sciendo Acta Marisiensis - Seria Medica 2024;70(3):112-117 DOI: 10.2478/amma-2024-0027

RESEARCH ARTICLE

Predictors of mortality in patients with early versus late onset of septic shock. A prospective, observational and comparative pilot study

Ioana Denisa Botoș[1#], Carmen Pantiș[1#], Marcel Ovidiu Negrău[1#], Constantin Bodolea[2*], Mihai Octavian Botea[1], Elisabeta Ioana Hirișcău[3], Cosmin Ion Puia[1,4]

1. Faculty of Medicine and Pharmacy. University of Oradea, Oradea, Romania
2. Department of Anesthesia and Intensive Care, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Romania
3. Department of Nursing, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Romania
4. Department of Surgery, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca. Romania

Introduction: Outcome and predictors of early- and late-onset septic shock are still controversial. The aim of the study was to compare the relevant predictors of 28-day mortality in early- and late-onset septic shock and other non-septic critical illnesses.
Material and Methods: We conducted a prospective, observational, pilot study. A group of 46 patients with early septic shock and 42 non-septic critically ill patients from the emergency department and 56 patients with late septic shock from the hospital were enrolled. On admission to the ICU, the most important potential predictors of 28-day mortality were assessed.
Results: In terms of predicting 28-day mortality, a higher mNUTRIC score was the only common predictor for all three groups. Multi-drug resistant (MDR) bacterial aetiology was a common predictor in both forms of septic shock. Older age, female gender, increased neutrophil-to-lymphocyte ratio (NLR) and increased need for vasoactive agents were common predictors in late septic shock and non-septic critically ill patients. Increased red blood cell distribution width coefficient of variation (RDW-CV) was predictor in early septic shock and non-septic critically ill patients. Central venous-arterial carbon dioxide difference (Pcv-aCO2) was predictor in patients with early septic shock. Inflammatory index and MDR carrier status were predictors in non-septic critically ill patients.
Conclusions:A higher mNUTRIC score is a predictor of 28-day mortality in early and late septic shock and in critically ill non-septic patients. MDR aetiology was predictive of 28-day all-cause mortality in both types of septic shock, and Pcv-aCO2 was predictive in patients with early septic shock.

Keywords: critical care, mortality, early onset, late onset, mNUTRIC score, mortality, predictors, septic shock

Received 30 August 2024 / Accepted 9 September 2024

Introduction

Approximately half of infected critically ill patients are estimated to die within 48 hours as a result of the development of sepsis and septic shock. [1]. The EPIC 3 study on the prevalence of infections in intensive care unit (ICU) patients found that 54% of patients had a suspected or proven infection, with an overall in-hospital mortality rate of 30%, with ICU-acquired infections having a significantly higher mortality rate than community-acquired infections [2]. Recent studies show that while mortality in ICU patients without hospital-acquired infections (HAIs) is 17%, mortality in critically ill patients with one HAI episode ranges from 30% to 48%, and mortality in patients with three concurrent HAIs can reach 63% [3,4].

However, if sepsis or septic shock occurs late in hospital and organ dysfunction develops, the absolute mortality may be 20% higher than for septic shock diagnosed in the ED [5]. The relationship between the timing of the onset of sepsis complicated by septic shock and morbidity and mortality has also been investigated in other previous studies. The results indicate a significantly higher rate of complications and mortality in patients who develop late-onset septic shock in hospital [6-10]. Various classes of demographic, clinical, laboratory and prognostic variables have been identified as predicting adverse outcome in sepsis and septic shock [7,10-12]. However, the pathophysiological complexity and highly variable interaction between host immunity and pathogen greatly complicates this approach [13] and conclusions are heterogeneous.

The aim of this study is to identify potential new predictors of 28-day mortality in ICU patients with early septic shock diagnosed in the emergency department and late septic shock in patients hospitalised longer than 48 hours. To better discriminate the value of these potential predictors, a group of critically ill non-septic patients were also compared.

Methods

Study design and population

A prospective, observational pilot study was conducted. The data collection was conducted in a single intensive care unit of a tertiary care hospital, from mid-February to mid-October 2023. Patients aged 18 years or older were included if they met the following criteria; (i) Patients presenting

* Correspondence to: Constantin Bodolea. E-mail: constantin.bodolea@umfcluj.ro
# These authors contributed equally to this work.

with septic shock and admitted to the ICU from the ED, where the diagnosis of septic shock has been established within 12 hours and in whom the onset of symptoms is less than 48 hours: Early Septic Shock Group (ii) Patients with septic shock who were transferred from a general medical ward to the ICU after a minimum of 48 hours of hospitalization: Late Septic Shock Group (iii) Patients admitted to the ICU from the ED for various severe conditions and not diagnosed with sepsis or septic shock within 48 hours of admission: Critically Ill Non-Septic Group. Pregnant women and patients declining enrolment were excluded. Only the initial ICU admission was taken into account if a patient had multiple admissions.

Ethical Considerations

This study was approved by the Ethics Council of the Oradea County Hospital Nr. 20470/ 22.06.2022 and Decision CEFMF-1/30.06.2023 of the Research Ethics Council of the University of Medicine and Pharmacy Oradea.

Data collection

Demographic data were collected at the time of admission to the intensive care unit. The Third International Consensus Definition of Sepsis and Septic Shock (Sepsis-3) [1] was used to diagnose septic shock. The severity of septic shock and the severity of illness was assessed on arrival at the ICU. A series of scores were calculated: Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, Modified Nutritional Risk Assessment in the Critically Ill (mNUTRIC) score, Vasoactive-Inotropic Score (VIS). We assessed the burden of comorbidities using the Charlson comorbidity index. Routine laboratory and biochemistry samples were taken on admission from the ED or ward. These included peripheral blood cell, inflammatory and infectious markers (C-reactive protein, procalcitonin). We considered the following prognostic biomarkers for mortality at ICU admission: a).Neutrophil-to-Lymphocyte Ratio (NLR); b).Systemic Immune-Inflammation index (SII) calculated by (N×P)/L (N, P and L represent neutrophil, platelets and lymphocyte counts); Clinical outcome data included bacterial aetiology, length of stay in the ICU and 28-day mortality, regardless of where it was recorded.

Statistical analysis

Statistical analysis was performed with SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Absolute values and percentages were used for categorical variables. Continuous variables with a normal distribution were expressed as mean and standard deviation (SD), whereas those without a normal distribution were expressed as median and interquartile range [IQR]. The Student's t-test, the Mann-Whitney U test and the chi-squared test were used to assess baseline characteristics. The association between the variables of interest and all-cause mortality was tested using binary logistic regression. A p-value of less than 0.05 was considered significant.

Results

A total of 144 patients were analysed and compared in the trial. These included 42 critically ill patients with non-septic shock and 102 patients with septic shock: 46 patients with early septic shock and 56 patients with late septic shock. Table I shows the baseline characteristics of the patients studied. Patients with septic shock were older, had significantly worse prognostic scores and indices, and had a significantly higher Charlson comorbidity index than patients with non-septic critical illness. Significant changes were seen in the peripheral blood cells of septic shock patients. These included neutrophilia, widening of the red blood cell distribution width (RDW-CV) and an increase in NLR.

Laboratory data show that biomarkers of inflammation and infection, and organ damage are significantly more severe in septic shock patients than in non-septic critically ill patients. The non-septic critically ill patients spent significantly longer in the ICU, but the overall 28-day mortality rate was not significantly different between the septic and non-septic groups (68.6%vs.57.1% p=0.532).

Table II shows the baseline characteristics, severity scores, biomarkers, laboratory data and clinical details of patients in the early and late septic shock arms. There is a significant increase in the mNUTRIC score in patients with late septic shock and a significant increase in the inotropic vasoactive score in patients with early septic shock. The peripheral blood cell profile showed a borderline significant increase in red blood cell distribution width (RDW-CV) in patients with late septic shock. The systemic immune inflammation index (SII) was significantly higher in patients with late septic shock. Central venous-arterial CO_2 difference is significantly higher in patients with early septic shock. In the late septic shock group, bacterial MDR aetiology was more common but not significant. ICU stay was significantly longer for patients in the late onset septic shock group. However, mortality did not differ between the early and late septic shock groups.

Furthermore, we aimed to identify the predictors of 28-day mortality in patients from the three groups studied using a binary logistic regression model based on the data from the descriptive analysis of the groups. Mortality was the dependent variable, and independent variables were potential mortality predictors. Table III shows the results.

With regard to demographic predictors, female sex is a predictor of 28-day mortality in patients with late septic shock [OR=6.890(95%CI=0.016-0.794);p=0.026)] in critical non-septic shock patients [OR=2.267(95%CI=0.042-4.631);p=0.459)] and to a lesser extent for patients in the early septic shock subgroup [OR=1.176(95%CI=0.067-20.721);p=0.912)]. Age showed reduced ability to predict mortality in the three patient subgroups.

Among the prognostic scores, the mNUTRIC score has the best predictive ability for death at 28 days in pa-

Table I. Baseline characteristics at time of ICU admission

Variable	Septic Shock Group (n=102)	Non-Septic Shock Group (n=42)	P value
Demographics			
Age (years)	70.0[56.0-76.0]	63.0[50.5-70.3]	0.007
Male sex nr.(%)	61(59.8)	25(59.5)	0.975
Scores and comorbidities			
APACHE II Score	27.73(7.4)	20.4(8.2)	<0.001
SOFA Score	11.15(2.9)	7.4(3.5)	<0.001
mNUTRIC Score	7.0[5.0-8.0]	4.0[2.0-6.0]	<0.001
Vasoactive Intropic Score	43.5[26.5-93.25]	0.0[0.0-10.5]	<0.001
CCI	5.0[3.0-7.0]	3.0[1.0-6.0]	0.018
Pheripheral blood cells profile			
Hemoglobin (g/dL)	10.4(2.8)	11.0(3.3)	0.202
Leukocytes (109/L)	17.0[8.9-26.5]	12.3[(9.5-17.2]	0.089
Neutrophils (109/L)	15.0[7.7-23.5]	10.6[7.6-14.0]	0.048
RDW-CV (%)	15.3[14.1-16.6]	14.6[13.5-15.6]	0.009
NLR	15.7[9.2-22.9]	11.6[6.9-17.6]	0.006
SII Index	2686.1 [1334.9-5656.4]	1829.1 [933.1-3753.6]	0.061
Laboratory values			
Albumin (g/dL)	2.2(0.6)	2.67(0.7)	<0.001
Blood urea nitrogen (mg/dL)	42.0[28.0-58.0]	23.0[12.0-41.0]	<0.001
Creatinine (mg/dL)	1.9(1.3-3.6)	1.1[0.7-1.9]	<0.001
C Reactive Protein (mg/L_)	224.1(100.2)	96.7(95.3)	<0.001
Procalciton in (mcg/L)	13.8[7.6-35.7]	0.5[0.2-2.0]	<0.001
Clinical Data			
ICU length of stay (days)	6.0[3.8-13]	9.0[6.0-14.3]	0.021
Mortality at 28 days nr. (%)	70(68.6)	2(57.1)	0.247

Table II Comparisons of baseline characteristics, severity scores, biomarkers and clinical data between groups of patients with septic shock.

Variable	Early Septic Shock Group (n=46)	Late Septic Shock Group (n=56)	P value
Demographics			
Age (years)	71.00[54.00-75.25]	69.50[61.00-77.75]	0.801
Male sex nr. (%)	26(56.5)	35(62.5)	0.542
Scores and comorbidities			
APACHE II Score	27.8(7.6)	27.6(7.1)	0.602
SOFA Score	11.4(3.0)	11.0(2.8)	0.396
mNUTRIC Score	6[5.00-7.00]	7[5.00-8.00]	0.011
CCI	5[2.00-7.00]	5[3.00-7.00]	0.554
Pheripheral blood cells profile			
Hemoglobin (g/dL)	10.6(2.8)	10.2(1,9)	0.316
Leukocytes (109/L)	17.8[6.2-24.1]	15.9[9.6-29.0]	0.459
Neutrophils (109/L)	15.7[5.2-21.7]	12.6[8.0-25.8]	0.532
RDW-CV (%)	14.8[13.7-16.4]	15.6[14.4-17.2]	0.050
NLR	15.5[8.8-27.9]	16.6[9.9-30.1]	0.484
SII Index	2095.4[1202.5-4162.6]	3823.9[1375.7-6250.0]	0.048
Laboratory values			
Albumin (g/dL)	2.2(0.6)	2.2(0.5)	0.617
Creatinine (mg/dL)	1.9[1,2-3.5]	1.97[1.4-3.7]	0.482
C Reactive Protein (mg/L_)	221.3(93.3)	226.2(106.1)	0.809
Procalcitonin (mcg/L)	20.5[9.0-39.0]	13.0[7,5-29.6]	0.362
Pv-aCO2 (mmHg)	7.0[5.0-9.0]	6[4.0-7.0]	0.011
Clinical Data			
MDR bacterial etiology of septic shock nr.(%)	8(17.3)	17(30.3)	0.167
ICU length of stay (days)	5.5[2.0-13.2]	7.0.0[4.0-13.0]	0.066
Mortality at 28-days nr.(%)	35(76.1)	35(62.5)	0.198

tients with late septic shock [OR=1.773 (95% CI=0.302-1.053);p=0.072)], followed by patients without septic shock [OR=1.626 (95% CI=0.338-1.117);p=0.110)] and patients with early septic shock [OR=1.520 (95% CI=0.266-1.615);p=0.359)].

The SII index is a significant independent variable in the prediction of death at 28 days in critically ill non-septic patients [OR=1.002(95% CI=0.998-1.000);p=0.041)], but the Inotropic Vasoactive Inotropic Score shows a relatively low value in predicting death in any of the

Tabel III.Predictors of mortality in the studied groups

Variable	Early septic shock (n=46)		Late septic shock (n=56)		Critically ill non septic (n=42)	
	Odd Ratio (95%CI)	P value	Odd Ratio (95%CI)	P value	Odd Ratio (95%CI)	P value
Age	1.040(0.916-1.182)	0.543	1.051(0.970-1.139)	0.222	1.005(0.909-1.087)	0.929
Female gender	1.176(0.067-20.721)	0.912	6.896(0.016-0.794)	0.026	2.267(0.042-4.631)	0.495
mNUTRIC Score	1.520(0.266-1.615)	0.359	1.773(0.302-1,053)	0.072	1.626(0.338-1.117)	0.110
SII Index	1.001(1.000-1.002)	0.124	1.000(1.000-1.000)	0.513	1.002(0.998-1.000)	0.041
VIS	1.022(0.941-1.016)	0.253	1.011(0.971-1.007)	0.390	1.025(0.937-1.015)	0.224
RDW-CV	1.460(0.380-1.224)	0.199	1.007(0.739-1,373)	0.965	1.127(0.494-1.593)	0.689
NLR	1.024(0.870-1.095)	0.675	1.011(0.960-1.085)	0.682	1.205(0.990-1.466)	0.062
Pv-aCO2	1.736(0.324-1.021)	0.059	1.077(0.721-1.194)	0.560	1.010(0.125-1.352)	0.950
MDR etiology/carriage	6.756(0.005-4.335)	0.267	3.594(0.453-28.510)	0.226	3.989(0.278-57.216)	0.309

subgroups studied. Looking at peripheral blood cells, an increase in RDW-CV showed a potential for predicting mortality in the early-onset septic shock subgroup [OR=1.460(95%CI=0.380-1.224);p=0.199)] and in critical non-septic shock [OR=1.127(95%CI=0.494-1.593); p=0.689)]. The increase in NLR is more predictive of mortality in non-septic critically ill patients [OR=1.205 (95%CI=0.990-1.466); p=0.062)] than in those with late [OR=1.101 (95%CI=0.960-1.085); p=0.682)] or early [OR=1.024 (95%CI=0.870-1.095); p=0.675)] septic shock. The predictive value of increased venous-arterial CO_2 difference (Pcv-aCO2) for mortality is highest in patients with early septic shock [OR=1.736 (95%CI=0.324-1.021); p=0.059)], followed by late septic shock [OR=1.077 (95%CI=0.721-1.194); p=0.560)]. MDR sepsis predicted mortality in both early [OR=6.756(95% CI=0.005-4.335); p=0.267)] and late [OR=3.594 (95% CI=0.453-28.510); p=0.226)] septic shock patients. MDR bacterial carriage on ICU admission also predicts mortality in non-septic critically ill patients [OR=3.989 (95%CI=0.278-57.216); p=0.309]. Receiving antibiotic therapy in the last 14 days prior to ICU admission is a strong predictor of mortality in patients with late septic shock [OR=6.250 (95%CI=0.023-1109); p=0.064)], in patients without septic shock [OR=4.081(95% CI=0.180-3.346); p=0.292)] and to a lesser extent in patients with early septic shock [OR=1.139 (95%CI=0.180-72.252); p=0.951)].

Discussions

This prospective exploratory pilot study aimed to identify predictors of 28-day mortality in patients with early septic shock admitted from the ED and late septic shock hospitalised for more than 48 hours. Mortality at 28 days was not significantly different between critically ill septic and non-septic patients, or between the two septic subgroups (early or late). A meta-analysis by Vicent JL et al. claims that overall mortality from septic shock may be as high as 52% at 28/30 days in ICU patients with septic shock defined by Sepsis-3 criteria [14]. Other studies have shown that all-cause mortality in ICU patients in the first 28 days after admission is closely related to the presence of sepsis and/or the presence of three or more organ dysfunctions, regardless of the cause of their occurrence [15,16]. Septic shock patients in our study were older and sicker than non-septic shock patients, as shown by a significant increase in severity scores. This may explain the higher overall 28-day mortality than reported in previous studies.

Decreased serum albumin concentration in septic shock patients is reflected in changes in certain prognostic ratios or scores correlated with short-term mortality [17]. Biomarkers of infection and inflammatory response represented by procalcitonin and C-reactive proteine, metabolic and organ dysfunction represented by albumin, blood urea nitrogen, creatinine, are strongly associated with the severity of organ dysfunction and mortality [18]. In our study, all these parameters were significantly altered when septic shock patients entered the ICU compared to critically ill non-septic patients. The relationship between the timing of the onset of septic shock and the subsequent outcome has been a topic of ongoing debate and remains incompletely understood.

Sakr and colleagues showed that patients who develop late septic shock have more severe organ dysfunction, higher dopamine requirements, and higher mortality [9]. Roman-Marchant et al. found that septic shock with ICU onset less than 24 hours is associated with more severe organ dysfunction, higher vasopressor requirements, but shorter hospital stay and slightly lower mortality than septic shock with onset more than 24 hours after ICU admission [6].

In our study, the use of vasopressors during ICU admission was also significantly higher in the septic group than in the critical nonseptic group, but the ability to predict mortality was not statistically significant between the groups. In a retrospective study in which septic shock mortality reached 57%, Huang et al. suggest that time of septic shock onset is an independent predictor of in-hospital outcome [7]. In another retrospective study, Sato et al. showed that the risk of mortality in patients with septic shock represents a „temporal continuum" in relation to the time of admission, with mortality increasing gradually over time [10]. In our regression analysis model, patient age was not significant in predicting mortality. Women with late septic shock had a higher risk of mortality than those with non-septic shock and those in the early septic shock subgroup.

Furthermore, a recent study found that the risk of death among older women with critical illness is multifactorial [19]. The mNUTRIC score has been shown to be an effective predictor of all-cause mortality in critically ill patients and at 28 days in patients with sepsis [20], findings that were confirmed in our study in septic and non-septic critically ill patients. The immunoinflammatory index was identified as a significant predictor of mortality in patients with late-onset shock and in nonseptic critically ill patients.

Altered ratios of peripheral blood cellular elements, represented by widened RDW-CV and increased NLR, are more significant in septic shock patients compared to non-septic critically ill patients. These results are in line with recent studies that have correlated all-cause mortality in septic shock patients [21-22]. We found that the increase in RDW-CV was an indicator of mortality in both the early septic shock subgroup and the critical non-septic cohort, in agreement with previous studies. In our study, in the non-septic critically ill group, the NLR value was recorded to predict mortality. This agrees with previous research where NLR was shown to be effective in predicting progression to septic shock and late mortality as shown in a previous study [12]. The difference between venous and arterial carbon dioxide (Pcv-aCO_2), considered a surrogate marker of cardiac index and tissue perfusion (23), was predictive of 28-day mortality in our patients with early septic shock. The MDR aetiology of septic shock has been shown to be a strong predictor of morbidity and mortality in our septic shock patients in both subgroups. This is strongly supported by the literature [3,24]. In addition, MDR carrier status in critically ill non-septic patients is a predictor of 28-day mortality on admission. This is a warning sign that these patients are likely to develop serious infections during their hospital stay.

Our study has strengths. As a prospective pilot study, it may suggest directions for future research to identify new predictors of outcome for categories of sepsis and septic shock with time-sensitive onset. Comparison of predictors between critically ill septic and non-septic patients may contribute to the identification of common risk predictors and specific short-term mortality predictors.

Our study had several limitations. The pilot study was conducted in small groups of patients at a single medical center. The management of patients in the admission areas was the responsibility of physicians of other specialties than intensivists, in accordance with local hospital protocols. In some cases, patients were admitted to the intensive care unit (ICU) under particularly difficult conditions due to a lack of ICU beds.. Also, the short follow-up of the outcome is an important limitation of the study.

Conclusions

An elevated mNUTRIC score and an MDR bacterial aetiology/carrier status have been identified as common predictors of 28-day mortality after admission to the ICU in critically ill patients with both septic shock and non-septic conditions. In patients with early-onset septic shock, central venous-arterial carbon dioxide difference (Pcv-aCO_2) and RDW-CV widening were predictors of 28-day mortality. Older age, female gender, increased vasoactive demand and increased NLR were predictors of mortality in patients with late septic shock admitted to the ICU. Predictors of 28-day mortality in critically ill patients without septic shock at the time of ICU admission were older age, female sex, increased inflammatory status, increased vasoactive demand, widening RDW-CV, increased NLR and MDR carrier status.

Authors' contribution

IDB (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)
CP (Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization)
MON (Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization)
CB (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)
MOB (Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization, Writing – original draft)
EIH (Data curation; Formal analysis, Software, Visualization,)
CIP (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)

Conflict of interest

None to declare

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(8):801-10.
2. Vincent JL, Sakr Y, Singer M, et al. EPIC III Investigators. Prevalence and Outcomes of Infection Among Patients in Intensive Care Units in 2017. JAMA. 2020 Apr 21;323(15):1478-1487.
3. Rosenthal VD, Yin R, Lu Y et al. The impact of healthcare-associated infections on mortality in ICU: A prospective study in Asia, Africa, Eastern Europe, Latin America, and the Middle East. Am J Infect Control. 2023 Jun;51(6):675-682.
4. Rosenthal VD, Yin R, Valderrama-Beltran SL, et al. Multinational Prospective Cohort Study of Mortality Risk Factors in 198 ICUs of 12 Latin American Countries over 24 Years: The Effects of Healthcare-Associated Infections. J Epidemiol Glob Health. 2022 Dec;12(4):504-515.
5. Sakr Y, Vincent JL, Schuerholz T, et al. Early- versus late-onset shock in European intensive care units. Shock. 2007 Dec;28(6):636-643.
6. Roman-Marchant O, Orellana-Jimenez CE, De Backer D, et al. Septic shock of early or late onset: does it matter? Chest. 2004 Jul;126(1):173-8.
7. Huang CT, Tsai YJ, Tsai PR, et al. Severe Sepsis and Septic Shock: Timing of Septic Shock Onset Matters. Shock. 2016 May;45(5):518-24.
8. Ahn YH, Lee J, Oh DK, et al. Korean Sepsis Alliance (KSA) Investigators.

Association between the timing of ICU admission and mortality in patients with hospital-onset sepsis: a nationwide prospective cohort study. J Intensive Care. 2023 Apr 21;11(1):16.

9. Ginestra JC, Coz Yataco AO, Dugar SP, Dettmer MR. Hospital-Onset Sepsis Warrants Expanded Investigation and Consideration as a Unique Clinical Entity. Chest. 2024 Jun;165(6):1421-1430.
10. Sato R, Dugar S, Han X, et al. A. TIME FROM HOSPITAL ADMISSION TO ONSET OF SEPTIC SHOCK IS ASSOCIATED WITH HIGHER IN-HOSPITAL MORTALITY. Shock. 2022 Sep 1;58(3):211-216.
11. Wu H, Cao T, Ji T, et al. Predictive value of the neutrophil-to-lymphocyte ratio in the prognosis and risk of death for adult sepsis patients: a meta-analysis. Front Immunol. 2024 Mar 18;15:1336456.
12. Botoş ID, Pantiş C, Bodolea Cet al. The Dynamics of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios Predict Progression to Septic Shock and Death in Patients with Prolonged Intensive Care Unit Stay. Medicina (Kaunas). 2022 Dec 23;59(1):32.
13. Bacârea A, Coman O, Bacârea VC, et al. Immune profile of patientsa new approach in management of sepsis and septic shock? Exp Ther Med. 2024 Mar 15;27(5):203.
14. Vincent JL, Jones G, David S. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Crit Care. 2019 May 31;23(1):196.
15. Mezzaroba AL, Larangeira AS, Morakami FK, et al. Evaluation of time to death after admission to an intensive care unit and factors associated with mortality: A retrospective longitudinal study. Int J Crit Illn Inj Sci. 2022 Jul-Sep;12(3):121-126.
16. Martin-Loeches I, Wunderink RG, Nanchal R, et al. Determinants of time to death in hospital in critically ill patients around the world. Intensive Care Med. 2016 Sep;42(9):1454-60.
17. Kendall H, Abreu E, Cheng AL. Serum Albumin Trend Is a Predictor of Mortality in ICU Patients With Sepsis. Biol Res Nurs. 2019 May;21(3):237-244.
18. Li S, Shen Y, Chang B, Wang N. Prognostic Value of Albumin-to-Fibrinogen Ratio for 28-Day Mortality among Patients with Sepsis from Various Infection Sites. Mediators Inflamm. 2022 Aug 10;2022:3578528.
19. Todorov A, Kaufmann F, Arslani K, et al. Swiss Society of Intensive Care Medicine. Gender differences in the provision of intensive care: a Bayesian approach. Intensive Care Med. 2021 May;47(5):577-587. doi: 10.1007/s00134-021-06393-3.
20. Jeong DH, Hong SB, Lim CM, et al. Comparison of Accuracy of NUTRIC and Modified NUTRIC Scores in Predicting 28-Day Mortality in Patients with Sepsis: A Single Center Retrospective Study. Nutrients. 2018 Jul 17;10(7):911.
21. Li X, Chen Y, Yuan Qet al. Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio associated with 28-day all-cause mortality in septic patients with coronary artery disease: a retrospective analysis of MIMIC-IV database. BMC Infect Dis. 2024 Jul 29;24(1):749.
22. Conway R, Byrne D, O'Riordan D et al.Red Cell Distribution Width as a Prognostic Indicator in Acute Medical Admissions. J Clin Med. 2023 Aug 21;12(16):5424.
23. Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please "mind the gap"! Intensive Care Med. 2013 Sep;39(9):1653-5.
24. Bassetti M, Carnelutti A, Peghin M. Patient specific risk stratification for antimicrobial resistance and possible treatment strategies in gram-negative bacterial infections. Expert Rev Anti Infect Ther. 2017 Jan;15(1):55-65.