT-4o in simulated scenarios was evaluated by calculating the mean success score across all cases. Bloom's 80% cut-off value was used to determine the success of ChatGPT-4o [6]. According to Bloom's cut-off value, achieving a success rate of over 80% was considered a "success", a success rate between 60-80% was considered "improvable", and a success rate below 60% was considered a "failure". A performance with a correct answer rate exceeding 60% is defined as a passing grade.

Outcomes

The primary objective of this study was to evaluate the appropriateness of the medical recommendations provided by ChatGPT-4o regarding current medical toxicology practices. The secondary goal is to evaluate ChatGPT-4o's capacity to interpret medical toxicology. The accuracy of the answers to the questions was evaluated using medical toxicology guidelines and reference sources, as used by toxicologists [7,8].

Results

In this study, the medical toxicology knowledge level of ChatGPT-4o was tested through a two-stage process using 10

different simulated case scenarios. In the first part of the study, it was observed that ChatGPT-4o achieved an average success rate of 90.88% across the simulated case scenarios. ChatGPT-4o was successful in 9 cases (90%) and received a "improvable" in only 1 case (10%). ChatGPT-4o achieved an excellent success rate (100%) in cases of poisoning with TCA in the first part. ChatGPT-4o also achieved the second highest success rate in the case of methanol toxicity, with an average success rate of 96.67% across the three categories. In addition, ChatGPT-4o achieved a high success rate in the following cases: digoxin poisoning, with an average of 95.83% success rate, CO poisoning with an average of 94.45% success rate. The only case in which ChatGPT-4o performed poorly was a snake bite, with a success rate of 67.5%. The average success rates of ChatGPT-4o in the simulated case scenarios are presented in Table 2.

The average success rate of ChatGPT-4o in the simulated case scenarios was evaluated separately for each of the three categories, and it was observed that ChatGPT-4o was successful in all categories. ChatGPT-4o achieved a success rate of 91.25% in the "general evaluation and stabilization" category, 86.15% in the "diagnostic activities" category, and 95.25% in the "medical treatment and follow-up" category. The average success rates of ChatGPT-4o at the case level, based on categories, were calculated, and the results are shown in Table 2. The results indicate that ChatGPT-4o achieved a perfect (100%) success rate in the "general evaluation and stabilization" category in all cases, except for snake bite. In the case of snake bites, ChatGPT-4o was unsuccessful in the "general evaluation and stabilization" category, with a success rate of 12.5%.

ChatGPT-4o was successful in 6 cases (60%) in the diagnostic activities category. We achieved a perfect (100%) success rate in cases of TCA poisoning, organophosphate toxicity, digoxin poisoning, and snake bite. In the category of "diagnostic activities", although ChatGPT-4o received a passing grade in the remaining cases, it demonstrated limited success, particularly in lithium poisoning (66.67%) and CCB poisoning (67.86%). The category in which ChatGPT-4o performed the least successfully was diagnostic activities, with an average success rate of 86.15%.

ChatGPT-4o was successful in 9 cases (90%) in the "medical treatments and follow-up" category. It achieved a perfect (100%) success rate in all cases (70%) except organophosphate toxicity, digoxin poisoning, and snake bite. ChatGPT-4o received a "passing grade" in the "medical treatments and follow-up" category for organophosphate poisoning with a 75% success rate. The statistical data on the success rates achieved by ChatGPT-4o in the simulated case scenarios are presented in Table 2.

During the initial phase of the study, questions that ChatGPT-4o failed to answer accurately in the simulated case scenarios were subsequently presented as knowledge-based questions in a separate second test. During the secondary test, the correct responses given by ChatGPT-4o for each case were scored in accordance with the evaluation criteria applied in the assessment of the simulated case scenarios. The overall success rate was then determined based on the results of the secondary tests. The success rates obtained from the secondary test and the simulated case scenarios are comparatively presented in Table 3.

It was observed that ChatGPT-4o's average success rate in all three categories and across all cases increased from 90.88% to 97.22% with the secondary test. In the secondary test,

Table 2. Analyzing the performance of ChatGPT-4o in simulated case scenarios across different categories

Simulated cases	General evaluation and stabilization		Diagnostics acitivies		Medical treatments and follow-up		Total	
Case number	**Points**	**Results**	**Points**	**Results**	**Points**	**Results**	**%**	**Result**
1. Acetaminophen overdose	100	Success	78.6	Improvable	100	Success	92.86	Success
2. TCA overdose	100	Success	100	Success	100	Success	100	Success
3. Methanol toxicity	100	Success	90	Success	100	Success	96.67	Success
4. Organophosphate toxicity	100	Success	100	Success	75	Improvable	91.67	Success
5. Digoxin poisoning	100	Success	100	Success	87.5	Success	95.83	Success
6. Sympathomimetic toxidrome	100	Success	75	Improvable	100	Success	91.67	Success
7. Lithium overdose	100	Success	66.67	Improvable	100	Success	88.89	Success
8. CO poisoning	100	Success	83.34	Success	100	Success	94.45	Success
9. CCB overdose	100	Success	67.86	Improvable	100	Success	89.29	Success
10. Snake bite	12.5	Failure	100	Success	90	Success	67.5	Improvable
Total (%)	**91.25**	**Success**	**86.15**	**Success**	**95.25**	**Success**	**90.88**	**Success**

CCB: Calcium channel blocker, CO: Carbon monoxide, TCA: Tricyclic antidepressant

Table 3. Comparison of success rates of ChatGPT-4o after simulated case scenarios and overall success rates following the secondary tests

	Success in simulated case scenarios				Overall success following the secondary test			
Simulated case scenarios	**Category I**	**Category II**	**Category III**	**Total (%)**	**Category I**	**Category II**	**Category III**	**Total (%)**
1. Acetaminophen overdose	100	78.6	100	92.86	100	85.74	100	95.25
2. TCA overdose	100	100	100	100	100	100	100	100
3. Methanol toxicity	100	90	100	96.67	100	100	100	100
4. Organophosphate toxicity	100	100	75	91.67	100	100	100	100
5. Digoxin poisoning	100	100	87.5	95.83	100	100	100	100
6. Sympathomimetic toxidrome	100	75	100	91.67	100	100	100	100
7. Lithium overdose	100	66.67	100	88.89	100	66.67	100	88.89
8. CO poisoning	100	83.34	100	94.45	100	100	100	100
9. CCB overdose	100	67.86	100	89.29	100	92.86	100	97.62
10. Snake bite	12.5	100	90	67.5	81.25	100	90	90.42
Total (%)	**91.25**	**86.15**	**95.25**	**90.88**	**98.13**	**94.53**	**99**	**97.22**

Category I: General evaluation and stabilization, Category II: Diagnostic activities, Category III: Medical treatments and follow-up, CCB: Calcium channel blocker, CO: Carbon monoxide, TCA: Tricyclic antidepressant

ChatGPT-4o achieved an average success rate of over 80% in all cases. As a result of the second test, ChatGPT-4o achieved 100% success in TCA overdose, methanol toxicity, organophosphate toxicity, digoxin poisoning, sympathomimetic toxidrome, and CO poisoning by answering all questions correctly in all three categories. Specifically, it improved the success rate from 67.5% to 90.42% in the case of snake bite. As a result, ChatGPT-4o's success grade in snake bite cases increased from "improvable" to "success". After the second test, ChatGPT-4o failed to increase success rates in cases of lithium overdose. Secondary tests did not contribute to the success rate in this case.

The success rates of ChatGPT-4o in the simulated case scenarios and after the secondary tests were compared, and the results are shown in Table 3. As indicated in the table, ChatGPT-4o demonstrated success in all three categories after the secondary tests, with a score of over 80%. By category, the success rates were 99% in category III (medical treatments and follow-up), 98.13% in category I (general assessment and stabilization), and 94.53% in category II (diagnostic activities). As a result of the secondary tests, the success rate of snake bite cases in category 1 increased from 12.5% to 81.25%. This resulted in a change of the success grade from "failure" to "success" in the case of snake bite. In category II, the success rates of acetaminophen overdose and CCB overdose increased to 85.74% and 92.86%, respectively. In these cases, ChatGPT-4o's success grade increased from "improvable" to "success" in category II. Similarly, in category III, the success rate of organophosphate toxicity increased from 75% to 100%.

Discussion

This study is the pioneering evaluation of ChatGPT-4o proficiency in medical toxicology through the use of simulated case scenarios. The results of our study indicate that ChatGPT-4o achieved high success rates in toxicology case scenarios. However, in a very small number of instances, it did not perform as well in specific categories. Given the potential for improvement in this aspect, it has emerged that ChatGPT has the potential to be used in areas where access to poison information centers and medical toxicologists is limited in the future.

The integration of AI with ChatGPT's advanced assessment and response capabilities demonstrates the contribution of AI in overcoming human workforce and time limitations. This contribution has prompted current research to focus on AI applications similar to ChatGPT. Recent studies utilizing ChatGPT encompass various areas, such as AI-assisted article writing, medical problem-solving, case analysis, exam/test solutions, triage, and generating differential diagnosis lists [9-12]. ChatGPT has no official approval for use in medicine and health [13]. In studies employing ChatGPT, there is frequently an emphasis on ChatGPT's CDS capabilities [10-12]. In these studies, ChatGPT draws conclusions about hypothetical variables, fictional cases, or scenarios and subsequently assesses the accuracy of the conclusions.

In our study, ChatGPT-4o demonstrated high success in providing medical recommendations for the diagnosis, treatment, and follow-up of overall poisoning cases. However,

it was also identified that there were scenarios in which it could be further improved and cases in which it was unsuccessful. In the "diagnostic activities" category, ChatGPT-4o gave insufficient responses concerning the diagnostic parameters that should be routinely requested and utilized for differential diagnosis in every overdose patient arriving at the emergency department. These parameters include serum acetaminophen, urine drug screen, serum salicylate level, serum ethanol level, and serum beta-HCG level in reproductive-age women during the prodromal period. Therefore, ChatGPT-4o did not achieve a perfect (100%) in the diagnostic activities stage of poisoning cases. The lack of appropriate diagnostic tests that should be routinely requested in toxicology had a significant impact on the overall success rate. However, even in such a situation, ChatGPT-4o provided highly successful responses in specific aspects of the diagnostic activities tailored to the individual case.

ChatGPT-4o failed in the "general evaluation and stabilization" category for snake bites. However, it received a satisfactory rating in the secondary tests. ChatGPT-4o demonstrated variable success rates in the categories of different cases. Some questions that were incorrectly answered in the initial assessment were correctly answered in the secondary tests (direct queries). In the secondary tests, the success rate increased from 90.88% to 97.22%. This demonstrates that ChatGPT-4o is capable of delivering highly accurate responses when directly queried with factual inquiries. The observation that previously unsuccessful phases yielded accurate responses when posed with direct factual inquiries emphasizes the importance of further enhancing ChatGPT's already well-regarded analytical prowess and interpretive capabilities.

The high analytical power of ChatGPT-4o stems from its ability to process the concrete data provided by users. Another noteworthy attribute of ChatGPT-4o is its capacity to generate intuitive or inferential judgments, in addition to processing concrete data, which is a capability that humans, as the most intelligent beings on earth, are also capable of. This feature plays a pivotal role in enhancing performance in case scenarios. The most illustrative examples of poisoning in our study are methanol poisoning, CO poisoning, and snake bites. In the case of methanol toxicity, it is explicitly stated that the individual consumed homemade alcohol with friends. Based on the patient's history, clinical, and laboratory findings, ChatGPT-4o hypothesized that the individual consumed methanol. In the simulated case scenario of CO poisoning while smoking hookah with friends at a café, ChatGPT-4o was able to diagnose CO poisoning. Similarly, in the simulated case scenario in which the person expressed feeling pain in her foot and the snake moved away afterwards, ChatGPT was able to infer that a snake bite had occurred.

One of the main drawbacks limiting the use of AI applications is that they give wrong answers to questions. In our study, ChatGPT-4o did not give incorrect answers to any questions. This supports that ChatGPT-4o can be used as a reference source. In our study, the reason for the low ChatGPT-4o score was its inability to provide the desired answer. For example, serum paracetamol level and serum ethanol level were not requested in patients with intentional overdose, and B-HCG was not requested in young women of childbearing age. These factors reduced the success of ChatGPT-4o. Another shortcoming is that ChatGPT-4o reacts to poisoning by ignoring the possibility that the patient may have taken more than one drug at the same time. This can be overcome by the clinical experience of the clinician. However, these shortcomings can also be overcome by training ChatGPT on topics such as "treatment approaches in poisoning patients" and "diagnostic approaches in poisoning patients."

GPTs (generative pre-trained transformers) represent one of the most significant indicators that ChatGPT can be used as a reliable reference in the future. On November 6, 2023, OpenAI announced the launch of custom versions of ChatGPT designed for specific purposes, which are referred to as GTPs. Thus, with a single click (chatgpt.com/create), users can train AI on a specific topic without coding knowledge. As in other professions, GPTs have been established in medicine and health. GPTs can also be trained in specific sub-branches of medicine, such as anatomy, biochemistry, and cardiology. The subject matter of the GPTs is limited only by the user's imagination. This indicates that if GPTs are developed in the field of medical toxicology, they could serve as a gateway for assessing patients with poisoning, offering the same level of expertise as a poison information center but with greater responsiveness.

Despite not being specifically trained in medical toxicology or medicine, ChatGPT's high analytical power and accurate response rates demonstrate its potential in medical decision-making. Although the reliability of AI in medical decision-making remains a topic of debate, the results of our study suggest that ChatGPT can be used by healthcare professionals in areas where access to poison information centers and medical toxicologists is limited. Furthermore, we believe that this study will shed light on the possibility of using ChatGPT as a portal for instant access to accurate and up-to-date information based on textbooks and guidelines.

Study of Limitations

The main limitation of this study is that ChatGPT-4o is not clinically approved for obtaining health information. Although ChatGPT-4o is competent in medical topics, it lacks specific training in medical toxicology. Another limitation of this study is that it was conducted using English questions. It is possible

that the results may be positive or negative depending on whether the clinician conducts the query in their native language.

Conclusion

The ability to query current medical toxicology information through ChatGPT showcases the potential of ChatGPT-4o to serve as a next-generation poison information center, providing a function that physicians can easily access, especially in areas where access to medical toxicologists is limited. The development of algorithms and innovations has made it possible to significantly enhance the success rate of ChatGPT in offering medical toxicology recommendations.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: İ.A., A.Ş., Design: İ.A., S.K., R.G., A.Ş., Data Collection or Processing: İ.A., R.G., A.Ş., Analysis or Interpretation: İ.A., S.K., R.G., Literature Search: İ.A., S.K., Writing: İ.A., S.K., R.G., A.Ş.

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SUPPLEMENTAL MATERIAL LINKS-1: https://d2v96fxpocvxx.cloudfront.net/2a4f1576-691d-4c9c-9173-1686c7aa9aea/documents/6-SUPPLEMENTAL-1-06025.pdf

SUPPLEMENTAL MATERIAL LINKS-2: https://d2v96fxpocvxx.cloudfront.net/2a4f1576-691d-4c9c-9173-1686c7aa9aea/documents/6-SUPPLEMENTAL-2-06025.pdf

SUPPLEMENTAL MATERIAL LINKS-3: https://d2v96fxpocvxx.cloudfront.net/2a4f1576-691d-4c9c-9173-1686c7aa9aea/documents/6-SUPPLEMENTAL-3-06025.pdf

ORIGINAL RESEARCH

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Investigation of Dynamic $ETCO_2$ Values With Side Stream in The Treatment of PTX: A Prospective Study

Safa Dönmez[1], Alp Sener[2], Nurullah İshak Işık[3], Mehmet Yılmaz[4], İlker Akbaş[5], Hakan Oguzturk[1]

[1]University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Clinic of Emergency Medicine, Ankara, Türkiye
[2]Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Emergency Medicine, Ankara, Türkiye
[3]Ministry of Health Ankara Etlik City Hospital, Clinic of Emergency Medicine, Ankara, Türkiye
[4]Ministry of Health Ankara Etlik Bilkent City Hospital, Clinic of Emergency Medicine, Ankara, Türkiye
[5]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Emergency Medicine, Kahramanmaraş, Türkiye

Abstract

Objective: Pneumothorax (PTX) is the accumulation of air in the pleural space, and it poses significant concerns in emergency settings. End-tidal carbon dioxide ($ETCO_2$) monitoring is potentially significant in PTX management, particularly regarding treatment response. This study aimed to elucidate the role of $ETCO_2$ monitoring in patients undergoing PTX, particularly in assessing treatment response following tube thoracostomy.

Materials and Methods: This prospective cross-sectional study was conducted at Ankara Bilkent City Hospital's emergency department. It included 43 patients diagnosed with spontaneous or traumatic PTX. $ETCO_2$ levels were measured before and after tube thoracostomy, along with other clinical parameters.

Results: Statistical analysis revealed significant differences in $ETCO_2$ values before tube insertion and at 2 and 4 hours post-insertion($p<0.001$). P-values were also less than 0.001 for all pairwise comparisons in the post hoc analysis. Changes in $ETCO_2$ levels post-treatment indicated the potential of this parameter for monitoring treatment efficacy. However, no significant difference was observed between spontaneous and traumatic PTX cases.

Conclusion: $ETCO_2$ monitoring emerges as a promising tool in PTX management, providing insights into treatment response. Further research is warranted to optimize its integration into clinical practice to enhance PTX patient care.

Keywords: PTX, tube thoracostomy, end-tidal carbon dioxide ($ETCO_2$)

Introduction

Pneumothorax (PTX) is defined as the accumulation of air in the pleural space [1]. PTX can develop secondary to various etiologies, and in some cases, there may be no identifiable lung abnormality[2]. PTX can be classified as spontaneous or traumatic [1]. The pathogenetic mechanisms leading to spontaneous PTX can be associated with lung-related abnormalities and environmental factors, such as smoking [2]. Traumatic PTX is another commonly encountered classification in the emergency department. Traumatic PTX can be further classified as iatrogenic or non-iatrogenic [3]. PTX can compromise lung tissue perfusion in the affected area and increase intrathoracic pressure, thereby impeding venous return and posing a potential life-threatening situation. Therefore, PTX necessitating urgent intervention is a significant concern in emergency departments [4].

End-tidal carbon dioxide ($ETCO_2$) provides insight into carbon dioxide levels resulting from lung perfusion and serves as a respiratory parameter providing information about the prognosis of many critical illnesses [5]. Physiologically, it is expected to be between 35-40 mmHg, with lower values expected in cases of impaired lung perfusion. One of the most important factors

Address for Correspondence: Safa Dönmez, University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Clinic of Emergency Medicine, Ankara, Türkiye
E-mail: drsafa0131@gmail.com **ORCID-ID:** orcid.org/0000-0003-1132-3617
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determining lung perfusion is the effective lung area [6]. The effective lung area can be influenced by many factors. One of the most important conditions for emergency departments is pneumothoraces. PTX resolves with emergency intervention, and an effective lung area is established. Perfusion and venous return improve. Based on the relationship between effective lung area and $ETCO_2$, it has been hypothesized that $ETCO_2$ may be affected in cases of PTX, and studies have explored the hypothesis that PTX can be monitored with $ETCO_2$ [5].

The present study aimed to investigate the changes in $ETCO_2$ levels following tube thoracostomy in patients undergoing PTX. Prior to tube insertion, we expected lower $ETCO_2$ values, and we measured them at intervals after tube insertion to assess the effectiveness of treatment and highlight the importance of etiology. We believe that the obtained data could be valuable for monitoring treatment response in patients with PTX.

Materials and Methods

Study Design

This study was conducted between August 15, 2023, and February 6, 2024, in patients diagnosed with isolated PTX who presented to the emergency department of Ankara Bilkent City Hospital, a tertiary care research hospital. The study has a prospective and cross-sectional design. Ethical approval was obtained from the Ankara Bilkent City Hospital No. 1 Clinical Research Ethics Committee (decision number: E1/387072023, date: 06.09.2023).

Patient Selection

The study included patients aged 18 years and above, without any comorbidities, diagnosed with spontaneous or traumatic PTX, who underwent tube thoracostomy, and did not have any other organ damage or injury. Participants were selected from volunteers who signed informed consent forms after being provided with detailed information about the study criteria. The study was completed in 43 patients.

Exclusion Criteria

- Patients aged below 18 years or over 65 years
- Patients who refused to participate in the study
- Pregnant women
- Individuals diagnosed with acute/chronic lung disease
- Patients with a history of advanced heart failure
- Patients with advanced systemic diseases
- Individuals with a history of malignancy (cancer)
- Chronic liver disease
- Individuals using sedative and analgesic drugs with neuropsychiatric effects
- Patients with a history of psychological or neurological diseases
- Patients with acute organ damage or failure other than PTX

The summary of the study and the flowchart are presented separately in Figure 1.

Study Variables and Definitions

In the study, a GE-brand patient monitor (GE Medical Systems Information Technologies, Germany) was used for vital parameter measurements, while a Medtronic-brand Capnostream 35 respiratory monitor device (Oridion Medical 1987 Ltd., Israel) was used for $ETCO_2$ measurement. $ETCO_2$ measurements of patients were conducted using a device that measures $ETCO_2$ levels in breaths delivered through the mouth and nose (sidestream measurement). $ETCO_2$ values were measured before tube thoracostomy insertion and at the 2nd and 4th hours after tube insertion in patients with indications for tube thoracostomy. The diagnosis of PTX was made using chest X-ray. The tube thoracostomy procedure was performed by chest surgeons or emergency physicians. Indications for tube thoracostomy were determined by chest surgeons.

Patients' age, gender, height, weight, vital signs, smoking history, PTX causes, lateral and apex collapse amount (in mm), procedures performed, $ETCO_2$ values before and after tube insertion at 2 and 4 hours, complete blood count, biochemistry, and arterial blood gas values were recorded on case report forms. Additionally, the length of hospital stay of patients was recorded using archive numbers through the hospital automation system.

According to the English guidelines, a large PTX is defined as a distance of more than 2 cm between the parietal and visceral pleura at the level of the hilum on chest X-ray, or a distance of more than 3 cm from the apex according to American guidelines [7]. Additionally, the percentage of PTX volume was calculated using the Collins method. The PTX percentage was calculated using the Collins method with the formula: % Collins="4.2 + 4.7(a + b + c)", where "a" represents the maximum apical interpleural distance, "b" represents the interpleural distance at the midpoint of the upper half of the lung, and "c" represents the interpleural distance at the midpoint of the lower half of the lung [8].

The first $ETCO_2$ ($ETCO_2$-0) was defined as the $ETCO_2$ measured during the emergency department visit. $PaCO_2$ was defined as the partial pressure of carbon dioxide measured during the first arterial blood gas analysis performed during the emergency department visit. After lung expansion, $ETCO_2$ was calculated as the average value of $ETCO_2$ measured 2 to 4 hours after tube thoracostomy ($ETCO_2$-1/$ETCO_2$-2). The increase in $ETCO_2$ after expansion was defined as the increase in $ETCO_2$ after closed

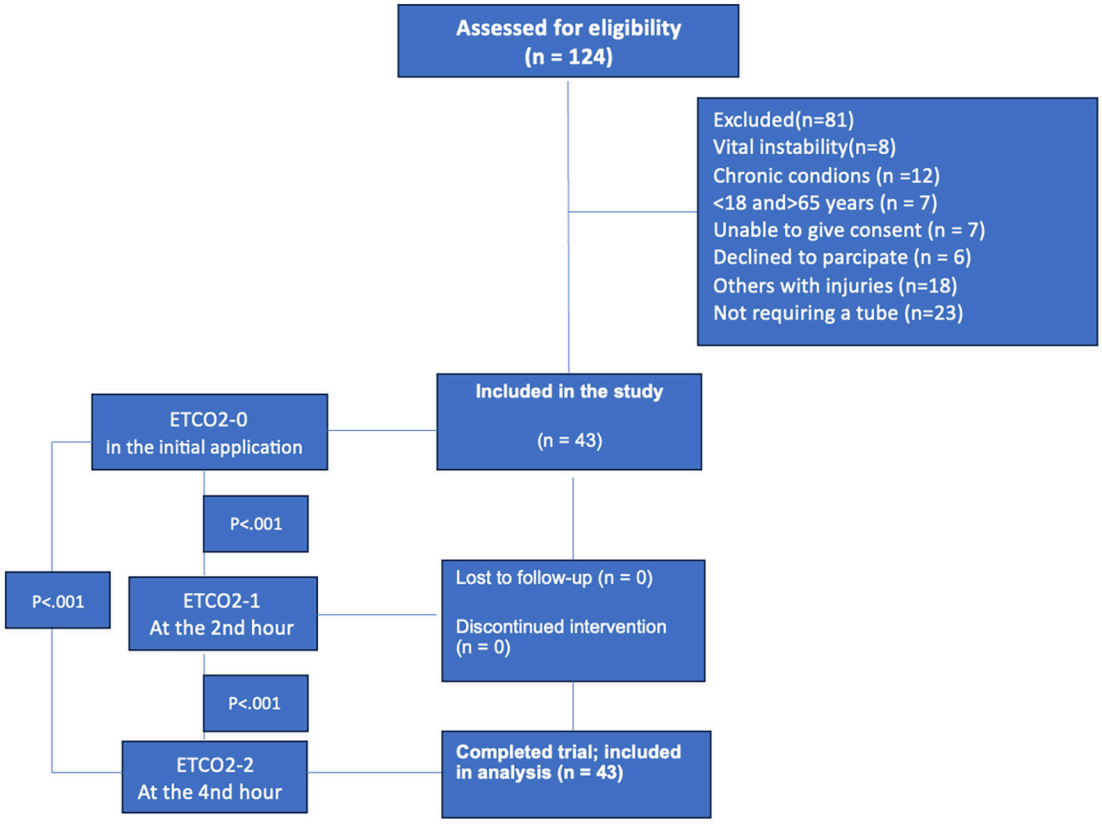

Figure 1. The flowchart and summary of the study

ETCO: End-tidal carbon dioxide

tube thoracostomy (Increase in $ETCO_2$ after drainage=$ETCO_2$ after tube thoracostomy-first $ETCO_2$). The change from $ETCO_2$-0 to $ETCO_2$-1 was determined as delta $ETCO_2$-1 ($\Delta ETCO_2$-1), and the change from $ETCO_2$-0 to $ETCO_2$-2 was determined as $\Delta ETCO_2$-2.

Outcomes

The primary endpoint of the study was the relationship between $ETCO_2$-0, $ETCO_2$-1, $ETCO_2$-2, $\Delta ETCO_2$-1, and $\Delta ETCO_2$-2 with Ac expansion after PTX treatment. The secondary endpoints included the differences between the traumatic and non-traumatic groups, relationship between hospital stay and $ETCO_2$ values, collapse percentage, PLR, and NLR indices.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for MacOS version 28.0 (Armonk, NY: IBM Corp). The normality of continuous data was assessed using the Shapiro-Wilk test, Q-Q plots, and histograms. Normally distributed parameters were presented as mean, standard deviation, and 95% confidence interval, whereas parameters with non-normal distributions were expressed as median and interquartile range. Independent Samples t-test was used to assess the mean and mean differences for parameters with normally distributed data between the two groups. Descriptive statistics for continuous data included mean standard deviation and median, while frequency percentages were provided for nominal variables. The suitability of $ETCO_2$ for consecutive measurements was confirmed, and repeated measures ANOVA was conducted with post hoc pairwise comparisons adjusted using the Bonferroni method. Finally, Spearman's correlation test was performed for $ETCO_2$ values and other parameters.

Sample Size

Lee et al. [5] calculated that a minimum of 32 patients should be included in the study based on their data, with an 80% power and a 5% type 1 error rate. However, considering possible data losses, the study was planned to be conducted with 45 patients (5).

Results

Patient Information and Blood Parameters

The demographic characteristics of the patients, along with their blood parameters upon admission and the percentage of PTX volume, are presented in Table 1.

$ETCO_2$ Measurements

The statistical analysis revealed a significant difference among all measurement groups in the $ETCO_2$ values obtained before

Table 1. Table showing the demographic characteristics of the patients

Variables		n (%)	Median (25-75%)	Mean (SD)
Gender	Male	36 (83.7)		
	Female	7 (16.3)		
PTX cause	Spontaneous	23 (53.5)		
	Traumatic	20 (46.5)		
Age			41 (24-60)	41.88 (17.61)
Height			174 (168-178)	173.07 (7.09)
Weight			75 (65-80)	73.26 (12.19)
SBP			125 (110-140)	127.09 (16.59)
DBP			80 (70-90)	79.19 (11.38)
SpO_2			89 (88-91)	87.56 (12.54)
Pulse rate			87 (80-94)	85.33 (15.27)
RR			19 (17-20)	18.93 (2.14)
Cigarettes (quantity)			10 (0-20)	13.72 (15.54)
Years of smoking			0 (0-20)	8.51 (12.48)
pH			7.36 (7.34-7.40)	7,36 (0.04)
PCO_2			42.9 (38.1-47.2)	42.96 (8.08)
PO_2			41.8 (35.4-50.4)	43.92 (10.82)
Laktat			1.64 (1.27-2.35)	1.96 (0.93)
Hemoglobin			14.6 (13.1-15.7)	14.21 (1.87)
WBC			11 (7.91-13.12)	11.05 (3.47)
Platelet			251 (211-288)	251.3 (59.78)
Hematocrit			42.5 (40-47.4)	42.93 (5.47)
Neutrophil			7.47 (6.3-10.77)	8.69 (3.69)
Lymphocyte			1.3 (0.81-1.65)	1.43 (0.88)
Na			140 (138-141)	139.2 (3.11)
K			4.3 (4.2-4.6)	4.34 (0.46)
Bun			30 (20-42)	33.12 (18.25)
Creatinine			0.84 (0.74-0.92)	0.88 (0.30)
Length of hospital stay			6 (4-8)	6.98 (3.73)
Volume percentage (%)			29.11 (23.99-42.79)	34.44 (14.47)

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SpO_2: Oxygen saturation, RR: Respiratory rate, WBC: White blood cell, Bun: Blood urea nitrogen , PLR: Platelet lymphocyte ratio, NLR: Neutrophil-lymphocyte ratio, PTX: Pneumothorax

tube insertion and at 2 and 4 hours after tube insertion ($p<0.001$). Further post hoc analysis indicated that all groups differed from each other (Table 2, Figure 2). Additionally, a statistically significant difference was found in the comparison of $\Delta ETCO_2$ values between $\Delta ETCO_2$-1 and $\Delta ETCO_2$-2 (Table 2).

When examining the correlations between length of hospital stay and $ETCO_2$, along with other parameters, a statistically significant relationship was found between the percentage of PTX volume and length of hospital stay. However, the relationship between length of hospital stay and other parameters was statistically insignificant (Table 3).

Statistically, no significant difference was found in both the $ETCO_2$ values and the $\Delta ETCO_2$ values when comparing spontaneous and traumatic PTX cases (Table 4).

Discussion

The evaluation of lung function based on $ETCO_2$ and its relationship with lung volume is an ongoing debate. This study aimed to elucidate the relationship between volume changes and $ETCO_2$ in patients with PTX. To the best of our knowledge, this study is the first prospective investigation of this hypothesis. According to the results obtained herein, the $ETCO_2$-0 value measured before tube thoracostomy, which was

Table 2. Distribution of $ETCO_2$ levels in patients and the relationship between values before and after tube thoracostomy

	Mean (SD)		p	95% CI	
				Lower bound	Upper bound
$ETCO_2$-0	26.86 (4.72)		<0.001*	25.408	28.313
$ETCO_2$-1	31.27 (4.97)			29.749	32.810
$ETCO_2$-2	32.97 (4.01)			31.741	34.212
Post-hoc pairwise comparisons		**Mean diff**	**p**		
$ETCO_2$-0	$ETCO_2$-1	-4.419	<0.001**	-6.199	-2.638
	$ETCO_2$-2	-6.116	<0.001**	-8.027	-4.205
$ETCO_2$-1	$ETCO_2$-2	-1.698	0.001**	-2.785	-0.611
Comparison of ΔETCO2 values					
ΔETCO-1	-4.42 (4.68)		<0.001†	0.818	2.577
ΔETCO-2	-6.12 (5.02)				

The mean difference is significant at the .05 level,

*Repeated Measured ANOVA (Greenhouse-Geisser), †Paired Sample T Test, **Adjustment for multiple comparisons: Bonferroni,

SD: Standard daviation, CI: Confidence interval, ETCO: End-tidal carbon dioxide

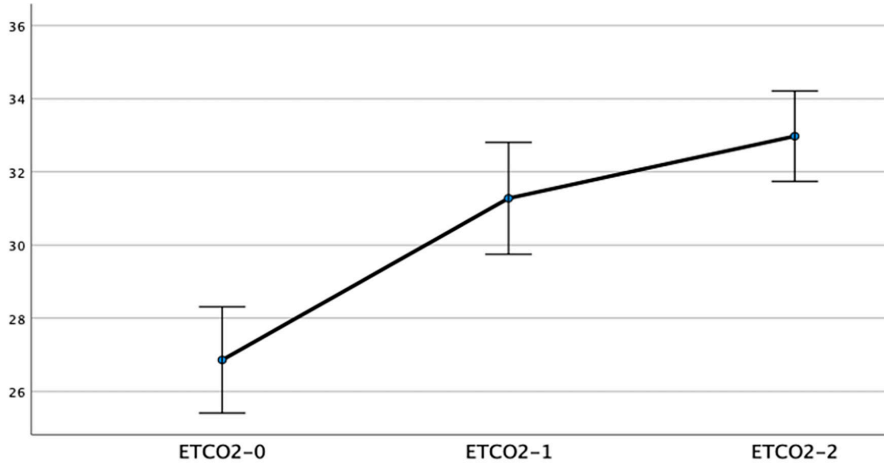

Figure 2. Changes in $ETCO_2$ levels following chest tube insertion

ETCO: End-tidal carbon dioxide

below the normal reference range and started to rise after tube thoracostomy, suggested a close relationship between $ETCO_2$ and lung volume, which may be significant for monitoring treatment efficacy.

When examining the characteristics of our study population, it is evident that there is a predominance of males and a representation of a young demographics. Concerning PTX, we observed that our population differed from the standard expected asthenic constitution. It is important to note that our population, which is consistent with the literature regarding gender distribution, exhibits differences in body morphology [9]. We can consider the increasingly sedentary lifestyle prevalent worldwide and in our country as a possible reason for this difference.

Normal healthy individuals typically have an expected normal range of $ETCO_2$ between 35 and 40 mm Hg, and values below or above these limits are considered pathological [6]. Studies have shown that $ETCO_2$ levels are a prognostic indicator in conditions such as severe infection, trauma, and cardiac arrest [10,11,12]. In patients with PTX, $ETCO_2$ values are expected to be lower than normal due to the dead space associated with the condition[6]. In a study conducted, differences between primary spontaneous and secondary spontaneous PTX were investigated, and it was reported that $ETCO_2$ values of all patients were lower before tube thoracostomy and higher after tube thoracostomy [5]. Our study findings support the existing literature, showing a similar relationship between patients' $ETCO_2$-0 and $ETCO_2$-1 and $ETCO_2$-2 values. This indicates how the

Table 3. Correlation of $ETCO_2$, collapse rates, and blood parameters with length of hospital stay

		$ETCO_2$-0	$ETCO_2$-1	$ETCO_2$-2	Volume percentage
Length of hospital stay	Spearman's rho	-0.202	0.022	-0.008	0.412
	p	0.193	0.891	0.961	0.006
		BUN	Laktat	HMG	WBC
	Spearman's rho	-0.226	-0.005	-0.225	0.134
	p	0.144	0.974	0.147	0.391

Table 4. Comparison of $ETCO_2$ between spontaneous and traumatic pneumothorax

		Mean (SD)	Mean diff	p	95% CI
ETCO-0	Spontaneous	27.30 (4.9)	0.95	0.5*	-1.979-3.888
	Traumatic	26.35 (4.6)			
ETCO-1	Spontaneous	30.96 (5.4)	-0.69	0.65*	-3.794-2.407
	Traumatic	31.65 (4.5)			
ETCO-2	Spontaneous	32.61 (4.4)	-0.69	0.53*	-3.288-1.705
	Traumatic	33.40 (3.6)			
$\Delta ETCO_2$-1	Spontaneous	-3.65 (4.62)	1.64	0.25*	-1.23-4.52
	Traumatic	-5.30 (4.70)			
$\Delta ETCO_2$-2	Spontaneous	-5.30 (4.81)	1.74	0.26*	-1.34-4.83
	Traumatic	-7.05 (5.21)			

*Independent Samples Test,

SD: Standard davitation, CI: Confidence interval, ETCO: End-tidal carbon dioxide

ventilation changes over time and returns to normal once full expansion is achieved. However, our results differ numerically from the literature. Our findings do not support the literature regarding pre- and post-expansion values and the amount of increase. The increased values at 2 and 4 h after expansion can be attributed to initial edema occurring acutely after expansion and its subsequent reduction over time. Follow-ups after PTX are typically based on clinical findings, vital parameters, and radiological findings. Although bedside X-rays are commonly used, they are not always readily available and involve radiation [13]. $ETCO_2$ measurement is a continuous and easily accessible method. Additionally, the increase observed over time is valuable for monitoring whether the tube is functioning properly and for tracking potential additional complications. When comparing the results of our study with those of the study conducted by Lee et al. [5] although they only included patients with primary and secondary spontaneous PTX and conducted their study retrospectively, there were similarities in terms of hospital stay durations and volume percentages. However, our $ETCO_2$ values did not show statistical significance with hospital stay duration. Only a statistically significant correlation was observed between volume percentage and hospital stay duration.

In a study of trauma patients, a comparison was made between patients with and without PTX. Parameters such as hemoglobin (Hgb), hematocrit (Hct), platelet, neutrophil, and lymphocyte counts, sodium (Na), potassium (K), and length of hospital stay were compared. It was noted that, except for Hgb and Hct, all other parameters were higher in the PTX group [14]. When the averages and standard deviations of patients in the PTX group in this study were examined numerically, Hgb and Hct were found to be higher. Among the other parameters, Na, K, platelet, and lymphocyte counts were found to be numerically close. However, in our study, the neutrophil count and average were numerically lower. Additionally, the average and standard deviation values for hospital stay in our study are similar to those in this previous study. We believe that these results are related to our study population. The reason for this discrepancy may be the inclusion of patients with isolated PTX without any additional diseases in our study.

In a study examining unilateral AC contusion, it was highlighted that changes in $ETCO_2$ levels are significant for evaluating the ventilation-perfusion (V/Q) balance of the lungs. Specifically, low $ETCO_2$ levels in diseased lungs can be an indicator of decreased ventilation [15]. Although our study focused on patients with isolated PTX, the findings are consistent with the existing literature. In cases of pulmonary embolism, a reduction in $ETCO_2$ is significantly associated with decreased pulmonary perfusion and increased alveolar dead space, leading to elevated venous CO_2 levels and consequently increasing the arterial CO_2-$ETCO_2$ gradient [16]. Although we did not present calculations for the CO_2-$ETCO_2$ gradient in our study, the direction of changes in $ETCO_2$ was consistent with that presented in the literature. An analysis involving patients with chronic obstructive pulmonary disease indicated that

higher $ETCO_2$ levels tend to decrease with treatment and may serve as a guide for intubation decisions; however, the changes observed in our study were in the opposite direction [17]. This discrepancy may be due to differences in pathophysiological mechanisms. Additionally, another study reported a decline in $ETCO_2$ levels among patients with pulmonary embolism [18]. The results of our study indicate that the collapse in AC caused a corresponding disruption in V/Q, which is in agreement with the literature. In conclusion, $ETCO_2$ monitoring can be used as a parameter for tube management and is a more convenient and harmless method than other existing methods. Conducting further studies on this topic would enhance our understanding.

Study Limitations

Our patient population primarily consisted of relatively young patients. Therefore, studies involving larger patient groups, including more elderly patients, or focusing specifically on elderly patients should be conducted. Another limitation is that we only included isolated PTX cases in our study; $ETCO_2$ values may vary in patients with multiple traumas, additional injuries, or other medical conditions. Hence, studies with a larger sample size that also include patients with such additional complaints or diseases can be conducted.

Conclusion

Our study provides valuable insights into the potential benefits of $ETCO_2$ monitoring in the management of PTX cases. By examining changes in $ETCO_2$ levels before and after tube thoracostomy, our aim was to evaluate treatment efficacy and underscore the significance of the etiology. Our results support the hypothesis that $ETCO_2$ values are influenced by PTX, suggesting that they could be a useful parameter for monitoring treatment response. Additionally, it offers a convenient and noninvasive approach. Further studies are needed to validate our findings and optimize patient care in the management of PTX. Overall, our study contributes to the growing body of evidence supporting the valuable role of $ETCO_2$ monitoring in the management and monitoring of patients with PTX. Further clinical research is required to fully elucidate its clinical implications and to integrate it into routine practice.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ankara Bilkent City Hospital No. 1 Clinical Research Ethics Committee (decision number: E1/387072023, date: 06.09.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.D., A.Ş., H.O., Concept: S.D., A.Ş., N.İ.I., M.Y., İ.A., H.O., Design: S.D., A.Ş., N.İ.I., M.Y., İ.A., H.O., Data Collection or Processing: S.D., A.Ş., H.O., Analysis or Interpretation: S.D., A.Ş., N.İ.I., M.Y., İ.A., Literature Search: S.D., A.Ş., N.İ.I., M.Y., İ.A., Writing: S.D., A.Ş., N.İ.I., İ.A.

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

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ORIGINAL RESEARCH

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Assessing Uterine Rupture: A Bibliometric Analysis of a Critical Emergency for Women's Health

Engin Yıldırım[1], Habibe Selmin Özensoy[2]

[1]Malatya Turgut Özal University, Department of Obstetrics and Gynecology, Malatya, Türkiye
[2]Ankara City Hospital, Clinic of Emergency Medicine, Ankara, Türkiye

Abstract

Objective: This study aimed to provide a comprehensive bibliometric analysis of academic literature related to uterine rupture, highlighting trends, publication productivity, and key contributors in this critical area of women's health.

Materials and Methods: A comprehensive analysis of the Web of Science (WoS) database was conducted, encompassing articles published from 1980 to 2023. Keywords "uterine rupture" and "uterus rupture" were utilized. Data visualization was facilitated using Datawrapper, while VosViewer 2019 was used to analyze coauthorship and citation networks.

Results: A total of 5.828 publications were identified, of which 5.745 were analyzed after excluding studies from 2024. The United States, England, and France emerged as the top contributing countries. The American Journal of Obstetrics and Gynecology was the leading journal. The publication rate has steadily increased, peaking in 2020. The most cited article, "risk of uterine rupture during labor among women with a prior cesarean delivery" reflects ongoing concerns in obstetric care. Collaborations between researchers and institutions are evident, with significant networks formed around key authors.

Conclusion: Uterine rupture remains a pressing clinical issue, increasingly prevalent due to rising cesarean rates. Emergency physicians and obstetricians should understand the risk factors and diagnostics. Continued growth in research publications is anticipated, with a focus on multidisciplinary approaches to enhance understanding and management strategies for uterine rupture.

Keywords: Uterine rupture, emergency medicine, gynecology, bibliometrics

Introduction

Uterine rupture is represents a serious gynecological and obstetric emergency linked to considerable maternal and perinatal complications and fatalities. Clinically, uterine rupture is defined as a complete tear through the uterine layers, including the parietal peritoneum. The incidence of peripartum uterine rupture ranges from 1 in 280 to 12.000 births, often leading to fetal death due to hemorrhage, the need for hysterectomy, and potentially maternal death [1]. In the United Kingdom (UK), it is reported in 0.2% of patients attempting vaginal birth after cesarean section and in 2 out of 10.000 of all births [2]. Perinatal risks associated with uterine rupture include damage to a cesarean scar and use of prostaglandins for labor induction [3]. Uterine rupture typically presents with signs such as fetal distress, maternal abdominal pain, and hypovolemic shock. Emergency intervention may require a laparotomy, cesarean delivery, scar repair, or hysterectomy. In some delayed cases, the fetus, placenta, and hematoma may be located in the abdominal cavity. Uterine scar dehiscence, a milder form of uterine rupture characterized by the partial separation of a preexisting uterine scar, is more common but less dangerous, rarely leading to significant fetal or maternal complications. Unlike full rupture, uterine scar dehiscence does not involve the overlying visceral peritoneum and typically does not result in significant bleeding. Moreover, in cases of dehiscence, the fetus, placenta, and umbilical cord remain contained within the uterine cavity.

Address for Correspondence: Engin Yıldırım, Malatya Turgut Özal University, Department of Obstetrics and Gynecology, Malatya, Türkiye
E-mail: dreyildirim@gmail.com **ORCID-ID:** orcid.org/000-0001-7937-4141
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Uterine rupture can also be caused by gynecological causes. Prior surgeries, such as myomectomy, hysteroscopic procedures, and adenomyoma excision, may weaken the uterine wall, leading to rupture in the scar area, with or without pregnancy. Advances in the imaging of cesarean scars, including assessments of uterine wall thickness and the identification of hypoechoic areas, have led to the introduction of the term "isthmocele" [4]. Proper surgical techniques during cesarean delivery can help reduce the incidence of uterine rupture, dehiscence, and ischiocele formation.

The clinical manifestations of uterine rupture vary according to the size and depth of the rupture. Patients may experience symptoms ranging from atypical lower abdominal pain to severe abdominal discomfort and from mild intra-abdominal hemorrhage to hematoma formation and hypovolemic shock. Research on the obstetric and gynecological causes, treatments, and follow-up protocols for uterine rupture is increasing, with an increasing number of publications annually. The objective of this study was to perform a comprehensive bibliometric analysis of academic articles on uterine rupture.

Materials and Methods

Our study utilized the Web of Science (WoS) database, incorporating sources such as the Korean journal database, the core collection index, the Russian Science Citation Index, and the Scientific Electronic Library Online citation index. We analyzed articles indexed between 1980 and 2023, deliberately excluding studies from 2024. This exclusion was made because the year 2024 is still in progress, and a complete view of its publications cannot yet be determined. Consequently, the citation metrics, publication frequencies, and impact factors for this year remain provisional. Including incomplete data from an ongoing year could introduce inconsistencies, thereby affecting the accuracy and comparability of trends across a stable time frame. The keywords "uterine rupture" and "uterus rupture" were employed during the database search. To visualize global research productivity, we employed the free open web-based application Datawrapper. The VosViewer 2019 software was used to evaluate the scientific significance of the obtained data.

This study analyzes the published literature on uterine rupture through a bibliometric approach, focusing on the characteristics of the reports. Bibliometric studies in medicine generally do not require ethical approval because they do not involve direct interaction with human participants, collection of personal data, or clinical interventions. Instead, they rely on publicly available data, such as published articles, citation metrics, and other scientific outputs, which pose no risk to individual privacy or welfare. Consequently, these studies fall outside the ethical review guidelines applicable to research involving human subjects.

Statistical Analysis

The statistical analysis for this bibliometric study was performed using descriptive and inferential methods to summarize and interpret the data retrieved from the WoS database. Descriptive statistics, such as frequencies, percentages, and averages, were used to quantify publication trends, citation metrics, and authorship patterns. Additionally, inferential techniques, such as regression analysis, were employed to identify significant trends over time and correlations between variables like publication year, citation counts, and journal impact factors. These methods ensured a robust and systematic evaluation of the bibliometric data.

Results

Overview of Characteristics and Worldwide Output: By examining the WoS database using the keywords "uterine rupture" and "uterus rupture", we found a total of 5.828 publications. In our study, we excluded 339 studies from 2024 because their citations were not yet complete. The remaining 5.745 articles published prior to 2023 were analyzed, with the first article dating back to 1980. This initial article examined the relationship between the use of hyperosmolar urea and prostaglandin in mid-trimester pregnancy abortion and uterine rupture [5]. The articles were published in 21 different languages, with English as the most prevalent, accounting for approximately 92.7% of all publications.

The majority of the documents (77.6%) were research articles, followed by reviews and meeting abstracts (Table 1). An analysis of the distribution of documents related to uterine rupture across scientific fields revealed studies in 40 different areas, with obstetrics and gynaecology being the most researched branch, comprising 64.1% of all documents. Subsequently, reproductive biology, emergency care, surgery, respiratory medicine, and medical imaging in radiology followed (Table 2). The number of publications related to uterine rupture has been increasing each year, with a significant increase starting

Table 1. Publication types of uterine rupture literature between 1980-2022

Research areas	Number of publications	% of 5745
Article	4463	77.6
Review	566	9.8
Proceedings paper	234	4.1
Letter	218	3.7
Editorial material	201	3.4
Meeting mbstracts	179	3.1
Note	49	0.8
Book mhapter	26	0.5
Early access	15	0.2
Corrections	8	0.1

in 1998. This trend culminated in 2020, with a record 383 publications, the majority being research articles (Figure 1). The most cited research article during this period was titled "risk of uterine rupture during labor among women with a prior cesarean delivery" published in the New England Journal of Medicine [6]. Upon evaluating the citations of documents related to uterine rupture, we found that the highest number of citations occurred in 2022. Among the articles published in the last 5 years, the most cited was "short-term and long-term effects of cesarean section on the health of women and children", which was published in The Lancet [7]. In total, 3.680 articles on uterine rupture have been published in the field of obstetrics and gynecology, with 885 of these articles appearing in the American Journal of Obstetrics and Gynecology, Obstetrics and Gynecology, and the Journal of Maternal-Fetal & Neonatal Medicine. The year 2022 was the most cited article on uterine rupture published in the American Journal of Obstetrics and Gynecology, with the most cited article being "incidence, risk factors, and temporal trends in severe postpartum hemorrhage" [8] (Figure 2).

We evaluated the countries responsible for publishing articles on uterine rupture and identified the USA, England, and France as the most productive countries. Approximately 27.0% of all publications originated from the United States

Table 2. The top 10 research areas of documents in uterine rupture according to the Web of Science database between 1980-2022

Research areas	Number of publications	% of 5745
Obstetrics and gynecology	3680	64.1
General internal medicine	752	13.1
Reproductive biology	427	7.4
Pediatrics	269	4.6
Radiology	250	4.3
Surgery	217	3.77
Public environmental and occupational health	149	2.5
Experimental medicine research	96	1.6
Multidisciplinary science	65	1.1
Emergency medicine	34	0.5

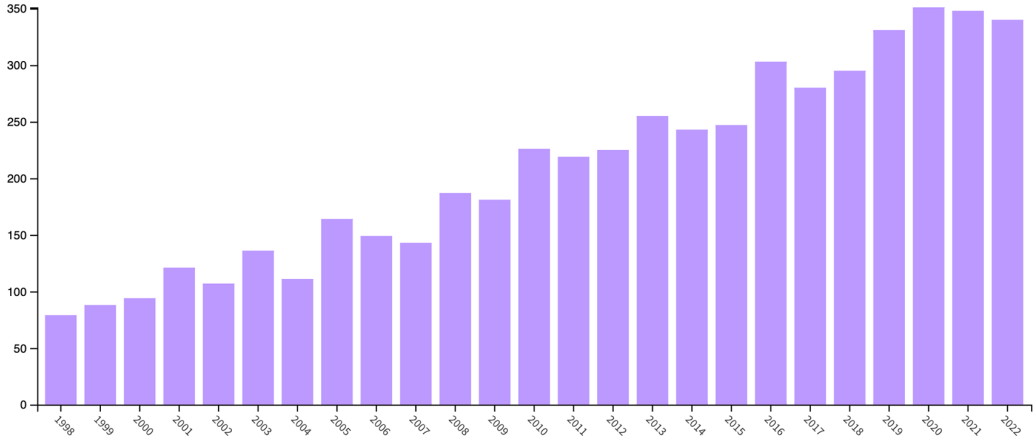

Figure 1. Graph of publications about uterine rupture by year

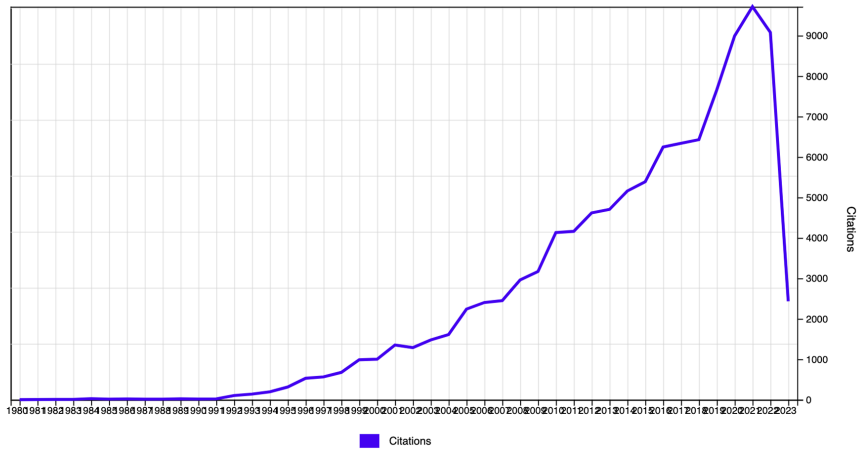

Figure 2. Graph of citations about uterine rupture by year

(Figure 3). We noted that the productivity of African and Central Asian countries regarding uterine rupture is relatively low, with the most productive countries being North America and Europe (Figure 4).

Productivity of Authors and Institutions: We compared author productivity, institutional output, and the h-index. Bujold E from Laval University, Canada was identified as the most productive researcher. The 10 most productive authors and countries are presented in Table 3. Furthermore, we compared the productivity of universities and organizations in the WoS database. The University of Texas System emerged as the most productive institution, with 127 publications (2.05%) in the field of uterine rupture (Figure 5).

Authorship and Institutions Co-citation: A co-citation analysis revealed that 44.708 authors have investigated uterine rupture. Organizations that published at least 10 documents and received 10 citations were classified, with 146 out of 4.949 organizations meeting these criteria. Among these, Wayne State University (USA) was identified as the most active. Collaboration and citation networks were noted between Wayne State University, Ohio State University, and University of Texas. Additionally, organizations from EU countries demonstrated collaborative efforts centered around the UK (Table 4, Figure 5).

In evaluating authors' collaborations, a total of 20.195 authors with at least 10 publications on uterine rupture were identified. After filtering, 67 active authors were identified, and their collaborative efforts were assessed. A clustering of collaboration around five active authors was observed, with Margaret Harper, Emmanuel Bujold, and Catherine Spong being the most collaborative (Figure 6).

Significant Publications: Articles concerning uterine rupture were reviewed, focusing on the most cited works, average citations per year, authors, and publishers. The document authored by Lydon-Rochelle, M. titled "risk of uterine rupture during labor among women with a prior cesarean delivery" ranked first in total citations and average citations per year [9]. The 10 most cited articles are listed in Table 5. The Citation relationships among the articles reflected the publishing trends and author preferences. A yearly examination of

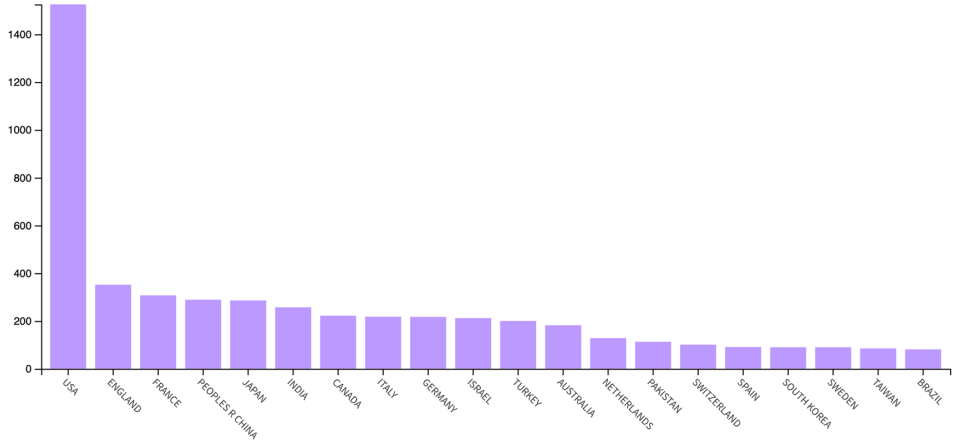

Figure 3. The top ten publishing country charts on uterine rupture

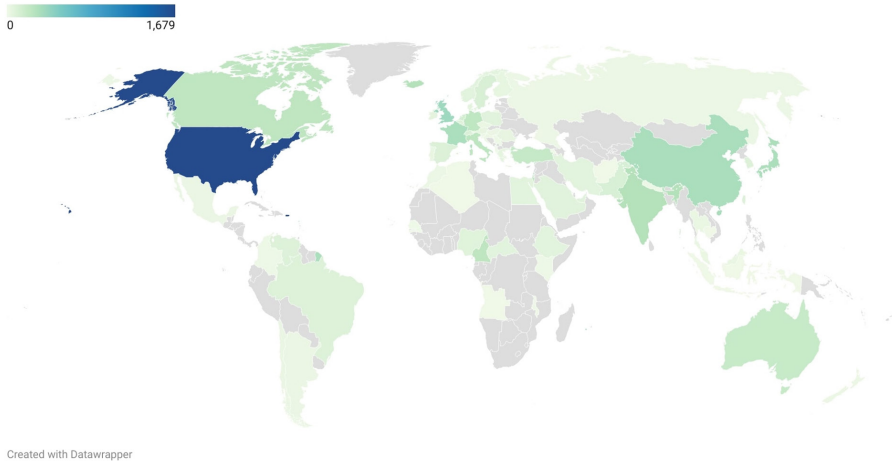

Figure 4. Uterine rupture publication density according to the countries

citations indicated that the most frequently cited articles were published between 2010 and 2015 (Figure 7).

Productivity of Journals: Journals featuring publications on uterine rupture were evaluated in terms of publication quantity and citation counts. The fifteen journals with the highest number of articles are detailed in Table 6, alongside their publication numbers and impact factors. A total of 923 journals publishing on uterine rupture were examined, of which 89 were identified as the most active, having published at least 10 articles. The American Journal of Obstetrics and Gynecology published 6.2% of all articles on uterine rupture. The 2023 impact factor for this journal was 8.7, indicating its significant influence on obstetrics and gynecology (Figure 8).

International Collaboration: An examination of research published by various countries on uterine rupture identified the United States as the most active contributor. Countries' collaborations were also explored, revealing that the United States served as the intersection point for researchers from other nations. France, Canada, and England are the most cooperative countries with the United States (Figure 9). A collaborative network centered around China included India, Japan, and Taiwan (Figure 9).

Table 3. The first ten authors with a record count in the literature on uterine rupture between 1980 and 2022

Authors	Institution	Record Count	% of 5745	H-index
Bujold E	Hutzel Hosp, Department of Obstetrics and Gynecology, 4707 St. Antoine Blvd, Detroit, MI 48201, USA	70	1.2	57
Macones GA	Washington University, Sch Med, Department of Obstetrics and Gynecology, St Louis, MO 63110, USA	37	0.6	56
Romero R	St. Josephs women Hospital, Florida Inst Fetal Diag & Therapy, Tampa, FL, USA	36	0.6	119
Sheiner E	Ben Gurion Univ Negev, Fac Hlth Sci, Soroka Univ Med Ctr, Dept Obstet & Gynecol, IL-84105 Beer Sheva, Israel	30	0.5	50
Gauthier RJ	Wayne State University, Department of Obstetrics and Gynecology, Detroit, MI 48202, USA	28	0.4	22
Landon MB	Ohio State University, Coll Med, Department of Obstetrics and Gynecology, Div Maternal Fetal Medicine, Columbus, OH 43210, USA	27	0.4	49
Caughey AB	Oregon Hlth & Sci Univ, Department of Obstetrics & Gynecology, 3181 Southwest Sam Jackson Pkwy, Portland, OR, 97239, USA	26	0.4	78
Mercer BM	Case Western Reserve University, Cleveland, Ohio 44106, USA	25	0.4	73
Odibo AO	Washington University, Sch Med, Department of Obstetrics and Gynecology, St Louis, MO 63110, USA	25	0.4	44
Spong CY	Icahn Sch Med Mt Sinai, Department of Populat Hlth, New York, NY, USA	25	0.4	63

Univ: University, USA: United States of America

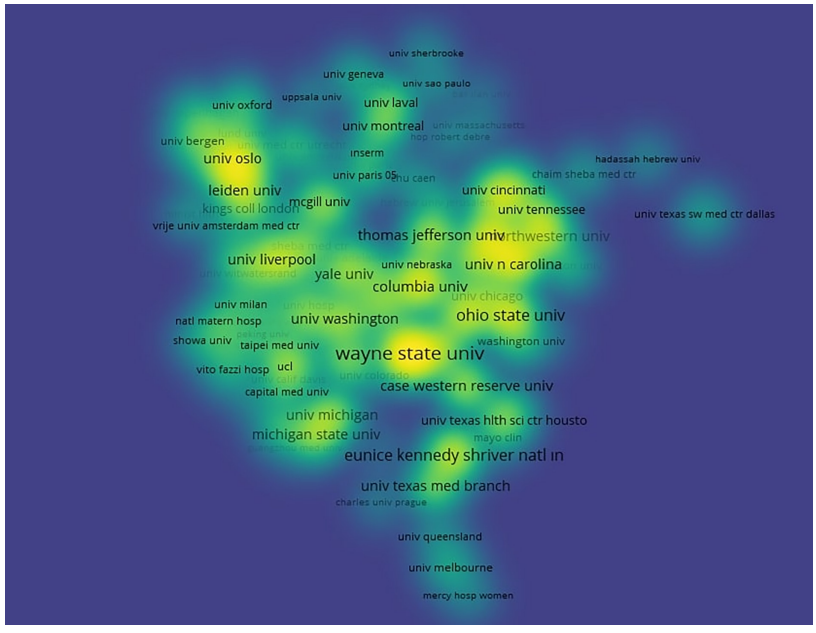

Figure 5. Intensity map of the cooperation analysis of the institutes

Table 4. The top 10 funding organizations by number of uterine rupture literature		
Institutions	**Number of Publications**	**% of 5745**
United States department of health human services	215	3.7
National institutes of health, USA	197	3.2
Nih eunice kennedy shriver, national institute of child health, human development	133	2.3
National natural science foundation of China	34	0.5
Canadian institutes of health research	33	0.5
National health and medical research council of Australia	29	0.3
National institute for health research	21	0.3
Ministry of education culture sports science and technology Japan	19	0.3
Japan society for the promotion of science	18	0.2
United Kingdom research innovation	18	0.2
USA: United States of America		

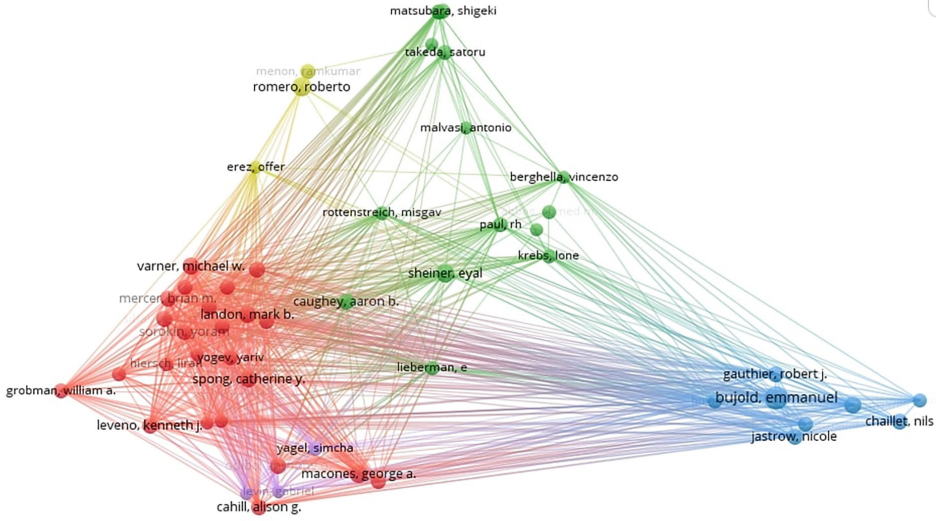

Figure 6. Network visualization map of co-citation analysis of active authors

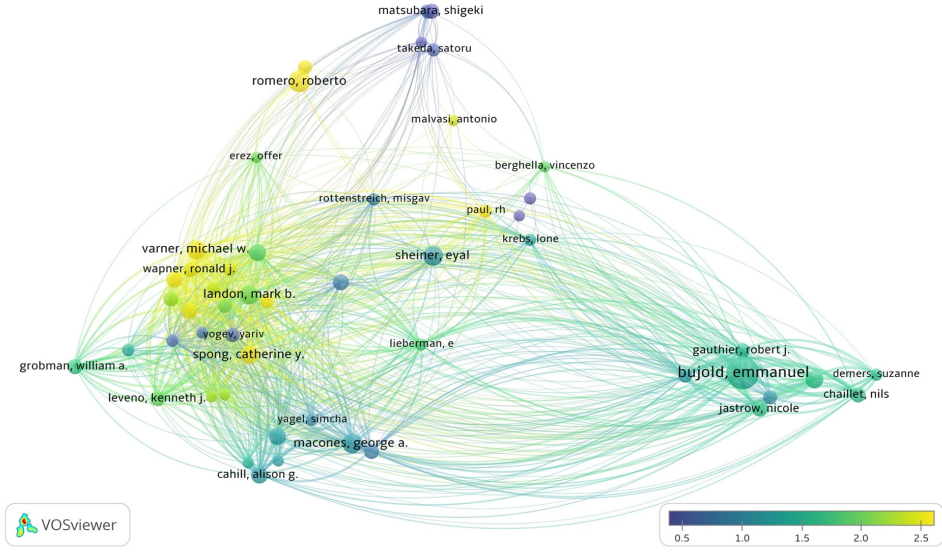

Figure 7. Network visualization map of co-citation analysis of most cited documents

Table 5. The top 10 most cited manuscripts about uterine rupture

No	Article	Author	Journal Name/Published	TC	ACY
1	Risk of uterine rupture during labor among women with a prior cesarean delivery.	Lydon-Rochelle, M., Holt, V. L., Easterling, T. R., and Martin, D. P.	New England Journal of Medicine, 2001	573	24.9
2	Incidences and predictors of severe obstetric morbidity: case–control study	Waterstone, Mark J. Deirdre Murphy, Susan Bewley, and Charles Wolfe.	BMJ, 2001	476	20.7
3	Comparison of a trial of labor with an elective second cesarean section	McMahon, M. J., Luther, E. R., Bowes Jr, W. A., & Olshan, A. F.	New England Journal of Medicine, 1996	457	16.3
4	Cesarean scar ectopic pregnancy: etiology, diagnosis, and management	Wittstein, IS; Thiemann, DR; Lima JAC; et al.	New England Journal of Medicine, 2005	406	22.5
5	Cesarean scar pregnancy: management issues	Seow, K. M., Huang, L. W., Lin, Y. H., Yan-Sheng Lin, M., Tsai, Y. L., Hwang, J. L.	Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology	391	19.5
6	Incidence, risk factors, and temporal trends in severe postpartum hemorrhage	Kramer, MS; Berg, C; Abenheim H, et al.	Amerıcan Journal of Obstetrıcs and Gynecology, 2008	365	33. 1
7	Cesarean scar pregnancy	Ash A; Smith A and Maxwell D.	BJOG International Journal of Obstetrics and Gynecology, 2007	358	21.44
8	Uterine rupture after previous cesarean delivery: maternal and fetal consequences	Leung, A.S.; Leung, E.K.and Paul, R.H.	American Journal of Obstetrics and Gynecology, 1993	234	7.31
9	Maternal complications of vaginal birth after cesarean delivery: a multicenter study	Macones GA; Peipert K; Nelson DB; et al	American Journal of Obstetrics and Gynecology 2005	215	10.75
10	WHO systematic review of maternal mortality and morbidity: the prevalence of uterine rupture	Hofmeyr GJ; Say L; Gulmezoglu AM	BJOG International Journal of Obstetrics and Gynecology, 2005	211	10.55

TC: Total citation, ACY: Average citations per year

Table 6. The first 15 journals by number of publications and citations on uterine rupture

Journal Name	No	% of 5828	JIF
American Journal of Obstetrics and Gynecology	383	6.2	8.8
Obstetrics and Gynecology	305	4.9	7.2
Journal of Maternal Fetal Neonatal Medicine	181	2.9	1.8
European Journal of Obstetrics Gynecology and Reproductive Biology	178	2.8	2.3
BJOG an an International Journal of Obstetrics and Gynecology	145	2.3	5.9
International Journal of Gynecology and Obstetrics	144	2.1	3.5
Archives of Gynecology and Obstetrics	133	2.0	2.3
ACTA Obstetricia et Gynecologica Scandinavica	126	1.7	2.6
Journal of Reproductive Medicine	108	1.7	0.2
Journal of Obstetrics and Gynecology Research	107	1.6	1.2
BMC Pregnancy and Childbirth	104	1.6	3.4
Journal of Obstetrics and Gynecology	99	1.4	1.3
Journal of Minimally Invasive Gynecology	91	1.2	1.3
Ultrasound in obstetrics and gynecology	79	1.1	6.4
Australian New Zealand Journal of Obstetrics Gynecology	73	1.1	1.7

No: Number of publications; JIF: Journal impact factor

Trend Topics: In examining articles on uterine rupture, we identified emerging trends and topics. Frequently used keywords, their frequencies, and interrelationships provide insights into new research areas. The terms "pregnancy" and "cesarean section" were found to have the strongest associations with uterine rupture. Clinical conditions such as "scarred uterus", "postpartum hemorrhage", "emergency medicine", and "hyperstimulation" were also identified as closely related to uterine rupture. The most commonly repeated clinical analyses in the literature included cesarean section, postpartum hemorrhage, and maternal mortality (Figure 10).

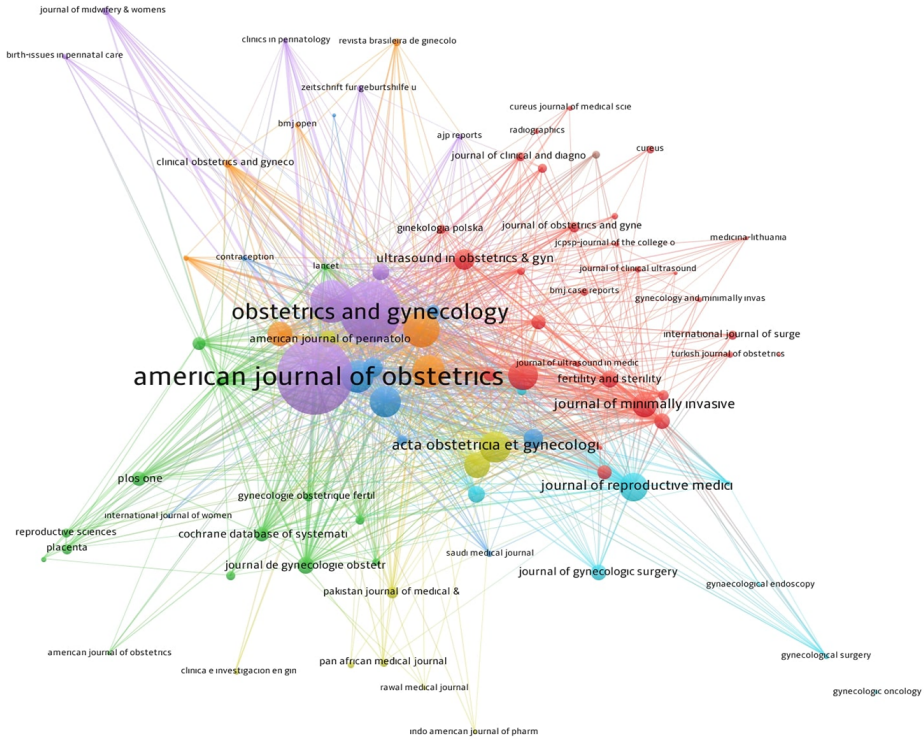

Figure 8. Network visualization of productivity of journals

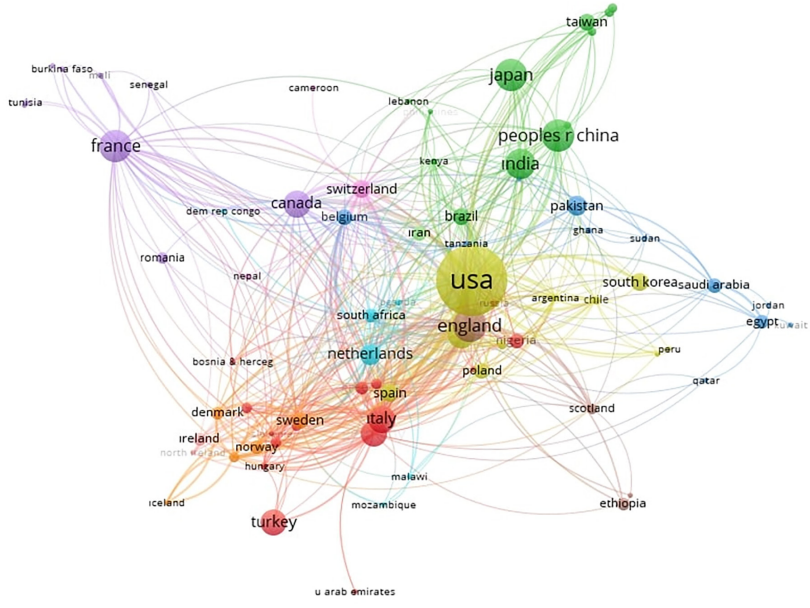

Figure 9. Network of co-contributing / collaborative countries on uterine rupture

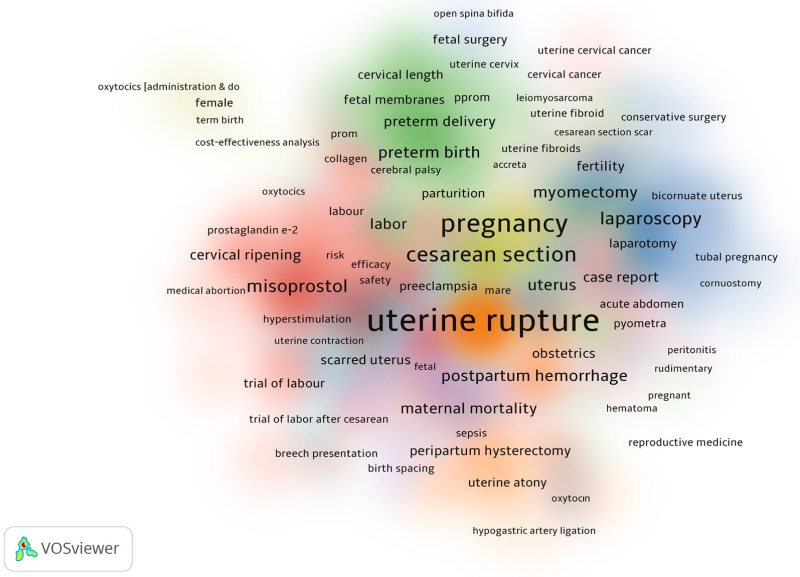

Figure 10. Network visualization map of relationships between the most commonly used trends keywords

Discussion

In our article, we conducted a bibliometric analysis of articles on “uterine rupture” in the WoS database. We reached a total of 5828 articles and reviewed the citations of these articles, the most active researchers, and the most active journals. The most active country was the United States. The most active researcher was Bujold, and the most active journal was the American Journal of Obstetrics and Gynecology. The most productive year was noted as 2020. The most cited study was “risk of uterine rupture during labor in women with a previous cesarean delivery”, a population-based, retrospective cohort analysis. The most cited study in the last three years is a meta-analysis published in BMC childbirth and pregnancy evaluating the use of oxytocin for uterine rupture in patients undergoing vaginal birth after cesarean section [9]. The etiology, diagnosis, and management of uterine rupture is multidisciplinary, and the medical team that first evaluates this symptom typically consists of obstetricians or emergency medicine specialists. The diagnosis of uterine rupture is challenging because of nonspecific uterine contractions, fetal movements, and atypical bowel movements during pregnancy [10]. Uterine rupture may cause acute abdominal symptoms, and this condition is triaged by emergency room specialists before obstetricians in emergency settings [11]. The types of uterine rupture may vary upon presentation to the emergency department (ED). For instance, full-thickness uterine rupture may occur in the ED without rupture of the membranes. Emergency physicians should maintain a presumptive diagnosis of uterine rupture in patients presenting with acute abdominal symptoms, regardless of gestational age. A holistic medical approach is required to diagnose uterine rupture. In addition to a complete history and examination in the ED, the correct use of imaging methods is also essential [12]. Uterine rupture is a clinical condition that has increased in frequency over the years, necessitating urgent diagnosis and intervention by obstetricians and emergency service clinicians. Factors contributing to this increase include higher rates of labor induction with oxytocin, scarred uteri from previous cesarean delivery, and labor induction using prostaglandins or prostaglandins combined with oxytocin [13]. Uterine rupture can range from dehiscence to full-thickness rupture. Clinical conditions on this scale may vary according to risk factors. The probability of developing full-thickness uterine rupture increases with vaginal delivery after cesarean section, pregnancy in women with a parity of 3 or more, and labor induction using oxytocin [14].

The triage of patients with uterine rupture in emergency services and obstetrics and gynecology clinics is based on the principles of thoroughly taking the patient’s medical history, conducting a physical examination, providing rapid monitoring, performing obstetric and abdominal imaging, and utilizing appropriate tests [10]. The most significant risk factor for uterine rupture, as agreed upon by gynecology and obstetrics associations, is scarring caused by uterine surgical procedures. Factors such as the number of scars, size, incision shape, and repair technique are determinants of potential rupture. Therefore, an obstetric history during patient triage is necessary to identify risk factors [15].

Uterine rupture may develop silently or may present as progressively increasing pain. This pain may occur alongside uterine contractions in women during labor, but it can sometimes manifest as persistent pain independent

of contractions. Persistent abdominal pain (present at all times, even outside of contractions, and intensifying during contractile activity) is the clinical presentation most commonly associated with uterine rupture. Symptoms indicative of full-thickness uterine rupture include persistent uterine bleeding, increased pain with contractions, a non-reassuring non-stress test, and a shift in the level of the fetus and placenta toward the abdomen.

Dehiscence or full-thickness rupture may lead to bleeding that dissects between the anterior uterine wall and the posterior bladder wall, causing urinary system complaints and hematuria. Patients experiencing urinary complaints should be evaluated during sonogram. Repeat sonographic evaluation may be necessary in the ED or upon hospitalization. This approach facilitates early diagnosis of the need for emergency laparotomy. Hemodynamic instability detected during patient evaluation may be an indication for emergency laparotomy [16,17].

Imaging methods for evaluating uterine rupture should be selected based on indication for emergency delivery. For patients with a history of uterine surgery, evaluation of the uterine wall is beneficial in establishing a clinical diagnosis. The detection of hemoperitoneum, pneumoperitoneum, uterine heterogeneity, and abscess formation on imaging may be associated with uterine rupture [18]. Ultrasonography can play a diagnostic role by demonstrating the hemoperitoneum and free fluid in the abdominal cavity where the fetal parts and their appendages are partially or completely expelled. Sonographic evaluation is typically the first-choice method for assessing uterine rupture due to its advantages, such as cost-effectiveness, ease of application, bedside applicability, and absence of ionizing radiation. The sonogram can easily identify the area of uterine rupture, assess fetal health, and estimate the volume of abdominal bleeding [19].

Transabdominal transducers are effective in visualizing intra-abdominal fluid and hematomas from a broader angle, whereas transvaginal use is more effective for visualizing uterine dehiscence and rupture areas. Color doppler and 3D sonograms can be used to visualize the active bleeding area and estimate the myometrial bleeding area. Sonograms are also frequently used to guide percutaneous diagnostic procedures [20].

Computed tomography (CT) can assist in the differential diagnosis when sonograms inadequately visualize the condition, in cases where the operator cannot diagnose, and in clinical situations that present similar symptoms. When sonography is inconclusive in diagnosing rupture during pregnancy, abdominal CT can be performed, considering the benefits and risks [21]. Compared with CT, sonography is advantageous for providing a broader view in evaluating intra-abdominal organs, visualizing pneumoperitoneum, offering multi-planar section capabilities, and enabling contrast applicability [22]. Magnetic resonance imaging (MRI) has limited utility in uterine rupture; it is generally reserved for clinically stable patients and should not delay urgent interventions. MRI is typically used in challenging cases and serves as a problem-solving tool when sonography and CT are inconclusive, especially when the suspicion of uterine injury is high [23].

The timing of intervention after the diagnosis of uterine rupture is critical. Maternal history and fetal intrapartum status may not reliably predict uterine rupture. Fetal mortality and morbidity increase as the duration of fetal bradycardia to cesarean delivery lengthens [24]. When uterine rupture is detected intrapartum or during pregnancy, the fetal status and maternal hemodynamics are the most critical factors determining the management of the rupture. Limited cases of uterine repair and pregnancy continuation have been reported when rupture or dehiscence was detected in second-trimester pregnancies. In cases involving hemodynamically unstable patients or those with fetal morbidity and mortality, laparotomy typically results in subtotal or total hysterectomy, with occasional hypogastric artery ligation performed [25,26].

Conclusion

Uterine rupture is a clinical challenge that is likely to become increasingly prevalent in the future, primarily due to rising rates of cesarean section and uterine surgery. Emergency physicians and obstetricians should be well-versed in the risk factors and diagnostic methods associated with uterine rupture. A comprehensive examination of existing studies reveals a steady annual increase in research on this topic, suggesting that high publication rates will persist, with future publications expected to achieve significant citation and impact. While there is a wealth of case reports and clinical studies focusing on risk factors and management, there remains a notable scarcity of meta-analyses and compilations that adopt a multidisciplinary approach. It is anticipated that the volume of research evaluating uterine rupture will continue to grow in the future, with an emphasis on integrating multidisciplinary strategies.

Ethics

Ethics Committee Approval: Not required

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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