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OLGU SUNUMLARI / CASE REPORTS

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Evaluation of outcomes of obstetric patients with COVID-19 disease followed up in the intensive care unit

Yoğun bakım ünitesinde takip edilen COVID-19 hastalığı olan obstetrik hastaların sonuçlarının değerlendirilmesi

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ABSTRACT

Objective: We aimed to evaluate the characteristics, prognosis, laboratory parameters, and mortality of severely ill obstetric patients due to severe COVID-19 disease and determine the factors affecting mortality.

Methods: Medical records of obstetric patients with COVID-19 infection were reviewed. Patients were admitted to the intensive care unit (ICU) and the outcomes of the newborns were evaluated furtherly.

Results: A total of 325 women were included. The ICU requirement was 8.6% (28/325). Among 28 women admitted to ICU maternal mortality rate was 53.6% (15/28), and preterm delivery rate was 88% (24/28). The 27 newborns were evaluated furtherly. Six stillbirths occurred. 40.7% (11/27) of the newborns had 1st minute APGAR scores lower than 7, while 33.3% (9/27) of them had 5th minute APGAR scores lower than 7. Body mass index, CRP, D-dimer, LDH, and CRP/Alb ratio were found to be significantly higher in the mortality cohort than surviving women requiring ICU. The CRP/Alb ratio was the most significant predictor of COVID-19-related maternal death in ICU.

Conclusion: The study revealed that COVID-19-related maternal mortality is considerably high in severely ill patients. The CRP/Alb ratio is a significant predictor of mortality. The cesarean section and preterm delivery rates were significantly high in severely ill mothers with COVID-19. Additionally, the severity of the mothers' illness negatively influenced neonatal outcomes.

Keywords: COVID-19, intensive care unit, mortality, obstetric

ÖZ

Amaç: Şiddetli COVID-19 hastalığı nedeniyle yoğun bakımda yatan obstetrik hastaların özelliklerini, prognozunu, laboratuvar parametrelerini ve mortalitesini değerlendirmeyi ve mortaliteyi etkileyen faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: COVID-19 enfeksiyonu olan obstetrik hastaların tıbbi kayıtları incelendi. Yoğun bakıma yatırılan hastalar ve yenidoğanların sonuçları ayrıntılı olarak değerlendirildi.

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Bulgular: Toplam 325 hasta çalışmaya dahil edildi. Yoğun bakım gereksinimi %8.6 (28/325) idi. Yoğun bakıma yatırılan 28 hasta arasında maternal mortalite oranı %53.6 (15/28) ve preterm doğum oranı %88 (24/28) idi. 27 yenidoğan ayrıntılı olarak değerlendirildi. Altı ölü doğum gerçekleşti. Yenidoğanların %40.7'sinin (11/27) 1. dakika APGAR skorları 7'den düşükken, %33.3'ünün (9/27) 5. dakika APGAR skorları 7'den düşüktü. Vücut kitle indeksi, CRP, D-dimer, LDH ve CRP/Alb oranının, yoğun bakıma ihtiyaç duyan hayatta kalan hastalara göre mortalite kohortunda anlamlı derecede daha yüksek olduğu bulundu. CRP/Alb oranı, YB'da COVID-19 ile ilişkili anne ölümünün en önemli predictor faktörü olarak bulundu.

Sonuç: Çalışmamız yoğun bakım hastalarında COVID-19 ile ilişkili anne ölümünün önemli ölçüde yüksek olduğunu ortaya koydu. CRP/Alb oranını mortalite için önemli bir prediktör olarak bulduk. Sezaryen ve erken doğum oranları COVID-19'lu yoğun bakım hastalarında anlamlı derecede yüksekti. Ek olarak, annelerin hastalığının ciddiyeti yenidoğan sonuçlarını olumsuz yönde etkiledi.

Anahtar kelimeler: COVID-19, obstetric, ölüm oranı, yoğun bakım ünitesi

Introduction

The World Health Organization (WHO) declared the new coronavirus disease (COVID-19) as an epidemic on March 11, 2020, and the first case of COVID-19 was detected in our country on the same date (1). By May 2022, WHO had announced more than 517.648.631 confirmed cumulative cases and approximately 6.261.708 cumulative deaths (2). On the same date, Turkey, reported more than 15.050.207 confirmed cumulative cases and about 98.878 cumulative deaths (2).

While the course of COVID-19 disease can be asymptomatic, it can also present a clinical manifestation that can range from mild symptoms to respiratory failure or multi-organ failure (1,3). Although yielding data provide us a point of view regarding the characteristics of COVID-19 infection in the general population, there are very little data exist in terms of risk factors concerning COVID-19 disease in specific patient groups, such as obstetric patients (4). Previous pandemics reports revealed that COVID-19 infection in pregnant women was associated with an increased risk for complications (5). After then, Li et al. (4) stated the COVID-19 disease usually presented mild respiratory symptoms in pregnant women, predominantly together with fever and pneumonia; on the other hand, other severe respiratory symptoms were reported to be less common. Furthermore, Antoun et al. (6) suggested that COVID-19 disease could lead to an increase in the prevalence of preterm birth, preeclampsia, and cesarean section, without increasing severe complications in newborns. Finally, it was concluded in another report that, despite the generally mild or asymptomatic course of COVID-19 disease in young patients, the risk of severe and complicated illness was higher in the pregnant population of the same age (7).

Although several studies are conducted in the general population researching the clinical and laboratory parameters predicting the progression to severe disease in COVID-19, the data are very few in obstetric patients. Therefore, we aimed to evaluate the characteristics, prognosis, laboratory parameters, and mortality of obstetric patients followed up in the intensive care unit (ICU) due to severe COVID-19 disease and to determine the factors affecting mortality.

Materials and Methods

The study was conducted in accordance with the Helsinki Declaration and registered to www.clinicaltrials.gov (NCT05264987). After the approval of the local ethics committee (2011-KAEK-25 2021/06-20), obstetric patients hospitalized in the ICU of Bursa Yuksek Ihtisas Training and Research Hospital between March 11, 2020 - September 15, 2021, were

reviewed retrospectively. Patients admitted to the ICU for COVID-19 during the pregnancy and postpartum period, from the beginning of pregnancy and up to 42 days after delivery, were included in the study. Patients with clinically suspected COVID-19 disease and having negative PCR tests were excluded from the study.

Demographic data, obstetric histories, comorbidities, treatments received in the ICU, delivery types, anesthesia types, and outcomes of newborns and mothers were retrospectively evaluated from the medical records. The need for the mechanical ventilator, the length of stay in the ICU, and outcomes of mothers were recorded. Laboratory findings were noted on the first day of admission to the ICU, including routine complete blood count, liver and kidney function, coagulation parameters, C-reactive protein (CRP), and albumin levels. Then neutrophil to lymphocyte (N/L) ratio, platelet to lymphocyte (P/L) ratio, and CRP to albumin (CRP/Alb) ratio were calculated. Deceased patients were evaluated in detail, and extreme cases were discussed.

The data were analyzed using SPSS Statistics for Windows version 19.0, 2010 (Armonk, NY: IBM Corp.). The Fisher's exact test was conducted to analyze categorical variables. Non-parametric tests were performed to analyze the small sample-sized data ($n<30$). The continuous maternal variables were compared using the Mann-Whitney-U test. The maternal characteristics and laboratory tests were presented as median (25-75 percentiles) and number (%). Poor neonatal outcomes were determined as 1st and 5th minute APGAR scores lower than 7, and poor maternal outcomes were identified as maternal death. The relation of the contributing factors with poor neonatal outcomes was analyzed using the Spearman correlation test. The statistically significant parameters in the maternal death were included in a further logistic regression model. After the multicollinearity analysis (tolerance >0.4), the Hosmer-Lemeshow test was performed to check the model's fitness. The effect sizes were presented as odds ratios (OR) and 95% confidence intervals (CIs). Additionally, receiver operating characteristic (ROC) curve analysis was conducted to find out optimal cut-off level and sensitivity and specificity of the demonstrated cut-off value of the independent parameters associated with maternal mortality. All tests were performed as two-tailed, and $p<0.05$ was considered significant.

Results

Ward patients

During the time process of this study, 516 patients were admitted to the COVID-19 obstetrics ward, and 325 patients with positive SARS CoV-2 PCR tests were included in the analysis. Of these, 271 (83.9%) were hospitalized during pregnancy, and 54 (16.6%) in the postpartum period. 296 (91.1%) of the hospitalized patients were discharged well from the hospital, 28 (8.61%) patients required admission to the ICU, and one died in the obstetrics ward. Of the 296 discharged patients, 137 patients were discharged with an ongoing pregnancy and 159 in the postpartum period. Of the159 postpartum patients, five aborted, 106 were delivered by cesarean section (general anesthesia rate 6.6% and spinal anesthesia rate 93.4%), and 48 were delivered vaginally (Figure 1).

The rate of asymptomatic patients at the time of admission to the hospital was 10.7%. Dyspnea 21.4%, cough 14.3%, anosmia and ageusia 3.6%, and vomiting 3.6% were observed in patients. Only one of our patients had received the COVID-19 vaccine. She was hospitalized and discharged during her pregnancy.

The Code Blue Case in the Obstetrics Ward

The case was a 35-years-old, 27 gestational weeks pregnant woman with no comorbidity who was being followed up in the obstetric ward. Due to respiratory distress, the patient was intubated in the ward following

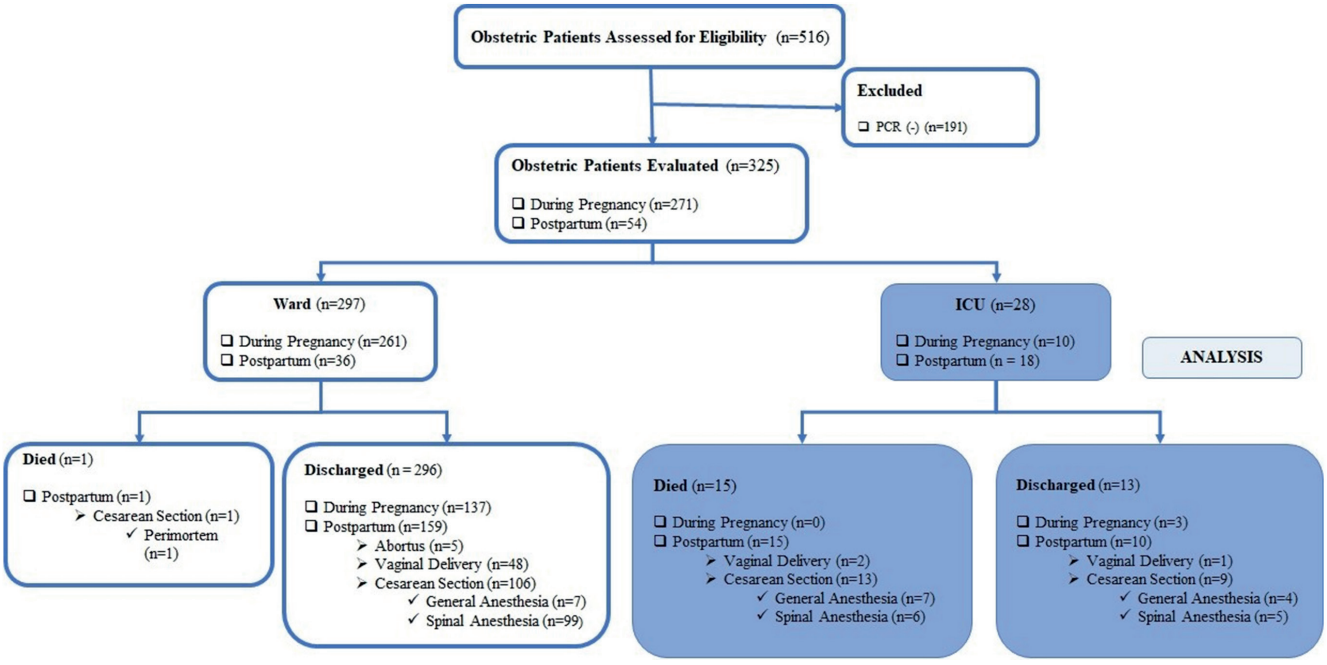

Figure 1. Flowchart of the study

the Code Blue emergency call. Then a sudden cardiac arrest was developed just before the transfer to the ICU. Cardiopulmonary resuscitation was immediately started, and a perimortem cesarean section was performed. A living neonate was delivered, with the 1st minute APGAR score of 0 and the 5th minute APGAR score of 4. This newborn was excluded from the neonatal outcomes analysis.

Difficult Airway in a Morbid Obese Patient

The case was a 25-years-old morbid obese patient with a BMI of 49.2 kg/m^2. The patient was consulted with the Anesthesiology and Reanimation team due to severe respiratory distress on the third postpartum day. The consultant team considered transferring the patient to ICU; however, it was decided to secure the airway first in the ward before the transfer because of the severe dyspnea. Both mask ventilation and intubation of this patient were difficult. Intubation was possible in the third attempt with gum elastic bougie. Seven healthcare personnel were infected with SARS-CoV-2 from the patient despite wearing Level-3 personal protective equipment. At that time, vaccination had not yet started in our country.

ICU patients

A total of 28 women were admitted to the ICU. Of these patients, 18 (64.29%) were postpartum patients, and 10 (35.71%) had ongoing pregnancies. The criteria for admission to ICU were respiratory rate ≥30 breaths per minute, oxygen saturation level ≤90%, and Horowitz index ≤300 mmHg. The maternal characteristics and the comparison of the data between mortality and survival patients were presented in Table 1. The comparison of the laboratory parameters at first admission to the ICU was presented in Table 2.

While 16 of our cases were followed up with high-flow nasal oxygen therapy, 22 patients were intubated due to refractory hypoxemia and needed invasive mechanical ventilation. The requirement for mechanical ventilation was 82.14% (n=23) in all our obstetric COVID-19 ICU patients. All the postpartum patients were placed in the prone position. Also, the other pregnant patients were placed in the prone position after delivery. The median (25-75 percentiles)

Table 1. Demographic data of the cases admitted to the ICU

	Total (n=28)	Survival (n=13)	Mortality (n=15)	p
Age, years	32.5 (27.0 – 35.8)	34.0 (27.5 – 37.0)	32.0 (27.0 – 35.0)	0.501
BMI, kg/m^2	27.5 (24.9 – 30.9)	25.0 (24.4 – 27.8)	29.4 (27.5 – 31.2)	0.019*
Gravidity, n	2.5 (2.0 – 3.0)	3.0 (2.0 – 3.0)	2.0 (2.0 – 3.0)	0.932
Parity, n	1.0 (1.0 – 2.0)	2.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	0.744
Gestational weeks, weeks	32.0 (28.0 – 35.0)	30.0 (25.0 – 34.5)	33.0 (28.0 – 36.3)	0.212
APACHE II, points	16.5 (15.0 – 23.5)	16.0 (14.5 – 20.0)	19,00 (15.0 – 25.0)	0.164
Comorbid diseases, yes	10 (35.7)	6 (46.2)	4 (26.7)	0.433
Pregnancy-induced hypertensive diseases	5 (17.6)	3 (23.1)	2 (13.3)	0.599
Cardiac diseases	1 (3.6)	1 (7.7)	0 (0.0)	
Diabetes mellitus	3 (10.7)	2 (15.4)	1 (6.7)	
Substance abuse	1 (3.6)	0 (0.0)	1 (6.7)	
Trimester, n				0.372
1st trimester	0 (0.0)	0 (0.0)	0 (0.0)	
2nd trimester	6 (21.4)	4 (30.8)	2 (13.3)	
3rd trimester	22 (78.6)	9 (69.2)	13 (86.7)	
Birth, n				0.183
None	3 (10.7)	3 (23.1)	0 (0.0)	
Vaginal	3 (10.7)	1 (7.7)	2 (13.3)	
Cesarean section	22 (78.6)	9 (69.2)	13 (86.7)	
Anesthesia†, n				0.665
General anesthesia	11 (50.0)	4 (44.4)	7 (53.8)	
Regional anesthesia	11 (50.0)	5 (55.6)	6 (46.2)	

Categorical variables are presented as n (%), continuous variables are presented as median (25–75 percentiles); APACHE II: Acute Physiology and Chronic Health Evaluation-II, BMI: *Body mass index*, ICU: Intensive care unit; *p<0.05; †Number of patients who delivered only by cesarean section.

length of stay in the ICU was 10.0 (4.0 – 15.0) days, and the median (25-75 percentiles) number of days spent on the mechanical ventilator was 4.0 (1.0 – 10.8) days.

A massive pulmonary embolism developed in a patient on the 6th day in the ICU despite thrombolytic therapy; then, she died in the ICU on the same day.

Outcomes of patients discharged from the ICU during pregnancy

We were able to discharge three patients to the obstetrics ward with an ongoing pregnancy. One of these patients gave birth by cesarean section under epidural anesthesia six weeks after discharge, and the other delivered vaginally eight weeks later. The records of the last patient could not be accessed because she did not give birth in our hospital.

Maternal mortality

The mortality rate of obstetric patients admitted to the ICU due to COVID-19 disease was found to be 53.57% (15/28). The all-over mortality rate of the hospitalized obstetric patients with COVID-19 disease was found to be 4.92% (16/325).

Factors that influence maternal mortality

The body mass index (BMI) was significantly higher in patients who died than survived patients (p=0.019). Cesarean section was performed in 22 of our cases, and general anesthesia was applied at a rate of 50%. The reasons for preferring general anesthesia were low platelets, cardiac causes, severe respiratory distress, and one case previously intubated in the ICU.

Table 2. Laboratory parameters at initial admission to the ICU

	Total (n=28)	Survival (n=13)	Mortality(n=15)	p
Hemoglobin, g/dL	10.8 (9.4 - 11.8)	10.5 (9.25 - 12.1)	10.9 (9.5 - 11.7)	0.955
White Blood Cell, mcl	12.9 (8.2 - 15.3)	14.6 (7.8 - 15.6)	12.2 (9.2 - 13.7)	0.555
Neutrophil count, $\times10^3$/mL	11.4 (7.3 - 13.8)	12.2 (7.0 - 14.2)	11.2 (8.1 - 12.5)	0.467
Lymphocyte count, $\times10^3$/mL	0.8 (0.6 - 1.2)	0.8 (0.4 - 1.2)	0.8 (0.7 - 1.2)	0.609
Platelet, mcl	288.0 (161.5 - 328.0)	302.0 (151.5 - 343.0)	274.0 (161.0 - 321.0)	0.856
Aspartate Aminotransferase, U/L	41.5 (28.5 - 55.5)	41.0 (30.5 - 71.5)	42.0 (26.0 - 56.0)	0.901
Alanine Aminotransferase, U/L	24.5 (16.0 - 41.5)	25.0 (15.0 - 43.0)	21.0 (16.0 - 43.0)	0.593
Blood Urea Nitrogen, mg/dL	7.0 (4.0 - 12.0)	6.9 (3.5 - 11.1)	9.0 (5.2 - 14.3)	0.187
Creatinine, *mg/dL*	0.5 (0.5 - 0.6)	0.5 (0.5 - 0.6)	0.6 (0.5 - 0.7)	0.066
C-Reactive Protein, mg/L	107.5 (63.0 - 143.3)	65.7 (25.1 - 92.9)	141.0 (110.0 - 169.0)	<0.001*
Fibrinogen, mg/dL	515.5 (399.0 - 661.0)	544.0 (386.5 - 656.0)	514.0 (388.0 - 684.0)	0.937
D-dimer, mg/mL	3.8 (1.7 - 7.2)	2.2 (0.7 - 4.8)	4.1 (2.6 - 8.9)	0.013*
Ferritin, ng/mL	240.9 (117.5 - 451.1)	191.8 (102.9 - 411.5)	261.4 (160.8 - 458.0)	0.316
Lactate Dehydrogenase, U/L	486.5 (362.5 - 806.3)	381.0 (282.5 - 468.0)	702.0 (490.0 - 819.0)	0.006*
Albumin, g/L	27.4 (24.7 - 29.2)	27.8 (25.0 - 29.0)	27.0 (24.4 - 29.4)	0.726
N/L ratio	13.7 (9.0 - 16.2)	13.8 (8.4 - 18.9)	13.7 (9.1 - 14.9)	0.683
P/L ratio	356.7 (215.7 - 458.4)	379.3 (204.0 - 729.9)	335.6 (220.5 - 442.4)	0.856
CRP/Alb ratio	3.9 (2.5 - 5.5)	2.4 (1.0 - 3.4)	5.3 (4.1 - 6.9)	<0.001*

The results are presented as median (25–75 percentiles). CRP/Alb: C-Reactive Protein/Albumin, ICU: Intensive care unit, N/L: Neutrophil/lymphocyte, P/L: Platelet/lymphocyte.

Among these, CRP ($p<0.001$), D-dimer ($p=0.013$), LDH ($p=0.006$), and CRP/Alb ratio ($p<0.001$) were found to be significantly higher in the mortality cohort than survival cohort. After then, BMI, D-dimer, LDH, and CRP/Alb ratio were included in further logistic regression analysis. The CRP was excluded from the final analysis due to the CRP/Alb ratio co-linearity. The model's fitness was verified with the Hosmer-Lemeshow test. The final model explained 79.8% (Nagelkerke R^2) of the variance in maternal death and correctly classified 85.7% of the cases (sensitivity: 86.7%, specificity: 84.6%). Accordingly, CRP/Alb ratio was found as the most significant predictor of COVID-19 maternal death in ICU (OR, [95% CI]: 6.924, [1.174 – 40.841]; p=0.033) (Table 3). Finally, the discriminative power for COVID-19 maternal death in ICU of CRP/Alb ratio was evaluated using ROC analysis (Figure 2). The AUC [95% CI] for prediction of mortality for CRP/Alb ratio was found to be 0.913 [0.811 – 1.000]; $p<0.001$.

Table 3. Logistic regression analysis of risk factors in died patients

	OR, [95% CI]	Wald	p
BMI	1.000, [0.718 – 1.393]	0.000	0.999
Lactate Dehydrogenase	1.003, [0.998 – 1.008]	1.301	0.254
D-dimer	1.762, [0.732 – 4.238]	1.598	0.206
CRP/ Alb ratio	6.924, [1.174 – 40.841]	4.567	0.033*

BMI: Body mass index, CRP/Alb: C-Reactive Protein/Albumin.

The cut-off value for predicting maternal mortality of CRP/Alb ratio was calculated as 3.99 with a sensitivity of 80.0% and specificity of 92.3%.

Neonatal outcomes

Two women gave birth to twins. Accordingly, a total of 27 newborns born from 25 mothers were included in the further analysis. The preterm delivery rate (<37 gestational weeks) was 88.0%. Six stillbirths occurred. The rate of the newborns having 1st minute APGAR scores lower than 7 was 40.7% (11/27), while

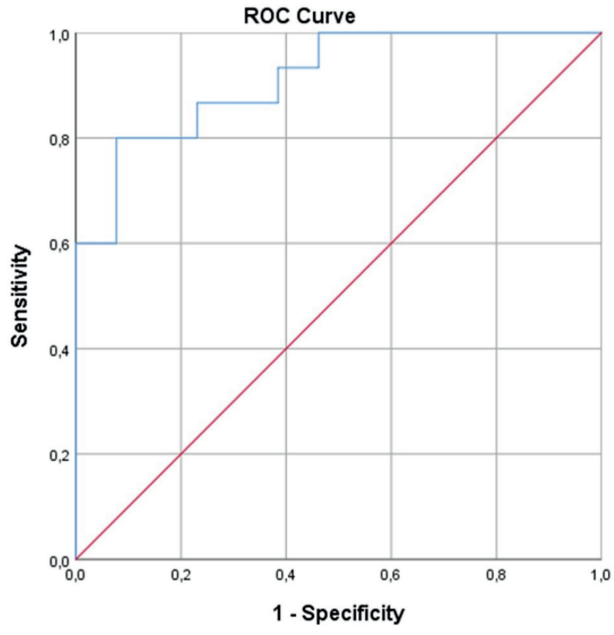

Figure 2. ROC analysis of CRP/Albumin ratio

the rate of the newborns having 5th minute APGAR scores lower than 7 was 33.3% (9/27). All newborns tested negative for SARS-CoV-2 with nasopharyngeal swabs. No congenital anomaly was observed in any of the newborns. The mean weight of newborn babies was 1985.96 ± 1050.72 kg; additionally, 59.3% of the newborns were girls, 40.7% were boys.

Factors that influence neonatal outcomes

Factors that influence neonatal outcomes were evaluated with correlation analysis (Table 4). Accordingly, low neonatal birth weight was moderately correlated with 1st minute APGAR scores lower than 7 (r=-0.643; p=0.000) and strongly correlated with 5th minute APGAR scores lower than 7 (r=-0.589; p=0.002). Furthermore, being in the second trimester and early gestational weeks were strongly correlated with 1st and 5th minute APGAR scores lower than 7 (Table 4).

Discussion

This report presented the outcomes of obstetric patients with confirmed COVID-19 disease admitted to the hospital. Additionally, the 28 obstetric patients requiring ICU follow-up and the newborns of these patients were evaluated furtherly. We found the mortality rate of obstetric patients due to COVID-19 disease in ICU as 53.57%. The cesarean section rate in severely ill obstetric patients was 78.57%. The BMI, CRP, D-dimer, LDH, and CRP/Alb ratio were significantly high in the mortality cohort. Among these parameters, the CRP/Alb ratio was found to be the most significant predictor of maternal death related

Table 4. The correlation of 1st and 5th minute APGAR scores with neonatal and maternal factors.

	APGAR 1st minute <7		APGAR 5th minute <7	
	r s	p	r s	p
Neonatal factors				
Weight, kg	-0.643	0.000*	-0.589	0.002*
Trimester, 3rd	-0.575	0.002*	-0.674	0.000*
Gestational weeks, weeks	-0.612	0.001*	-0.557	0.003*
Maternal factors				
Age, years	0.088	0.664	0.015	0.940
BMI, kg/m^2	-0.111	0.580	-0.091	0.652
Gravidity, n	-0.122	0.545	0.037	0.854
Parity, n	-0.047	0.817	0.113	0.573
Comorbidity, yes	0.213	0.286	0.167	0.406
Perinatal complication, yes	-0.053	0.792	0.167	0.406
APACHE-II, score	-0.024	0.904	-0.167	0.405
Death, yes	-0.080	0.693	-0.053	0.792

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, BMI: *Body mass index*.

to COVID-19 disease in the ICU. The cut-off value for predicting maternal mortality of CRP/Alb ratio was calculated as 3.99 with a sensitivity of 80.0% and specificity of 92.3%.

Although it is well documented that infectious diseases can cause varying degrees of both maternal and neonatal complications in the pregnant patient group, it was a matter of curiosity to what extent and how COVID-19 would affect pregnant women at the onset of the pandemic. The presented data in the later pandemic stages have shown that the mortality rate due to infection varied in a wide range between 0.3-12.7% in obstetric patients with positive SARS CoV-2 PCR test (8-15). However, the indications for admission to the ICU and the inclusion criteria of the patients in these reports varied widely, which could explain the high variability in mortality rates. While the mortality rate decreased with the inclusion of asymptomatic or patients with mild symptoms in the analysis, this rate increased when only the patients admitted to the ICU were evaluated. Accordingly, the results of our study indicated the mortality rate of test-positive pregnant women ranged from 4.92% to 53.57%.

Andrikopoulou et al. (16) reported in their study that one in five of the COVID-19 obstetric patients developed moderate or severe symptoms, while ten patients required respiratory support without intubation. Additionally, they stated the only patient was intubated for general anesthesia for cesarean section (16). Also, a previous report suggested that 67.2% of patients undergoing cesarean section were asymptomatic, and 14% had pneumonia (17). In our study, the rate of asymptomatic patients at the time of admission to the hospital was 10.7%, and severe disease requiring ICU was 8.61%, while the remaining had mild to moderate disease. All pregnant women with moderate disease followed up in the COVID-19 Obstetrics ward received respiratory support with a nasal cannula or nonrebreather mask. Patients who needed high flow oxygen or mechanical ventilatory respiratory support in addition to the previously mentioned ICU-admission criteria were followed up in the ICU. 78.57% of our patients were intubated in the ICU. Akinosoglou et al. (18) studied 60 pregnant women who presented to the emergency department with COVID-19 and reported that none of the patients survived the pregnancy and 6.6% required invasive mechanical ventilation.

Although no vertical transmission of SARS CoV-2 has been reported in any of the studies conducted until April 2020, the possibility of a vertically-transmitted illness started to be mentioned in the reports up to August 2020 (19,20). Significantly; the third trimester has been emphasized as the most unprotected period for infection (19). Oncel et al. (12) stated that COVID-19 was a risk for maternal death, vertical transmission, and neonatal disease. Additionally, the authors reported 3.3% (4/120) of newborns had tested positive for SARS CoV-2 (12). However, none of the newborns delivered from any of the COVID-19 positive mothers had positive PCR results in our study. It was postulated in a study that symptomatic parturients with COVID-19 were at increased risk of preterm birth, cesarean section, and peripartum ICU admission (21). In this report, the preterm delivery rate of parturients with severe disease was 88.0% (22 of the 25 patients), and six were stillbirths. While 40.7% (11/27) newborns had low 1st minute APGAR scores, 33.3% (9/27) had low 5th minute APGAR scores.

Takemoto et al. (13) indicated that 48.4% of fatal cases had at least one comorbidity and suggested postpartum ARDS, obesity, diabetes, and cardiovascular disease were the main risk factors for COVID-19-related maternal deaths. Also, they asserted that white ethnicity provided a protective effect (13). Additionally, Hazari et al. (10) pointed out that half of their pregnant COVID-19 ICU patients had BMI higher than 30 kg/m^2. Moreover, Chu et al. (22) concluded in their meta-analysis that obesity was strongly associated with poor outcomes of COVID-19, including increased ICU admissions, mechanical ventilation support, and disease progression. Similarly, the BMI was significantly higher in dead patients than the survived patients in our study.

Many clinical parameters and laboratory tests have been evaluated in the general population to predict the progression to severe COVID-19 disease. Ganesan et al. (23) showed Charlson comorbidity index, sequential organ failure assessment score, D-dimer, LDH, and N/L ratio were independently associated with mortality in COVID-19 patients admitted to the ICU. Ozer et al. (24) reported hypertension, malignancy (solid and hematological), neurological disease, age, APACHE-II and SOFA scores, and N/L ratio as factors affecting mortality in patients with COVID-19 in ICU. Subsequently, Li Y et al. (25) reported a higher N/L ratio, P/L ratio, CRP/Alb ratio, and systemic immune-inflammation index in those with progressive disease than those with stable disease. Moreover, they demonstrated a CRP/Alb ratio greater than 1.843 was closely associated with higher hospital mortality rates, ICU admission, invasive mechanical ventilation, and longer hospital stays. In our study, the CRP/Alb ratio was found as the most significant predictor of COVID-19 maternal death in the ICU. The cut-off value of the CRP/Alb ratio was calculated as 3.99 with a sensitivity of 80.0% and specificity of 92.3%.

Pregnant patients tend to have difficult airways due to increased oropharyngeal edema; thus, preparations should be made accordingly. We observed difficult mask ventilation in a case with a BMI of 49.2 kg/m^2 and both difficult mask ventilation and intubation in the ward. Mask ventilation of those patients was possible with two practitioners. The case was intubated with gum elastic bougie in the third attempt. Even though all the team members helping the management of the intubation case wore Level-3 personal protective equipment, the disease was transmitted to seven of the nine staff.

During the worldwide spread of the COVID-19, regional anesthesia techniques are encouraged over aerosol-generating procedures (26). Moreover, the benefits of regional anesthesia in the cesarean section are well-known. However, the risk and benefit balance should be tailored for the patients individually. In a previous study on COVID-19 positive patients delivering by cesarean section, the general anesthesia rate was 4.9% (17). Nevertheless, in this report handling the obstetric COVID-19 ICU patients, the general anesthesia rate in patients undergoing cesarean section was found to be 50%, while the overall general anesthesia rate for cesarean section in COVID-19 patients was 14.06%. The choice of anesthesia technique may vary depending on viral contamination, the clinical condition of the patient, and the clinical experience and expertise of the anesthesiologist.

Dashraath et al. (27) suggested that pregnant women with COVID-19 infection are at a higher risk of thromboembolic disorders during the third trimester. After then, Goudarzi et al. (28) published a case report of maternal death due to pulmonary embolism during COVID-19 infection. In one case of our report, despite receiving antithrombotic therapy, a massive pulmonary embolism developed on the 6th day of her admission to the ICU; then, she died on the same day.

Vaccination rates among pregnant women vary by region. The vaccination rate among pregnant women was low in our country when vaccination was first started. But, the vaccination rate in pregnant women began to increase as the pandemic spread. Only one of our patients presented in this report had received the COVID-19 vaccine. After two days of high flow oxygen treatment, this vaccinated patient was discharged from the ICU. Pecks et al. (29) reported that vaccinated pregnant women required less hospitalization for COVID-19 than unvaccinated women.

The strength of this study was the relatively large sample size enough to comment on the overall COVID-19-related maternal morbidity and mortality. Additionally, the presented extreme cases set up examples of the challenging situations that may be encountered in pregnant women with COVID-19. On the other hand, its retrospective nature was a weakness of the study. The small sample size of the ICU patients included in the further evaluation might fail to demonstrate modest differences.

In conclusion, this study found the overall COVID-19-related maternal mortality rate as 4.92%, but this rate rose to 53.57% among patients requiring ICU care. The BMI, CRP, D-dimer, LDH, and CRP/Alb ratio were the independent predictors of mortality; besides, the CRP/Alb ratio was the strongest predictor of mortality in severely ill obstetric patients with COVID-19. The cesarean section and preterm delivery rates were significantly high in severely ill mothers with COVID-19. Additionally, the severity of the mothers' illness negatively influenced neonatal outcomes.

Ethical approval

This study has been approved by the Institutional Ethics Committee (2011-KAEK-25 2021/06-20). The trial was also retrospectively registered at ClinicalTrials.gov (NCT05264987). Patient informed consent was waived due to the retrospective study design. Researchers analyzed only anonymized data.

Author contribution

Study conception and design: DK, İC, HES; data collection: KT, ŞEÖ, ŞE; analysis and interpretation of results: DK, HG, BD; draft manuscript preparation: DK, İC, HES, HG, BD. The author(s) reviewed the results and approved the final version of the article.

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The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. World Health Organization (WHO). Q&A on coronaviruses (COVID-19). 2022. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (Accessed on May 16, 2022).
2. World Health Organization (WHO). Coronavirus (COVID-19). 2022. Available at: https://covid19.who.int/ (Accessed on May 16, 2022).
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506. [Crossref]
4. Li N, Han L, Peng M, et al. Maternal and neonatal outcomes of pregnant women with coronavirus disease 2019 (COVID-19) pneumonia: a case-control study. Clin Infect Dis. 2020;71:2035-41. [Crossref]
5. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009;374:451-8. [Crossref]
6. Antoun L, Taweel NE, Ahmed I, Patni S, Honest H. Maternal COVID-19 infection, clinical characteristics, pregnancy, and neonatal outcome: a prospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2020;252:559-62. [Crossref]
7. Celewicz A, Celewicz M, Michalczyk M, et al. Pregnancy as a risk factor of severe COVID-19. J Clin Med. 2021;10:5458. [Crossref]
8. Papapanou M, Papaioannou M, Petta A, et al. Maternal and neonatal characteristics and outcomes of COVID-19 in pregnancy: an overview of systematic reviews. Int J Environ Res Public Health. 2021;18:596. [Crossref]
9. Metz TD, Clifton RG, Hughes BL, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). Obstet Gynecol. 2021;137:571-80. [Crossref]
10. Hazari KS, Abdeldayem R, Paulose L, et al. Covid-19 infection in pregnant women in Dubai: a case-control study. BMC Pregnancy Childbirth. 2021;21:658. [Crossref]
11. BahaaEldin H, El Sood HA, Samy S, et al. COVID-19 outcomes among pregnant and nonpregnant women at reproductive age in Egypt. J Public Health (Oxf). 2021;43:iii12-18. [Crossref]
12. Oncel MY, Akın IM, Kanburoglu MK, et al. A multicenter study on epidemiological and clinical characteristics of 125 newborns born to women infected with COVID-19 by Turkish Neonatal Society. Eur J Pediatr. 2021;180:733-42. [Crossref]
13. Takemoto M, Menezes MO, Andreucci CB, et al. Clinical characteristics and risk factors for mortality in obstetric patients with severe COVID-19 in Brazil: a surveillance database analysis. BJOG. 2020;127:1618-26. [Crossref]
14. Di Toro F, Gjoka M, Di Lorenzo G, et al. Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis. Clin Microbiol Infect. 2021;27:36-46. [Crossref]

15. Lassi ZS, Ana A, Das JK, et al. A systematic review and meta-analysis of data on pregnant women with confirmed COVID-19: clinical presentation, and pregnancy and perinatal outcomes based on COVID-19 severity. J Glob Health. 2021;11:05018. [Crossref]

16. Andrikopoulou M, Madden N, Wen T, et al. Symptoms and critical illness among obstetric patients with coronavirus disease 2019 (COVID-19) infection. Obstet Gynecol. 2020;136:291-9. [Crossref]

17. Karasu D, Kilicarslan N, Ozgunay SE, Gurbuz H. Our anesthesia experiences in COVID-19 positive patients delivering by cesarean section: a retrospective single-center cohort study. J Obstet Gynaecol Res. 2021;47:2659-65. [Crossref]

18. Akinosoglou K, Schinas G, Papageorgiou E, et al. COVID-19 in pregnancy: perinatal outcomes and complications. World J Virol. 2024;13:96573. [Crossref]

19. Diriba K, Awulachew E, Getu E. The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical maternal-fetal transmission: a systematic review and meta-analysis. Eur J Med Res. 2020;25:39. [Crossref]

20. Salem D, Katranji F, Bakdash T. COVID-19 infection in pregnant women: review of maternal and fetal outcomes. Int J Gynaecol Obstet. 2021;152:291-8. [Crossref]

21. Bhatia K; Group of Obstetric Anaesthetists of Lancashire, Greater Manchester and Mersey Study Collaborators. Obstetric analgesia and anaesthesia in SARS-CoV-2-positive parturients across 10 maternity units in the north-west of England: a retrospective cohort study. Anaesthesia. 2022;77:389-97. [Crossref]

22. Chu Y, Yang J, Shi J, Zhang P, Wang X. Obesity is associated with increased severity of disease in COVID-19 pneumonia: a systematic review and meta-analysis. Eur J Med Res. 2020;25:64. [Crossref]

23. Ganesan R, Mahajan V, Singla K, et al. Mortality prediction of COVID-19 patients at intensive care unit admission. Cureus. 2021;13:e19690. [Crossref]

24. Özer B, Arslan Yıldız Ü, Kavaklı AS, Cengiz M, Temel H, Yılmaz M. Factors affecting mortality in COVID-19. Turk J Intensive Care. 2025;23:38-52. [Crossref]

25. Li Y, Li H, Song C, et al. Early prediction of disease progression in patients with severe COVID-19 using c-reactive protein to albumin ratio. Dis Markers. 2021;2021:6304189. [Crossref]

26. Macfarlane AJR, Harrop-Griffiths W, Pawa A. Regional anaesthesia and COVID-19: first choice at last? Br J Anaesth. 2020;125:243-7. [Crossref]

27. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222:521-31. [Crossref]

28. Goudarzi S, Firouzabadi FD, Mahmoudzadeh F, Aminimoghaddam S. Pulmonary embolism in pregnancy with COVID-19 infection: a case report. Clin Case Rep. 2021;9:1882-6. [Crossref]

29. Pecks U, Mand N, Kolben T, et al. SARS-CoV-2 infection during pregnancy-an analysis of clinical data from Germany and Austria from the CRONOS registry. Dtsch Arztebl Int. 2022;119:588-94. [Crossref]

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

The impact of window on delirium, sedation, and sleep quality of intensive care patients: a prospective study

Pencerenin yoğun bakım hastalarının deliryumu, sedasyonu ve uyku kalitesi üzerindeki etkisi: prospektif bir çalışma

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ABSTRACT

Objective: The aim of this study was to assess the impact of window on delirium, sedation, and sleep quality of intensive care patients.

Materials and Methods: This prospective study was conducted with 140 patients admitted to anesthesia intensive care units from April to September 2023. The data collection tools included the patient information form, the Visual Analog Scale for Pain, the Delirium Screening Scale, the RAMSAY Sedation Scale, and the Richards–Campbell Sleep Questionnaire. Multiple linear regression analysis was used.

Results: In the 72nd hour evaluation of the patients, the most important predictors of nighttime delirium were determined to be agitation (β=0.40), non-compliance with treatment (β=0.26), and antipsychotic use (β=0.14) (p<.05). The predictors of daytime delirium were agitation (β=0.41) and non-compliance with treatment (β=0.26, p<.05). In the 7th day evaluation, the predictors of nighttime delirium were determined to be non-compliance with treatment (β=0.28), age (β=–0.26), gender (β=–0.22), and sedative use (β=0.18) (p<.05). Predictors of daytime delirium were age (β=–0.25) and gender (β=–0.19, p<.05).

Conclusion: Having a window in the room is not a significant predictor of delirium and sedation, but it is important for sleep quality. Sleep quality and sedation are significant predictors of each other. Intensive care healthcare professionals should plan and implement psychosocial interventions to reduce the frequency of delirium, sleep problems, and sedation use in patients.

Keywords: delirium, sleep, anesthesia, intensive care, prospective studies

ÖZ

Amaç: Bu çalışmanın amacı, pencerenin yoğun bakım hastalarının deliryumu, sedasyonu ve uyku kalitesi üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Bu prospektif çalışma, Nisan-Eylül 2023 tarihleri arasında anestezi yoğun bakım ünitelerine yatırılan 140 hasta ile yürütülmüştür. Veri toplama araçları arasında hasta bilgi formu, Ağrı İçin Görsel Analog Skala, Deliryum Tarama Skalası, RAMSAY Sedasyon Skalası ve Richards-Campbell Uyku Anketi yer almıştır. Çoklu doğrusal regresyon analizi kullanılmıştır.

Bulgular: Hastaların 72. saatte yapılan değerlendirmesinde, gece ortaya çıkan deliryumun en önemli yordayıcıları ajitasyon (β=0,40), tedaviye uyumsuzluk (β=0,26) ve antipsikotik kullanımı (β= 0,14) olarak belirlenmiştir (p<,05). Gündüz görülen deliryumun yordayıcıları ise ajitasyon (β=0,41) ve tedaviye uyumsuzluktur (β=0,26, p<,05). Yedinci gün yapılan değerlendirmede, gece deliryumunun yordayıcıları tedaviye uyumsuzluk (β=0,28), yaş (β= –0,26), cinsiyet (β=–0,22) ve sedatif kullanımı (β=0,18) olarak saptanmıştır (p<,05). Gündüz görülen deliryumunun yordayıcıları ise yaş (β=–0,25) ve cinsiyettir (β=–0,19, p<,05).

Sonuç: Odada pencere olması deliryum ve sedasyonun önemli bir yordayıcısı değildir, ancak uyku kalitesi için önemlidir. Uyku kalitesi ve sedasyon birbirlerinin önemli yordayıcılarıdır. Yoğun bakım sağlık profesyonelleri, hastalarda deliryum, uyku sorunları ve sedasyon kullanımının sıklığını azaltmak için psikososyal müdahaleler planlamalı ve uygulamalıdır.

Anahtar kelimeler: deliryum, uyku, anestezi, yoğun bakım, prospektif çalışmalar

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Introduction

Delirium is one of the most common clinical conditions in intensive care units and can impair brain function (1). The pathogenesis of delirium is associated with neuro inflammation, abnormal stress responses, neurotransmitter imbalances, and changes in neural networks. Delirium in the intensive care unit is also linked to cognitive problems, such as memory loss, difficulty in concentration, and reduced awareness (2). The prevalence of delirium in coronary and internal medicine intensive care patients is 15%, but it can rise to 50% in internal medicine intensive care units (3). In one study, the incidence of delirium was 32%, with the frequency of the hypoactive subtype reaching 42% (4). Similarly, in another study, delirium was reported in 31% of patients, with the frequency of the hypoactive subtype reaching 56% (5). Another study reported a delirium incidence of 32%, with disease severity being the most significant predictor (6).

It has also been reported that delirium increases mortality and morbidity rates in intensive care patients and prolongs hospital stays (1,6). Furthermore, it has been noted that the frequency of occurrence varies based on personal characteristics, such as age and gender, but the use of physical restraints is the strongest predictor (7). In another study, variables such as age and gender did not predict delirium, but mechanical ventilation, benzodiazepine use, and certain physiological variables significantly predicted delirium (5). Long stays in the intensive care unit, frequent use of physical restraints, increased use of fentanyl, and poor sleep quality are described as important risk factors (8,9).

Delirium is often accompanied by pain and agitation in intensive care patients. It has been suggested that the drugs used to treat these symptoms, such as steroids, sedatives, anticholinergics, and opioids, are precipitating factors for delirium (10). Sleep disturbances are also among the risk factors. They are associated with delirium, but factors such as pain, discomfort, anxiety/fear, noise, and light are said to contribute to sleep problems (11). Sleep disturbances may be associated with emotional stress and cognitive problems, such as delirium, or with mechanical ventilation (12).

To reduce agitation resulting from delirium and mechanical ventilation in intensive care, minimal sedation is recommended. The goal of minimal sedation is to keep patients easily arousable, comfortable, and experiencing low levels of pain when deep sedation is not necessary (13). However, some studies suggest that the use of sedation increases delirium rates and can even be an accelerating factor (1,14). Medications such as midazolam, propofol, dexmedetomidine, and fentanyl are used for sedation. Benzodiazepines, such as midazolam and fentanyl, are more strongly associated with delirium (15). Therefore, reducing sedative use, organizing the intensive care environment, and implementing psychosocial nursing interventions are essential.

In intensive care environments, environmental conditions affecting vision, hearing, and perception are crucial, and poor environmental conditions that disrupt these functions are known to accelerate delirium (14). Windows that provide daylight and views of the outside have been shown to positively impact individuals' well-being (16). Ensuring that people can see objects and activities is the primary purpose of daylight and also facilitates the performance of daily life activities. Moreover, it contributes to well-being through physiological relaxation, enhances attention, improves mood, and increases satisfaction (17). Sleeping in a room with windows also increases patient satisfaction and shortens hospital stays (18). Cumulative delirium incidence in intensive care patients with windows in their rooms is lower than in those without windows (19).

The potential effect of windows on delirium and sleep quality could also be related to the circadian rhythm. The circadian rhythm is an internal biological clock that regulates various physiological processes, including the secretion of melatonin and cortisol, hormones essential for sleep regulation and stress response. Disturbances in this rhythm, such as altered melatonin

and cortisol secretion patterns, have been associated with the development of delirium, especially in ICU patients (20). Sleep deprivation and circadian disruption can impair immune function, cognition, and increase mortality risk, all of which contribute to delirium onset (21). Exposure to natural light through windows plays a significant role in synchronizing the circadian rhythm by influencing melatonin secretion and promoting a normal sleep-wake cycle. Patients in rooms with windows receive more direct sunlight, which can help regulate their circadian rhythm and potentially reduce delirium risk by improving sleep quality and cognitive function (22).

The aim of this study was to assess the impact of window on delirium, sedation, and sleep quality of intensive care patients.

The main research questions are as follows:

1. Is there a difference in the average scores of the nighttime and daytime delirium screening scales between patients in rooms with windows and those without windows?

2. Is there a difference in the average scores of the RAMSAY sedation scale between patients in rooms with windows and those without windows?

3. Is there a difference in the average scores of the Richards–Campbell sleep questionnaire between patients in rooms with windows and those without windows?

4. What are the predictors of delirium, sedation, and sleep quality?

Materials and Methods

Study design

This research is a prospective study. This study was reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

Setting and sample

This study was conducted with patients hospitalized in Anesthesia Intensive Care I and II units at Giresun University Training and Research Hospital from April to September 2023. There are 12 beds in the Anesthesia Intensive Care I unit and 12 beds in the Anesthesia Intensive Care II unit. Fifteen of these beds are in rooms with windows and nine are in rooms without windows. A total of 42 certified intensive care nurses and 8 anesthesia and reanimation doctors work in both intensive care units.

The number of samples calculated with anticipated effect size (*f2*): 0.15, desired statistical power level: 0.8, number of predictors: 12, and probability level: 0.05 is 127 patients (https://www.danielsoper.com/statcalc/calculator.aspx?id=1). One hundred forty patients who met the inclusion criteria between the specified dates were included in the sample. In the post hoc analysis conducted with G*Power 3.1.9.7, taking into account the RSS averages, the effect size was determined as 0.9793 with power (1 - β)=81.0% margin of error. In Post-hoc Statistical Power Calculator for Multiple Regression, observed statistical power calculated with number of predictors: 12, Observed R^2: 0.25, probability level: 0.05 and sample size: 140 is 0.9984 (https://www.danielsoper.com/statcalc/calculator.aspx?id=9). Patients were divided into two groups: those who hospitalized in rooms with and without windows.

The inclusion criteria for the study were agreeing to participate in the study, length of stay in intensive care unit ≥24 hours, and being ≥18 years old. Exclusion criteria from the study included patients who were diagnosed with delirium upon admission, were unconscious, had a mental and cognitive problem, and had serious hearing and vision problems.

Ethical consideration

This study was approved by the Institutional Review Board of a state university (Approval Date: 21.03.2023, Approval Number: KAEK-40/7). The principles of the Declaration of Helsinki were taken into consideration

in conducting the research. After the purpose of the research was explained, verbal and written consents were obtained from all the patients.

Instruments

The data collection tools included the patient information form, the Visual Analog Scale for Pain (VAS), the Delirium Screening Scale (DSS), the RAMSAY Sedation Scale (RSS), and the Richards–Campbell Sleep Questionnaire (RCSQ).

The Patient Information Form was prepared by the researchers. It consists of questions such as whether there is a window in the patient's room, the day of admission, age, gender, education level, marital status, pulse, blood pressure, respiration and oxygen saturation, whether there is agitation and pain, the severity of the pain, whether sedative and antipsychotic medication is given.

The VAS is a unidimensional scale used to record patients' pain progression or assess pain severity. It is scored from 0 (no pain) to 10 (very severe pain) (23).

The DSS was developed by Gaudreau et al. (24). The validity and reliability of the scale in Turkish was conducted by Karataş and Baglama (25). The DSS is a five-item instrument consisting of disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations, and psychomotor retardation. Cronbach's α internal consistency coefficient was calculated as 0.74. In this study, the 72nd Hour was calculated as night DSS .67 and daytime DSS .64, and the 7th Day was calculated as night DSS .75 and daytime DSS .75.

The RSS was developed by Ramsay (26). Turkish reliability and validity were evaluated by Esen et al. made by (27). The scale includes a total of six items, the first three items indicating the level of alertness and the three items indicating the level of sleep. Answers are scored from 1 to 6. An increase in the score obtained from the scale indicates an increase in the level of sedation.

The RCSQ was developed by Richards et al. (28). Turkish reliability and validity were conducted by Özlü and Özer (29). A minimum of 0 and a maximum of 100 points can be obtained from the scale. An increase in the score obtained from the scale indicates that sleep quality increases. The Cronbach's α internal consistency number of the scale is .91. In this study, it was found to be .97 at the 72nd hour and .97 at the 7th day.

Procedure

The data were collected face to face in the intensive care unit by the primary investigator, who is an anesthesia and reanimation physician from April to September 2023. Evaluations were made at the 72nd hour and on the 7th day, which is the time period when delirium is most common according to sources. Patients were evaluated twice, between 08:00-10:00 in the morning and 20:00-22:00 at night. Physiological findings were evaluated between 08:00 and 10:00 in the morning. Additionally, the 28-day mortality status of the patients was evaluated. The forms were filled in approximately 20 minutes by observation. Both daytime and nighttime assessment for delirium was performed.

Data analysis

The data were analyzed using the SPSS (Statistical Package for Social Sciences) for Windows 25.0 program. Number, percentage, mean and standard deviation values are given in the presentation of demographic data, physiological findings and scale score averages. In comparing the demographic data, physiological findings and scale averages of patients who were and were not hospitalized in a windowed room, Chi-square analysis was used for categorical variables and independent sample t-test was used for numerical and continuous variables. According to Skewness and Curtosis values, it was determined that the data showed normal distribution. With Multiple Linear Regression analysis, early and late term predictors of day and night delirium, sedation and sleep levels were tried to be determined in patients

sleeping and not sleeping in a windowed room. The evaluation for the early period was made at the 72nd hour, and the evaluation for the late period was made on the 7th day. In each model, Adjusted R^2 values were examined to determine how much of the variance the independent variables explained. The 28-day mortality status of all patients included in the study was examined. Independent samples t test was used to compare physiological findings and scale score averages according to 28-day mortality status. Statistical significance level was accepted as $p<.05$.

Results

The demographic characteristics of intensive care patients who stayed in rooms with windows and of those who stayed in rooms without windows are compared and presented in Table 1. There were no significant differences in demographic features—age, gender, marital status, smoking, alcohol use, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and heart disease—between the two groups ($p>.05$).

Table 1. Comparison of patients' demographics

Variable	Patients treated in a room with window (n=87)	Patients treated in a room without window (n=52)	Test value	p value
Age (M±SD)	64±18.03	65.40±17.73	0.44	.656
	n (%)	**n (%)**		
Sex				
Female	27 (31.0)	21 (40.4)	1.25	.262
Male	60 (69.0)	31 (59.6)		
Marital status				
Single	17 (19.5)	9 (17.3)	0.10	.744
Married	70 (80.5)	43 (82.7)		
Smoking				
Yes	35 (40.2)	23 (44.2)	0.21	.643
No	52 (59.8)	29 (55.8)		
Alcohol				
Yes	14 (16.1)	9 (17.3)	0.03	.852
No	73 (83.9)	43 (82.7)		
Hypertension				
Yes	32 (36.8)	24 (46.2)	1.18	.276
No	55 (63.2)	28 (53.8)		
Diabetes mellitus				
Yes	12 (13.8)	8 (15.4)	0.06	.796
No	75 (86.2)	44 (84.6)		
COPD				
Yes	17 (19.5)	16 (30.8)	2.26	.132
No	70 (80.5)	36 (69.2)		
Cardiac disease				
Yes	18 (20.7)	11 (21.2)	0.00	.948
No	69 (79.3)	41 (78.8)		

Table 2. Comparison of patients' clinical findings (72nd hour)

Clinical Properties	Patient treated in a room with window (n=87)	Patient treated in a room without window (n=52)	Test value	p value
	M±SD	M±SD		
Pulse	89.32±18.58	84.88±15.88	1.43	.153
Systolic blood pressure	130.69±19.34	126.40±19.48	1.26	.210
Diastolic blood pressure	72.13±11.36	70.44±11.70	0.83	.405
Respiratory rate	22.39±6.04	21.94±5.06	0.44	.654
Oxygen saturation (Sp02)	95.61±2.41	95.38±2.91	0.49	.625
Visual Analoq Scale	21.57±23.31	14.02±20.53	1.93	.056
Ramsay Sedation Scale	1.86±0.57	1.81±0.44	0.58	.559
Delirium Screening Scale (nighttime)	7.26±1.11	7.63±0.74	2.12	.035
Delirium Screening Scale (daytime)	7.31±1.05	7.63±0.74	1.93	.055
Richards–Campbell Sleep Questionnaire	235.22±107.59	221.34±108.46	0.73	.464
	n (%)	n (%)		
Ventilatory support				
No	7 (8.0)	5 (9.6)	5.05	.282
Mask	51 (58.6)	38 (73.1)		
NIMV	27 (31.0)	8 (15.4)		
HFNC	1 (1.1)	1 (1.9)		
Tracheostomized patient with easy-breathe	1 (1.1)	0 (0.0)		
Agitation				
Yes	23 (26.4)	11 (21.2)	0.49	.483
No	64 (73.6)	41 (78.8)		
Non-compliance with treatment				
Yes	23 (26.4)	9 (17.3)	1.53	.216
No	64 (73.6)	43 (82.7)		
Pain				
Yes	45 (52.3)	19 (36.5)	3.24	.072
No	41 (47.7)	33 (63.5)		
Sedative				
Yes	13 (14.9)	4 (7.7)	1.84	.398
No	74 (85.1)	48 (92.3)		
Antipsychotic				
Yes	12 (13.8)	2 (3.8)	3.55	.081
No	75 (86.2)	50 (96.2)		

The initial assessment of intensive care patients who stayed in rooms with windows versus those who stayed in rooms without windows was conducted at 72h (Table 2). There were no significant differences in the average values of pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, oxygen saturation (SPO_2), and VAS, RSS, and RCSQ scores between the two groups ($p>.05$). While there were no statistically significant differences in the average scores of the daytime delirium observation scale (DSS) ($p>.05$), a significant difference was observed in the average scores of nighttime DSS ($p=.035$). There were no statistically significant differences between patients staying in rooms with

Table 3. Comparison of clinical findings in patients based on 28-day mortality rates

Values	72nd Hour (n=140)			7th Day (n=104)		
	Excitus	Survived	p	Excitus	Survived	p
	M±SD	M±SD		M±SD	M±SD	
Pulse	92.19±22.45	86.95±16.65	.211	90.58±24.61	83.58±14.42	.154
Systolic Blood Pressure	120.86±21.53	130.56±18.68	.034	118.59±25.52	130.26±18.03	.043
Diastolic Blood Pressure	66.62±11.33	72.44±11.31	.032	65.23±14.39	72.49±9.57	.019
Respiratory rate	24.81±6.45	21.82±5.45	.026	24.08±6.76	21.38±4.37	.057
Oxygen saturation	94.67±3.56	95.65±2.39	.113	94.00±2.48	95.42±3.90	.207
Visual Analog Scale	17.24±26.04	18.92±21.90	.753	9.62±18.08	14.35±17.48	.365
Ramsay Sedation Scale	2.10±0.76	1.80±0.46	.017	2.00±0.71	1.81±0.47	.213
Delirium Screening Scale (nighttime)	7.23±0.99	7.43±1.00	.404	6.30±1.37	7.39±1.09	.002
Delirium Screening Scale (daytime)	7.28±0.90	7.46±0.97	.440	6.38±1.32	7.41±1.08	.002
Richards–Campbell Sleep Questionnaire	249.76±119.26	225.75±105.60	.348	231.15±108.30	227.33±110.12	.907

windows and those without windows in terms of respiratory support, agitation, non-compliance with treatment, pain status, and the use of sedatives and antipsychotics ($p>.05$).

When patients' findings were compared according to their 28-day mortality status (Table 3), at the 72-h assessment, patients who subsequently expired had lower measurements of SBP (120.86±21.53) and DBP (66.62±11.33) compared to the surviving patients (130.56±18.68 and 72.44±11.31) ($p<.05$). The respiratory rate (24.81±6.45) and RSS score averages (2.10±0.76) of patients who later expired were higher than those of surviving patients (21.82±5.45 and 1.80±0.46) ($p<.05$). At the day-7 assessment (Table 3), surviving patients had higher values of SBP (130.26±18.03) and DBP (72.49±9.57) compared to those who expired (118.59±25.52 and 65.23±14.39) ($p<.05$). The nighttime delirium observation scale (DSS) (7.39±1.09) and daytime DSS (7.41±1.08) averages of surviving patients were higher than those of patients who ultimately expired (6.30±1.37 and 6.38±1.32) ($p<.05$).

Early predictors were evaluated at 72 h (Table 4), and the most significant variables were included in the model. The most important predictors of nighttime delirium were agitation (β=0.40), non-compliance with treatment (β=0.26), and antipsychotic use (β=0.14, $p<.05$). This model explained 50.1% of the variance in nighttime delirium ($p<.001$). The most important predictors of daytime delirium were agitation (β=0.41) and non-compliance with treatment (β=0.26, $p<.05$). This model explained 45.5% of the variance in daytime delirium ($p<.001$). The most important predictors of sleep quality were daytime DSS (β=0.76), the presence of pain (β=0.38), and agitation (β=0.35, $p<.05$). For RCSQ, the model explained 22.7% of the variance ($p<.001$). The most important predictors of sedation level were agitation (β=0.56), non-compliance with treatment (β=0.19), age (β=0.14), and antipsychotic use (β=–0.16, $p<.05$). This model explained 55.9% of the variance for RSS ($p<.001$).

The evaluation of late predictors was performed on day 7 (Table 5). The most important predictors of nighttime delirium on day 7 were non-compliance with treatment (β=0.28), age (B=–0.26), gender (β=–0.22), and sedative use (β=0.18, $p<.05$). This model explained 35.0% of the variance in nighttime delirium on day 7 ($p<.001$). The most important predictors of daytime delirium were age (β=–0.25) and gender (β=–0.19, $p<.05$). This model explained 28.3% of the variance in daytime delirium on day 7 ($p<.001$). The most important predictors of sleep quality on day 7 were RSS (β=0.38), pain (β=0.30), and staying in a

Table 4. Early predictors of delirium, sleep, and sedation levels (n=140)

Variable	B	S.E.	β	t	p
Nighttime Delirium Screening Scale (R^2=0.545, Adjusted R^2=0.501, F=12.46, p<.001)					
Window	0.233	0.131	0.112	1.78	.077
Sex	-0.037	0.137	-0.018	-0.27	.786
Age	-0.003	0.004	-0.053	-0.74	.460
Agitation	0.961	0.265	0.408	3.62	<.001
Non-compliance with treatment	0.620	0.219	0.260	2.83	.005
Pain	0.102	0.220	0.050	0.46	.645
Visual Analog Scale	0.005	0.005	0.121	1.16	.245
Sedative	0.047	0.204	0.017	0.22	.820
Antipsychotic	0.488	0.225	0.147	2.17	.032
Ramsay Sedation Scale	0.051	0.182	0.027	0.28	.780
Richards–Campbell Sleep Questionnaire	0.000	0.001	0.021	0.29	.766
Daytime Delirium Screening Scale (R^2=0.502, Adjusted R^2=0.455, F=10.51, p<.001)					
Window	0.214	0.131	0.108	1.63	.105
Sex	-0.019	0.138	-0.009	-0.13	.890
Age	-0.002	0.004	-0.042	-0.55	.577
Agitation	0.934	0.266	0.414	3.51	.001
Non-compliance with treatment	0.601	0.219	0.263	2.74	.007
Pain	0.021	0.221	0.011	0.09	.925
Visual Analog Scale	0.005	0.005	0.111	1.02	.308
Sedative	-0.020	0.204	-0.007	-0.09	.922
Antipsychotic	0.402	0.225	0.126	1.78	.077
Ramsay Sedation Scale	-0.024	0.182	-0.013	-0.13	.896
Richards–Campbell Sleep Questionnaire	0.001	0.001	0.063	0.85	.396
Richards–Campbell Sleep Questionnaire (R^2=0.300, Adjusted R^2=0.227, F=4.09, p<.001)					
Window	-22.327	17.572	-0.100	-1.27	.206
Sex	-17.377	18.269	-0.077	-0.95	.343
Age	-0.688	0.532	-0.114	-1.29	.198
Agitation	89.185	36.338	0.353	2.45	.016
Non-compliance with treatment	-17.328	30.065	-0.068	-0.57	.565
Pain	83.817	28.617	0.388	2.92	.004
Visual Analog Scale	0.640	0.630	0.131	1.01	.311
Sedative	-24.377	27.258	-0.081	-0.89	.373
Antipsychotic	26.336	30.612	0.074	0.86	.391
Ramsay Sedation Scale	30.438	24.309	0.148	1.25	.213
Nighttime Delirium Screening Scale	-78.967	42.381	-0.737	-1.86	.065
Daytime Delirium Screening Scale	85.667	42.196	0.766	2.03	.044
Ramsay Sedation Scale (R^2=0.601, Adjusted R^2=0.559, F=14.35, p<.001)					
Window	-0.073	0.065	-0.067	-1.12	.262
Sex	0.007	0.067	0.006	0.10	.920
Age	0.004	0.002	0.140	2.12	.036
Agitation	0.689	0.122	0.562	5.66	<.001
Non-compliance with treatment	0.246	0.108	0.198	2.27	.025
Pain	0.009	0.109	0.009	0.08	.932
Visual Analog Scale	0.003	0.002	0.140	1.43	.153
Sedative	-0.028	0.100	-0.019	-0.27	.781
Antipsychotic	-0.285	0.110	-0.165	-2.59	.010
Nighttime Delirium Screening Scale	0.228	0.156	0.437	1.45	.148
Daytime Delirium Screening Scale	-0.224	0.156	-0.412	-1.43	.154
Richards–Campbell Sleep Questionnaire	0.000	0.000	0.084	1.25	.213

Table 5. Late predictors of delirium, sleep, and sedation levels (n=104)

Variable	B	S.E.	B	t	p
Nighttime Delirium Screening Scale (R^2=0.426, Adjusted R^2=0.350, F=5.57, p<.001)					
Window	0.176	0.218	0.071	0.80	.421
Sex	-0.547	0.225	-0.224	-2.43	.017
Age	-0.017	0.006	-0.266	-2.65	.009
Agitation	0.324	0.376	0.122	0.86	.391
Non-compliance with treatment	0.892	0.410	0.280	2.17	.032
Pain	0.373	0.338	0.157	1.10	.272
Visual Analog Scale	0.007	0.009	0.100	0.71	.478
Sedative	0.619	0.294	0.187	2.10	.038
Antipsychotic	0.304	0.255	0.118	1.19	.237
Ramsay Sedation Scale	-0.125	0.288	-0.053	-0.43	.665
Richards–Campbell Sleep Questionnaire	0.000	0.001	-0.022	-0.22	.822
Daytime Delirium Screening Scale (R^2=0.367, Adjusted R^2=0.283, F=4.35, p<.001)					
Window	0.139	0.225	0.057	0.61	.538
Sex	-0.478	0.233	-0.199	-2.05	.043
Age	-0.016	0.007	-0.257	-2.44	.017
Agitation	0.273	0.389	0.105	0.70	.485
Non-compliance with treatment	0.749	0.423	0.240	1.77	.080
Pain	0.367	0.349	0.156	1.05	.296
Visual Analog Scale	0.007	0.010	0.109	0.74	.461
Sedative	0.443	0.303	0.136	1.46	.148
Antipsychotic	0.366	0.263	0.145	1.38	.168
Ramsay Sedation Scale	-0.043	0.297	-0.019	-0.14	.885
Richards–Campbell Sleep Questionnaire	0.000	0.001	-0.041	-0.39	.695
Richards–Campbell Sleep Questionnaire (R^2=0.349, Adjusted R^2=0.254, F=3.66, p<.001)					
Window	-46.410	20.920	-0.205	-2.21	.029
Sex	-11.274	22.995	-0.050	-0.49	.625
Age	0.279	0.651	0.048	0.42	.669
Agitation	19.077	37.022	0.079	0.51	.608
Non-compliance with treatment	-17.751	41.731	-0.061	-0.42	.672
Pain	67.170	32.559	0.308	2.06	.042
Visual Analog Scale	1.287	0.919	0.209	1.40	.165
Sedative	-55.418	30.147	-0.183	-1.83	.069
Antipsychotic	31.480	25.104	0.134	1.25	.213
Ramsay Sedation Scale	82.436	27.097	0.385	3.04	.003
Nighttime Delirium Screening Scale	37.094	49.162	0.406	0.75	.453
Daytime Delirium Screening Scale	-38.997	47.555	-0.420	-0.82	.414
Ramsay Sedation Scale (R^2=0.587, Adjusted R^2=0.527, F=9.73, p<.001)					
Window	0.086	0.079	0.081	1.07	.284
Sex	-0.037	0.086	-0.035	-0.43	.668
Age	-0.001	0.002	-0.052	-0.58	.561
Agitation	0.514	0.127	0.453	4.05	<.001
Non-compliance with treatment	0.357	0.151	0.263	2.36	.020
Pain	-0.061	0.124	-0.060	-0.49	.622
Visual Analog Scale	0.005	0.003	0.164	1.38	.170
Sedative	0.024	0.114	0.017	0.21	.831
Antipsychotic	0.078	0.094	0.071	0.82	.410
Nighttime Delirium Screening Scale	-0.252	0.182	-0.589	-1.38	.169
Daytime Delirium Screening Scale	0.233	0.176	0.536	1.32	.189
Richards–Campbell Sleep Questionnaire	0.001	0.000	0.244	3.04	.003

room with a window (β=–0.20, p<.05). This model explained 25.4% of the variance in RCSQ ($p<.001$). The most important predictors of patients' sedation levels on day 7 were agitation (β=0.45), non-compliance with treatment (β=0.26), and RCSQ (β=0.24, $p<.05$). This model explained 52.7% of the variance in RSS on day 7 ($p<.001$).

Discussion

This comparison of patients in intensive care units with and without windows revealed interesting findings. While no statistically significant differences were observed in physiological parameters, pain assessments, sedation, sleep quality, agitation, treatment compliance, or the use of sedatives and antipsychotics at the 72-h assessment, a significant discrepancy was identified in delirium levels, particularly in the average night delirium rating scale (DSS) scores. Patients in windowless rooms had higher average night DSS scores compared to those in windowed rooms. This result aligns with prior research indicating that patients benefit from natural daylight in intensive care units, experiencing a lower incidence of delirium (19). A prospective study highlighted that patients exposed to daylight through windows experienced less agitation and hallucinations compared to those in dark rooms, who were thus likelier to use antipsychotics (30). Additionally, some studies have suggested that nighttime light levels may be a more powerful predictor of delirium than daytime light levels (31,32). In another study, no difference was found in terms of delirium development between in patients with and without a window (21). It should be noted that conflicting findings exist in the literature, necessitating further research in future studies, including measuring the intensity of daylight through the windows.

Regarding 28-day mortality, the study found that surviving patients had higher systolic and diastolic blood pressure (SBP and DBP) values compared to those of patients who ultimately expired. At the 72-h assessment, patients who eventually died had higher respiratory rates and sedation score averages than survivors. On day 7, survivors also had higher night and day DSS score averages than patients who ultimately expired. Nevertheless, no direct relationship was observed between 28-day mortality rates and the presence of windows in the intensive care unit. Similarly, no significant difference in 28-day mortality rates was noted between patients in windowed versus windowless intensive care unit rooms (19). However, some physiological parameters were linked to mortality. Specifically, in one study, there was a significant association between high mortality rates and low SBP and DBP values in intensive care unit patients (33). Another study found that deceased patients in the intensive care unit had previously had higher respiratory rates compared to surviving patients. Additionally, this study had reported higher pulse rates and lower SpO_2 levels previously among patients who died (34). These findings suggest that 28-day mortality rates are not directly influenced by the presence of windows, and further research is warranted to better understand the intricate relationship between patient outcomes and windowed environments.

In this study, the assessment conducted at 72 h revealed that the most significant predictors of nighttime delirium were agitation, non-compliance with treatment, and the use of antipsychotic medication. On day 7, the important predictors were non-compliance with treatment, age, gender, and sedative use. For daytime delirium, the crucial predictors were agitation at 72 h and non-compliance with treatment on day 7, along with age and gender. These findings align with recent advances in delirium prediction emphasizing multifactorial risk models that incorporate clinical, demographic, and treatment-related variables (35,36). Machine learning models have further demonstrated the value of integrating physiological and clinical data for early delirium detection, supporting the importance of continuous monitoring of agitation and medication effects (35). The identification of non-compliance as a consistent predictor suggests that interventions to improve patient engagement and adherence could be

pivotal in delirium prevention strategies. Overall, this study reinforces the need for dynamic, time-sensitive assessment protocols in the ICU that address modifiable factors such as agitation and medication use while considering patient-specific characteristics to reduce delirium incidence and improve outcomes.

Regarding the use of antipsychotic medication, this study showed that as the average delirium score increased at 72 h, antipsychotic use also increased. This increase paralleled the rise in agitation and non-compliance with treatment. In one study, approximately half of the patients who developed delirium were administered antipsychotic drugs, which were found to be effective in managing delirium (37). However, one study suggested that psychoactive drugs, such as antipsychotics and anticonvulsants, pose a moderate risk factor for delirium (38). In contrast, a review of randomized controlled trials found no significant difference in delirium frequency, duration, length of hospital stay, or mortality rates between haloperidol use and a placebo. Additionally, there was insufficient evidence to support the efficacy of haloperidol regarding delirium severity, cognitive function, and sedation (39). In one study, approximately 45% of delirious patients were administered antipsychotics, and it was found that haloperidol and olanzapine increased the likelihood of delirium persistence and mortality; only quetiapine reduced mortality rates (40). While antipsychotics play a significant role in delirium treatment, further studies are needed to evaluate their long-term effects, including mortality rates.

In this study, the day-7 evaluation indicated that delirium was less common in older individuals, but females had a higher incidence compared to males. These findings differ from those of other studies, which have reported different risk factors. One study reported that advanced age is a risk factor for delirium without gender differences (38). Another study found that older individuals were more prone to persistent delirium, alongside factors such as the use of physical restraint, severe illness, prolonged mechanical ventilation, hospitalization, and repeated admissions (7). Some studies found that while the incidence of delirium in intensive care unit patients did not differ by age and gender, it was associated with prolonged mechanical ventilation, hypoxia, extended intensive care unit stays, severe pain, increased agitation, and sedation (9,41). Different results were obtained in the studies. In this study, the risk of delirium decreased with increasing age. In one study, patients younger than 55 years of age in intensive care were more affected by biological and environmental factors (42). These varying results emphasize the need for further research, particularly to clarify the relationships between age and gender in different group comparisons.

In this study, the assessment conducted at 72 h indicated that the most critical predictors of sleep quality were daytime intensive care unit (ICU) stay, the presence of pain, and agitation. On day 7, the most important predictors of sleep quality were the Richmond Agitation-Sedation Scale (RSS), the presence of pain, and staying in a room with windows. The relationship between sleep deprivation and delirium has been observed, especially in older patients (43). In one study evaluating risk factors for delirium in elderly patients, poor sleep quality was found in delirious patients (9). In older patients who underwent surgical procedures for femur fractures, experiencing sleep disturbances was identified as a predictive factor for delirium (44). Changes in sleep quality and quantity have been recognized as one of the factors accelerating delirium in ICU patients (45). Hence, it is crucial to continually assess sleep and delirium in patients, implement psychosocial interventions for those experiencing sleep problems or delirium symptoms, and make environmental adjustments.

In this study, in addition to delirium, pain and agitation were also significant predictors of sleep quality. In ICU patients, agitation can result from factors such as pain and delirium (46). Factors like pain have been reported to disturb a patient's sleep in the ICU and increase anxiety, leading to agitation (10). In a systematic review, the severity of the disease, age, pain, delirium,

comorbidities, gender, and pre-hospitalization sleep problems were identified as individual factors affecting sleep disorders (47). ICU patients have reported that factors such as pain, discomfort, anxiety/fear, noise, light, and ICU care-related activities contribute to sleep disturbances (11). Identifying and supporting pain and agitation early with psychosocial nursing interventions can help effectively manage symptoms and address the problems they cause, such as sleep disorders.

This study found that patients who stayed in rooms with windows had better sleep quality. Some sources have reported that factors such as light and noise are significant factors that reduce sleep quality, particularly continuous exposure to strong light (11,12,48,49). In a cohort study, environmental factors, such as noise and artificial lighting, were found to have a more substantial impact on sleep quality in ICU patients compared to biological factors (42). In ICU patients, circadian rhythm is considered crucial, with the circadian rhythm most affected by light. Environmental factors, such as strong lighting, have been reported to disrupt circadian rhythm, leading to problems with sleep duration and quality (50). Most studies seem to focus on the relationship between light intensity and sleep quality. Therefore, conducting studies comparing patients who stayed in rooms with windows to those who did not is recommended to further explore this issue.

In this study, the predictors of sedation level at 72 h included agitation, non-compliance with treatment, age, and antipsychotic medication use. On day 7, the most important predictors of patients' sedation levels were agitation, non-compliance with treatment, and sleep quality. In ICU patients, agitation can arise from various factors, including pain, delirium, and medication. Agitation can lead to unintended removal of tubes and catheters, prolonged ICU stays, and various secondary complications (46). To calm patients, facilitate procedures such as mechanical ventilation and tracheal intubation, and promote their adaptation to daily care and nursing practices, sedation is often administered (51). While it is recommended to use sedatives at very low doses, interventions such as improving the patient's environment, reducing nighttime noise and light, and enhancing sleep quality are also advised (10). It is possible to prevent or minimize factors predicting sedation through nursing interventions. Before resorting to medication, proper interventions should be planned and implemented, and making the necessary assessments and adjustments in the ICU.

Strengths and limitations

One of the strengths of this study is that it is a prospective study. Prospective studies allow researchers to collect future data which helps to better assess cause-and-effect relationships. Additionally, conducting two separate assessments on the same patients contributed to a better understanding of predictors for both early and late dependent variables, enhancing the internal validity of the research. Another strength is the validation and reliability of the assessments, which used standardized tools. This ensures that the data collected are accurate and reliable.

Nevertheless, a significant limitation of the study is that it was conducted in a single center. Therefore, the results obtained may only be applicable to the sampled population in that specific center, and different results may be obtained in other hospitals. Multicenter studies are recommended to increase the likelihood of obtaining generalizable results.

Conclusion

This study examined predictors associated with delirium, sedation, and sleep quality in anesthesia intensive care unit patients. In general, the most important predictors for delirium, sedation, and sleep quality include factors such as pain, agitation, non-compliance with treatment, and sleep quality. Notably, sleeping in a room with a window did not emerge as a significant predictor for delirium or sedation, but was found to be a significant predictor for sleep quality. In light of these findings, further research on the subject is recommended. The findings of the study

provide guidance for managing important factors related to delirium, sedation, and sleep quality in the ICU. In daily practice, pain and agitation should be regularly assessed and effectively controlled, while individualized sedation plans should be implemented to prevent over-sedation. To improve treatment compliance, patient and family education should be provided, treatment regimens simplified where possible, and adherence supported through multidisciplinary teamwork. To enhance sleep quality, rooms with windows should be preferred when feasible, noise and light disturbances minimized during nighttime, and non-pharmacological sleep-promoting methods utilized. Additionally, routine screening for delirium should be conducted for early detection, modifiable risk factors actively managed, and the environment maintained calm, well-lit, and orienting. Finally, raising healthcare staff awareness on these issues and encouraging interprofessional collaboration play a critical role in improving patient outcomes.

Ethical approval

This study was approved by the Institutional Review Board of Giresun University Training and Research Hospital (Approval Date: 21.03.2023, Approval Number: KAEK-40/7). The principles of the Declaration of Helsinki were taken into consideration in conducting the research. After the purpose of the research was explained, verbal and written consents were obtained from all the patients.

Author contribution

Study conception and design: AB, EBY; data collection: AB, EBY; analysis and interpretation of results: AB, EBY; draft manuscript preparation: AB, EBY. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Mart MF, Williams Roberson S, Salas B, Pandharipande PP, Ely EW. Prevention and management of delirium in the intensive care unit. Semin Respir Crit Care Med. 2021;42:112-26. [Crossref]
2. Sadhu A, Valencia C, Fatima H, et al. Haloperidol versus atypical antipsychotics for treating delirium in intensive care unit patients: a systematic review. Cureus. 2022;14:e30641. [Crossref]
3. dın ZD, Yıldırım H. Delirium and associated factors among older patients in coronary and internal medicine intensive care units of a university hospital. Eur J Geriatr Gerontol. 2019;1:87-93. [Crossref]
4. Erbay Dalli Ö, Kelebek Girgin N, Kahveci F. Incidence, characteristics and risk factors of delirium in the intensive care unit: an observational study. J Clin Nurs. 2023;32:96-105. [Crossref]
5. Jayaswal AK, Sampath H, Soohinda G, Dutta S. Delirium in medical intensive care units: incidence, subtypes, risk factors, and outcome. Indian J Psychiatry. 2019;61:352-58. [Crossref]
6. Alzoubi E, Shaheen F, Yousef K. Delirium incidence, predictors and outcomes in the intensive care unit: a prospective cohort study. Int J Nurs Pract. 2024;30:e13154. [Crossref]
7. Kooken RWJ, van den Berg M, Slooter AJC, Pop-Purceleanu M, van den Boogaard M. Factors associated with a persistent delirium in the intensive care unit: a retrospective cohort study. J Crit Care. 2021;66:132-37. [Crossref]
8. Li Y, Yuan D, Li X, Wang S. Risk factors for delirium in intensive care unit and its duration. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020;32:62-66. [Crossref]
9. Li X, Zhang L, Gong F, Ai Y. Incidence and risk factors for delirium in older patients following intensive care unit admission: a prospective observational study. J Nurs Res. 2020;28:e101. [Crossref]
10. Govern C, Cowan R, Appleton R, Miles B. Pain, agitation and delirium in the intensive care unit. Anaesth. Intensive Care Med. 2021;22:799-06. [Crossref]
11. Honarmand K, Rafay H, Le J, et al. A systematic review of risk factors for sleep disruption in critically ill adults. Crit Care Med. 2020;48:1066-74. [Crossref]
12. Grimm J. Sleep deprivation in the intensive care patient. Crit Care Nurse. 2020;40:e16-24. [Crossref]

13. Page V, McKenzie C. Sedation in the intensive care unit. Curr Anesthesiol Rep. 2021;11:92-100. [Crossref]

14. Mart MF, Pun BT, Pandharipande P, Jackson JC, Ely EW. ICU survivorship-the relationship of delirium, sedation, dementia, and acquired weakness. Crit Care Med. 2021;49:1227-40. [Crossref]

15. Casault C, Soo A, Lee CH, et al. Sedation strategy and ICU delirium: a multicentre, population-based propensity score-matched cohort study. BMJ Open. 2021;11:e045087. [Crossref]

16. Zadeh RS, Shepley MM, Williams G, Chung SSE. The impact of windows and daylight on acute-care nurses' physiological, psychological, and behavioral health. HERD. 2014;7:35-61. [Crossref]

17. Veitch JA, Galasiu AD. The physiological and psychological effects of Windows, daylight, and view at home: review and research agenda. National Research Council of Canada. Technical Report, 2012. [Crossref]

18. Mihandoust S, Joseph A, Kennedy S, MacNaughton P, Woo M. Exploring the relationship between window view quantity, quality, and ratings of care in the hospital. Int J Environ Res Public Health. 2021;18:10677. [Crossref]

19. Li J, Cai S, Liu X, et al. Circadian rhythm disturbance and delirium in ICU patients: a prospective cohort study. BMC Anesthesiol. 2023;23:203. [Crossref]

20. Boyko Y, Jennum P, Toft P. Sleep quality and circadian rhythm disruption in the intensive care unit: a review. Nat Sci Sleep. 2017;9:277-84. [Crossref]

21. Aomura D, Yamada Y, Harada M, Hashimoto K, Kamijo Y. Hospital admission to a window-side bed does not prevent delirium: a retrospective cohort study of older medical inpatients in general wards. Front Med (Lausanne). 2021;8:744581. [Crossref]

22. Lee HJ, Bae E, Lee HY, Lee SM, Lee J. Association of natural light exposure and delirium according to the presence or absence of windows in the intensive care unit. Acute Crit Care. 2021;36:332-41. [Crossref]

23. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health. 1990;13:227-36. [Crossref]

24. Gaudreau JD, Gagnon P, Harel F, Tremblay A, Roy MA. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. J Pain Symptom Manage. 2005;29:368-75. [Crossref]

25. Karataş G, Samancıoğlu Bağlama S. Validity and reliability study of the Turkish version of the nursing-Delirium Screening Scale. Gümüşhane University Journal of Health Sciences. 2023;12:918-29. [Crossref]

26. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974;2:656-59. [Crossref]

27. Esen H, Öntürk ZK, Badır A, Aslan FE. Pain behaviours of intubated and sedated intensive care patients during positioning and aspiration. ACU Sağlık Bil Derg. 2010;1:89-93.

28. Richards KC, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. J Nurs Meas. 2000;8:131-44.

29. Özlü ZK, Özer N. Richard-Campbell sleep questionnaire validity and reliability study. Journal of Turkish Sleep Medicine. 2015;2:29-32. [Crossref]

30. Smonig R, Magalhaes E, Bouadma L, et al. Impact of natural light exposure on delirium burden in adult patients receiving invasive mechanical ventilation in the ICU: a prospective study. Ann Intensive Care. 2019;9:120. [Crossref]

31. Bandyopadhyay S, Cecil A, Sena J, Davidson A, Guan Z, Nerella S, et al. Predicting risk of delirium from ambient noise and light information in the ICU. 2023. [Crossref]

32. Junior MM, Kumar A, Kumar P, Gupta P. Assessment of delirium as an independent predictor of outcome among critically ill patients in intensive care unit: a prospective study. Indian J Crit Care Med. 2022;26:676-81. [Crossref]

33. Khanna AK, Kinoshita T, Natarajan A, et al. Association of systolic, diastolic, mean, and pulse pressure with morbidity and mortality in septic ICU patients: a nationwide observational study. Ann Intensive Care. 2023;13:9. [Crossref]

34. Abate SM, Assen S, Yinges M, Basu B. Survival and predictors of mortality among patients admitted to the intensive care units in southern Ethiopia: a multi-center cohort study. Ann Med Surg (Lond). 2021;65:102318. [Crossref]

35. Park C, Han C, Jang SK, et al. Development and validation of a machine learning model for early prediction of delirium in intensive care units using continuous physiological data: retrospective study. J Med Internet Res. 2025;27:e59520. [Crossref]

36. Esumi R, Funao H, Kawamoto E, et al. Machine learning-based prediction of delirium and risk factor identification in intensive care unit patients with burns: retrospective observational study. JMIR Form Res. 2025;9:e65190. [Crossref]

37. Shoulders BR, Elsabagh S, Tam DJ, Frantz AM, Alexander KM, Voils SA. Risk factors for delirium and association of antipsychotic use with delirium progression in critically ill trauma patients. Am Surg. 2023;89:1610-15. [Crossref]

38. Poulsen LM, Estrup S, Mortensen CB, Andersen-Ranberg NC. Delirium in intensivecare. Curr Anesthesiol Rep. 2021;11:516-23. [Crossref]

39. Oh ES, Needham DM, Nikooie R, et al. Antipsychotics for preventing delirium in hospitalized adults: a systematic review. Ann Intern Med. 2019;171:474-84. [Crossref]

40. Boncyk CS, Farrin E, Stollings JL, et al. Pharmacologic management of intensive care unit delirium: clinical prescribing practices and outcomes in more than 8500 patient encounters. Anesth Analg. 2021;133:713-22. [Crossref]

41. Ali MA, Hashmi M, Ahmed W, Raza SA, Khan MF, Salim B. Incidence and risk factors of delirium in surgical intensive care unit. Trauma Surg Acute Care Open. 2021;6:e000564. [Crossref]

42. Miranda-Ackerman RC, Lira-Trujillo M, Gollaz-Cervantez AC, et al. Associations between stressors and difficulty sleeping in critically ill patients admitted to the intensive care unit: a cohort study. BMC Health Serv Res. 2020;20:631. [Crossref]

43. Farasat S, Dorsch JJ, Pearce AK, et al. Sleep and delirium in older adults. Curr Sleep Med Rep. 2020;6:136-48. [Crossref]

44. Cho MR, Song SK, Ryu CH. Sleep disturbance strongly related to the development of postoperative delirium in proximal femoral fracture patients aged 60 or older. Hip Pelvis. 2020;32:93-8. [Crossref]

45. Carvalho LAC, Correia MDL, Ferreira RC, Botelho ML, Ribeiro E, Duran ECM. Accuracy of delirium risk factors in adult intensive care unit patients. Rev Esc Enferm USP. 2022;56:e20210222. [Crossref]

46. Aubanel S, Bruiset F, Chapuis C, Chanques G, Payen JF. Therapeutic options for agitation in the intensive care unit. Anaesth Crit Care Pain Med. 2020;39:639-46. [Crossref]

47. Cho YS, Joung S. Influencing factors for sleep disturbance in the intensive care unit patients: A systematic review. J Korean Crit Care Nurs. 2023;16:1-14. [Crossref]

48. Bernat Adell MD, Galarza Barrachina L, Bisbal Andrés E, et al. Factors affecting sleep quality in intensive care units. Med Intensiva (Engl Ed). 2021;45:470-6. [Crossref]

49. Bani Younis M, Hayajneh F, Alshraideh JA. Effect of noise and light levels on sleep of intensive care unit patients. Nurs Crit Care. 2021;26:73-8. [Crossref]

50. Durrington HJ, Clark R, Greer R, et al. 'In a dark place, we find ourselves': light intensity in critical care units. Intensive Care Med Exp. 2017;5:9. [Crossref]

51. Rasheed AM, Amirah MF, Abdallah M, P J P, Issa M, Alharthy A. Ramsay sedation scale and richmond agitation sedation scale: a cross-sectional study. Dimens Crit Care Nurs. 2019;38:90-5. [Crossref]

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Current utilization, training and barriers to point of care ultrasound in intensive care units: a national survey

Yoğun bakımlarda yatak başı klinik ultrasonografi kullanımı, eğitimi ve engeller: ulusal anket çalışması

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ABSTRACT

Objective: This study examines the training and utilization of Point-of-Care Ultrasound (POCUS) among intensive care physicians in Türkiye, assessing its clinical use, training and barriers to implementation.

Materials and Methods: A prospective, observational, cross-sectional survey was conducted between November 10–25, 2024, among adult tertiary intensive care unit (ICU) physicians in Türkiye. The structured online questionnaire collected demographic data, POCUS training experiences, and clinical applications.

Results: A total of 152 ICU physicians participated. Lung ultrasound (78.3%) and cardiac ultrasound (71.0%) were the most frequently used POCUS applications, while cranial ultrasound (20.4%) was the least. Over half (52.6%) had no POCUS training during residency, and 53.3% had never attended a certified course; among attendees, 64.8% found the training duration insufficient. Online digital platforms were the primary self-learning resource (75.0%), and 92.1% expressed interest in further education.

Conclusion: The study highlights the need for structured POCUS training during residency and post-specialization. The absence of a standardized curriculum and experienced instructors were key barriers. Expanding post-specialization courses and improving access to high-quality digital resources may enhance POCUS competency.

Keywords: intensive care unit, POCUS, point of care ultrasound, bedside ultrasound, training

ÖZ

Giriş: Bu çalışma, Türkiye'deki yoğun bakım hekimleri arasında Yatak Başı Ultrason (POCUS) eğitimi ve kullanımını inceleyerek, klinik uygulamalarını, eğitim olanaklarını ve uygulamadaki engelleri değerlendirmektedir.

Gereç ve Yöntem: Türkiye'deki üçüncül erişkin yoğun bakım ünitelerinde (YBÜ) çalışan hekimler arasında 10-25 Kasım 2024 tarihleri arasında prospektif, gözlemsel ve kesitsel bir anket çalışması yürütüldü. Yapılandırılmış çevrimiçi anket, katılımcıların demografik verilerini, POCUS eğitimi ile ilgili deneyimlerini ve klinik

Bulgular: Çalışmaya toplam 152 YBÜ hekimi katıldı. En sık kullanılan POCUS uygulamaları akciğer ultrasonu (%78,3) ve kardiyak ultrason (%71,0) iken, en az kullanılan uygulama kraniyal ultrason (%20,4) oldu. Katılımcıların %52,6'sı uzmanlık eğitimi sırasında POCUS eğitimi almadığını, %53,3'ü ise sertifikalı bir kursa katılmadığını belirtti. Kurslara katılanların %64,8'i ise eğitim süresini yetersiz buldu. Katılımcıların %75,0'i çevrimiçi dijital platformları kendi kendine öğrenme kaynağı olarak kullanırken, %92,1'i ileri düzeyde POCUS eğitimi almakla ilgilendiğini ifade etti.

Sonuç: Çalışma, POCUS eğitiminin hem uzmanlık eğitimi hem de uzmanlık sonrası dönemde yapılandırılmış bir şekilde artırılması gerektiğini ortaya koymaktadır. Standart bir eğitim müfredatının olmaması ve deneyimli eğitmen eksikliği önemli engeller olarak belirlenmiştir. Uzmanlık sonrası POCUS kurslarının genişletilmesi ve yüksek kaliteli dijital eğitim materyallerine erişimin artırılması, POCUS kullanım yeterliliğini geliştirebilir.

Anahtar kelimeler: yoğun bakım ünitesi, POCUS, yatak başı ultrasonografi, yatak başı ultrason, eğitim

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Introduction

Ultrasonography (USG) is a rapidly expanding imaging modality in clinical practice due to its advantages, including the absence of radiation risk, low cost, and bedside applicability (1). Point-of-Care Ultrasonography (POCUS), is a practical and easily performed technique widely utilized by clinicians in intensive care units (ICUs) and operating rooms for the rapid assessment of targeted pathologies in the brain, airway, thorax, abdomen, and extremities as well as for guiding interventional procedures (2-5).

However, every USG technique requires comprehensive theoretical and practical training. Insufficient training can limit the accuracy of clinical assessments and lead to misleading results (6). Therefore, to ensure standardization in certain applications of POCUS, skill levels and corresponding minimum training requirements have been established (7).

The increasing global utilization of POCUS has necessitated its integration into training programs across various medical specialties. However, POCUS training varies not only between countries but also among different centers within the same country (3,6). The lack of standardization limits the reliability of POCUS applications and impacts the quality of patient care (8). Furthermore, gaps in knowledge regarding the adequacy of training programs, the effectiveness of teaching methods, and the availability of specialized assessment tools hinder the advancement of POCUS education (8).

The aim of this study is to investigate the current frequency of POCUS use among intensive care physicians in Türkiye, assess available training opportunities, and identify barriers to its utilization.

Materials and Methods

This study was designed as a prospective, observational, and cross-sectional research. Prior to the initiation of the study, ethical approval was obtained from the Necmettin Erbakan University Ethics Committee for Non-Pharmaceutical and Non-Medical Device Research (Approval No: 2024/5318). Data were collected between November 10 and November 25, 2024, through an web based survey administered via "Google Forms" to physicians working in adult tertiary ICUs across Türkiye. Structured questionnaire, consisting of multiple-choice, Likert-scale, and forced-choice questions (yes, no, or undecided), was used as the data collection tool (see Appendix A for the full questionnaire). The survey included participants' demographic characteristics, POCUS training, experience and use in practice, institutional resources for education and equipment, and potential barriers to POCUS implementation.

Statistical analysis

Statistical analyses were performed using SPSS 27.0 software (IBM Inc., Chicago, IL, USA). Categorical (qualitative) variables were expressed as frequency (n) and percentage (%), while quantitative variables were presented as the interquartile range and median (min-max).

Results

This study was announced through the social media platforms of relevant associations and researchers, making it impossible to determine the exact number of ICU physicians who received the invitation. A total of 152 intensive care physicians completed the survey. The demographic and professional characteristics of the participants are summarized in Table 1. The diagnostic areas in which POCUS is utilized in intensive care units are detailed in Table 2.

Table 1. Demographic characteristics of the participants

Question	Answer	Frequency	Percent (%)
Age	25-45	123	80,92%
	≥ 45	29	19,08%
Gender	Male	78	51,32%
	Female	74	48,68%
Work experience in the ICU	> 10 year	39	25,66%
	< 10 year	113	74,34%

Table 2. POCUS applications in diagnostic procedures

Application Area	Frequency (N)	Percent (%)
Lung	119	78,3%
Cardiac	108	71,0%
Abdomen	92	60,5%
Airway	78	51,3%
Ocular	65	42,7%
Cranial	31	20,4%

Comprehensive information regarding the POCUS training received by participants, including courses attended and their related perspectives, is provided in Table 3. Physicians' evaluations of POCUS training and competency during their intensive care specialization are presented in Table 4. Data on equipment availability, frequency of clinical use, preferences, and individual learning approaches are outlined in Table 5.

Table 3. Participants' POCUS training

Question	Answer	Frequency (N)	Percent (%)
Have you attended a certified POCUS course?	Yes	71	46,7%
	No	81	53,3%
If your answer to the previous question is 'No,' what are the primary reasons preventing you from attending POCUS courses and training programs? *	High course fees	21	25,9%
	The distant locations of the courses	24	29,6%
	Insufficient number of courses	23	28,4%
	Not feeling the need for a course	13	16,1%
What was the total duration of the POCUS courses you attended?	1 day only	49	69%
	2 days only	22	31%
Was the duration of the POCUS courses you attended sufficient?	Yes	25	35,2%
	No	46	64,8%
What was the duration of the workshop training in the POCUS courses you attended?*	A few hours	27	38%
	Half a day	34	47,9%
	1 day	10	14,1%
Was the duration of the workshop training in the POCUS courses you attended sufficient?	Yes	26	36,6%
	No	45	63,4%
How many trainees were assigned per instructor during the workshop sessions in the POCUS courses you attended?	>10	10	14,1%
	5-10	49	69%
	<5	12	16,9%

* Multiple response options were allowed for this question, and percentages were calculated based on the total frequencies of the selected responses.

Table 4. POCUS training and competency during residency

Question	Answer	Frequency (N)	Percent (%)
Did you receive POCUS training at your hospital during your residency?	Yes	72	47,4%
	No	80	52,6%
If your answer to the previous question is "Yes," who mentored you during your POCUS training throughout your residency?	Faculty Members	66	%85,71
	Senior Research Fellows	11	14.3%
Was the POCUS training provided during your residency sufficient?	Yes	49	32,2%
	No	103	67,7%
Would you have found a radiology rotation beneficial during your training	Yes	23	15,1%
	No	129	84,8%

Table 5. Equipment, frequency of clinical use, and individual learning preferences of POCUS

Question	Answer	Frequency (N)	Percent (%)
Is the number of ultrasound devices in your clinic sufficient?	Yes	78	51,3%
	No	74	48,7%
What is your frequency of POCUS usage?	Never	30	19,7%
	Daily	19	12,5%
	Several times a week	103	67,8%
Do you use POCUS in intensive care for purposes other than vascular interventional procedures?	Yes	115	75,7%
	No	37	24,3%
Would you like to receive further training in POCUS?	Yes	140	92,1%
	No	12	7,9%
Which additional learning methods do you use for ultrasound training?	Online trainings	71	46,7%
	Youtube	114	75,0%
	Textbook	49	32,2%
	Articles	51	33,5%
	Course	61	40,1%
If you detect a lung point and barcode sign during POCUS in a patient with suspected pneumothorax, would you proceed with an interventional procedure without additional imaging?	Yes	54	35,5%
	No	63	41,4%
	Undecided	35	23,0%

Discussion

This study represents the first national-level research evaluating the knowledge, training status, and perceived barriers to POCUS utilization among physicians working in adult intensive care units (ICUs) in our country. A total of 68% of participants reported that the current POCUS training was insufficient. More than half of the participants reported not receiving POCUS training during their residency, and over half had never attended a certified POCUS course. Among those who had participated in a POCUS course, 64.8% considered the training duration inadequate. Notably, the vast majority of participants (92.1%) expressed a strong desire for additional POCUS training.

Consistent with the findings of this study, research conducted in Canada, one of the most developed countries, has also highlighted variability in POCUS training within intensive care residency programs and identified significant educational gaps (9). A Canadian study reported that while 64% of intensive care programs provided PUS training in accordance with national recommendations, challenges such as a lack of qualified instructors and limited hands-on training opportunities remained prevalent.

Similar studies have also identified the most frequently cited barriers to POCUS education as the shortage of trained faculty members and the absence of a standardized curriculum (10). The adequacy of teaching faculty plays a crucial role in improving the quality of training. Both in our study and previous research, one of the most prominent shortcomings is the lack of a widely accepted, structured, and standardized POCUS curriculum, along with an insufficient number of competent instructors.

According to the results of this study, the most frequently used POCUS applications for diagnostic purposes were lung ultrasound (78.3%) and cardiac ultrasound (71.0%), while cranial ultrasound (20.4%) was the least utilized. Although the lower frequency of cranial ultrasound use compared to lung ultrasound is expected, the lack of adequate training in this area may also contribute to this finding.

Only 12.5% of participants reported using POCUS daily, while 19.7% stated that they never used it, and 67.8% reported using it several times a week. Regarding POCUS use in interventional procedures, 24.3% of participants indicated that they used it exclusively for vascular access. A national survey conducted in Brazil found that POCUS was primarily used for central venous catheterization (49.4%) and bedside echocardiographic evaluation (33.9%) (11).

Both national and international societies organize numerous postgraduate training courses on POCUS. In this study, half of the participants reported not attending such courses, citing high course fees, limited course availability, and the distant locations of these courses as the primary barriers. The findings of this study indicate that residents prefer digital platforms (e.g., YouTube) over traditional textbook-based learning methods. This trend highlights the increasing demand for digital resources in medical education. Therefore, it is recommended that educational materials be enriched and adapted for digital platforms to enhance accessibility. Additionally, ensuring the accuracy and reliability of content on these platforms through supervision by academic institutions and experts would be beneficial.

Lung USG is frequently utilized in the ICU due to its ease of bedside application, its ability to provide reliable diagnostic information, its advantage of avoiding radiation exposure compared to chest radiography, and its cost-effectiveness (12). In this study, lung USG was identified as the most frequently used ultrasound technique in intensive care units, with 78% of participants reporting regular use.

However, when asked, *'If you detect a lung point and barcode sign during POCUS in a patient with suspected pneumothorax, would you proceed with an interventional procedure without additional imaging?',* only 35% of physicians responded affirmatively. This finding suggests that the majority of physicians prefer to integrate ultrasound findings with other diagnostic parameters rather than relying solely on USG, even when the findings are highly suggestive.

Additionally, nearly half of the participants reported that their clinical settings lacked a sufficient number of ultrasound devices. This indicates that equipment shortages may be one of the limiting factors in the widespread utilization of POCUS.

This study highlights the need for a more standardized POCUS training program, particularly for intensive care physicians. The guidelines provided by the European Society of Intensive Care Medicine (ESICM) define the essential ultrasound skills that intensive care physicians should acquire for the assessment of critically ill patients (13). Such guidelines can serve as a fundamental framework for intensive care training programs and help address existing educational deficiencies

Conclusion

This study evaluates the training level, attitudes, preferences, frequency of use, and perspectives of intensive care physicians in Türkiye regarding POCUS, highlighting both the current state and existing gaps in education that require improvement. The primary barriers to POCUS utilization include the lack of technical equipment, an insufficient number of experienced instructors for resident training, and the absence of a standardized national curriculum. Our findings underscore the need to increase the frequency and duration of postgraduate POCUS courses, as well as to enhance the availability and quality of digital educational materials under the supervision of academic institutions and experts. We believe that these steps are essential for the widespread adoption and improved effectiveness of POCUS in clinical practice.

Ethical approval

This study has been approved by the Necmettin Erbakan University Ethics Committee for Non-Pharmaceutical and Non-Medical Device Research (approval date: 01.10.2024, number: 2024/5318).

Author contribution

Study conception and design: MA; data collection: ÖK, TA; analysis and interpretation of results: AK; draft manuscript preparation: MNK, AY. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Coker BJ, Zimmerman JM. Why anesthesiologists must incorporate focused cardiac ultrasound into daily practice. Anesth Analg. 2017;124:761-5. [Crossref]
2. Moore CL, Copel JA. Point-of-care ultrasonography. N Engl J Med. 2011;364:749-57. [Crossref]
3. Perera P, Mailhot T, Riley D, Mandavia D. The RUSH exam: rapid ultrasound in shock in the evaluation of the critically ill. Emerg Med Clin North Am. 2010;28:29-56. [Crossref]
4. Moylan M, Newgard CD, Ma OJ, Sabbaj A, Rogers T, Douglass R. Association between a positive ED FAST examination and therapeutic laparotomy in normotensive blunt trauma patients. J Emerg Med. 2007;33:265-71. [Crossref]
5. Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med. 2012;38:577-91. [Crossref]
6. Galarza L, Wong A, Malbrain MLNG. The state of critical care ultrasound training in Europe: a survey of trainers and a comparison of available accreditation programmes. Anaesthesiol Intensive Ther. 2017;49:382-6. [Crossref]
7. Wong A, Galarza L, Forni L, et al. Recommendations for core critical care ultrasound competencies as a part of specialist training in multidisciplinary intensive care: a framework proposed by the European Society of Intensive Care Medicine (ESICM). Crit Care. 2020;24:393. [Crossref]
8. Brady AK, Spitzer CR, Kelm D, Brosnahan SB, Latifi M, Burkart KM. Pulmonary critical care fellows' use of and self-reported barriers to learning bedside ultrasound during training: results of a national survey. Chest. 2021;160:231-7. [Crossref]
9. Slemko JM, Daniels VJ, Bagshaw SM, Ma IWY, Brindley PG, Buchanan BM. Critical care ultrasound training: a survey exploring the "education gap" between potential and reality in Canada. Ultrasound J. 2021;13:48. [Crossref]
10. Schott CK, Wetherbee E, Khosla R, et al. Current use, training, and barriers to point-of-care ultrasound use in intensive care units in the department of veterans affairs. CHEST Critical Care. 2023;1:100012. [Crossref]
11. Pellegrini JAS, Cordioli RL, Grumann ACB, Ziegelmann PK, Taniguchi LU. Point-of-care ultrasonography in Brazilian intensive care units: a national survey. Ann Intensive Care. 2018;8:50. [Crossref]
12. Laursen CB, Sloth E, Lassen AT, et al. Point-of-care ultrasonography in patients admitted with respiratory symptoms: a single-blind, randomised controlled trial. Lancet Respir Med. 2014;2:638-46. [Crossref]
13. Robba C, Wong A, Poole D, et al. Basic ultrasound head-to-toe skills for intensivists in the general and neuro intensive care unit population: consensus and expert recommendations of the European Society of Intensive Care Medicine. Intensive Care Med. 2021;47:1347-67. [Crossref]

Appendix A. Survey questions

1) What is your age?
2) What is your gender?
3) What is your medical specialty?
4) How long have you been working in intensive care units?
5) What is your academic title at your current institution?
6) What is your current workplace?
7) Have you attended any certified course on Point-of-Care Ultrasonography (POCUS)?
8) Do you think the POCUS courses conducted in our country are beneficial?
9) What was the duration of the POCUS courses you attended?
10) Do you think the duration of the POCUS courses you attended was sufficient?
11) Were hands-on workshop sessions on mannequins included in the POCUS courses you attended?
12) What was the duration of the hands-on workshop sessions on mannequins in the POCUS courses you attended?
13) Do you think the duration of the hands-on workshop sessions on mannequins was sufficient?
14) How many trainees were assigned per instructor during the hands-on workshop sessions in the POCUS courses you attended?
15) What is the primary reason preventing you from attending POCUS courses and training programs?
16) Did you receive POCUS training at your hospital during your residency?
17) If your answer to question 16 is "Yes," who mentored you during your POCUS training?
18) Did you receive POCUS training outside of your hospital during your residency?
19) Did you receive POCUS training after completing your residency?
20) How many ultrasound procedures did you perform during your residency?
21) Do you think the use of POCUS was sufficient during your residency?
22) Do you think the POCUS training provided during your residency was adequate?
23) Which ultrasound applications have you received theoretical training on during courses or at your hospital? (Please select all that apply.)
24) Would you like to receive further training in POCUS?
25) Do you use additional learning methods for ultrasound training?
26) Should a radiology rotation be included in the intensive care fellowship training program?
27) Is the number of ultrasound devices in your clinic sufficient?
28) How frequently do you use POCUS?
29) Do you use POCUS for diagnostic and therapeutic purposes (excluding interventional procedures) in intensive care?
30) Do you use POCUS while performing interventional procedures in intensive care?
31) Do you feel competent enough to make independent clinical decisions using POCUS?
32) How important do you consider POCUS skills in your professional career?
33) In which clinical situations do you use lung ultrasound?
34) In a scenario where you detect a lung point and barcode sign during POCUS in a patient with suspected pneumothorax, would you proceed with an interventional procedure without requesting any additional imaging?
35) In which clinical situations do you use cardiac ultrasound?
36) In which clinical situations do you use abdominal ultrasound?
37) In which clinical situations do you use cranial ultrasound?
38) In which clinical situations do you use airway ultrasound?
39) In which clinical situations do you use ocular ultrasound?

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Sepsis outcomes and predictive factors of mortality in ICU: A single center experience for four years

Yoğun bakım ünitesinde sepsis sonuçları ve mortaliteyi etkileyen faktörler: Dört yıllık tek merkez deneyimi

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ABSTRACT

Introduction: Sepsis, defined by Sepsis-3 as a life-threatening organ dysfunction due to infection, has high mortality rates worldwide. Early diagnosis and treatment are challenging due to its heterogeneous nature. Identifying predictive factors is crucial for improving outcomes. This study aims to analyze sepsis patients in the intensive care units (ICU) of Lokman Hekim University Ankara Hospital.

Methods: A retrospective analysis of 400 patients diagnosed with sepsis (Sepsis-3 criteria) between April 2020 and April 2024 was conducted. Data included demographics, clinical parameters, laboratory results, comorbidities, treatments and outcomes.

Results: The median age was 81 years (range: 21–101), with 214 patients (53.5%) aged 80 years and above. Hypertension (56.5%), diabetes mellitus (38.3%), and coronary artery disease (26.5%) were common comorbidities. Lactate levels were significantly higher in non-survivors (2.7 vs. 1.7 mmol/L, p=0.006). Non-survivors had higher Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, while Glasgow Coma Score (GCS) scores were higher in survivors. Invasive mechanical ventilation was required in 98.6% of non-survivors. Overall ICU mortality was 86.5%. The total culture positivity rate was 65.5%, with blood cultures positive in 32.8% of cases. *Staphylococcus epidermidis*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* were common blood isolates. In respiratory cultures, K. pneumoniae and A. baumannii predominated, while *E. coli* and *Candida species* were frequent in urine cultures. However, culture positivity in blood, urine, or respiratory samples did not significantly impact mortality. Logistic regression identified age, APACHE II score, serum procalcitonin level, and Mean arterial pressure (MAP) as independent mortality risk factors.

Conclusion: Key predictors of mortality in sepsis include age, APACHE II score, procalcitonin, and MAP. Therefore, early identification and tailored interventions may improve outcomes in sepsis management. Further research is needed to refine prognostic models.

Keywords: sepsis, prognosis, mortality, critical care

ÖZ

Giriş: Sepsis, Sepsis-3 tanımına göre enfeksiyona bağlı yaşamı tehdit eden organ disfonksiyonu olarak tanımlanmakta olup, dünya genelinde yüksek mortalite oranlarına sahiptir. Heterojen yapısı nedeniyle erken tanı ve tedavisi zorludur. Sonuçları iyileştirmek amacıyla prediktif faktörlerin belirlenmesi önemlidir. Bu çalışma, Lokman Hekim Üniversitesi Ankara Hastanesi yoğun bakım ünitelerinde yatan sepsis hastalarının analizini amaçlamaktadır.

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Yöntem: Nisan 2020 ile Nisan 2024 tarihleri arasında Sepsis-3 kriterlerine göre sepsis tanısı alan 400 hastanın retrospektif analizi yapılmıştır. Demografik veriler, klinik parametreler, laboratuvar sonuçları, eşlik eden hastalıklar, uygulanan tedaviler ve sonuçlar kaydedilmiştir.

Bulgular: Medyan yaş 81 yıl (aralık: 21–101) olup, hastaların 214'ü (%53,5) 80 yaş ve üzerindeydi. En sık görülen komorbiditeler hipertansiyon (%56,5), diabetes mellitus (%38,3) ve koroner arter hastalığı (%26,5) idi. Laktat seviyeleri sağ kalanlara kıyasla sağ kalmayanlarda anlamlı olarak yüksekti (2,7 vs. 1,7 mmol/L, p=0,006). Sağ kalmayan hastalarda APACHE II ve SOFA skorları daha yüksekken, Glasgow Koma Skoru (GKS) sağ kalanlarda yüksekti. İnvaziv mekanik ventilasyon ihtiyacı sağ kalmayanların %98,6'sında görüldü. Yoğun bakım ünitesi mortalitesi genel olarak %86,5 olarak saptandı. Toplam kültür pozitiflik oranı %65,5 olup, kan kültürleri %32,8 oranında pozitifti. Kan kültürlerinde *Staphylococcus epidermidis*, *Acinetobacter baumannii* ve *Klebsiella pneumoniae* yaygın olarak izole edildi. Solunum yolu kültürlerinde K. pneumoniae ve A. baumannii, idrar kültürlerinde ise *E. coli* ve *Candida* türleri sık görüldü. Ancak kan, idrar veya solunum yolu kültürlerindeki pozitiflik mortalite üzerinde anlamlı etki göstermedi. Lojistik regresyon analizinde yaş, APACHE II skoru, serum prokalsitonin düzeyi ve ortalama arter basıncı (OAB) bağımsız mortalite risk faktörleri olarak belirlendi.

Sonuç: Sepsis hastalarında mortalitenin başlıca belirleyicileri yaş, APACHE II skoru, prokalsitonin ve ortalama arter basıncıdır. Erken tanı ve kişiselleştirilmiş müdahaleler, sepsis yönetiminde sonuçların iyileştirilmesi için kritik öneme sahiptir. Prognostik modellerin geliştirilmesi ve antimikrobiyal direnç sorunlarının çözümü için ileri araştırmalara ihtiyaç vardır.

Anahtar kelimeler: sepsis, prognoz, mortalite, yoğun bakım

Introduction

According to the Sepsis-3 definition, sepsis is a life-threatening condition caused by an abnormal host response to infection, leading to organ dysfunction (1). Mortality from sepsis shows significant regional variation; in Europe, the rate is approximately 41%, whereas in the United States, it is around 28.3% (2).

An epidemiological study examining sepsis across intensive care units in Turkey revealed that 15.8% of patients had infections without Systemic Inflammatory Response Syndrome (SIRS), while 10.8% had infections accompanied by SIRS. Additionally, the study showed 17.3% of patients had severe sepsis without shock, whereas 13.5% had septic shock. When the researchers regrouped according the Sepsis-3 criteria, they found that 6.9% of patients were in septic shock and this subgroup had a high mortality rate (75.9%) (3). In another study carried out in Turkey, when culture results were categorized, Gram-negative bacteria were identified in 48% of cases, Gram-positive bacteria in 15%, and fungi in 8%, and 29% of patients had negative cultures. The reported in-hospital mortality rate was 51% (4). The heterogeneous nature of sepsis revealed in these studies is the key factor that complicates early diagnosis and treatment planning (5).

Due to its heterogeneous nature, identifying predictive factors in sepsis can help clinicians intervene early, improve patient outcomes, and reduce mortality rates. (6). Although studies on predictive biomarkers in sepsis have increased in recent years, identifying effective predictive factors for sepsis management remains challenging due to the limitations of these studies. In a study investigating the predictive value of the Lactate/Albumin ratio, it was found to be more predictive of 28-day mortality in critically ill sepsis patients than a single lactate measurement, and was recommended as a strong prognostic marker independent of the initial lactate level (7). While systematic reviews and meta-analyses highlight the effectiveness of machine learning models in predicting the onset of sepsis, the variability across studies complicates the evaluation of results; nevertheless, these models provide alternatives to traditional scoring systems. Therefore, there remains a need for systematic reporting and clinical research to further investigate this area (8).

The aim of the study was to review the demographic, characteristics and comorbidities effect on outcomes.

Methods

This study was designed retrospectively and carried out at the intensive care units (ICUs) at Lokman Hekim University Ankara Hospital between 01.04.2020 and 01.04.2024. Ethical approval was obtained from the Lokman Hekim University Scientific Research Ethics Committee (approval date: 01/03/2024, number: 2024/75).

The patient's data were obtained from the hospital's database system and intensive care follow-up form. When searching hospital system, International Classification of Diseases 10th Revision (ICD 10) codes (A40.0-A41.9), the key words "sepsis and septicemia" were used. For the patient's selection, 2016 Sepsis-3 diagnostic criteria were used for the definitions of sepsis, septic shock and patient selection (1). The patients having clinical and laboratory findings compatible with sepsis according to the sepsis-3 criteria and aged over 18 years old were included in the study. Exclusion criteria were defined as being under 18 years old and pregnant. The selection criteria of the patients are shown in the flow chart in Figure 1.

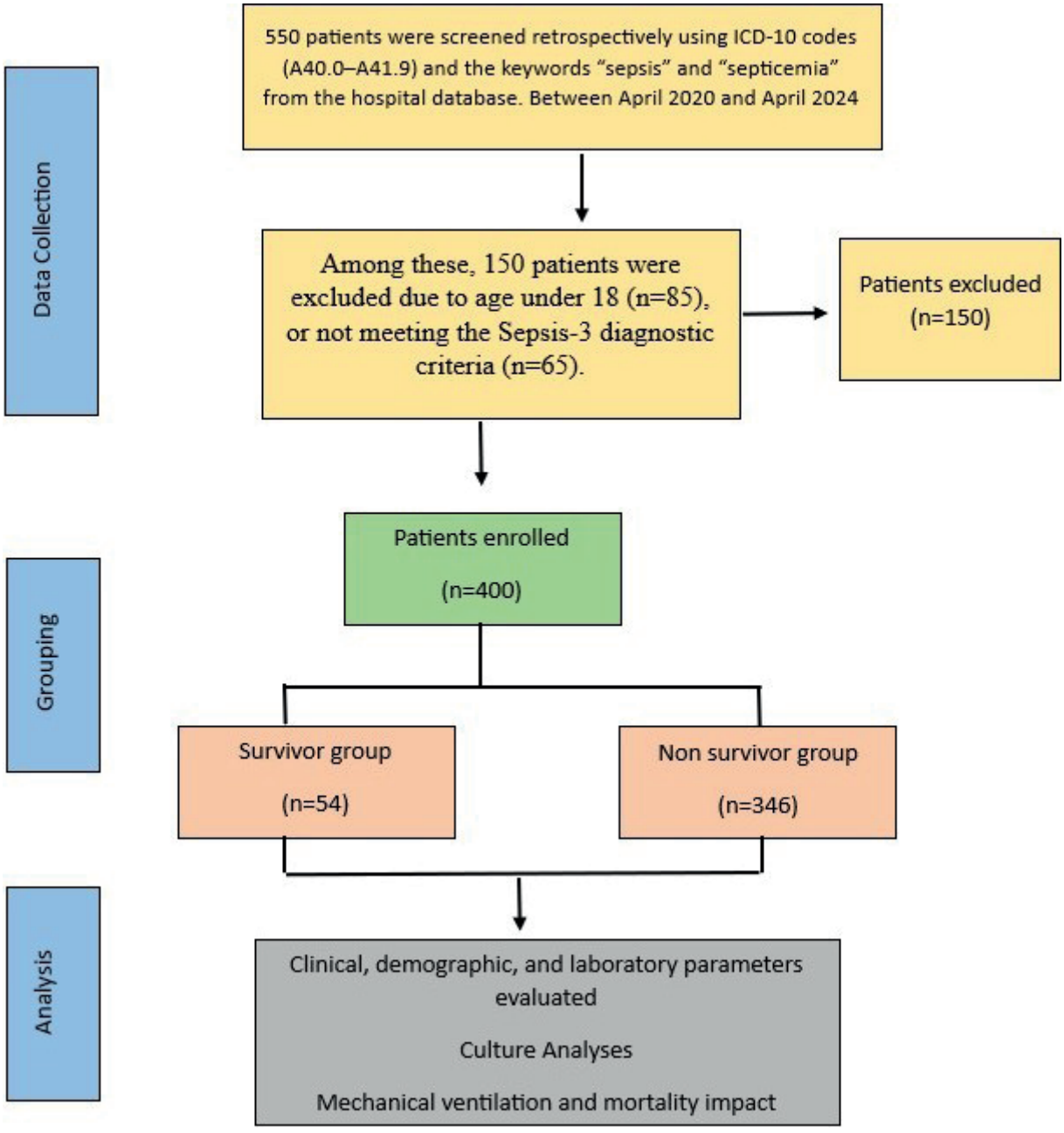

Figure 1. Flow diagram of patient selection

The demographic information of the cohort, such as age and gender, Glasgow Coma Score (GCS) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the Sequential Organ Failure Assessment (SOFA) Score at admission, serum levels of lactate, procalcitonin (PCT), C-reactive protein (CRP), leukocyte, lymphocyte, platelet, albumin, D-dimer, comorbidities, identified infection sources, documented pathogens and antimicrobial resistance results, need for mechanical ventilation and its duration, mortality were recorded. Clinical and laboratory parameters impact on mortality were analyzed. For analysis, patients were grouped retrospectively based on ICU survival status as survivors and non-survivors. The primary outcome of the study was ICU mortality. Secondary outcomes included the evaluation of demographic, clinical, and laboratory parameters as potential predictors of mortality.

Statistical analysis

The statistical analysis of the study data was performed using IBM SPSS (IBM Corp., Armonk, NY, USA) version 27.0. The normality of continuous variables was assessed using the Shapiro-Wilk test, histograms, and skewness-kurtosis coefficients. Continuous variables were presented as median (minimum–maximum) due to non-normal distribution, while categorical variables were expressed as frequencies and percentages. For the comparison of continuous variables between two groups, the Mann-Whitney U test was used. Categorical variables were compared using the Chi-square test. Binary logistic regression analysis was performed to identify independent risk factors for mortality. A p-value <0.05 was considered statistically significant.

Results

A total of 400 patients diagnosed with sepsis and septic shock were included in this study. Of the patients, 48.3% were male. The median age was 81 years (range: 21-101) and 214 cases were aged 80 years and over. Table 1 summarizes the demographic characteristics of patients. The most common comorbidities were hypertension (56.5%), diabetes mellitus (38.3%), and coronary artery disease (26.5%). However, no significant relationship was found between the presence of comorbid diseases and mortality (p>0.05).

Initially, 550 patients were screened retrospectively using ICD-10 codes (A40.0–A41.9) and the keywords “sepsis” and “septicemia” from the hospital database. Among these, 150 patients were excluded due to age under 18 (n=85), or not meeting the Sepsis-3

Table 1. The total number of patients with sepsis patients included in the study, along with their sociodemographic profiles and associated chronic conditions.

Characteristic	Total	Survivors	Non-survivors	p-value
Male (No, %)	193 (48.3%)	25 (46,3%)	168 (48,6%)	0.950
Age (median, min, max)	81 (21-101)	76 (32-98)	81 (21-101)	0.056
Comorbidities				
Hypertension	226 (56,5%)	29 (53,7%)	197 (56,9%)	0.656
Diabetes Mellitus	153 (38,3%)	21 (38,9%)	132 (38,2%)	0.917
Coronary Artery Disease	106 (26,5%)	17 (31,5%)	89 (25,7%)	0.372
Heart Failure	82 (20,5%)	13 (24,1%)	69 (19,9%)	0.484
Chronic Obstructive Pulmonary Disease	65 (16,3%)	7 (13,0%)	58 (16,8%)	0.481
Stroke	60 (15,0%)	5 (9,3%)	55 (15,9%)	0.201
Chronic Kidney Disease	64 (16,0%)	11 (20,4%)	53 (15,4%)	0.351

Data are presented as number (%) for categorical variables and median (minimum–maximum) for continuous variables.

diagnostic criteria (n=65). No patients were excluded due to incomplete data during chart review. The remaining 400 patients were then divided into two groups based on ICU survival status: survivors (n=54) and non-survivors (n=346).

Clinical and laboratory findings

When evaluating the clinical and laboratory parameters of the patients, significant differences were observed between survivors and non-survivors. Parameters such as heart rate, mean arterial pressure (MAP), PCT, CRP, and CRP/albumin ratio (CAR) had statistically significant effects on mortality ($p<0.001$, Table 2). The lactate levels were found to be 1.7 (0.5-93) mmol/L in survivors and 2.7 (0.2-113) mmol/L in non-survivors, with this difference being statistically significant (p:0.006). However, no significant difference was detected in terms of other parameters such as neutrophil/lymphocyte ratio (NLR) and albumin levels ($p>0.05$).

Culture analyses

The total culture positivity rate was 65.5%, and the blood culture positivity rate was 32.8%. The most frequently isolated bacteria from blood cultures were *Staphylococcus epidermidis* (19.08%), *Acinetobacter baumannii* (11.45%), and *Klebsiella pneumoniae* (10.69%). In respiratory secretion cultures, the most frequently isolated microorganisms were *K. pneumoniae* (27.41%), *A. baumannii* (20.00%), and *Candida species* (11.85%). In urine cultures, the most commonly isolated pathogens were *E. coli* (27.41%), *K. pneumoniae* (20.00%), and *Candida species* (23.70%) (Table 3). The presence of at least one positive culture in any sample did not significantly affect mortality. Similarly, having a positive blood, urine, or respiratory secretion culture did not have a statistically significant impact on mortality when assessed separately ($p>0.05$, Table 2). There was no statistically significant difference between survivors and non-survivors in terms of blood, respiratory secretion, or urine culture

Table 2. Analysis of the clinical characteristics and laboratory parameters of sepsis patients.

Variable	Total	Survivors	Non-survivors	p-value
Sepsis	126 (31.5%)	54 (42.9%)	72 (57.1%)	<0.001
Septic shock	274 (68.5%)	0 (0%)	100 (100%)	
Heart rate (bpm)	130 (75-145)	95 (75-110)	130 (110-145)	<0.001
MAP (mmHg)	60 (45-90)	80 (75-90)	57 (45-80)	<0.001
PCT (ng/mL)	1.155 (9-76)	9.015 (0.109-100)	0.952 (0.02-100)	<0.001
WBC (x10^9/L)	12.67 (0.42-85.57)	13.25 (4.15-45.4)	12.5 (0.42-85.5)	0.529
PLT (x10^9/L)	214 (8-801)	216 (21-459)	211 (8-801)	0.636
CRP (mg/L)	103.45 (0.16-460.36)	201 (0.16-460.3)	97.7 (0.4-421)	<0.001
Albumin (g/dl)	2.95 (0.78-68)	2.92 (2-32.5)	2.95 (0.78-68)	0.854
CRP/Albumin (CAR)	34 (1-268)	59 (1-173)	31 (1-268)	<0.001
Neutrophils (x10^9/L)	10.64 (1.27-90.1)	11.1 (3.65-42.4)	10.6 (1.27-90)	0.527
Lymphocytes (x10^9/L)	0.96 (0.1-66.42)	0.96 (0.2-4.09)	0.96 (0.1-66.4)	0.771
NLR	11 (1-160)	11 (2-73)	11 (1-160)	0.844
Lactate (mmol/L)	2.5 (0.2-113)	1.7 (0.5-93)	2.7 (0.2-113)	0.006
Positive Culture	262 (65.5%)	29 (53.7%)	233 (67.3%)	0.050
Positive Respiratory Secretion Culture	135 (33.8%)	12 (22.2%)	123 (35.5%)	0.054
Positive Blood Culture	131 (32.8%)	14 (25.9%)	117 (33.8%)	0.251
Positive Urine Culture	135 (33.8%)	15 (27.8%)	120 (34.7%)	0.318

MAP; Mean Arterial Pressure, PCT; Procalcitonin, WBC; White Blood Cell count, PLT; Platelets, CRP; C-reactive Protein, CAR: C-Reactive Protein/Albumin Ratio, NLR; Neutrophil-to-Lymphocyte Ratio.
Data are presented as number (%) for categorical variables and median (minimum–maximum) for continuous variables.

Table 3. Distribution of microorganisms isolated from patients with sepsis.

Microorganisms	Respiratory Secretion Culture, n (%)	Blood Culture, n (%)	Urine Culture, n (%)
Gram-negative bacteria			
Klebsiella pneumoniae	37 (27.41)	14 (10.69)	27 (20.00)
Acinetobacter baumannii	27 (20.00)	15 (11.45)	4 (2.96)
Escherichia coli	20 (14.81)	8 (6.11)	37 (27.41)
Enterobacter spp.	13 (9.63)	4 (3.05)	12 (8.89)
Pseudomonas aeruginosa	10 (7.41)	2 (1.53)	7 (5.19)
*Others**	10 (7.41)	4 (3.05)	1 (0.74)
Gram-positive bacteria			
Staphylococcus epidermidis	-	25 (19.08)	-
Staphylococcus aureus	2 (1.48)	13 (9.92)	4 (2.96)
Enterococcus spp.	-	11 (8.40)	2 (1.48)
Streptococcus haemolyticus	-	11 (8.40)	-
Staphylococcus capitis	-	9 (6.87)	-
Staphylococcus hominis	-	9 (6.87)	8 (5.93)
*Others **	-	4 (3.05)	1 (0.74)
Fungi			
Candida spp.	16 (11.85)	2 (1.53)	32 (23.70)
Total	135 (100)	131 (100)	135 (100)

** Citrobacter, Hafnia alvei, Serratia, Stenotrophomonas maltophilia, Providencia rettgeri, Pantoea agglomerans, Cedecea lapagei, Corynebacterium striatum, Raoultella ornithinolytica*

*** Staphylococcus simulans, Streptococcus agalactiae, Enterococcus faecium, Streptococcus spp., Aerococcus viridans*

Data are presented as number (%).

Table 4. Evaluation of outcomes among patients with sepsis.

Variable	Total	Survivors	Non-survivors	p-value
Length of stay (days)	8 (1-114)	9 (2-83)	8 (1-114)	0.228
Invasive MV Requirement	352 (88%)	11 (20.4%)	341 (98.6%)	<0.001
IMV/days	4 (0-103)	0 (0-83)	4 (0-103)	<0.001
APACHE II	27 (9-76)	22 (10-38)	28 (9-76)	<0.001
SOFA	12 (2-20)	3 (2-5)	14 (8-20)	<0.001
GCS	9 (1-15)	12 (3-15)	9 (3-15)	<0.001

APACHE II; Acute Physiology and Chronic Health Evaluation II, SOFA; Sequential Organ Failure Assessment, GCS; Glasgow Coma Scale, IMV; Invasive Mechanical Ventilation.

positivity (p>0.05). Although total culture positivity was higher in non-survivors (67.3% vs. 53.7%), the difference was borderline significant (p=0.050).

Outcomes

The median duration of ICU stay for the patients was 8 days (range:1-114). There was no statistically significant difference in the length of hospital stay between survivors and non-survivors (p:0.228). The need for invasive mechanical ventilation (IMV) was significantly higher in non-survivors (98.6%) compared to survivors (20.4%) (p<0.001). The duration of IMV was significantly longer in non-survivors (median 4 days) than in survivors (median 0 days, p<0.001). In terms of disease severity criteria such as APACHE II and SOFA scores, non-survivors had significantly higher values, while GCS scores were significantly higher in survivors. (p<0.001, Table 4).

Table 5. A comprehensive list of variables identified as potential predictors for ICU mortality, derived from univariate binary logistic regression, alongside the independent ICU mortality predictors established through multivariate binary logistic regression analysis.

Variables	Univariate binary logistic regression				Multivariate binary logistic regression			
	p-value	Exp (B)	95% C.I. for EXP (B)		p-value	Exp (B)	95% C.I. for EXP (B)	
			Lower	Upper			Lower	Upper
Age	0.010	1.026	1.006	1.046	0.039	1.041	1.002	1.081
APACHE II	<0.001	1.128	1.078	1.180	0.004	1.162	1.049	1.286
SOFA	0.980	20364.304	0.000	-	-	-	-	-
GCS	<0.001	0.774	0.702	0.853	0.723	0.969	0.812	1.155
PCT	<0.001	0.977	0.969	0.985	0.007	0.974	0.955	0.993
WBC	0.998	1.000	0.971	1.030	-	-	-	-
Platelets	0.770	1.000	0.998	1.001	-	-	-	-
CRP	<0.001	0.995	0.992	0.997	0.067	0.989	0.978	1.001
Albumin	0.294	1.037	0.969	1.110	-	-	-	-
CRP/Albumin (CAR)	0.001	0.990	0.984	0.996	0.412	1.010	0.987	1.033
Neutrophils	0.873	1.002	0.973	1.032	-	-	-	-
Lymphocytes	0.510	1.098	0.832	1.448	-	-	-	-
NLR	0.899	1.001	0.986	1.016	-	-	-	-
Lactate	0.760	1.001	0.997	1.004	-	-	-	-
IMV Days	0.003	1.113	1.036	1.195	-	-	-	-
MAP	<0.001	0.680	0.577	0.801	<0.001	0.666	0.540	0.820

APACHE II; Acute Physiology and Chronic Health Evaluation II, SOFA; Sequential Organ Failure Assessment, GCS; Glasgow Coma Scale, WBC; White Blood Cell count, CRP; C-reactive Protein, CAR; C-Reactive Protein/Albumin Ratio, NLR; Neutrophil-to-Lymphocyte Ratio, IMV; Invasive Mechanical Ventilation, MAP; Mean Arterial Pressure, PCT; Procalcitonin.

In logistic regression analysis, age (p:0.039), APACHE II score (p:0.004), PCT (p:0.007), and MAP (p<0.001) were identified as independent risk factors for mortality (p<0.05, Table 5).

Among the 400 cases included in the study, 346 patients (86.5%) died in the ICU, with a mortality rate of 86.5%. The mortality rates were significantly higher in patients diagnosed with septic shock when compared to those diagnosed with sepsis (p<0.001).

Discussion

The study findings highlight critical factors influencing patient outcomes and provide insights into the epidemiology, clinical characteristics and microbial landscape of sepsis in a tertiary care setting. Age, APACHE II score, PCT levels and MAP emerged as independent predictors of mortality. The previous studies show the role of severity scoring systems and biomarkers in prognosticating sepsis outcomes. Elevated APACHE II scores and low MAP underscore the need for aggressive hemodynamic monitoring and management in critically ill patients. Recent studies have further supported the use of multimodal biomarker combinations and advanced scoring systems to refine mortality predictions in sepsis patients (9-12).

Despite SOFA scores being found to be high in the non-survivor group in our study, it was not found to be an independent risk factor for mortality in the analyses performed. However, when the literature is examined, prospective studies on lactate are important in the management of sepsis. In addition, a prospective study identified factors such as decreased mobility, delayed sepsis diagnosis in the emergency department, higher SOFA scores at admission and inappropriate antimicrobial treatment as key risk factors for ICU mortality (13). Another meta-analysis revealed that each one-point increase in the SOFA score was

associated with a 2.4 increase in 90-day mortality in patients with septic shock, and that elevated SOFA scores were linked to higher 30-day mortality in both sepsis and septic shock. These studies underscore the prognostic role of the SOFA score in sepsis (14). Furthermore, both MAP and elevated heart rate at admission were found to significantly increase the likelihood of ICU mortality, as indicated by the analysis of these clinical parameters. These findings underscore the importance of early identification and comprehensive clinical assessment in improving outcomes for sepsis patients (13).

Lactate levels and the lactate/albumin ratio, as markers of tissue hypoperfusion, are valuable indicators for investigating poor prognosis in sepsis. Advances in omics-based technologies are enabling the characterization of sepsis endotypes, and pave the way for integrating molecular biomarkers with clinical parameters to improve outcome predictions (9–11). Although lactate was not found to be an independent risk factor for mortality in our study, recent research suggests that lactate plays a key role in sepsis, not only as a disease marker but also by promoting increased inflammation. These findings indicate that lactate may serve as a valuable target for both the diagnosis and treatment of sepsis (15).

Current studies have suggested that biomarkers such as NLR and plasma lactate levels are strong predictors of 28-day mortality in sepsis patients. A study by Liu et al. (16) reported that both NLR and lactate levels are independently associated with poor outcomes in sepsis. However, the lack of significant differences in other markers suggests that combining multiple biomarkers may provide more reliable predictive value. This notion aligns with findings from other studies, which support the use of multimodal biomarkers to enhance the sensitivity and specificity of sepsis prediction models. These findings indicate that plasma lactate levels are a significant biomarker in the prognosis of sepsis and suggest that this parameter could be more widely utilized in clinical practice. However, the lack of a significant association between NLR and mortality in our study implies that the prognostic value of NLR may vary depending on the patient population, clinical context or stage of sepsis. Considering the limitations of assessments based on a single biomarker, combining reliable biomarkers such as lactate with NLR and other potential indicators could enable the development of models that better predict sepsis outcomes. This approach may facilitate the development of individualized treatment plans and help reduce mortality rates.

Emerging biomarkers such as IL-6 and circular RNAs are showing promise in enhancing diagnostic and prognostic accuracy (11,12). Even though it is not possible to examine blood tests that are not routinely used in retrospective analyses, future studies should investigate the clinical utility of jointly evaluating biomarkers and explore how such combined approaches can be optimized in the diagnosis and management of sepsis.

The most commonly isolated microorganisms, *K. pneumoniae* and *A. baumannii*, reflect the challenges posed by multidrug-resistant organisms in ICU settings. The high prevalence of Gram-negative bacteria underscores the importance of antimicrobial stewardship programs to curb resistance rates. Literature highlights the global burden of antimicrobial resistance in sepsis management, further emphasizing the need for rapid diagnostic techniques (9,12,17). In our study, the absence of a significant relationship between positive or negative results in respiratory secretion, blood, and urine cultures and mortality ($p>0.05$) suggests that other clinical and patient-related factors may play a more decisive role in influencing mortality.

In our study, non-survivors required IMV significantly more often than survivors. Timely and effective management strategies of respiratory failure including the judicious use of mechanical ventilation and other therapeutic modalities, are essential for mitigating the risk of mortality. These interventions not only improve patient outcomes by stabilizing respiratory function, but also underscore the need for proactive care to

escalation of respiratory compromise. Studies have demonstrated that early recognition and intervention in cases of respiratory distress are essential for improving survival rates and reducing the need for more invasive treatments (10,11). Consistent with the literature and our findings revealed a higher IMV in the non-survivor group.

In our study, the mortality rate appears to be much higher than the rates typically reported in the literature. According to the literature, mortality in sepsis is generally high, and increases further in cases of septic shock (4,7,13,14,18,19). The higher mortality rate in our cohort may be attributed to several factors that differentiate this study population from those in other studies. The higher mortality rate observed in our study may be related to the severity of the patients included in our cohort. It is likely that our patients had more advanced stages of sepsis or septic shock, or were affected by multiple underlying conditions, which are known to increase mortality risk. In comparison, studies with lower mortality rates may have focused on patients with less severe forms of sepsis or those who received early, aggressive interventions.

Additionally, the heterogeneous nature of septic shock (characterized by multi-organ failure, hemodynamic instability, and metabolic disturbances) may have contributed to the high mortality rate observed in our cohort. Although survival rates for septic shock have improved in recent years with advancements in medical treatment, the prognosis remains poor in many cases, particularly in patients with delayed diagnosis or treatment (1).

Study limitations

Retrospective studies, which rely on pre-existing data, are susceptible to certain limitations, such as selection bias and the accuracy of available clinical information. In this study, for instance, the inclusion of patients who were already critically ill and the use of historical clinical records may have made it more challenging to account for all potential influencing factors.

Additionally, as the data were collected from a single center, the findings may not be generalizable to other settings or populations. Furthermore, incomplete or missing data for certain parameters could introduce bias, potentially affecting the accuracy and reliability of the results.

Conclusion

In conclusion, our study identified, age, APACHE II score, PCT and MAP as independent risk factors for ICU mortality. The findings shown the importance of early recognition, individualized management and a multidisciplinary approach in improving sepsis outcomes. The study underscores the heterogeneity of sepsis and the need for tailored therapeutic approaches. Early identification of high-risk patients using validated scoring systems and biomarkers is crucial to optimize outcomes.

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Ethical approval

This study has been approved by the Lokman Hekim University Scientific Research Ethics Committee (approval date: 01.03.2024, number: 2024/75).

Author contribution

Study conception and design: OD; data collection: OD, OZY; analysis and interpretation of results: OD; draft manuscript preparation: OD, BEY. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-10. [Crossref]
2. Levy MM, Artigas A, Phillips GS, et al. Outcomes of the surviving sepsis campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis. 2012;12:919-24. [Crossref]
3. Baykara N, Akalın H, Arslantaş MK, et al. Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study. Crit Care. 2018;22:93. [Crossref]
4. Sipahioğlu H, Onuk S, Dirik H, Bulut K, Sungur M, Gündoğan K. Evaluation of non-intensive care unit acquired sepsis and septic shock patients in intensive care unit outcomes. Erciyes Med J. 2022;44:161-6. [Crossref]
5. van Amstel RB, Kennedy JN, Scicluna BP, et al. Uncovering heterogeneity in sepsis: a comparative analysis of subphenotypes. Intensive Care Med. 2023;49:1360-9. [Crossref]
6. Liu Q, Zheng HL, Wu MM, et al. Association between lactate-to-albumin ratio and 28-days all-cause mortality in patients with acute pancreatitis: a retrospective analysis of the MIMIC-IV database. Front Immunol. 2022;13:1076121. [Crossref]
7. Shin J, Hwang SY, Jo IJ, et al. Prognostic value of the lactate/albumin ratio for predicting 28-day mortality in critically ILL sepsis patients. Shock. 2018;50:545-50. [Crossref]
8. Fleuren LM, Klausch TLT, Zwager CL, et al. Machine learning for the prediction of sepsis: a systematic review and meta-analysis of diagnostic test accuracy. Intensive Care Med. 2020;46:383-400. [Crossref]
9. Giamarellos-Bourboulis EJ, Aschenbrenner AC, Bauer M, et al. The pathophysiology of sepsis and precision-medicine-based immunotherapy. Nat Immunol. 2024;25:19-28. [Crossref]
10. Peters van Ton AM, Kox M, Abdo WF, Pickkers P. Precision immunotherapy for sepsis. Front Immunol. 2018;9:1926. [Crossref]
11. He RR, Yue GL, Dong ML, Wang JQ, Cheng C. Sepsis biomarkers: advancements and clinical applications-a narrative review. Int J Mol Sci. 2024;25:9010. [Crossref]
12. Luka S, Golea A, Vesa SC, Leahu CE, Zaganescu R, Ionescu D. Can we improve mortality prediction in patients with sepsis in the emergency department? Medicina (Kaunas). 2024;60:1333. [Crossref]
13. Vucelić V, Klobučar I, Đuras-Cuculić B, et al. Sepsis and septic shock - an observational study of the incidence, management, and mortality predictors in a medical intensive care unit. Croat Med J. 2020;61:429-39. [Crossref]
14. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019-results from a systematic review and meta-analysis. Crit Care. 2020;24:239. [Crossref]
15. Yang K, Fan M, Wang X, et al. Lactate promotes macrophage HMGB1 lactylation, acetylation, and exosomal release in polymicrobial sepsis. Cell Death Differ. 2022;29:133-46. [Crossref]
16. Liu Y, Zheng J, Zhang D, Jing L. Neutrophil-lymphocyte ratio and plasma lactate predict 28-day mortality in patients with sepsis. J Clin Lab Anal. 2019;33:e22942. [Crossref]
17. Slim MA, van Mourik N, Bakkerus L, et al. Towards personalized medicine: a scoping review of immunotherapy in sepsis. Crit Care. 2024;28:183. [Crossref]
18. Amrein K, Zajic P, Schnedl C, et al. Vitamin D status and its association with season, hospital and sepsis mortality in critical illness. Crit Care. 2014;18:R47. [Crossref]
19. Alabay S, Ulu Kilic A, Cevahir F, Alp E, Doğanay M. Evaluation of clinical course and outcomes of severe sepsis and septic shock in elderly patients. J Clin Pract Res. 2024;46:84-91. [Crossref]

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Global trends in sepsis and artificial intelligence studies in intensive care units: Bibliometric analysis with Biblioshiny

Yoğun bakım ünitelerinde yapay zeka ile sepsis çalışmalarının küresel trend konuları: Biblioshiny ile bibliyometrik analiz

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ABSTRACT

Objective: The aims of the study was to identify and visualize studies conducted between 2006 and 2025 in the fields of sepsis and artificial intelligence in intensive care units, with the aim of revealing trends in this area.

Materials and Methods: The data were obtained from the Web of Science Core Collection database on May 2, 2025. Performance analysis, visualization, mapping, and bibliometric analyses were performed using the R software program Biblioshiny interface. For bibliometric data, a search was conducted in the WoS database using the keywords "intensive care" OR "ICU" OR "intensive care unit" OR "ICUs" AND "artificial intelligence" OR "machine learning" OR "deep learning" AND 'Sepsis' OR "sepsis prediction" in all files. The analysis of the study was conducted using 1,072 publication data.

Results: The study found that the average annual number of articles produced in intensive care units in the fields of sepsis and artificial intelligence obtained from the WoS database was 2.76, with an annual growth rate of 27.63. A total of 1,072 articles were produced in 371 journals between 2006 and 2025. A total of 1,531 keywords were used. The average number of citations per publication was 18.13. It was observed that authors used 2,255 keywords across all publications, 7,015 authors were involved in these publications, only 6 articles had a single author, the average number of co-authors per article was 8.95, and the international co-authorship rate was 21.64%.

Conclusions: The results of the bibliometric analysis showed that studies in this field are extremely recent. Studies conducted between 2006 and 2025 on sepsis and artificial intelligence in intensive care units have been included in the literature.

Kewords: Artificial intelligence, bibliometric, Bibliyoshiny, intensive care unit, machine learning, sepsis

ÖZ

Amaç: Araştırmanın amacı, yoğun bakım ünitelerinde sepsis ve yapay zeka alanında 2006-2025 yılları arasında yapılmış çalışmaları belirlemek, görselleştirmek ve bu alandaki eğilimleri ortaya koymaktır.

Gereç ve Yöntem: Veriler 2 Mayıs 2025 tarihinde Web of Science Core Collection veri tabanından elde edildi. Performans analizi, görselleştirme, haritalama ve bibliyometrik analizler R yazılım programı Biblioshiny arayüzü kullanılarak yapıldı. Bibliyometrik veriler için WoS veri tabanında tüm dosyalarda "yoğun bakım" VEYA "YBÜ" VEYA "yoğun bakım ünitesi" VEYA "YBÜ'ler" VE "yapay zeka" VEYA "makine öğrenmesi" VEYA "derin öğrenme" VE 'Sepsis' VEYA "sepsis tahmini" anahtar kelimeleri kullanılarak arama yapıldı. Araştırma evreni 1.896 olarak bulundu. Science Citation Index Expanded, Social Sciences Citation Index ve Emerging Sources Citation Index'te yayın dili, yıl, ülkeler, kurumlar, yazarlar ve yayın türü aratıldığında ve yayın yılı 2006-2025 ile sınırlandırıldığında örneklem büyüklüğünün 1.072 olduğu görüldü. Çalışmanın analizi 1.072 yayın verisi kullanılarak yapılmıştır.

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Bulgular: Çalışmada WoS veri tabanından elde edilen sepsis ve yapay zeka alanlarında yoğun bakım ünitelerinde üretilen yıllık ortalama makale sayısının 2,76 olduğu, yıllık büyüme hızının ise 27,63 olduğu tespit edilmiştir. 2006-2025 yılları arasında 371 dergide toplam 1.072 makale üretilmiştir. Toplam 1.531 anahtar kelime kullanılmıştır. Yayın başına ortalama atıf sayısı 18,13'tür. Yazarların tüm yayınlarda 2.255 anahtar kelime kullandığı, bu yayınlarda 7.015 yazarın yer aldığı, yalnızca 6 makalede tek yazarın yer aldığı, makale başına ortalama ortak yazar sayısının 8,95 olduğu ve uluslararası ortak yazarlık oranının %21,64 olduğu görülmüştür.

Sonuç: Bibliyometrik analiz sonuçları bu alandaki çalışmaların son derece yeni olduğunu göstermiştir. Yoğun bakım ünitelerinde sepsis ve yapay zeka konusunda 2006-2025 yılları arasında yapılmış çalışmalar literatüre dahil edilmiştir. Çalışma, yayın sayısının 2019 yılından itibaren arttığını ve 2024 yılında en yüksek sayıya ulaştığını göstermiştir. Çalışmada elde edilen sonuçların sepsis ve yapay zeka alanında yoğun bakım ünitelerindeki mevcut durumu değerlendirmek, alana genel bir bakış sağlamak ve bu alanda yapılacak gelecekteki araştırmalara rehberlik etmek amacıyla kullanılabileceği düşünülmektedir.

Anahtar Kelimeler: Yapay zeka, bibliyometrik, Bibliyoshiny, yoğun bakım ünitesi, makine öğrenmesi, sepsis

Introduction

Sepsis is a life-threatening condition resulting from a dysregulated host response to infection and remains one of the leading causes of morbidity and mortality worldwide (1-5). In intensive care units (ICUs), where the most critically ill patients are treated, early diagnosis and prompt intervention are crucial to reducing mortality (6). Although clinical tools such as the Systemic Inflammatory Response Syndrome (SIRS), Modified Early Warning Score (MEWS), and Sequential Organ Failure Assessment (SOFA) are used to aid in sepsis diagnosis, early detection remains a major challenge due to the syndrome's heterogeneous nature and variable presentation (7,8).

The widespread adoption of electronic health records (EHRs) has resulted in the accumulation of large volumes of patient information; however, the heterogeneous and unstructured nature of these data presents significant analytical challenges. In this context, artificial intelligence (AI), particularly machine learning (ML) techniques, has emerged as a promising approach for handling complex clinical data and facilitating earlier identification of sepsis (9- 11). Previous studies indicate that these AI-driven approaches contribute to improved clinical outcomes, such as decreased mortality rates and reduced lengths of stay in intensive care units, by supporting timely clinical interventions (12,13).

Although several systematic reviews and retrospective analyses have explored the application of artificial intelligence in sepsis prediction (14,15), no bibliometric investigation has been conducted to comprehensively evaluate global research patterns, collaborative networks, and the evolution of key themes in this domain. This lack of bibliometric evidence underscores the necessity of a detailed mapping of the existing literature to inform and guide the future development of AI-supported sepsis management strategies in intensive care settings.

The present study seeks to map and critically assess worldwide scientific trends in research on artificial intelligence applications for sepsis in intensive care units by employing bibliometric techniques through the Biblioshiny platform. By identifying the most influential publications, authors, and collaboration networks, this study intends to provide guidance for future interdisciplinary research and emphasize the value of integrating AI into critical care practices.

Research questions

- What is the publication trend by year?
- What is the annual number of citations?
- What is the co-occurrence map of author keywords?
- What are the nodes and clusters formed by keywords?
- Who are the most productive authors?
- What are the most influential journals?
- Which country is the most influential for publications?
- What are the thematic maps like?
- What is the thematic evolution like?

Methods

Study design

In this study, a descriptive and evaluative bibliometric analysis of articles published on sepsis and AI in ICU was performed. The bibliometric analysis method provides researchers with a broader literature profile through performance analysis, visualization and relationship analysis (16). Therefore, bibliometric analysis was used in this study for a deeper research and to reveal the relationship of social networks with the tracking of trends.

Data collection

This study consists of a dataset of 1,072 open access articles obtained from the WoS database. In this study, research published in the Web of Science Core Collection (WoSCC) database on sepsis and artificial intelligence in intensive care units was examined from a bibliometric perspective with the aim of revealing the current situation at the international level. An important point in bibliometric analyses is the databases from which the data set will be obtained. Currently, there are multiple databases available for bibliometric analyses. Among the most frequently used databases are PubMed, Embase, Scopus, SpringerLink, Google Scholar, and ScienceDirect. These databases possess distinct characteristics (17). Compared to Scopus and Google Scholar, the WoS database is a more reliable database due to its broader journal and citation archive, which dates back to earlier years, its inclusion of journals with higher impact values, its effective access to bibliographic data, and its larger number of publications. Therefore, as in many bibliometric studies, it has been the preferred database for obtaining data in this study (18-22). The data for the study were obtained from the "Web of Science (WoS) Core Collection" database on May 2, 2025, from among the open access publications found between 2006 and 2025. For bibliometric data, an advanced search was performed in all files in the WoS database (((((((((ALL=("intensive care")) OR ALL=("ICU")) OR ALL=("intensive care unit")) OR ALL=('ICUs')) AND ALL=("artificial intelligence ")) OR ALL=("Machine Learning")) OR ALL=("deep learning")) AND ALL=("Sepsis")) OR ALL=("Sepsis Prediction")) and Open Access and Article (Document Types) and Science Citation Index Expanded (SCI-EXPANDED) or Emerging Sources Citation Index (ESCI) or Social Sciences Citation Index (SSCI) and English (Languages) The research universe was found to be 1896. When the publication language, year, countries, institutions, authors, and publication type were searched in the Science Citation Index Expanded, Social Sciences Citation Index, Emerging Sources Citation Index, and the publication year was limited to 2006-2025, the sample was found to be 1072. The analysis of the study was performed on 1072 publication data. The studies comprising the research dataset were selected from the WoS database according to publication acceptance criteria and are presented in the publication flow diagram (Figure 1).

Data analysis

All information related to publications has been filtered according to research acceptance criteria. After filtering, the record contents of 1,072 publications obtained from the WoS database were selected as full records and references. Publications between 1 and 500 were exported as file 1, those between 501 and 1,000 as file 2, and those between 1,001 and 1,072 as file 3 in BibTEX format. The files containing the exported data were combined into a single file in the BibTEX file for analysis and organized in the R software program interface to be suitable for analysis. The Biblioshiny program, which is preferred for bibliometric analysis, was loaded into the R software program interface as the analysis tool. Biblioshiny facilitates the visual representation of interconnections among scientific publications, allowing documents to be organized according to shared thematic characteristics (23). By offering a user-friendly interface, Biblioshiny streamlines the otherwise complex process of thematic analysis, rendering it more accessible, interpretable, and efficient. Identifying thematic

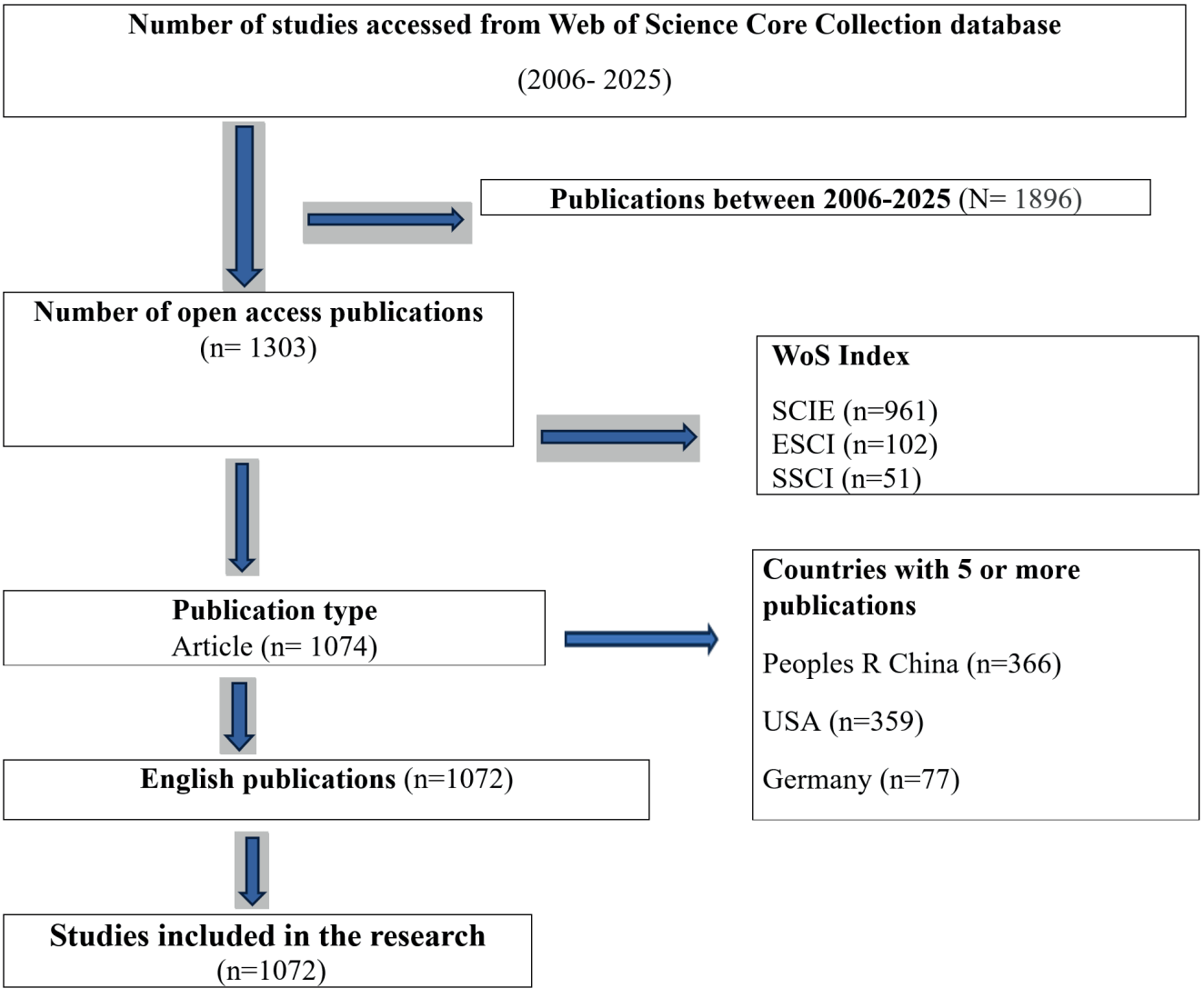


Figure 1. Publication selection flow diagram

patterns and emerging trends within the scientific literature is essential for supporting researchers and policymakers in recognizing both current priorities and prospective research trajectories (24).

Within the framework of general structure analysis, Biblioshiny provides comprehensive information on datasets, journals, and authors, alongside descriptive bibliometric indicators and analyses of intellectual structure. These evaluative bibliometric analyses encompass conceptual, social, and intellectual dimensions of the literature. In network visualizations, nodes denote the core analytical units, such as keywords, authors, or research topics (25). For instance, keyword-based analyses enable the examination of popularity trends within specific research domains. Connections between nodes, represented as links, reflect the relationships and associations among these elements, with the existence of a link indicating a meaningful connection (26).

Clustering techniques group nodes with similar or related characteristics, thereby highlighting collections of elements that converge around particular themes or subject areas (27). Furthermore, node attributes such as size or color are used to represent quantitative

or qualitative metrics; for example, the frequency of a keyword within the literature can be inferred from node size (28). Finally, the overall topology of the bibliometric map illustrates the structural relationships among themes, providing insight into how different research areas are interconnected.

Clusters connected by dense links may indicate a strong relationship (23). Obvious gaps or anomalies in the map may indicate areas that have not been sufficiently researched in the literature or unexpected relationships (28). In this study, thematic maps, trend topics, and thematic evolution analyses were used to focus on thematic trends and the evolution of studies. The four quadrants in the thematic map are defined as follows:

1. Motor themes: The clusters in the upper right quadrant are highly developed and important themes. This quadrant consists of strong themes. The centrality and density of the clusters are high.

2. Niche themes: The upper left quadrant consists of clusters with low centrality and high density. These clusters have few but strong connections with other themes.

3. Basic themes: The clusters in the lower right are themes that have many connections with other themes but weak relationships.

4. Emerging or declining themes: Clusters in the lower left quadrant represent themes with few and weak connections to other themes (29,30).

Results

Characteristics of publications

When examining the distribution of publications by year, it was observed that the first publication within the data set was made in 2006 (n=1) and contributed 0.093 to the current publications, that there has been an upward trend in the number of publications since 2019, and that there has been significant growth in the number of publications between 2021 and 2022.

Table 1. Distribution of publications by years (2006-2025)

Publication Years	Record Count	% of 1.072
2024	247	23.041
2023	211	19.683
2022	178	16.604
2021	157	14.646
2025	98	9.142
2020	80	7.463
2019	47	4.384
2017	18	1.679
2018	18	1.679
2016	8	0.746
2014	4	0.373
2015	2	0.187
2006	1	0.093

In 2024, the highest number of publications was recorded (n=247), accounting for 23.041% of the total (Table 1).

As a result of bibliometric analysis, it was found that there were 1,072 articles published, with an average of

Table 2. Basic information on bibliometric analysis

Description	Results
Main Information About Data	
Timespan	2006:2025
Sources (Journals)	371
Documents	1072
Annual Growth Rate %	27,63
Document Average Age	2,76
Average citations per doc	18,13
References	1
Document Contents	
Keywords Plus (ID)	1531
Author's Keywords (DE)	2255
Authors	
Authors	7015
Authors of single-authored docs	6
Authors Collaboration	
Single-authored docs	6
Co-Authors per Doc	8,95
International co-authorships %	21,64
Document Types	
Article	1072

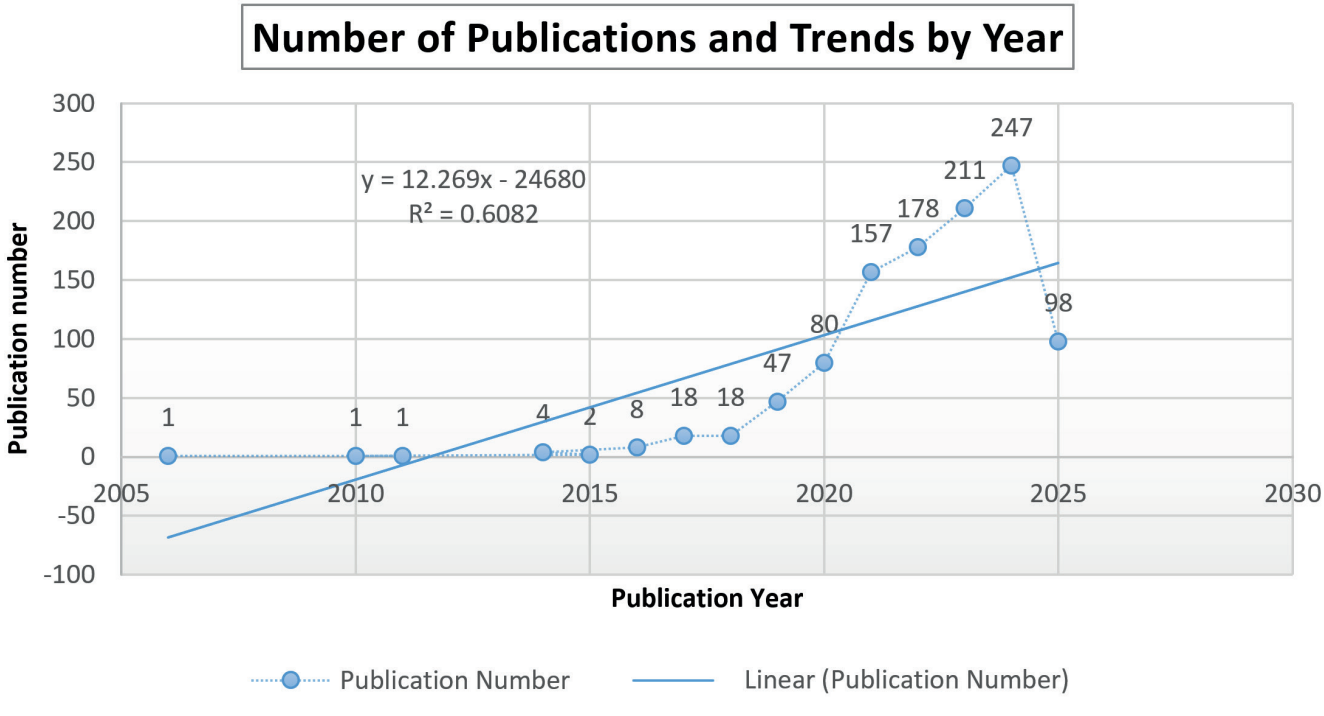
2.76 articles produced annually in the field of sepsis and artificial intelligence, and an annual growth rate of 27.63. Between 2006 and 2025, 1,072 articles were produced in 371 journals. A total of 1,531 keywords were used. The average number of citations per publication was 18.13. It was observed that authors used 2,255 keywords for all publications, 7,015 authors were involved in these publications, there were only 6 single-authored articles, the average number of co-authors per article was 8.95, and the international co-authorship rate was 21.64% (Table 2).

Regression analysis results regarding the accuracy of trends in publication growth

Linear regression analysis was performed to evaluate the change in the number of publications over the years. As a result of the analysis, it was found that there was a statistically significant increase in the number of publications over the years (Trend coefficient = 12.27; $R^2 = 0.6082$; $p = 0.0006$). These findings reveal that the increase in publications is not random and shows a consistent development in time. In addition, the explanatory power of the model is moderately strong, which supports the relationship between the regression line and the number of publications. The addition of these statistical tests increased the rigor of our analysis. "As a result of the linear regression analysis, it was determined that the number of publications increased significantly over the years ($\beta = 12.27$, $p = .0006$, $R^2 = .608$). This situation reveals that the productivity in the literature increased by an average of 12.27 publications per year during the period covered by the study. The 95% confidence interval of the trend coefficient is [6.92, 17.62], which indicates a steady growth in academic production." (Graphic 1).

Interpretation of Publication Trend Coefficient

1. Trend Coefficient ($\beta_1 = 12.27$ publications/year): This coefficient shows that there has been an average increase of 12.27 publications per year throughout the years examined. This indicates that academic interest in the relevant scientific field has been increasing and productivity has been steadily increasing.



Graphic 1. Linear regression analysis

2. R^2 (0.608): The explanatory power of the model, R^2, is 60.8%. This means that approximately 61% of the changes in the number of publications are explained by the time (year) variable. In other words, the model shows a medium-high level of fit with the data.

3. p-value (0.0006): The trend coefficient obtained is statistically significant ($p < 0.05$). This shows that the increase in the number of publications over the years is not random, but rather a consistent and significant upward trend over time.

4. 95% Confidence Interval ([6.92, 17.62]): This interval shows that the annual publication increase is between 6.92 and 17.62 with a 95% probability. This proves that the increase is not only significant in the average but also in a safe interval (Graphic 1).

Trend topics and most influential journals

It has been reported that 1414 keywords were used as author keywords in studies conducted in intensive care units in the field of sepsis and artificial intelligence. The most frequently used author keyword cloud in studies conducted in intensive care units in the field of sepsis and artificial intelligence is shown in Figure 2. As the frequency of words increases, the keywords appear larger in the word distribution. Accordingly, the most frequently used author keywords are machine learning (429 times), sepsis (414 times), artificial intelligence (93 times), prediction (67 times), mortality (67 times), deep learning (42 times), critical care (40 times), intensive care unit (43 times), machine (38 times), learning (42 times), and septic shock (28 times) (Figure 2).

Figure 3 shows the co-occurrence map of author keywords. When creating this map, the number of nodes was set to 50 and the word co-occurrence ratio was set to 2. The higher the word co-occurrence ratio, the larger the nodes and words. The color of the nodes indicates the word co-occurrence. Sepsis and machine learning were the most frequently co-occurring words.

Figure 2. Author keyword clouds

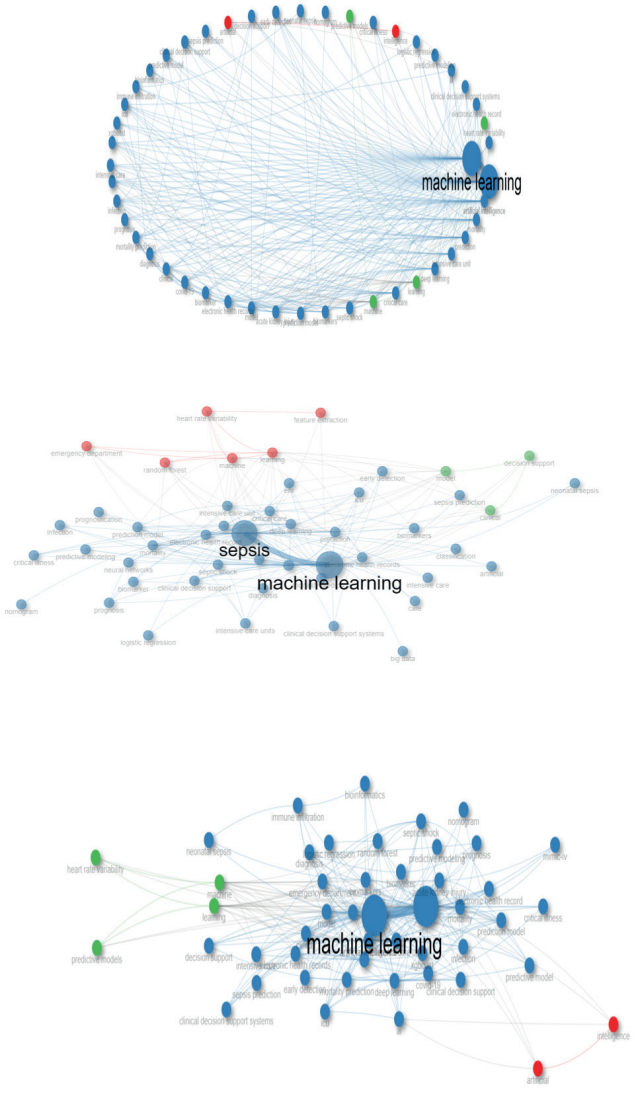


Figure 3. Keyword node and co-occurrence map

The co-occurrence network of studies conducted in intensive care units in the fields of sepsis and artificial intelligence can be categorized into three clusters. The first cluster (red) contains the words Artificial (Betw = 0.15) and intelligence (Betw = 0). The second cluster (blue) includes machine learning (Betw = 408.98), sepsis (Betw = 409.43), artificial intelligence (Betw = 20.52), prediction (Betw = 5.04), mortality (Betw = 5.88), deep learning (Betw = 1.91), critical care (Betw =1.27), intensive care unit (Betw =1.10), septic shock (Betw =0.49), prediction model (Betw =0.45), acute kidney injury (Betw =0.67), biomarkers (Betw =3.87), electronic health records (Betw =1.15), COVID-19 (Betw =0.20), mortality prediction (Betw =0.16), biomarker (Betw =3.87), mortality prediction (Betw =0.16), clinical decision support (Betw =0.03), infection (Betw =0.06), prognosis (Betw =0.04), diagnosis (Betw =0.13), intensive care (Betw =0.003), predictive modeling (Betw =0), electronic health record (Betw =1.15), ICU (Betw =0.17), sepsis prediction (Betw =0), early detection (Betw =0), neonatal sepsis (Betw =0), prognostication (Betw =0), artificial (Betw = 0), big data (Betw = 0), care (Betw = 0), clinical decision support systems (Betw = 0), critical illness (Betw = 0), EHR (Betw = 0), intensive care units (Betw = 0.04), logistic regression (Betw = 0), AI (Betw = 0.19). The third cluster (green) consists of the words learning (Betw = 3.42), machine (Betw = 3.28), predictive models (Betw = 0.005), and heart rate variability (Betw = 0.004). The keywords in the second cluster are more suitable for researchers conducting studies in the field of intensive care sepsis artificial intelligence (Figure 3). The analysis revealed that “machine learning” was mentioned 428 times and “sepsis” 414 times among the most frequently studied trending topics between 2021, 2023, and 2024 (Figure 4).

Kamaleswaran R (17 publications), Nemati S (16 publications), Das R (16 publications), and Wang Y (15 publications) were found to be the most prolific authors. Most of the studies were produced in Peoples R China (n=366), USA (n=359), and Germany (n=77). Most of the studies were published in Scientific Reports (68 publications; H index 17), Frontiers in

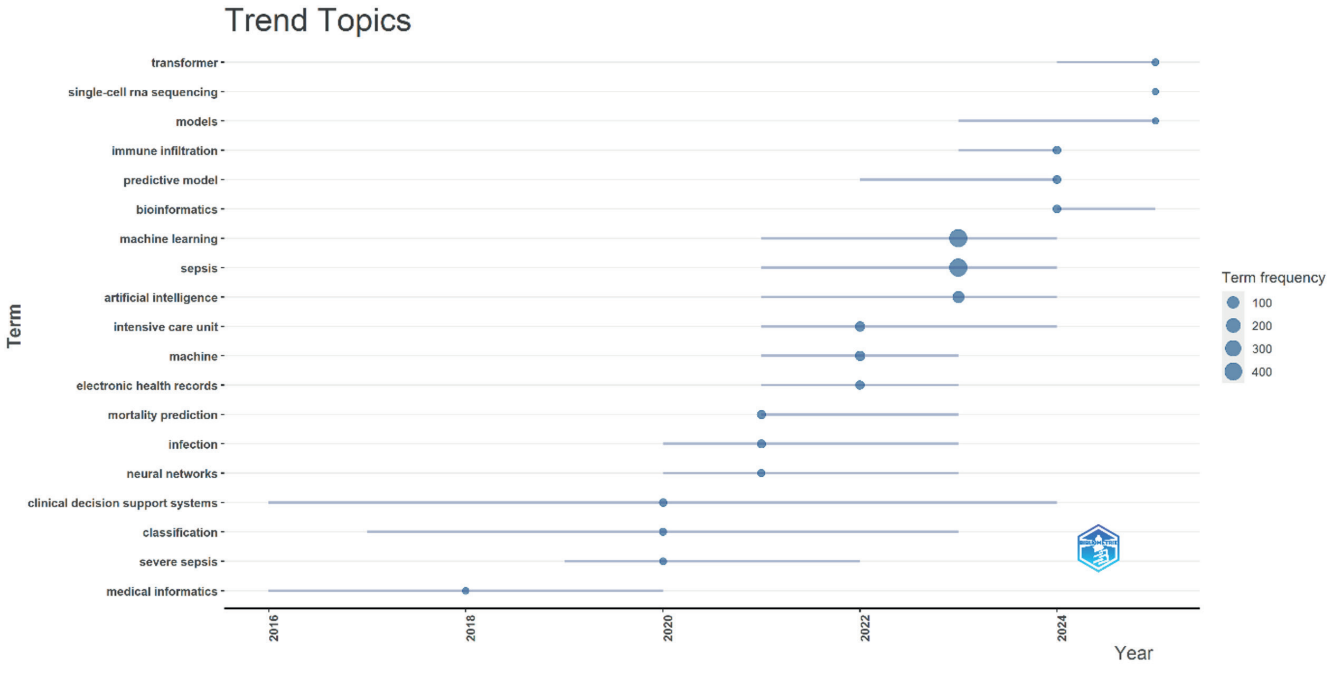


Figure 4. Trend topics

Medicine (48 publications; H index 12), Frontiers in Immunology (40 publications; H-index 11), Critical Care (21 publications; H-index 11), and PLOS ONE (30 publications; H-index 11) (Figure 5 and Figure 6).

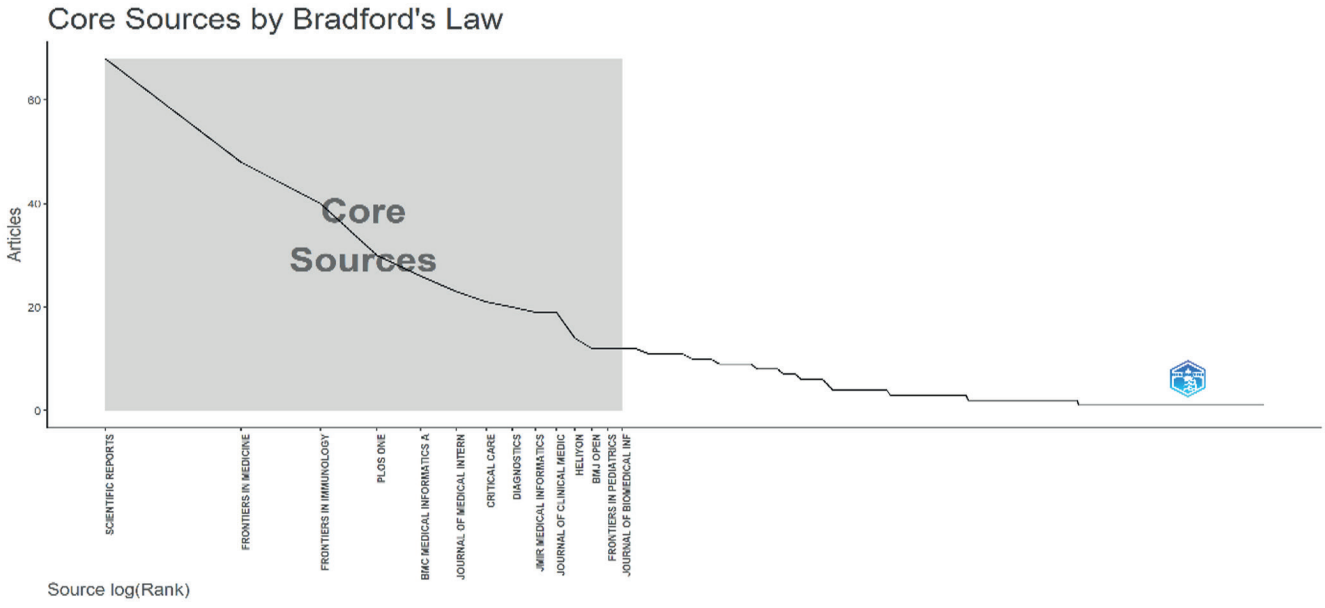


Figure 5. Distribution of most influential journals (Bradfor's Law)

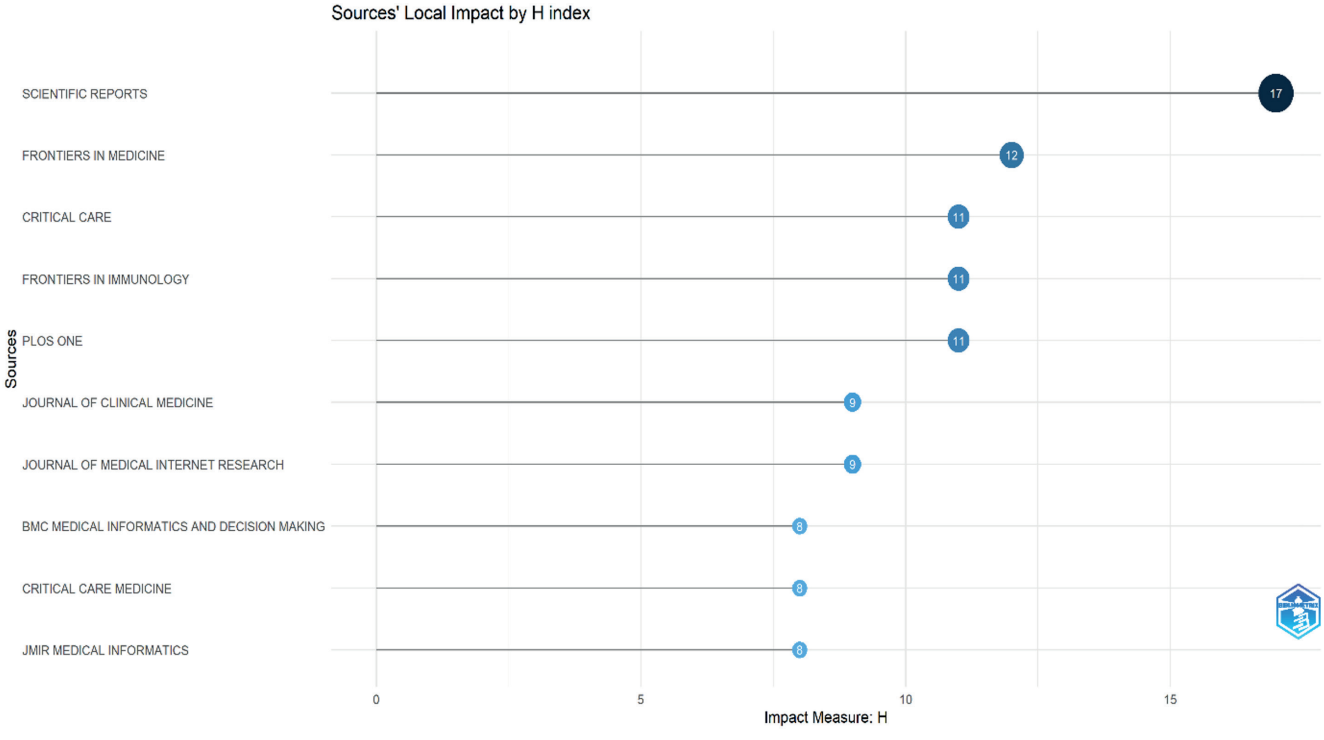


Figure 6. Impact of journals according to H index

It is a model defined by Samuel C. Bradford in 1934 that predicts the exponentially decreasing returns of searching for references in scientific journals. According to Bradford's Law, core journals containing the largest number of publications on a given topic are followed by second and third groups of journals containing fewer and fewer related publications, respectively. This law indicates that scientific knowledge is concentrated in a limited number of journals. Articles published on a scientific topic are distributed in journals containing progressively fewer articles, starting with core journals. This distribution follows a specific logarithmic pattern (31,32).

Tematic map

The theme typology of research in intensive care units in the field of sepsis and artificial intelligence is shown in Figure 7. In the thematic map analysis, the number of words is 100, the minimum cluster frequency is 3, and the number of levels per cluster is 3 (Figure 7). The motor themes in the upper right quadrant are characterized by both higher density and higher centrality and consist of words such as prevention intensive care unit and deep learning. The upper left quadrant, on the other hand, has lower centrality and higher density, contains niche themes, and shows insignificant external connections of limited importance, such as bioinformatics, immune, infiltration, heart rate variability, feature extraction pediatrics, and emergency. The lower right quadrant shows basic themes with lower density but higher centrality and includes words such as machine learning, sepsis, artificial intelligence, and sepsis prediction. The lower left quadrant shows themes with lower centrality and lower density. In particular, it includes words related to sepsis and artificial intelligence in intensive care units, which have low centrality and low density.

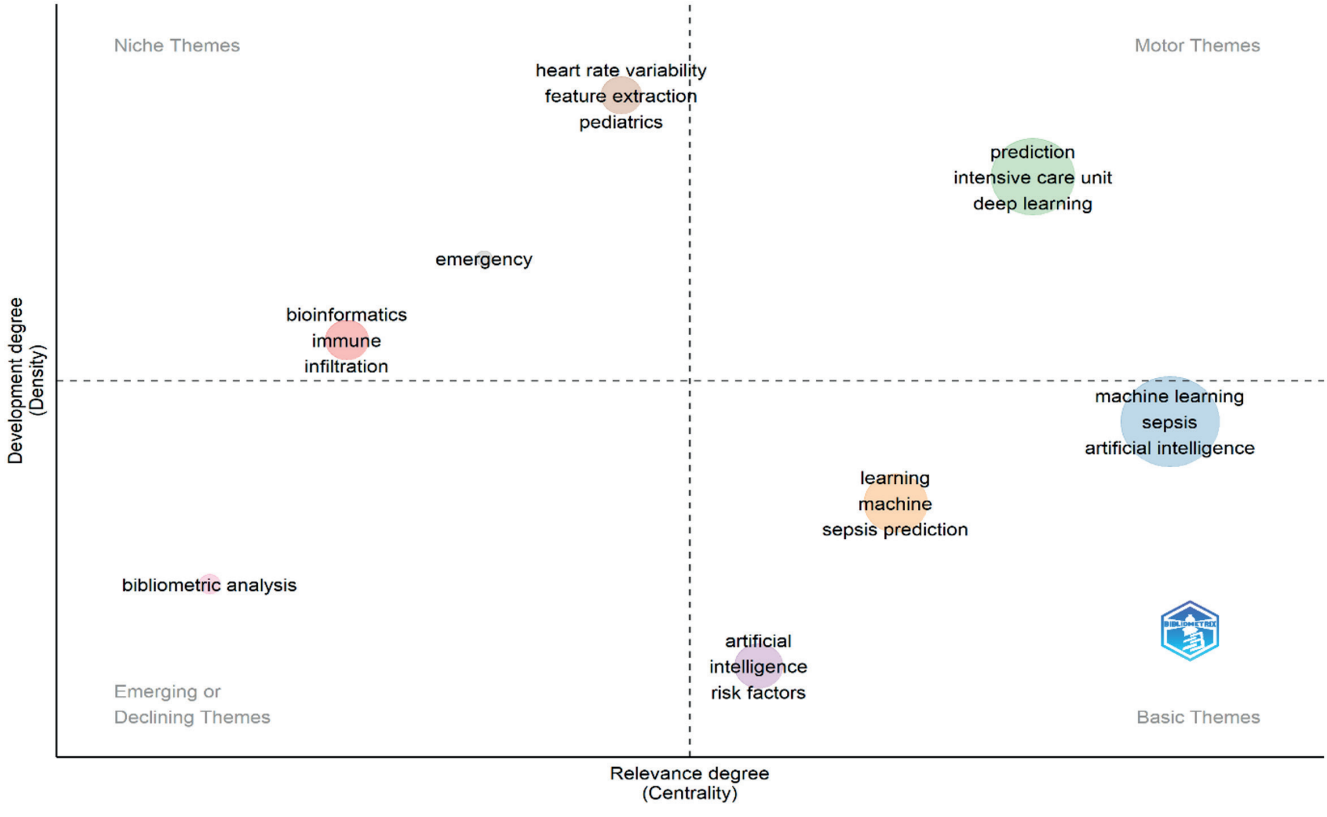


Figure 7. Thematic map

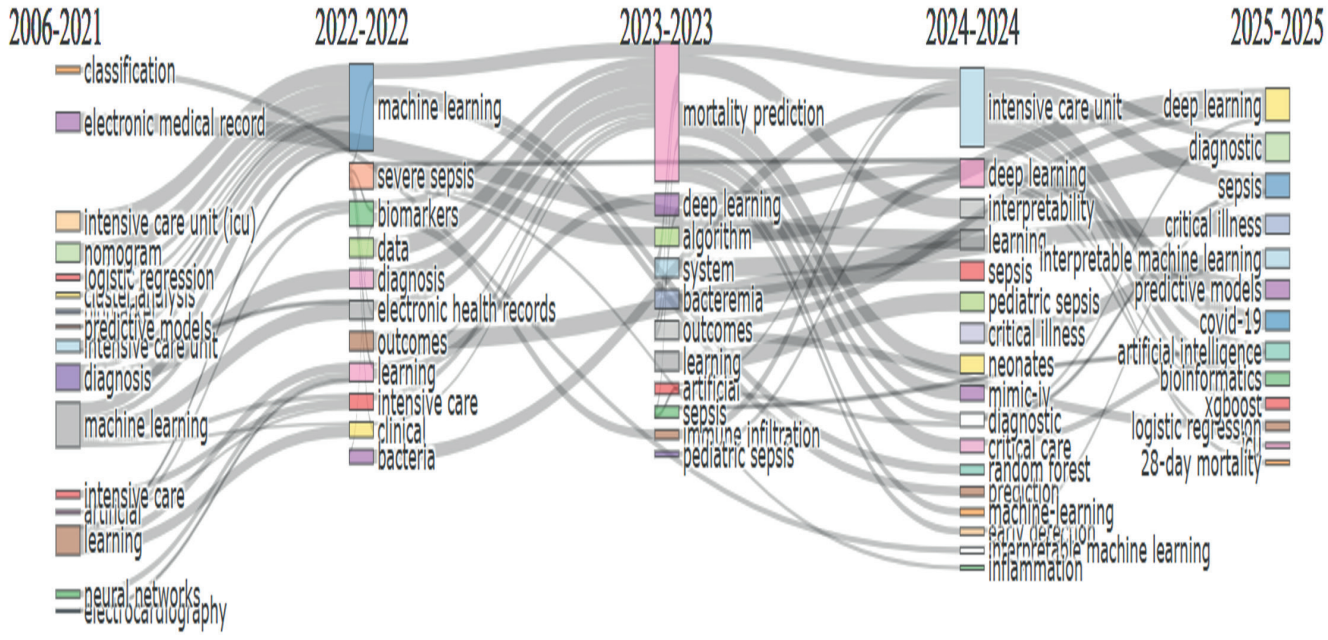


Figure 8. Thematic evaluation of keywords by year

Figure 8 shows the thematic evolution of author keywords in four stages. Thematic evolution analysis enables the discovery of evolutionary correlations and trends in thematic contexts and evolutionary trends in structures (18). Figure 8 shows the correlation between different themes and their progress over a period of approximately 19 years: 2006-2021; 2022-2022; 2023-2023; 2024-2024 and 2025; 2025, divided into five stages. Between 2006 and 2021, the most frequently used keywords in the early years were electronic records, intensive care unit, intensive care, diagnosis, and machine learning, while in 2022, the keywords were machine learning, diagnosis, electronic records, intensive care, and bacteria. In 2023, the keywords that stood out were mortality rate prediction, deep learning, system, and bacteremia. In 2024, studies using author keywords such as intensive care unit, pediatric sepsis, sepsis, and deep learning are prominent. In 2025, the keywords deep learning, diagnosis, sepsis, artificial intelligence, and neonatal deaths are prominent (Figure 8).

Discussion

This bibliometric review, encompassing 599 publications published between 2006 and 2025, offers an in-depth depiction of the progression and transformation of artificial intelligence (AI) research related to sepsis within intensive care unit (ICU) settings. A substantial growth in the number of publications has been evident from 2019 onward, reaching its highest point in 2022. This escalation is likely associated with the expanding adoption of digital health technologies and the heightened emphasis on early sepsis identification during the COVID-19 pandemic.

In contrast to conventional bibliometric analyses focusing on sepsis research (32,33), the present study identifies a distinct evolution in thematic priorities. Earlier investigations predominantly highlighted terms such as “ICU” and “septic shock,” whereas more recent literature increasingly concentrates on concepts including “machine learning,” “predictive modeling,”

and “deep learning.” This transition underscores the growing reliance on data-driven methodologies for early sepsis recognition, which may address the inherent limitations of traditional clinical scoring systems, such as SIRS and SOFA (34-36). The rising prominence of predictive modeling further suggests a research response to clinical demands for earlier and more personalized interventions among critically ill patients.

Moreover, the frequent occurrence of keywords such as “mortality,” “biomarkers,” and “electronic health records” reflects a multidisciplinary orientation that combines AI techniques with clinical diagnostic processes. Analytical approaches including logistic regression, neural networks, and nomogram-based models are commonly applied in model construction, indicating a shift from purely conceptual development toward practical implementation in real-world ICU environments. Supporting this progression, prior studies have demonstrated that machine learning algorithms are capable of predicting sepsis up to 12 hours before clinical onset (11), and systems such as the NAVOY Sepsis model have shown promising proof-of-concept performance in intensive care contexts (6).

Nevertheless, despite the considerable potential of artificial intelligence, only a limited number of predictive models have undergone sufficient validation for routine clinical application. Factors such as heterogeneity in data sources, limited model transparency and interpretability, and regulatory constraints continue to impede broad implementation (9,12,13). Furthermore, a substantial proportion of AI-driven sepsis research relies on retrospective datasets and lacks rigorous external validation, which restricts the generalizability of reported findings.

When the expansion rate of AI-focused sepsis studies (31.19%) is compared with bibliometric patterns observed in other intensive care conditions, including pneumonia and cardiac arrest (20,36,37), a broadly comparable growth pattern emerges. However, research on AI applications in sepsis demonstrates a notably sharper increase over the past five years. This accelerated growth indicates that sepsis may function as a sentinel condition, signaling broader innovation and adoption of artificial intelligence within the critical care domain.

According to the results of this analysis, Das R. was identified as the most productive author in this research field, while Scientific Reports was recognized as the leading journal in terms of influence. Together, these findings highlight key contributors and publication platforms that play a central role in shaping the development and dissemination of AI-based sepsis research.

Several limitations of this study should be acknowledged. First, restricting the data source to the Web of Science database may have led to the omission of relevant publications indexed in other repositories, such as PubMed, Scopus, or leading artificial intelligence–oriented conference proceedings. This restriction may have resulted in selection bias, favoring certain journals and geographic regions. Additionally, while bibliometric approaches are effective for examining publication patterns and citation performance, they do not provide an assessment of the methodological rigor or the clinical effectiveness of individual studies.

In summary, the present analysis offers a systematic depiction of research focal points and developmental trends in AI-supported sepsis research within intensive care units. The growing focus on predictive analytics, early detection strategies, and clinical decision support systems suggests a trajectory in which artificial intelligence may substantially influence future sepsis management. Nonetheless, further prospective investigations and validation studies conducted in real-world clinical settings are essential to close the gap between technological advancement and practical implementation in routine care.

Study limitations and strengths

The most important limitation of this study is that the literature review is limited to the data obtained from the WoS database. Another limitation is that the publications belong to the time period between 2006 and 2025 when the literature review was conducted. If a similar study is conducted in a different time period, different results may be obtained. Apart from the limitations, the study also has some strengths. The current study shows that publications can achieve a high level of visibility even in subspecialty journals. This once again emphasizes the potential value of the methodology used in the study, as further examination of publications outside of high-impact publications that receive high levels of attention could help researchers to better understand how to promote their work. Furthermore, the interaction with sources reflected in the bibliometric analysis result could support the creation of potential studies for researchers if grant funders start to take them into account despite the acknowledged limitations.

Conclusion

This study provides important data on sepsis and artificial intelligence applications in intensive care units. The results of the bibliometric analysis show that studies in this field are extremely recent. Studies on sepsis and artificial intelligence in intensive care units between 2006 and 2025 have been included in the literature. The number of publications has increased steadily since 2019, reaching its highest number in 2024. After the COVID-19 pandemic, sepsis and artificial intelligence applications have emerged as an important field of study. Recent studies have focused on clinical models, decision support systems, and machine learning. While studies in the fields of mortality, sepsis, and intensive care were prevalent in the early days, in recent years, studies using keywords such as machine learning, clinical decision support, output, big data, artificial intelligence machine learning, sepsis, and COVID-19 have become more common. Therefore, the results of this study are quite important in guiding researchers regarding gaps in the literature. It is thought that the results obtained in this study can evaluate the current situation in intensive care units in the field of sepsis and artificial intelligence, provide a general overview of the field, and guide future research in this area.

There are gaps between research and clinical application of AI-based sepsis prediction models. To bridge these gaps; it is recommended that prospective clinical studies be conducted to evaluate AI-sepsis models, that AI models that include multimodal data (e.g. vital signs, genomics, imaging) be developed, and that ethical concerns and explainability of AI be addressed in the clinical decision-making process.

Ethical approval

This study includes a retrospective review of previously published studies and their visualization by bibliometric analysis. The study did not involve any human or animal study. Therefore, this study does not require ethics committee approval.

Author contribution

Study conception and design: BT, FA; data collection: BT, FA; analysis and interpretation of results: BT, FA; draft manuscript preparation: BT, FA. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Centers for Disease Control and Prevention. What is sepsis? Available at: https://www.cdc.gov/sepsis/about/index.html (Accessed on November 27, 2023).
2. Rhee C, Jones TM, Hamad Y, et al. Prevalence, underlying causes, and preventability of sepsis-associated mortality in US acute care hospitals. JAMA Netw Open. 2019;2:e187571. [Crossref]
3. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395:200-11. [Crossref]
4. Liu V, Escobar GJ, Greene JD, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA. 2014;312:90-2. [Crossref]
5. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing Sepsis as a Global Health Priority - A WHO Resolution. N Engl J Med. 2017;377:414-7. [Crossref]
6. Persson I, Östling A, Arlbrandt M, Söderberg J, Becedas D. A machine learning sepsis prediction algorithm for intended intensive care unit use (NAVOY Sepsis): proof-of-concept study. JMIR Form Res. 2021;5:e28000. [Crossref]
7. Al-Mualemi BY, Lu L. A deep learning-based sepsis estimation scheme. IEEE Access. 2021;9:5442-52. [Crossref]
8. Schinkel S, Schouten BC, Kerpiclik F, Van Den Putte B, Van Weert JCM. Perceptions of barriers to patient participation: are they due to language, culture, or discrimination? Health Commun. 2019;34:1469-81. [Crossref]
9. Yuan KC, Tsai LW, Lee KH, et al. The development an artificial intelligence algorithm for early sepsis diagnosis in the intensive care unit. Int J Med Inform. 2020;141:104176. [Crossref]
10. Alanazi A, Aldakhil L, Aldhoayan M, Aldosari B. Machine learning for early prediction of sepsis in intensive care unit (ICU) patients. Medicina (Kaunas). 2023;59:1276. [Crossref]
11. Nemati S, Holder A, Razmi F, Stanley MD, Clifford GD, Buchman TG. An interpretable machine learning model for accurate prediction of sepsis in the ICU. Crit Care Med. 2018;46:547-53. [Crossref]
12. Burdick H, Pino E, Gabel-Comeau D, Gu C, Huang H, Lynn-Palevsky A, Das R. Evaluating a sepsis prediction machine learning algorithm in the emergency department and intensive care unit: a before and after comparative study. BioRxiv. 2017:224014. [Crossref]
13. Moor M, Rieck B, Horn M, Jutzeler CR, Borgwardt K. Early prediction of sepsis in the ICU using machine learning: a systematic review. Front Med (Lausanne). 2021;8:607952. [Crossref]
14. Islam MM, Nasrin T, Walther BA, Wu CC, Yang HC, Li YC. Prediction of sepsis patients using machine learning approach: A meta-analysis. Comput Methods Programs Biomed. 2019;170:1-9. [Crossref]
15. Fleuren LM, Klausch TLT, Zwager CL, et al. Machine learning for the prediction of sepsis: a systematic review and meta-analysis of diagnostic test accuracy. Intensive Care Med. 2020;46:383-400. [Crossref]
16. Esen M, Bellibas MS, Gumus S. The evolution of leadership research in higher education for two decades (1995-2014): a bibliometric and content analysis. International Journal of Leadership in Education. 2020;23(3):259-73. [Crossref]
17. Moral-Munoz JA, Herrera-Viedma E, Santisteban-Espejo A, Cobo MJ. Sofware tools for conducting bibliyometric analysis in sience: An -up-to-date rewiew. El Profesional de La Informacion. 2020;29(1):273-89. [Crossref]
18. Guleria D, Kaur G. Bibliometric analysis of ecopreneurship using VOSviewer and R Studio Bibliometrix, 1989-2019. Library Hi Tech. 2021;1(24):1001-24. [Crossref]
19. Karagöz B, Şeref İ. Bibliometric profile of Journal of Values Education (2009-2018). Journal of Values Education. 2019;17(37):219-46. [Crossref]
20. Ramos-Rincón JM, Pinargote-Celorio H, Belinchón-Romero I, González-Alcaide G. A snapshot of pneumonia research activity and collaboration patterns (2001-2015): a global bibliometric analysis. BMC Med Res Methodol. 2019;19:184. [Crossref]
21. Zavadskas EK, Skibniewski MJ, Antucheviciene J. Performance analysis of civil Engineering Journals based on the web of science® database. Archives of Civil and Mechanical Engineering. 2014;14(4):519-27. [Crossref]
22. Zhu J, Song LJ, Zhu L, Johnson RE. Visualizing the landscape and evolution of leadership research. The Leadership Quarterly. 2019;30(2):215-32. [Crossref]
23. Waltman L, Van Eck NJ. A smart local moving algorithm for large-scale modularity-based community detection. The European Physical Journal B. 2013;86(11):1-14. [Crossref]
24. Aria M, Cuccurullo C. Bibliometrix: An R-tool for comprehensive science mapping analysis. Journal of Informetrics. 2017;11(4):959-75. [Crossref]
25. Mingers J, Leydesdorff L. A review of theory and practice in scientometrics. European Journal of Operational Research. 2015;246(1):1-19. [Crossref]
26. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2010;84:523-38. [Crossref]

27. Chen C. CiteSpace II: Detecting and visualizing emerging trends and transient patterns in scientific literature. Journal of the American Society for Information Science and Technology. 2006;57(3):359-77. [Crossref]

28. Börner K, Chen C, Boyack KW. Visualizing knowledge domains. Annual Review of Information Science and Technology. 2003;37(1):179-255. [Crossref]

29. López-Robles JR, Cobo MJ, Gutiérrez-Salcedo M, Martínez-Sánchez MA, Gamboa-Rosales NK, Herrera-Viedma E. 30th anniversary of applied intelligence: a combination of bibliometrics and thematic analysis using SciMAT. Applied Intelligence. 2021;51(9):6547-68. [Crossref]

30. Sott MK, Bender MS, Furstenau LB, Machado LM, Cobo MJ, Bragazzi NL. 100 years of scientific evolution of work and organizational psychology: A bibliometric network analysis from 1919 to 2019. Front Psychol. 2020;11:598676. [Crossref]

31. Bradford SC. Sources of information on specific subjects. Engineering: An Illustrated Weekly Journal. 1943;137:85-6.

32. Bradford SC. Information sources on specific topics. Journal of Information Science. 1985;10(4):173-80. [Crossref]

33. Jabaley CS, Groff RF, Stentz MJ, et al. Highly visible sepsis publications from 2012 to 2017: Analysis and comparison of altmetrics and bibliometrics. J Crit Care. 2018;48:357-71. [Crossref]

34. Zhang Z, Van Poucke S, Goyal H, Rowley DD, Zhong M, Liu N. The top 2,000 cited articles in critical care medicine: a bibliometric analysis. J Thorac Dis. 2018;10:2437-47. [Crossref]

35. Rosenberg AL, Tripathi RS, Blum J. The most influential articles in critical care medicine. J Crit Care. 2010;25:157-70. [Crossref]

36. Tao T, Zhao X, Lou J, et al. The top cited clinical research articles on sepsis: a bibliometric analysis. Crit Care. 2012;16:R110. [Crossref]

37. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for Sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-10. [Crossref]

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Drug-induced hepatotoxicity among critically ill patients in the intensive care unit

Yoğun bakım ünitesindeki kritik hastalarda ilaç kaynaklı hepatotoksisite

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ABSTRACT

Background: Drug-induced liver injury (DILI) is a significant complication in intensive care unit (ICU) patients, driven by polypharmacy and critical illness. This study aimed to investigate the incidence, clinical characteristics, implicated agents, and outcomes of DILI in ICU patients.

Methods: This retrospective, cross-sectional study included patients with abnormal liver function tests admitted to a tertiary ICU between October 2023 and October 2024. Patients with viral, alcoholic, autoimmune, tumor-related, or other non-drug-related liver diseases were excluded. Data on demographics, clinical scores, medications, and outcomes were analyzed. Causality was assessed using the RUCAM scale.

Results: Among 475 ICU patients, 16 cases (9.89%) were identified as DILI. The mean age was 47.1±23.6 years; 43.8% were female. Antibiotics were the most frequently implicated agents (62.5%), followed by anticoagulants and antipsychotics. The predominant pattern of liver injury was hepatocellular (81.3%). DILI developed approximately 9.5±5.2 days after ICU admission. Mortality among DILI patients was 56.3%, emphasizing the critical nature of hepatotoxicity in this population.

Conclusion: DILI in ICU patients is strongly associated with anti-infectives, particularly β-lactam antibiotics, and predominantly manifests as hepatocellular injury. High mortality underscores the need for vigilant liver monitoring, timely withdrawal of suspected drugs, and a multidisciplinary approach where clinical pharmacists can play a key supportive role. DILI may contribute to morbidity and mortality in critically ill patients, highlighting the importance of early recognition and proactive management.

Keywords: Drug-induced hepatotoxicity, critically ill patients, Hepatocellular injury, Polypharmacy

ÖZ

Amaç: İlaç kaynaklı karaciğer hasarı (DILI), yoğun bakım ünitesi (YBÜ) hastalarında polifarmasi ve kritik hastalık nedeniyle önemli bir komplikasyondur. Bu çalışma, YBÜ hastalarında DILI insidansı, klinik özellikleri, etkilenen ilaçlar ve sonuçlarını araştırmayı amaçladı.

Yöntem: Retrospektif, kesitsel olarak tasarlanan çalışmaya, Ekim 2023–Ekim 2024 arasında YBÜ'ye yatışı yapılan ve anormal karaciğer fonksiyon testleri görülen hastalar dahil edildi. Viral, alkolik, otoimmün, tümör ilişkili veya diğer ilaç dışı karaciğer hastalıkları olanlar çalışma dışı bırakıldı. Demografik veriler, klinik skorlar, kullanılan ilaçlar ve sonuçlar analiz edildi. Nedensellik değerlendirmesi RUCAM skalası ile yapıldı.

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Bulgular: 475 YBÜ hastası arasında 16 (%9,89) DILI vakası tespit edildi. Ortalama yaş 47,1±23,6 yıl; ve hastaların %43,8'i kadın idi. Hasara en sık yol açan ilaç grubu antibiyotikler (%62,5) olup, bunu antikoagülanlar ve antipsikotikler izledi. Karaciğer hasarı çoğunlukla hepatosellüler (%81,3) idi ve DILI yatıştan ortalama 9,5±5,2 gün sonra gelişti. DILI hastalarında mortalite %56,3 olarak gözlendi.

Sonuç: Yoğun bakım hastalarında görülen ilaç kaynaklı karaciğer hasarı (DILI), özellikle β-laktam antibiyotikler olmak üzere anti-infektiflerle güçlü bir ilişki göstermekte ve çoğunlukla hepatoselüler hasar şeklinde ortaya çıkmaktadır. Yüksek mortalite nedeni ile, karaciğer fonksiyonlarının dikkatle izlenmesi, şüpheli ilaçların zamanında kesilmesi ve klinik eczacıların kilit destek rolü üstlendiği çok disiplinli bir yaklaşım gereklidir. DILI, kritik hastalarda morbidite ve mortaliteyi arttırabilir; bu da erken tanı ve proaktif yönetimin önemini ortaya koymaktadır.

Anahtar kelimeler: İlaç kaynaklı hepatotoksisite, Kritik hastalar, Hepatosellüler hasar, Polifarmasi

Introduction

Drug-induced hepatotoxicity (DIH), also known as drug-induced liver injury (DILI), represents a pathological response to both synthetic and natural compounds, which can be acute or chronic (1). While its incidence is relatively low, DILI remains a major cause of acute liver failure in Europe, the United States, and Australia (2). The global annual incidence of DILI is estimated to range between 14 and 19.1 cases per 100,000 individuals exposed to potential hepatotoxic agents, with approximately 30% of affected patients developing jaundice (3). Key risk factors for DILI include female sex, advanced age, and an elevated body mass index (BMI) (4,5). More than 1,000 pharmaceutical drugs and herbal compounds are known to be hepatotoxic and are cataloged in the LiverTox database, a searchable resource (6). Other factors that may increase susceptibility to DILI include pre-existing liver disease, concomitant medication use, high dosages, the lipophilicity of the drug, and genetic predispositions (7).

DILI is typically classified into two mechanisms: predictable intrinsic (dose-dependent) and unpredictable (dose-independent). Unpredictable reactions, also known as immune-mediated hypersensitivity or non-immune reactions, occur in a smaller proportion of individuals (8). Intrinsic DILI is usually dose-dependent, affects a significant number of individuals, and has a short onset (hours to days) (9). Idiosyncratic DILI, on the other hand, is dose-independent but typically requires a threshold dose of 50-100 mg/day. It can be classified into hepatocellular, cholestatic, or mixed patterns and further divided into immune-mediated (allergic) or non-immune-mediated reactions. Immune-mediated cases are characterized by fever, rash, eosinophilia, and autoantibodies, whereas non-immune-mediated cases lack these features and have a delayed onset (10).

Approximately half of DILI cases are attributed to acetaminophen overdose. In addition to acetaminophen, DILI can be induced by various agents, with commonly reported ones being anti-tuberculosis agents such as isoniazid and rifampicin; antibiotics such as amoxicillin-clavulanate, tetracyclines, and macrolides; NSAIDs such as diclofenac; antifungal agents; antiepileptics; and halothane (8,11).

Liver injury is typically detected through biochemical tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBL). In a 2011 expert working group, a new definition for drug-induced liver injury (DILI) was proposed, including ALT elevation ≥5 times the upper limit of normal (ULN), ALP elevation ≥2 times ULN (with an accompanying increase in gamma-glutamyltransferase (GGT)), or ALT ≥3 times ULN with a simultaneous increase in total bilirubin concentration above 2 times ULN. Hepatocellular injury is classified when the ALT/ALP ratio is ≥5, cholestatic injury occurs with ALP ≥2 times ULN or an ALT/ALP ratio of ≤2, and mixed injury is identified when the ALT/ALP ratio is between 2 and 5.

Total bilirubin (TBL) is typically normal until the later stages of DILI, and alkaline phosphatase (ALP) levels are generally normal, although mild elevations (usually <2× ULN) may occur. Gamma-glutamyltransferase (GGT) levels can vary widely, with values ranging from low normal to >400 U/L. It is important to note that the

majority of clinical trials utilize the ULN values from the central laboratory employed for the study, which can vary due to differences in reference populations and analytical variations in commercial assays (12,13)

A variety of scales have been developed to assess the causality of drug toxicity objectively (14). Among these, the CIOMS Roussel-Uclaf Causality Assessment Method (RUCAM) scale, the Maria & Victorino System, and the Clinical and Diagnostic Scale (CDS) are widely used, with RUCAM being the most commonly applied (15). Since drug-induced hepatotoxicity can present with symptoms similar to hepatobiliary disorders, it is crucial to conduct a comprehensive drug history when DILI is suspected. The diagnostic process begins by collecting detailed information, including the type of drug, dosage details (such as frequency, duration, and any adjustments), and the timing of symptom onset. A multidisciplinary approach involving the doctor, clinical pharmacist, and nurse is necessary for diagnosis, and regulatory agencies must be informed to evaluate the possibility of removing suspect drugs from the market (5). Clinical pharmacists play a pivotal role in the patient-centered diagnosis and treatment process, offering professional pharmaceutical expertise and comprehensive medication management. At our hospital, clinical pharmacists are integral in optimizing the DILI management model, providing timely and appropriate treatment recommendations for patients with DILI (16).

The aim of our study is to investigate the various causes of drug-induced liver injury, analyze the different patterns and outcomes of DILI in patients, and assess the role of the clinical pharmacist in managing this condition.

Methods

Study design

This retrospective, cross-sectional study was conducted between October 1, 2023, and October 1, 2024, on patients admitted to the third-level intensive care unit of a training and research hospital. The study focused on patients with elevated liver function and investigated DILI. The sample size of the study was determined based on the existing dataset without prior statistical power calculations. The number of patients included in the study was based on the available data.

Data collection

Data were collected from the hospital's information management system. The study investigated the potential liver injury associated with the medications used in the treatment process of patients with elevated liver function. During data collection, liver function tests of patients were examined without specifically focusing on the presence of a clear drug relationship with DILI.

Inclusion criteria

Patients who fulfilled at least one of the clinical biochemical criteria for the diagnosis of drug- DILI were included in the study. These criteria include abnormal results in biochemical tests such as ALT, AST, ALP, and total bilirubin. Patients meeting these criteria were included to allow for the investigation of drug-induced liver injury.

Exclusion criteria

Patients with viral liver diseases, alcoholic liver disease, autoimmune liver disease, cholestatic liver diseases, infections (e.g., liver abscess), sepsis induced liver dysfunction, hepatobiliary pancreatic tumors, pancreatitis, direct liver injury, osteopathy, cirrhosis, and other drug-independent or unknown liver injuries were excluded from the study.

Diagnostic criteria

DILI is typically diagnosed and confirmed through abnormal results in biochemical tests such as ALT, AST, ALP, and total bilirubin. In 2011, an international expert working group proposed new criteria for the diagnosis of DILI. According to these criteria, an

increase in ALT ≥5 times the upper limit of normal (ULN) or ALP ≥2 times the ULN, particularly in the presence of elevated gamma-glutamyltransferase (GGT), and in the absence of known bone pathologies influencing ALP elevation, should raise suspicion for DILI. Additionally, a simultaneous elevation of ALT ≥3 times the ULN and total bilirubin concentration >2 times the ULN is considered a significant diagnostic criterion for DILI.

In our study, the type of liver injury is determined by the ALT/ALP ratio and ALT levels. When the ALT/ALP ratio is ≥5, the clinical condition is classified as hepatocellular. A rise in ALP of twofold or more, or an ALT/ALP ratio of ≤2, indicates a cholestatic condition. When the ALT/ALP ratio falls between 2 and 5, the clinical condition is considered mixed liver injury.

Ethical approval

The study was approved by the Marmara University Medical Faculty Research and Ethics Committee (09.2024.1229). The confidentiality of personal data was maintained, and all data were collected while ensuring patient anonymity. Informed consent was not obtained due to nature of the study.

Statistical analysis

The data collected in this study were analyzed using SPSS version 22.00. The Shapiro-Wilk test was employed to assess the normality of the distribution for numerical variables. Categorical variables were expressed as frequencies and percentages. Numerical variables with normal distribution were presented as mean ± standard deviation, whereas non-normally distributed variables were expressed as median and interquartile ranges (IQR). For comparisons of numerical variables, the Independent Samples t-test was used; if the assumptions of this test were not met, the Mann-Whitney U test was applied instead. The Chi-square test was used for comparisons of categorical variables; when the assumptions of the Chi-square test were not fulfilled, Fisher's exact test was performed. A p-value of <0.05 was considered statistically significant.

Results

Among 475 patients admitted to the intensive care unit, altered liver test results were detected in 47 patients. Of these, 31 cases of hepatic enzyme elevation were attributed to non-drug-related causes, while 16 cases were identified as drug-induced liver injury (DILI) (Figure 1). The one-year incidence of DILI was calculated as 9.89%. The mean age of patients with DILI was 47.1±23.6 years; 7 patients (43.75%) were female and 9 (56.25%) were male (Table 1). The median Charlson Comorbidity Index (CCI) score was 1 (1–3).

The most common ICU admission diagnoses among patients who developed DILI were intracranial hemorrhage or cerebral lesions (4 patients; 25%) and postoperative follow-up (4 patients; 25%). Additionally, 3 patients (18.8%) were admitted due to status epilepticus. The median APACHE II score was 18 (15–21) and the median SOFA score was 6 (4–8).

More than half of the patients with DILI (9 patients; 56.3%) were receiving eight different medications during treatment. The minimum number of medications administered was five. More than half of the patients (9; 56.3%) required vasopressor support. Table 2 shows each patient's SOFA score on the day of peak liver enzyme elevation, vasopressor use, and average daily dose of paracetamol. Of the 16 DILI patients, 15 received paracetamol, with a mean daily dose of 1.16 g/day (range: 0–4 g/day).

On ICU admission, the average ALT was 29±16 U/L, AST was 33±18 U/L, ALP was 77±26 U/L, and total bilirubin was 0.44±0.14 mg/dL. The average albumin level was 3.9±0.6 g/dL, INR was 1.09±0.15, and creatinine was 0.99±0.39 mg/dL. DILI developed approximately 9.5±5.2 days after ICU admission. After DILI onset, the average ALT was 375±152 U/L, AST was 283±157 U/L, and ALP was 141±88 U/L.

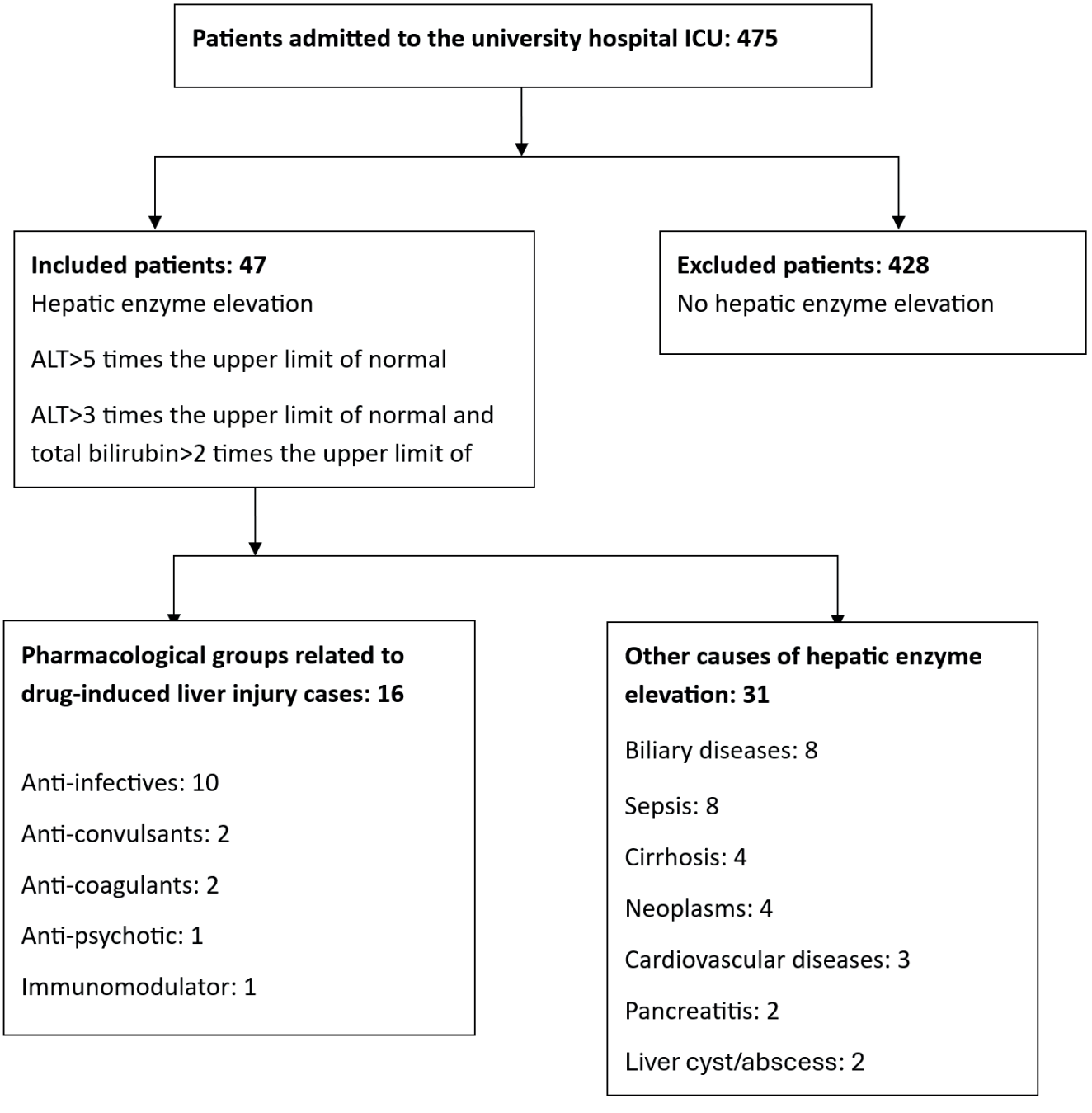

Figure 1. Flow diagram of patients selection

ICU: Intensive care unit.

Among the drugs associated with DILI, antibiotics accounted for 62.5% (10 drugs). Other frequently associated drug classes included anticoagulants (2; 12.5%) and antipsychotics (2; 12.5%). The most commonly implicated agents were ampicillin-sulbactam (2; 12.5%), cefoperazone-sulbactam (2; 12.5%), enoxaparin (2; 12.5%), and quetiapine (2; 12.5%) (Table 3). The median duration of use for the suspected drugs was 8.5 days (5.25–14.75).

Table 1. Cases of drug-induced liver injury

Patient number	Age, year	Sex	CCI	Suspected Drug	R score	Type of liver injury	Duration of drug, day	Mortality
1	48	Male	1	Cefoperazone-sulbactam	12,0	Hepatocellular	10,0	No
2	84	Male	5	Cefoperazone-sulbactam	7,0	Hepatocellular	7,0	Yes
3	19	Male	0	Quetiapine	16,0	Hepatocellular	11,0	Yes
4	79	Female	1	Enoxaparin	11,0	Hepatocellular	61,0	Yes
5	26	Male	0	Enoxaparin	5,1	Hepatocellular	15,0	No
6	29	Male	1	Ampicillin-sulbactam	6,7	Hepatocellular	6,0	No
7	78	Female	4	Ampicillin-sulbactam	13,5	Hepatocellular	7,0	No
8	26	Male	1	Valproic acid	28,0	Hepatocellular	34,0	Yes
9	58	Female	2	Ceftriaxone	12,0	Hepatocellular	2,0	Yes
10	75	Female	4	Clindamycin	12,8	Hepatocellular	3,0	No
11	56	Male	3	Imipenem	5,6	Hepatocellular	14,0	Yes
12	23	Female	0	IVIG	11,5	Hepatocellular	5,0	No
13	48	Male	1	Daptomycin	12,0	Hepatocellular	2,0	Yes
14	20	Male	0	Quetiapine	3,1	Cholestatic	26,0	No
15	24	Female	1	Tigecycline	3,7	Cholestatic	14,0	Yes
16	60	Female	3	Ceftazidim	2,1	Mixed	7,0	Yes

CCI: Charlson Comorbidity Index.

Table 2. DILI patients' SOFA scores, vasopressor use, and paracetamol doses

Patient No	SOFA (peak day)	Vasopressor	Paracetamol (g/day)
1	8	Yes	2.2
2	7	Yes	1.18
3	4	No	0.62
4	5	No	0.32
5	6	Yes	0.55
6	6	Yes	1.07
7	4	No	1.06
8	6	Yes	0.54
9	5	No	0.2
10	6	Yes	0.3
11	8	Yes	0
12	6	No	1.6
13	4	No	4
14	5	Yes	0.28
15	4	Yes	3.5
16	5	No	0.28

The median R ratio used to assess injury type was 11.25 (5.35–12.4). The injury pattern was hepatocellular in 13 patients (81.25%), cholestatic in 2 patients (12.5%), and mixed in 1 patient (6.25%). In our cohort, the hepatocellular pattern of injury together with the latency period (median 9.5±5.2 days after ICU admission) and RUCAM scores (≥6) strongly supported the diagnosis of drug-induced liver injury. Importantly, although nine patients were receiving vasopressors at the time of peak enzyme elevation, the biochemical profile was not consistent with ischemic hepatitis or sepsis-associated liver dysfunction. In particular, transaminase elevations did not exceed 1000 U/L, bilirubin levels remained largely within normal limits (0.3–0.9 mg/dL), and the pattern of injury was not compatible with sepsis-related cholestasis, where conjugated hyperbilirubinemia and cholestatic enzyme elevations usually predominate. These findings indicate that the observed liver injury was more plausibly attributable to DILI rather than sepsis or ischemia.

Table 3. Values in liver tests

Suspected Drug	ALT, first (U/L)	AST, first (U/L)	ALP, first (U/L)	ALT, high (U/L)	AST, high (U/L)	ALP, high (U/L)	Total bilirubin, mg/dl
Cefoperazone-sulbactam	23	29	48	364	291	89	0,38
Cefoperazone-sulbactam	15	25	81	680	551	292	0,37
Quetiapine	73	87	88	624	446	111	0,39
Enoxaparin	12	10	43	246	121	67	0,40
Enoxaparin	50	18	108	280	147	163	0,54
Ampicillin-sulbactam	18	24	81	245	212	101	0,30
Ampicillin-sulbactam	15	24	67	665	447	145	0,45
Valproic acid	36	24	57	348	111	36	0,26
Ceftriaxone	35	44	98	421	394	82	0,30
Clindamycin	29	47	59	298	270	70	0,47
Imipenem	45	32	144	270	336	121	0,34
IVIG	30	31	84	441	349	115	0,58
Daptomycin	29	20	51	361	525	69	0,50
Quetiapine	19	32	84	247	91	241	0,87
Tigecycline	16	54	50	264	130	216	0,52
Ceftazidim	26	31	88	252	118	345	0,45

Among DILI cases, 7 patients (43.75%) showed clinical improvement and normalization of liver tests after liver-protective and supportive therapy. However, 9 patients (56.3%) died. Demographic characteristics such as age and gender were not associated with mortality. Likewise, ALT, AST, and ALP levels at both admission and during DILI episodes were not significantly associated with mortality ($p>0.05$).

Discussion

This study provides valuable insight into the incidence, clinical characteristics, implicated agents and outcomes of drug-induced liver injury (DILI) among critically ill patients in a tertiary intensive care unit (ICU) over the span of one year. Our findings indicate a DILI incidence of 9.89% among ICU patients presenting with elevated liver enzymes. In a recent study from a university hospital in Colombia, the 1-year incidence of drug-induced liver injury (DILI) was approximately 6%. Similar to our findings, antibiotics and anticonvulsants were reported as the main pharmacological groups associated with DILI. These results are in line with our observations, further supporting the notion that careful patient selection, close monitoring, and rational prescribing are essential in minimizing the risk of DILI. Consistent with the recommendations of this study, the prompt suspension of the suspected agent should be considered the first protective measure, followed, when appropriate, by modification of pharmacotherapy or the initiation of supportive treatment strategies (17).

In critically ill patients, liver enzyme elevations and drug-related hepatotoxicity are increasingly recognized as significant contributors to morbidity and mortality. A study reported that intensive care unit (ICU) patients with elevated liver enzymes at admission had significantly higher mortality compared to those with normal levels, emphasizing the prognostic relevance of hepatic dysfunction in critical illness (18). In our cohort, the liver enzyme abnormalities predominantly exhibited a hepatocellular pattern, with transaminase elevations exceeding cholestatic markers and bilirubin levels largely within normal limits. This biochemical profile contrasts with sepsis-associated cholestatic liver injury, which typically presents with conjugated

bilirubin and ALP/GGT predominance and only mild transaminase elevation (8,19).

R values and RUCAM scores further support the attribution of these abnormalities to drug-induced liver injury (DILI) rather than sepsis or ischemic hepatopathy (6). Even among patients receiving vasopressors, the biochemical profiles remained inconsistent with sepsis-related liver dysfunction. These findings underscore that hepatocellular injury observed in the ICU can be differentiated from hemodynamic or infection-related liver damage.

Overall, this emphasizes the importance of vigilant monitoring, rigorous causality assessment, and early recognition of DILI in critically ill populations. These findings support the notion that both underlying critical illness and complex pharmacotherapy contribute to liver injury in ICU settings. In addition, findings highlight that critically ill patients are particularly susceptible to hepatotoxicity due to complex pharmacotherapy and polypharmacy, underscoring the need for vigilant monitoring, early detection, and rigorous causality assessment to mitigate potential adverse outcomes.

One of the factors potentially contributing to elevated liver enzyme levels is drug–drug interactions. The clinical relevance of these interactions in intensive care units has been emphasized in several studies (20). For example, some studies (21) have demonstrated that co-administration of interacting drugs can lead to increases in liver enzyme levels. In our study, however, no significant elevations in liver enzymes attributable to such interactions were observed. Nevertheless, this potential risk should be carefully considered in the management of intensive care patients.

A notable observation was the predominance of hepatocellular injury (81.25%) in our cohort, which is consistent with existing literature that identifies hepatocellular injury as the most common form of DILI (19,22). The onset of DILI approximately 9.5 days following ICU admission underscores the critical need for heightened vigilance during the second week of ICU stay, particularly when multiple high-risk medications are being administered.

In terms of causative agents, anti-infectives, particularly β-lactam antibiotics (e.g., ampicillin-sulbactam, cefoperazone-sulbactam, ceftriaxone), were the most commonly implicated drugs (19). This is unsurprising given the routine and extensive use of broad-spectrum antibiotics in ICU settings. Interestingly, the involvement of antipsychotics (such as quetiapine) and anticoagulants (like enoxaparin) as potential culprits despite being less frequently reported in the general population merits attention (23-25). Paracetamol use was common among patients with suspected DILI, but the daily doses were generally low and well below levels typically associated with hepatotoxicity in adults (26). These agents are more commonly used in ICUs, where off-label or extended-use practices are frequent. This emphasizes the need for ICU-specific DILI monitoring protocols, as opposed to relying solely on generalized hepatotoxicity data.

The mortality rate observed in our study (56.3%) was alarmingly high, significantly surpassing the mortality rates seen in non-ICU DILI cohorts. This increase likely reflects the severity of baseline illness among ICU patients, rather than DILI being the primary cause of death. However, it is important to acknowledge that DILI may exacerbate multi-organ dysfunction and increase susceptibility to sepsis, thereby indirectly worsening patient outcomes. Remarkably, neither demographic factors (age, gender) nor baseline liver enzyme levels were predictive of mortality, suggesting that DILI in the ICU is a multifactorial phenomenon intricately linked with the progression of critical illness (27,28).

An important strength of this study is the application of rigorous diagnostic criteria, including internationally recognized thresholds for DILI (ALT ≥5× ULN or ALT ≥3× ULN + total bilirubin >2× ULN), ensuring consistency and comparability with other studies. Furthermore, causality assessment was systematically performed using the RUCAM scale, which is considered the gold standard in hepatotoxicity

causality assessment. Despite these strengths, the retrospective design introduces certain limitations, such as the potential underreporting of subtle DILI cases and the inability to account for confounding variables like parenteral nutrition, ischemic hepatitis, or undiagnosed infections (6,19,29).

From the clinical pharmacy perspective, this study underscores the pivotal role of clinical pharmacists in the early detection, risk stratification, and management of DILI in ICU. Routine medication profile reviews, proactive deprescribing strategies, and advocacy for liver-friendly therapeutic alternatives could significantly reduce the incidence of DILI in ICUs. In light of our findings, it is plausible to consider the implementation of prospective DILI screening protocols, led by clinical pharmacists with the collobration of intensivists, as a standard practice within ICU settings (16).

A critical revelation from our study is the often subtle, insidious onset of DILI in ICU patients. At ICU admission, liver function tests were predominantly normal or near-normal. Relying solely on initial admission laboratory results could create a false sense of security. Therefore, dynamic and repeated liver function tests should be an integral part of ongoing ICU pharmacovigilance (30,31).

Study strengths and limitations

This study's strengths include its focus on a high-risk ICU patient population, the use of internationally validated diagnostic and causality tools, and its strong practical relevance to real-world clinical practice. However, the relatively small sample size and single-center design limit the generalizability of our findings. Additionally, the absence of liver biopsy data and the retrospective nature of the study preclude the definitive exclusion of all potential causes of liver injury.

Future research should focus on multicenter prospective studies to validate these findings and identify predictive biomarkers for early detection of DILI in ICU patients. Machine learning approaches that analyze large, multicenter datasets could provide insights into subtle risk patterns that may elude conventional analysis.

Conclusion

DILI remains an important, yet often underrecognized, complication in ICU patients. Anti-infectives, particularly β-lactam antibiotics, dominate the list of implicated drugs, with hepatocellular injury being the most common manifestation. Clinical vigilance, dynamic liver function monitoring, and the active involvement of clinical pharmacists are essential for mitigating DILI-related morbidity and mortality. Establishing structured DILI surveillance programs in ICUs is a forward-thinking strategy that can significantly enhance patient safety and improve clinical outcomes.

Highlights

- DILI incidence among ICU patients was 9.89% emphasizing that hepatotoxicity is a significant yet often overlooked complication in critically ill patients.
- Antibiotics were the most frequently implicated drug class (62.5%), particularly β-lactam antibiotics, highlighting the need for cautious use in ICU settings.
- Hepatocellular injury was the dominant pattern (81.25%), and DILI onset occurred approximately 9.5 days after ICU admission, underscoring the importance of dynamic liver monitoring beyond initial hospitalization.
- The mortality rate among DILI patients reached 56.3%, indicating the critical role of early detection and interdisciplinary management, particularly involving clinical pharmacists.

Ethical approval

This study has been approved by the Marmara University Medical Faculty Research and Ethics Committee (approval date: 18.10.2024, number: 09.2024.1229).

Author contribution

Study conception and design: FG, DÜ; data collection: FG, DÜ; analysis and interpretation of results: FG, DÜ; draft manuscript preparation: FG, DÜ. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Fisher K, Vuppalanchi R, Saxena R. Drug-Induced Liver Injury. Arch Pathol Lab Med. 2015;139:876-87. [Crossref]
2. McGill MR, Jaeschke H. Biomarkers of drug-induced liver injury. Adv Pharmacol. 2019;85:221-39. [Crossref]
3. Garcia-Cortes M, Robles-Diaz M, Stephens C, Ortega-Alonso A, Lucena MI, Andrade RJ. Drug induced liver injury: an update. Arch Toxicol. 2020;94:3381-407. [Crossref]
4. Njoku DB. Drug-induced hepatotoxicity: metabolic, genetic and immunological basis. Int J Mol Sci. 2014;15:6990-7003. [Crossref]
5. Real M, Barnhill MS, Higley C, Rosenberg J, Lewis JH. Drug-Induced Liver Injury: Highlights of the Recent Literature. Drug Saf. 2019;42:365-87. [Crossref]
6. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
7. Germani G, Battistella S, Ulinici D, et al. Drug induced liver injury: from pathogenesis to liver transplantation. Minerva Gastroenterol (Torino). 2021;67:50-64. [Crossref]
8. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70:1222-61. [Crossref]
9. Bessone F, Hernandez N, Tagle M, et al. Drug-induced liver injury: A management position paper from the Latin American Association for Study of the liver. Ann Hepatol. 2021;24:100321. [Crossref]
10. Chitturi S, Farrell GC. Drug-Induced Liver Disease. In: Schiff's Diseases of the Liver. 2011. [Crossref]
11. David S, Hamilton JP. Drug-induced Liver Injury. US Gastroenterol Hepatol Rev. 2010;6:73-80.
12. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89:806-15. [Crossref]
13. Regev A, Palmer M, Avigan MI, et al. Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis. Aliment Pharmacol Ther. 2019;49:702-13. [Crossref]
14. Lucena MI, Camargo R, Andrade RJ, Perez-Sanchez CJ, Sanchez De La Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity. Hepatology. 2001;33:123-30. [Crossref]
15. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR, Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. Am J Gastroenterol. 2021;116:878-98. [Crossref]
16. Li D, Dong J, Xi X, et al. Impact of pharmacist active consultation on clinical outcomes and quality of medical care in drug-induced liver injury inpatients in general hospital wards: A retrospective cohort study. Front Pharmacol. 2022;13:972800. [Crossref]
17. Cano-Paniagua A, Amariles P, Angulo N, Restrepo-Garay M. Epidemiology of drug-induced liver injury in a University Hospital from Colombia: Updated RUCAM being used for prospective causality assessment. Ann Hepatol. 2019;18:501-7. [Crossref]
18. Yiğit E, Çetin T, Taşkıran G, et al. Elevation of liver enzymes in intensive care patients is significantly related with the increased mortality. Turk J Gastroenterol. 2019;30(Suppl 1):S94. [Crossref]
19. Björnsson ES. The epidemiology of newly recognized causes of drug-induced liver injury: an update. Pharmaceuticals (Basel). 2024;17:520. [Crossref]
20. Gülen D, Dağdelen MŞ, Ceylan İ, Kelebek Girgin N. Potential drug-drug interactions in intensive care units in Turkey: a point prevalence study. Turk J Intensive Care. 2023;21(2):93-9. [Crossref]
21. Ho YF, Chou HY, Chu JS, Lee PI. Comedication with interacting drugs predisposes amiodarone users in cardiac and surgical intensive care units to acute liver injury: a retrospective analysis. Medicine (Baltimore). 2018;97:e12301. [Crossref]
22. Jiang F, Yan H, Liang L, et al. Incidence and risk factors of anti-tuberculosis drug induced liver injury (DILI): Large cohort study involving 4652 Chinese adult tuberculosis patients. Liver Int. 2021;41:1565-75. [Crossref]

23. Roger C, Louart B. Beta-Lactams Toxicity in the Intensive Care Unit: An Underestimated Collateral Damage? Microorganisms. 2021;9:1505. [Crossref]

24. He S, Chen B, Li C. Drug-induced liver injury associated with atypical generation antipsychotics from the FDA Adverse Event Reporting System (FAERS). BMC Pharmacol Toxicol. 2024;25:59. [Crossref]

25. Eze IE, Adidam S, Gordon DK, Lasisi OG, Gajjala J. Probable enoxaparin-induced liver injury in a young patient: a case report of a diagnostic challenge. Cureus. 2023;15:e36869. [Crossref]

26. Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA. 2006;296:87-93. [Crossref]

27. Abid A, Subhani F, Kayani F, Awan S, Abid S. Drug induced liver injury is associated with high mortality-A study from a tertiary care hospital in Pakistan. PLoS One. 2020;15:e0231398. [Crossref]

28. Sunil Kumar N, Remalayam B, Thomas V, Ramachandran TM, Sunil Kumar K. Outcomes and Predictors of Mortality in Patients With Drug-Induced Liver Injury at a Tertiary Hospital in South India: A Single-Centre Experience. J Clin Exp Hepatol. 2021;11:163-70. [Crossref]

29. Tajiri K, Shimizu Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. World J Gastroenterol. 2008;14:6774-85. [Crossref]

30. Tiwari V, Shandily S, Albert J, et al. Insights into medication-induced liver injury: Understanding and management strategies. Toxicol Rep. 2025;14:101976. [Crossref]

31. Sehrawat SS, Premkumar M. Critical care management of acute liver failure. Indian J Gastroenterol. 2024;43:361-76. [Crossref]

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CASE REPORT / *OLGU SUNUMU*

A rare clinical manifestation of lactate elevation explained by the Warburg effect: report of two lymphoma cases and literature review

Laktat yüksekliğinin nadir görülen sebebi: Warburg etkisiyle açıklanan iki lenfoma vakası ve literatür taraması

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ABSTRACT

Type B lactic acidosis is a rare life-threatening condition associated with hematological malignancies. This condition is of great clinical importance because it requires rapid diagnosis and treatment. Its association with malignancies is based on the Warburg effect. The Warburg effect is a condition in which tumor cells prefer glycolysis over oxidative phosphorylation for energy production, which may lead to severe lactic acidosis.

Here, we report two cases of patients who presented with severe lactic acidosis and hypoglycemia that could be explained by Warburg phenomenon, were followed up in the intensive care unit and subsequently diagnosed with lymphoma. We aim to contribute to the literature on Warburg phenomenon by detailing the rapid and successful management of these cases.

Keywords: type B lactic acidosis, hypoglycemia, hematologic malignancy, intensive care

ÖZ

Tip B laktik asidoz, nadir görülen, hayatı tehdit eden ve hematolojik malignitelerle ilişkilendirilmiş bir tablodur. Bu tablo, hızlı tanı ve tedavi gerektirmesi nedeniyle klinik açıdan büyük önem taşır. Malignitelerle ilişkisinin temelinde Warburg etkisi yer alır. Warburg etkisi, tümör hücrelerinin enerji üretimi için oksidatif fosforilasyon yerine glikoliz yolunu tercih etmesi durumudur ve bu durum ciddi laktik asidoz gelişimine yol açabilir.

Burada Warburg fenomeni ile açıklanabilecek şekilde ciddi laktik asidoz ve hipoglisemi ile başvuran, yoğun bakımda takip edilen ve ardından lenfoma tanısı alan iki vakayı paylaşacağız. Vakaların hızlı ve başarılı bir şekilde yönetilmesini detaylandırarak, Warburg fenomeni ile ilgili literatüre katkıda bulunmayı amaçlıyoruz.

Anahtar kelimeler: tip B laktik asidoz, hipoglisemi, hematolojik malignite, yoğun bakım

Introduction

Hyperlactatemia is defined as a serum lactate level exceeding 2.0 mmol/L without acidemia (1). Lactic acidosis is characterized with a pH of <7.35 accompanied by lactate elevation. The etiology of lactic acidosis needs to be clarified early because it carries an ominous prognosis (2). There are two types of lactic acidosis; Type A being the most common one associated with hypoxia or hypoperfusion and Type-B lactic acidosis which is rare compared to type-A and is associated with liver disease, vitamin B1 deficiency, alcoholism, medications such as metformin and

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adrenalin, and malignancies (3). Lactic acidosis developing due to the high turnover of malignant cells is called the Warburg effect (4). Otto Warburg first described this phenomenon in the 1920s, and it is mainly since tumor cells prefer the glycolytic pathway even in the presence of oxygen (4,5).

Herein, we present 2 cases admitted with hypoglycemia and lactate elevation and subsequently diagnosed with lymphoma. In these cases, we observed that serum lactate decreased gradually and hypoglycemia resolved after chemotherapy initiation. We also report this a literature review, emphasizing the relationship between the Warburg phenomenon and malignancy.

Patients and Methods

We utilized the retrospective medical records of two patients admitted to the intensive care unit (ICU) who developed type-B lactic acidosis and hypoglycemia as a complication of hematologic malignancy. Literature review was conducted by searching "PubMed" and "Google Scholar" in English literature from January 2002 to June 2022 using ''Warburg effect and lymphoma'' and ''type-B lactic acidosis, hypoglycemia and lymphoma'' keywords.

Case Series

Case 1

A 19 years-old female was admitted to the emergency department at 22 weeks of pregnancy presenting with fever, abdominal pain, and generalized fatigue. Her physical examination revealed generalized lymphadenopathy. Laboratory examination showed normocytic anemia (hemoglobin (Hb) 6.8 g/dL, mean corpuscular volume (MCV) 86 fL), neutrophilic leukocytosis (leukocyte count 26x10^3/µL, neutrophil count 18.2x 10^3/µL), lymphopenia (lymphocyte count 0.79x10^3/µL) and elevated inflammatory markers (C-reactive protein 35 mg/dL [normal <0.5mg/dL] and erythrocyte sedimentation rate 61 mm/h). Lactic acidosis (pH 7.27, bicarbonate 9 mmol/L, and lactate 8 mmol/L) and asymptomatic hypoglycemia (glucose level 55 mg/dL) were noted. There was no coagulopathy, encephalopathy and jaundice. Sepsis was suspected and broad-spectrum antibiotics were started. Infectious work-up, including blood and urine cultures, have not revealed any meaningful results. Fluid resuscitation and thiamine (vitamin B1) were also administered to the patient. She was intubated due to severe metabolic acidosis. The patient became anuric and continuous renal replacement therapy was started. She was extubated after metabolic acidosis recovered and her bicarbonate level returned to normal range. However, serum lactate levels did not normalize despite optimal treatment. Even with 25 cc/h 30% dextrose infusion was administered, serum glucose levels remained low. Spontaneous abortion occurred at the 22nd week of gestation.

After the abortion, the patient was evaluated by computerized tomography (CT). Numerous lymph nodes were reported in cervical tomography, suggesting lymphoproliferative disease. A cervical lymph node biopsy was performed. As infectious causes were excluded, 6 mg dexamethasone therapy was started with the initial diagnosis of lymphoproliferative disease. In a few days, clinical recovery was observed. Cervical lymph node biopsy pathology revealed "anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma", stained positive for CD30, CD4, CD2, ALK, and granzyme. Small cells were stained positive for CD20, CD3, CD8, and CD5 and negative for CD56. Ki67 index was found as 70%.

The Cyclophosphamide, Vincristine, Prednisone chemotherapy protocol was initiated and after that resistant hypoglycemia resolved, and lactate levels returned to normal range (Figure 1a). The patient received multiple chemotherapy regimens. However, she passed away due to septic shock approximately 1 year after the diagnosis.

Case 2

A 19 years-old female was admitted to the emergency department with nausea, vomiting, and abdominal pain. Her vital signs were within normal range except hypotension. Physical examination showed epigastric tenderness with moderate ascites. Lung sounds were diminished at the subzone of the lungs, and a bilateral 2-3 positive pretibial edema was observed.

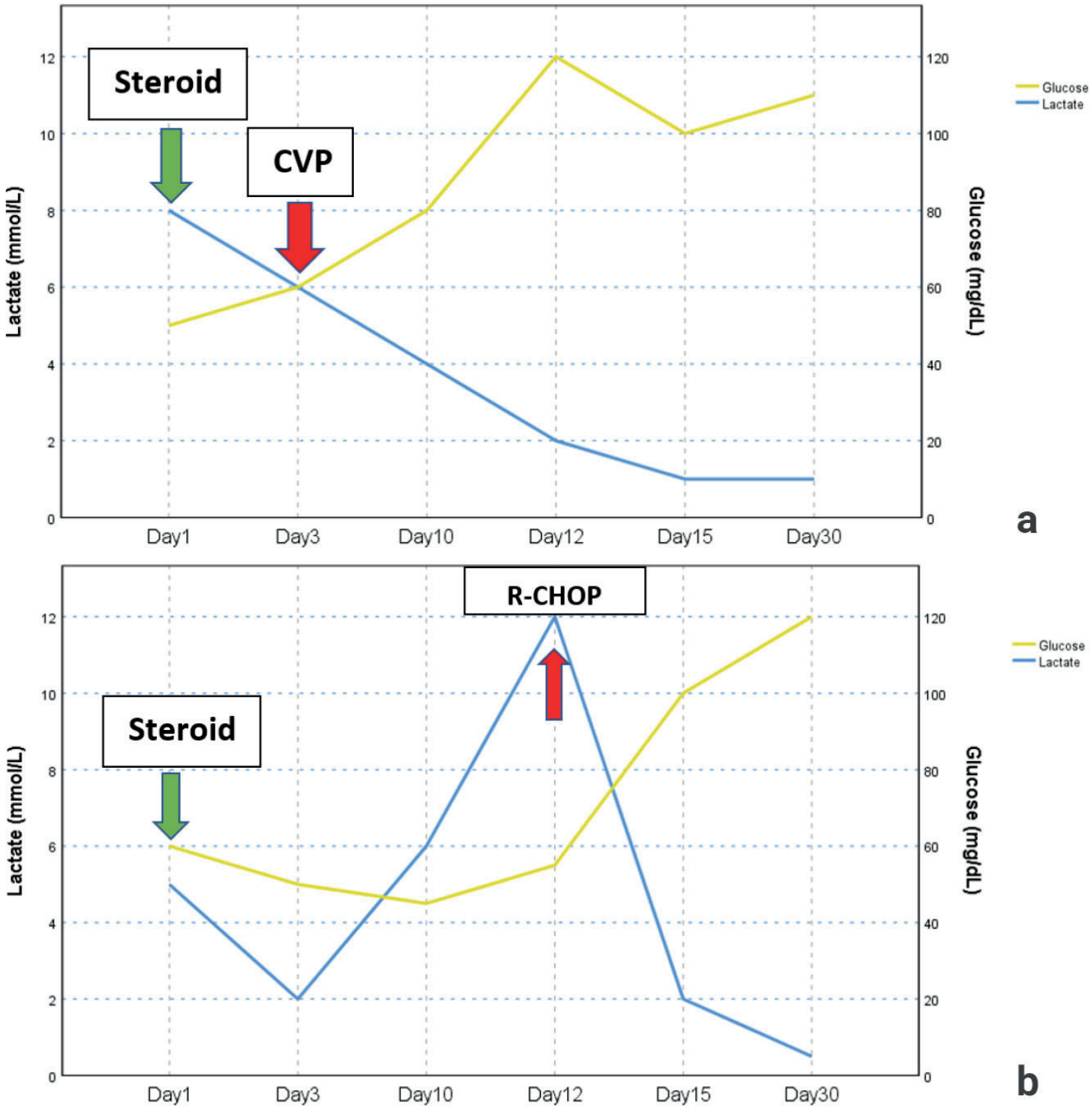

Figure 1. represent pre and post treatment serum levels of lactic acid (blue line) and glucose (yellow line). The green arrows indicate the beginning of steroid therapy and the red arrows indicate the beginning of chemotherapy

CVP: Cyclophosphamide, Vincristine, Prednisone; R CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone

Laboratory assessment revealed microcytic anemia (Hb 9.9 g/dL, MCV 72 fL), neutrophilic leukocytosis (neutrophil count 11.2x10^3/µL), lymphopenia (0.21x10^3/µL), thrombocytosis (426x10^3/µL), elevated inflammatory markers (C-reactive protein 6.2 mg/dL) and pancreatic enzymes (amylase 357 U/L [normal 28-100 U/L], pancreatic amylase 270 U/L [normal 8-53 U/L], lipase 425 U/L [normal <67 U/L]). There was no coagulopathy, encephalopathy and jaundice.

CT scan of the abdomen performed at the admission to the emergency department revealed diffuse thickening of the head of the pancreas and an appearance compatible with periaortitis. With the preliminary diagnosis of sepsis, broad-spectrum antibiotic therapy was initiated as the lactate level raised to 12.0 mmol/L during the patient's follow-up. One-gram methylprednisolone was commenced with the initial diagnosis of IgG4-related disease. There was no improvement in lactate levels despite optimal fluid resuscitation, antibiotic therapy and thiamine replacement. Infection workup, including blood and urine cultures, were negative. During her ICU stay, multiple hyperemic nodular lesions appeared in whole body with approximately 3x3 cm diameter in which the biggest lesion was seen on her abdominal skin, and punch biopsies were obtained from there.

After the methylprednisolone dose had started to be reduced to 48 mg, her abdominal pain recurred, and pancreatic enzymes and lactate levels increased. Therefore, the methylprednisolone dose was increased again to 64 mg/day. Despite oral intake and administration of IV dextrose solution, the patient had persistent hypoglycemia (lowest level 41 mg/dL). Endoscopic retrograde cholangiopancreatography (ERCP) was performed to exclude intrahepatic cholestasis and duodenal biopsy was obtained. The pathology of both skin and duodenal biopsy revealed high-grade diffuse large B cell lymphoma. The skin biopsy specimen stained positive for CD20, BCL6 and negative for CD3, CD5, Cyclin D1, CD23, MUM1 and CD10. The proliferative index (Ki67) was found over 90%. Duodenal biopsy stained positive for CD20, BCL6 and negative for MUM1 and CD10 . The proliferative index (Ki67) was found as 90%. The biopsy results excluded the diagnosis of IgG4-related disease. The Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone chemotherapy protocol was immediately initiated. After initiation of chemotherapy, resistant hypoglycemia resolved and serum lactate level decreased dramatically (Figure 1b). After she had received 5 cycles of chemotherapy, febrile neutropenia developed. She passed away due to septic shock approximately 1 year after initial diagnosis.

Literature review

There have been 30 cases of Warburg effect associated malignancies reported in the last 21.5 years that we have reviewed (Table 1). Twenty-three cases had lymphoma, three had multiple myeloma, two had chronic lymphocytic leukemia (CLL), one with acute myeloid leukemia (AML) and one with adenoma of unknown origin. Diffuse large B cell lymphoma (DLBCL) was the most common cause (46%) among the defined cases. Twenty-one of the cases were male. The median age was 58 (min-max, 19-79 years). The median lactate level was 13.5 mmol/L (min-max, 3.24-29). Hypoglycemia was reported in 43% of cases. Eight of the cases were followed in the ICU. Twenty-three of 30 patients had received treatment (22 received chemotherapy and one received only steroid treatment). Others could not receive chemotherapy due to deterioration in their clinical status, refusal of treatment or postmortem diagnosis. The overall mortality was 76%, whereas it was reported that mortality was 69% in patients who received chemotherapy.

Discussion

Current case reports demonstrated that lactate elevation and hypoglycemia might be associated with occult lymphomas in critically ill patients admitted to ICU, which has been described as so-called "Warburg phenomenon". Lymphomas are a heterogeneous

Table 1. Case reports associated with type B lactic acidosis and lymphoma in the literature

No	Year	Ref	Sex/ Age	Max. lactate pre-treatment (mmol/L)	Hypoglycemia	Diagnosis	ICU admission	Chemotherapy	Lactate Post-treatment (mmol/L)	Outcome
1	2002	(16)	M/55	11.7	NR	MM	-	VAD	3	Death
2	2007	(17)	M/28	11.2	+	NK/ T-cell lymphoma	NR	CHOP	1.05	Death
3	2007	(9)	M/79	19	+	AML	NR	No	NR	Death
4	2007	(9)	F/75	5.4	NR	FL	NR	Etoposide	NR	Death
5	2007	(9)	F/54	12	-	DLBCL	NR	Rituximab, cyclophosphamide, doxorubicin	NR	Death
6	2007	(9)	M/54	12	-	Extranodal -T cell lymphoma	NR	CHOP	NR	Death
7	2007	(9)	F/66	7.5	-	CLL	NR	CHOP	NR	Death
8	2007	(9)	F/61	11.6	-	Intravascular lymphoma	+	High dose dexamethasone, Rituximab	NR	Death
9	2007	(9)	M/54	18	+	DLBCL	+	No	NR	Death
10	2011	(18)	F/55	19	+	DLBCL	+	CHOP	<2.0	Death
11	2012	(19)	F/64	28.5	+	DLBCL	-	R-CHOP	4.3	Death
12	2013	(20)	M/50	14.4	NR	DLBCL	NR	R-CHOP	2.2	Death
13	2013	(21)	M/58	21.5	NR	MM	NR	VRD-PACE	NR	Death
14	2013	(22)	M/73	14.7	+	DLBCL	-	No	NR	Death
15	2013	(23)	M/58	7.3	NR	MM	NR	VRD-PACE	5.5	Death
16	2014	(24)	M/76	7.7	NR	Adenocarcinoma of unknown origin	+	No	NR	Death
17	2014	(25)	M/19	11.2	NR	T cell lymphoma	NR	CHOP	<2.0	Discharged
18	2014	(26)	F/54	18.3	NR	DLBCL	NR	EPOCH	2.6	Unknown
19	2015	(27)	M/67	24	+	CLL	NR	Rituximab	NR	Death
20	2018	(28)	M/67	11.3	-	Mantle cell lymphoma	NR	VR-CAP	3.5	Discharged
21	2018	(29)	M/54	18.7	NR	DLBCL	NR	Methylprednisolone, doxorubicin, cyclophosphamide, etoposide	NR	Death
22	2018	(30)	M/24	9.4	NR	DLBCL	NR	EPOC-RR	1	Discharged
23	2019	(31)	F/74	>20	+	Haematolymphoid leukemia/ lymphoma	NR	No	NR	Death

ICU: Intensive care unit, M: Male, NR: Not reported, MM: Multiple myeloma, VAD: Vincristine, Adriamycin and Dexamethasone, NK/T-cell lymphoma: Natural killer/T cell lymphoma, CHOP: Cyclophosphamide, doxorubicin, vincristine (or oncovin) and prednisone, AML: acute myelocytic leukemia, F: Female, FL: Follicular lymphoma, DLBCL: Diffuse large B cell lymphoma, CLL: Chronic lymphocytic leukemia, R-CHOP: Rituximab, Cyclophosphamide, doxorubicin, vincristine (or oncovin) and prednisone, VRD-PACE Bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide, EPOCH: etoposide, epirubicin, vincristine, cyclophosphamide, and prednisolone, VR-CAP: Bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone, EPOC-RR: Rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, R-EPOCH: Rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone, CV: Cyclophosphamide and vincristine.

Table 1. Continued

No	Year	Ref	Sex/ Age	Max. lactate pre-treatment (mmol/L)	Hypoglycemia	Diagnosis	ICU admission	Chemotherapy	Lactate Post-treatment (mmol/L)	Outcome
24	2020	(32)	F/73	12.7	+	DLBCL	-	CHOP	<2.0	Day 226, hospitalized
25	2021	(33)	M/65	18.8	+	DLBCL	+	Steroid	36	Death
26	2021	(34)	M/52	16	+	DLBCL	+	R-EPOCH	1.2	6 cycles of chemotherapy no sign of relapse
27	2021	(35)	M/53	3.2	-	DLBCL	NR	No	NR	Death
28	2021	(36)	M/60	7.4	+	Burkitt lymphoma	+	CV	NR	One year follow-up CT normal
29	2021	(37)	M/63	14.5	NR	Burkitt lymphoma	+	R-EPOCH	NR	Death
30	2022	(38)	M/42	18	+	DLBCL	-	No	NR	Death

ICU: Intensive care unit, M: Male, NR: Not reported, MM: Multiple myeloma, VAD: Vincristine, Adriamycin and Dexamethasone, NK/T-cell lymphoma: Natural killer/T cell lymphoma, CHOP: Cyclophosphamide, doxorubicin, vincristine (or oncovin) and prednisone, AML: acute myelocytic leukemia, F: Female, FL: Follicular lymphoma, DLBCL: Diffuse large B cell lymphoma, CLL: Chronic lymphocytic leukemia, R-CHOP: Rituximab, Cyclophosphamide, doxorubicin, vincristine (or oncovin) and prednisone, VRD-PACE Bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide, EPOCH: etoposide, epirubicin, vincristine, cyclophosphamide, and prednisolone, VR-CAP: Bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone, EPOC-RR: Rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, R-EPOCH: Rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone, CV: Cyclophosphamide and vincristine.

group of malignancies of the lymphoid system. The majority of lymphomas are non-Hodgkin lymphomas (NHL) ranging from low-grade to rapidly growing and high-grade histology (6). NHL usually presents with painless lymphadenopathy, whereas some may have accompanying systemic symptoms. The definite diagnosis is made by histopathological examination of the appropriate and adequate biopsy specimen (7). It is not always possible to diagnose with appropriate lymph node sampling in patients with rapidly progressive clinics, eventually it may be fatal if not diagnosed and treated. High lactate levels and lactic acidosis during lymphoma are associated with poor prognosis. Mortality is more than 80% when Warburg effect is present (8). Although the best treatment for patients with malignancies who develop type-B lactic acidosis is not clear yet, chemotherapy seems to be the most appropriate first choice (9). The Warburg Effect is visually summarized in Figure 2.

The first stage of oxidative phosphorylation is known as glycolysis and takes place in the cytoplasm. As a result of glycolysis, 2 molecules of pyruvic acid are formed and converted to acetyl-coenzyme A (acetyl-co A). Acetyl-co A enters the Krebs cycle in the mitochondria. By entering the electron transport chain (ETC) in the inner membrane of the mitochondria, 36 adenosine-three-phosphate (ATP) is obtained at the end and a water molecule is also formed. In the absence of oxygen, pyruvate was not converted to Acetyl-co A, but transformed to lactic acid, known as anaerobic glycolysis. In this way, the net energy balance is only two ATP molecules (10). On the other hand, in cancer cells, the glycolytic pathway is preferred even in the presence of oxygen, which is known as aerobic glycolysis or the Warburg effect (11). As a result, only 2 ATP is obtained. More glucose must be consumed in cancer cells for the same amount of energy. This mechanism why cancer cells

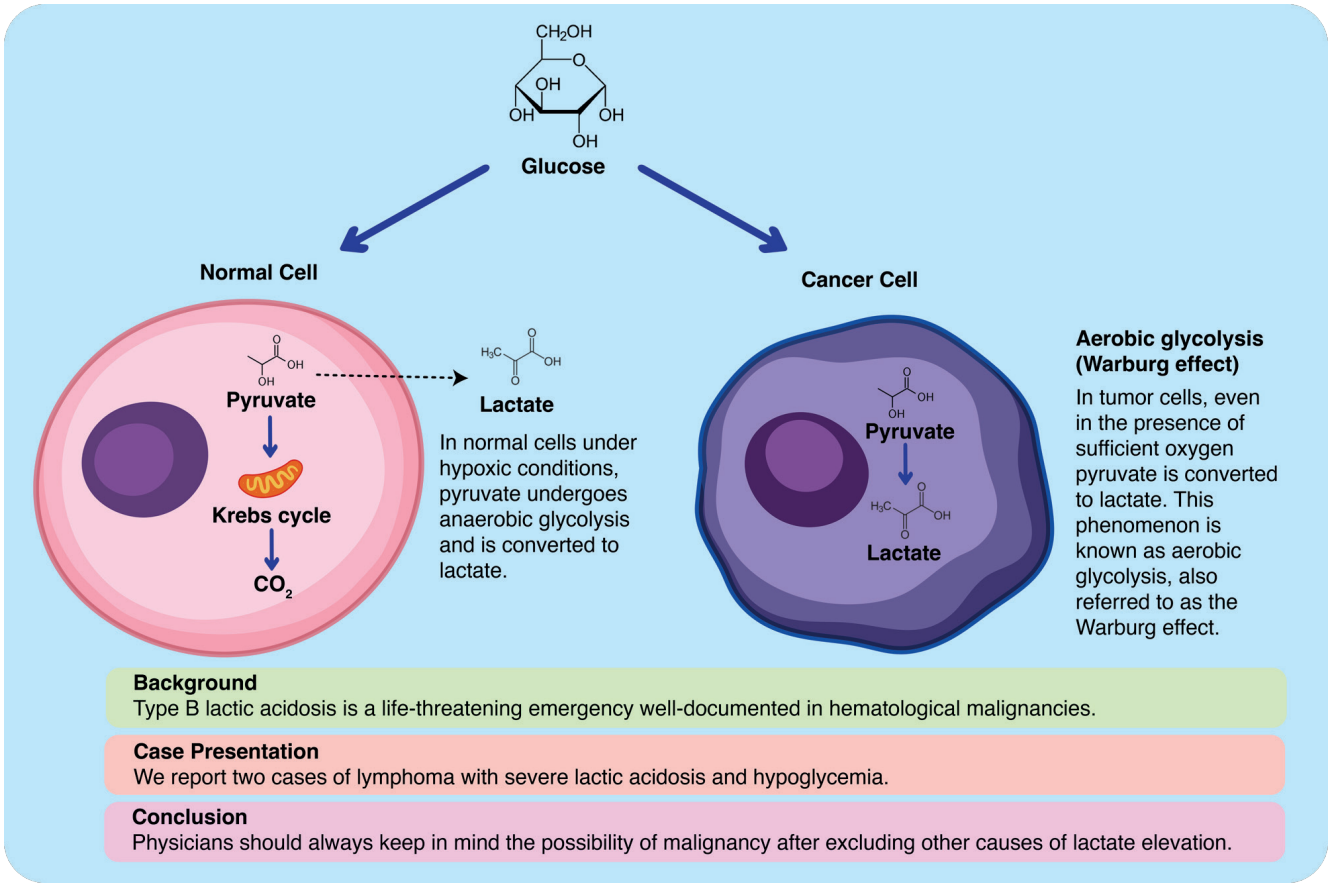

Figure 2. Schematic representation of the Warburg Effect

prefer a less efficient pathway has not fully been understood yet. The plausible hypothesis is that cancer cells use the formed carbon chains derived from aerobic glycolysis for amino acids, nucleotides, and lipid synthesis which are significant for cancer cell proliferation (12). In addition, an acidic environment is created with the activation of the glycolytic pathway in cancer cells, which paves the way for tumor invasion with local toxicity (13). Warburg effect also forms the basis of the fluorodeoxyglucose and positron emission tomography (FDG-PET) system, which is based on increased glucose metabolism and utilized for the diagnosis and follow-up of several tumors (14).

Remarkably, 2 patients in this report were younger than the other reports. Although most of the cases in the literature were male, 2 of our cases were female. The pre-treatment lactate levels were 8 and 12.6 mmol/l, and hypoglycemia was present in both of our cases. One of our cases was diagnosed with DLBCL and the other one with ALK+ lymphoma in the ICU. Lactic acidosis and hypoglycemia disappeared with appropriate early chemotherapy and both of our patients received chemotherapy and passed away 1 year after admission.

We know that lactic acidosis can have numerous causes. Septic shock is the most common etiology of lactic acidosis in ICUs (15). We could not rule out septic shock in these patients and started fluid replacement and antibiotic therapy. We also administered thiamine. Despite this, the persistence of lactic acidosis and the deterioration of the clinical condition of the patients in addition to the presence of hypoglycemia despite continuous glucose infusion directs the potential role of the Warburg effect.

In both of our patients, imaging could not be performed with PET-CT, as it was deemed necessary to make a quick diagnosis and to start the treatment as quick as possible. Biopsy was planned as a result of CT imaging. There was no hepatic failure in the differential diagnosis of hypoglycemia. Since both of our patients were under steroid treatment, cortisol levels were not tested. Unfortunately, patients were not tested for insulin and c-peptide levels for the differential diagnosis of hypoglycemia.

Conclusions

We wanted to emphasize the relationship between the Warburg effect and lymphoma, which has been known for years. Clinicians should always keep in mind the possibility of malignancy after excluding other potential causes of lactate elevation. Lactic acidosis and hypoglycemia could resolve with rapid initiation of efficient chemotherapy in chemo-sensitive tumors.

Ethical approval

This study has been approved by the Hacettepe University Health Sciences Research Ethics Committee (approval date: 09.12.2025, number: SBA25/991).

Author contribution

Study conception and design: BH; data collection: ZÖÖ, EÖ; analysis and interpretation of results: ZÖÖ; draft manuscript preparation: ZÖÖ, EÖ, BH, GG, AT. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. J Intensive Care Med. 2005;20:255-71. [Crossref]
2. de Groot R, Sprenger RA, Imholz ALT, Gerding MN. Type B lactic acidosis in solid malignancies. Neth J Med. 2011;69:120-3.
3. Foucher CD, Tubben RE. Lactic Acidosis. In: statPearls. Treasure Island (FL): StatPearls Publishing; 2022.
4. Potter M, Newport E, Morten KJ. The warburg effect: 80 years on. Biochem Soc Trans. 2016;44:1499-505. [Crossref]
5. Pascale RM, Calvisi DF, Simile MM, Feo CF, Feo F. The warburg effect 97 years after its discovery. Cancers (Basel). 2020;12:2819. [Crossref]
6. Shankland KR, Armitage JO, Hancock BW. Non-hodgkin lymphoma. Lancet. 2012;380:848-57. [Crossref]
7. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F. Non-Hodgkin lymphoma. Lancet. 2017;390:298-310. [Crossref]
8. Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. Ann Intensive Care. 2013;3:12. [Crossref]
9. Friedenberg AS, Brandoff DE, Schiffman FJ. Type B lactic acidosis as a severe metabolic complication in lymphoma and leukemia: a case series from a single institution and literature review. Medicine (Baltimore). 2007;86:225-32. [Crossref]
10. Granchi C, Bertini S, Macchia M, Minutolo F. Inhibitors of lactate dehydrogenase isoforms and their therapeutic potentials. Curr Med Chem. 2010;17:672-97. [Crossref]
11. Devic S. Warburg effect - a consequence or the cause of carcinogenesis? J Cancer. 2016;7:817-22. [Crossref]
12. Liberti MV, Locasale JW. The warburg effect: how does it benefit cancer cells? Trends Biochem Sci. 2016;41:211-18. [Crossref]
13. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? Nat Rev Cancer. 2004;4:891-99. [Crossref]
14. Pauwels EK, Sturm EJ, Bombardieri E, Cleton FJ, Stokkel MP. Positron-emission tomography with [18F] fluorodeoxyglucose. Part I. Biochemical uptake mechanism and its implication for clinical studies. J Cancer Res Clin Oncol. 2000;126:549-59. [Crossref]

15. Ferreruela M, Raurich JM, Ayestarán I, Llompart-Pou JA. Hyperlactatemia in ICU patients: incidence, causes and associated mortality. J Crit Care. 2017;42:200-05. [Crossref]

16. Ustun C, Fall P, Szerlip HM, et al. Multiple myeloma associated with lactic acidosis. Leuk Lymphoma. 2002;43:2395-97. [Crossref]

17. He YF, Wei W, Sun ZM, et al. Fatal lactic acidosis and hypoglycemia in a patient with relapsed natural killer/T-cell lymphoma. Adv Ther. 2007;24:505-09. [Crossref]

18. Ruiz JP, Singh AK, Hart P. Type B lactic acidosis secondary to malignancy: case report, review of published cases, insights into pathogenesis, and prospects for therapy. ScientificWorldJournal. 2011;11:1316-24. [Crossref]

19. Elhomsy GC, Eranki V, Albert SG, et al. "Hyper-warburgism," a cause of asymptomatic hypoglycemia with lactic acidosis in a patient with non-Hodgkin's lymphoma. J Clin Endocrinol Metab. 2012;97:4311-16. [Crossref]

20. Martinez-Outschoorn UE, Whitaker-Menezes D, Valsecchi M, et al. Reverse warburg effect in a patient with aggressive B-cell lymphoma: is lactic acidosis a paraneoplastic syndrome? Semin Oncol. 2013;40:403-18. [Crossref]

21. Tang P, Perry AM, Akhtari M. A case of type B lactic acidosis in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2013;13:80-82. [Crossref]

22. Buppajarntham S, Junpaparp P, Kue-A-Pai P. Warburg effect associated with transformed lymphoplasmacytic lymphoma to diffuse large B-cell lymphoma. Am J Emerg Med. 2013;31:999.e5-6. [Crossref]

23. Sia P, Plumb TJ, Fillaus JA. Type B lactic acidosis associated with multiple myeloma. Am J Kidney Dis. 2013;62:633-37. [Crossref]

24. El Imad T, El Khoury L, Geara AS. Warburg's effect on solid tumors. Saudi J Kidney Dis Transpl. 2014;25:1270-77. [Crossref]

25. Yun S, Walker CN, Vincelette ND, Anwer F. Acute renal failure and type B lactic acidosis as first manifestation of extranodal T-cell lymphoblastic lymphoma. BMJ Case Rep. 2014;2014:bcr2014205044. [Crossref]

26. Kuo CY, Yeh ST, Huang CT, Lin SF. Diffuse large B-cell lymphoma presenting with type B lactic acidosis and hemophagocytic syndrome. Kaohsiung J Med Sci. 2014;30:428-29. [Crossref]

27. Claudino WM, Dias A, Tse W, Sharma VR. Type B lactic acidosis: a rare but life threatening hematologic emergency. A case illustration and brief review. Am J Blood Res. 2015;5:25-29.

28. Wahab A, Kesari K, J Smith S, Liu Y, Barta SK. Type B lactic acidosis, an uncommon paraneoplastic syndrome. Cancer Biol Ther. 2018;19:101-04. [Crossref]

29. Arif H, Zahid S, Kaura A. Persistent lactic acidosis: thinking outside the box. Cureus. 2018;10:e2561. [Crossref]

30. Mejia M, Perez A, Watson H, et al. Successful treatment of severe type B lactic acidosis in a patient with HIV/AIDS-associated high-grade NHL. Case Reports Immunol. 2018;2018:9093623. [Crossref]

31. Talwalkar PG. Severe and persistent hypoglycemia with lactic acidosis in an elderly lady with type 2 diabetes mellitus and lymphoma\leukemia: a rare case report. Diabetes Metab Syndr. 2019;13:648-50. [Crossref]

32. Hamada T, Kaku T, Mitsu S, Morita Y, Ohno N, Yamaguchi H. Lactic acidosis and hypoglycemia in a patient with gastric diffuse large B-Cell lymphoma due to the warburg Effect. Case Rep Oncol. 2020;13:1047-52. [Crossref]

33. Al Maqrashi Z, Sedarous M, Pandey A, Ross C, Wyne A. Refractory hyperlactatemia and hypoglycemia in an adult with non-hodgkin's lymphoma: a case report and review of the warburg effect. Case Rep Oncol. 2021;14:1159-67. [Crossref]

34. Goyal I, Ogbuah C, Chaudhuri A, Quinn T, Sharma R. Confirmed hypoglycemia without whipple triad: a rare case of hyper-warburgism. J Endocr Soc. 2020;5:bvaa182. [Crossref]

35. Hwang CS, Hwang DG, Aboulafia DM. A clinical triad with fatal implications: recrudescent diffuse large B-cell non-hodgkin lymphoma presenting in the leukemic phase with an elevated serum lactic acid level and dysregulation of the TP53 tumor suppressor gene - a case report and literature review. Clin Med Insights Blood Disord. 2021;14:2634853521994094. [Crossref]

36. Looyens C, Giraud R, Neto Silva I, Bendjelid K. Burkitt lymphoma and lactic acidosis: a case report and review of the literature. Physiol Rep. 2021;9:e14737. [Crossref]

37. Salcedo Betancourt JD, Garcia Valencia OA, Becerra-Gonzales VG, et al. Severe type-B lactic acidosis in a patient with bilateral renal Burkitt's lymphoma. Clin Nephrol Case Stud. 2021;9:49-53. [Crossref]

38. Wang C, Lv Z, Zhang Y. Type B lactic acidosis associated with diffuse large B-cell lymphoma and the Warburg effect. J Int Med Res. 2022;50:3000605211067749. [Crossref]

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CASE REPORT / *OLGU SUNUMU*

Use of midodrine for treatment of hypotension: a case report

Hipotansiyon tedavisi için midodrin kullanımı: bir olgu sunumu

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ABSTRACT

Midodrine is an orally approved α-agonist increasingly utilized in intensive care units for the treatment of refractory hypotension with peripheral effects. The current case report presents the clinical manifestation of midodrine utilization in a female patient experiencing refractory hypotension. She was admitted to the intensive care unit of a university hospital due to confusion and suspicion of intoxication.

Due to the patient's hypotensive condition, vasopressor support (norepinephrine) was initiated to address shock of unidentified cause. Midodrine was recommended by the clinical pharmacist to the patient due to the persisting need for norepinephrine. This case report highlights that, based on the clinical judgement of the clinician, midodrine can be used during vasopressor weaning when no other specific cause of hypotension has been identified.

Keywords: midodrine, hypotension, vasopressors, intensive care unit

ÖZ

Midodrin, periferik etkili bir α-agonist olup, dirençli hipotansiyonun tedavisinde yoğun bakım ünitelerinde giderek daha sık kullanılan, oral yolla uygulanan onaylı bir ajandır. Bu olgu sunumunda, refrakter hipotansiyon gelişen kadın bir hastada midodrin tedavisinin klinik etkileri değerlendirilmiştir. Hasta, konfüzyon ve zehirlenme şüphesiyle bir üniversite hastanesinin yoğun bakım ünitesine kabul edilmiştir. Hipotansif durumu nedeniyle, etiyolojisi net olarak belirlenemeyen şoka yönelik vazopresör tedavi (norepinefrin) başlanmıştır. Norepinefrin gereksiniminin devam etmesi üzerine, klinik eczacı tarafından hastaya midodrin tedavisi önerilmiştir. Bu olgu, hipotansiyonun belirgin ve spesifik bir nedeninin saptanamadığı durumlarda, klinisyenin klinik yargısına dayanarak vazopresör tedavinin kesilme sürecinde midodrinin destekleyici bir seçenek olarak kullanılabileceğini ortaya koymaktadır.

Anahtar kelimeler: midodrin, hipotansiyon, vazopressörler, yoğun bakım ünitesi

Introduction

Patients admitted to intensive care unit (ICU) often require intravenous vasoactive drugs to maintain normotension or other clinically indicated blood pressure targets. In hypotensive patients without impairment of tissue oxygenation, there is a need for the use of oral agents that could facilitate weaning from intravenous vasopressors and assist in earlier discharge. Midodrine, an oral α_1-adrenergic agonist, received accelerated approval by the U.S. Food and Drug Administration (FDA) in 1996 for the treatment of symptomatic orthostatic hypotension (1).

In this case report, it was indicated that midodrine may be considered as an option during vasopressor weaning in an ICU patient when no other specific cause of refractory hypotension is identified.

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Case Report

A 54-year-old woman with a known diagnosis of schizophrenia was admitted to ICU of a university hospital with confusion and suspicion of intoxication. A suspicious box was found by relatives in the patient's residence. Box was submitted to Drug and Poison Information Unit (HIZBIB), but due to lack of necessary infrastructure, the sample could not be analyzed. Given the initial presentation and suspicion of intoxication; ethanol, methanol, and urine toxicology analyses were performed as part of the differential diagnosis. Toxicological screening revealed no abnormalities; both ethanol and methanol levels were negative. Cardiac evaluation, including transthoracic echocardiography, demonstrated preserved left ventricular systolic function, with an ejection fraction of approximately 60%. The patient's initial Glasgow Coma Score (GCS) was 14, which later deteriorated, requiring elective intubation. Following admission to the ICU, urinalysis revealed the presence of leukocyturia, a finding that prompted clinicians to consider the possibility of urosepsis as a potential diagnosis. Due to escalating vasopressor requirements, with norepinephrine titrated up to 0.87 mcg/kg/min, empirical antibiotic therapy was initiated with ampicillin-sulbactam, followed by piperacillin-tazobactam. No microbial growth was detected in urine or blood cultures. Despite adequate fluid resuscitation, the patient remained hemodynamically unstable. As a result, additional vasoactive agents—adrenaline and dobutamine—were introduced. Critical illness related corticosteroid insufficiency was not ruled out and methylprednisolone was also administered. Given a serum albumin level of 2.3 mg/dL, albumin replacement therapy was administered. However, due to progressive neurological deterioration and increasing vasopressor requirements, elective endotracheal intubation was performed. On ICU day 3, the patient was successfully extubated. Vasopressor requirement varied between 0.01-0.5 mcg/kg/min throughout the patient's hospitalization. Following improvement in clinical status and a decline in acute-phase reactants, antibiotic therapy was discontinued. Nevertheless, the patient remained hypotensive, necessitating ongoing vasopressor support. Midodrine was recommended by the clinical pharmacist to the patient due to the persisting need for norepinephrine and administered to the patient as 2*2.5 mg/day posology. While midodrine was given, 0.1 mcg/kg/min of norepinephrine was continued to the patient. 4 days after starting midodrine, the patient's norepinephrine requirement decreased to 0.03 mcg/kg/min. On the eighth day, the patient's norepinephrine was stopped and midodrine was increased to 2*5 mg/day. During this period, the patient did not need a vasopressor. On the fourteenth day, the dose of midodrine was reduced to 2*2.5 mg/day because the patient's blood pressure was within the normal range and the patient was transferred to ward, where midodrine treatment was was maintained at the same dose.

Discussion

Midodrine is an oral α_1-adrenergic agonist which undergoes enzymatic hydrolysis to form its active metabolite desglymidodrine. It exerts its sympathomimetic effect via activation of alpha adrenergic receptors in the blood vessels which causes an increase in venous return and blood pressure (2). FDA proposed to withdraw approval of midodrine because of lack of studies that verify the clinical benefit of the drug in August 2010. However, there were many studies declaring that midodrine is effective in the treatment of refractory hypotension. Anstey et al. showed that the rate of decline in vasopressor requirements increased after initiation of midodrine treatment. They hypothesize that midodrine administration is effective to wean intravenous vasopressors and shorten ICU and hospital length of stay (3). According to the results of another study carried out by Levine et al., midodrine treatment was associated with an improve in the magnitude of decline of the IV vasopressor dose (4). According to the MIDAS trial conducted by Santer et al. midodrine did not accelerate the discontinuation of intravenous vasopressors. The median time to vasopressor

discontinuation was 23.5 hours in the midodrine group compared to 22.5 hours in the placebo group, a difference that was not statistically significant (p=0.62). These findings do not support the routine off-label use of midodrine for facilitating weaning from intravenous vasopressors in critically ill patients. Therefore, in cases such as the one presented, where midodrine is considered for the management of persistent hypotension in the intensive care setting, it is essential to discuss the negative findings of the MIDAS trial. While earlier small-scale observational studies and case reports have suggested potential benefits, the results of this randomized controlled trial—providing a higher level of evidence—cast doubt on the clinical efficacy of midodrine in this context (5).

Our case report indicates that four days after initiating midodrine, the patient's requirement for norepinephrine was reduced. These findings imply that although the evidence supporting the use of midodrine in the treatment of refractory hypotension is limited and of low quality, midodrine may be used based on physicians' clinical judgement to wean patients from vasopressor therapy when another specific cause of hypotension cannot be identified (6).

Conclusion

In patients who remain hypotensive despite vasopressor therapy, there is limited and low-quality evidence to support the use of midodrine when weaning patients from vasopressors. It should be considered that midodrine may be used to wean hypotensive patients from vasopressor support when all other clinical causes have been ruled out (6).

Ethical approval

Written informed consent was obtained from the patient's sister for publication of the data in this case report.

Author contribution

Study conception and design: KD, AT, BH; analysis and interpretation of results: ZÖY; draft manuscript preparation: ZÖY, BH. The authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Dhruva SS, Redberg RF. Accelerated approval and possible withdrawal of midodrine. JAMA. 2010;304:2172-3. [Crossref]
2. Palma JA, Kaufmann H. Management of orthostatic hypotension. Continuum (Minneap Minn). 2020;26:154-77. [Crossref]
3. Anstey MH, Wibrow B, Thevathasan T, et al. Midodrine as adjunctive support for treatment of refractory hypotension in the intensive care unit: a multicenter, randomized, placebo controlled trial (the MIDAS trial). BMC Anesthesiol. 2017;17:47. [Crossref]
4. Levine AR, Meyer MJ, Bittner EA, et al. Oral midodrine treatment accelerates the liberation of intensive care unit patients from intravenous vasopressor infusions. J Crit Care. 2013;28:756-62. [Crossref]
5. Santer P, Anstey MH, Patrocínio MD, et al. Effect of midodrine versus placebo on time to vasopressor discontinuation in patients with persistent hypotension in the intensive care unit (MIDAS): an international randomised clinical trial. Intensive Care Med. 2020;46:1884-93. [Crossref]
6. Barber DB, Rogers SJ, Fredrickson MD, Able AC. Midodrine hydrochloride and the treatment of orthostatic hypotension in tetraplegia: two cases and a review of the literature. Spinal Cord. 2000;38:109-11. [Crossref]