

# The six scoring systems' prognostic value in predicting 24-hour mortality in septic patients

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**Abstract. – OBJECTIVE:** The use of scoring systems contributes to the faster identification of septic patients, especially those at a high risk of a fatal outcome. The best scoring system does not exist, so the search for the optimal one is always current. The aim of this study is to estimate the prognostic value of the six scoring systems in predicting 24-hour mortality among septic patients presented at the emergency department.

**PATIENTS AND METHODS:** An observational retrospective study was conducted in the Emergency Triage Room (ETR) of the Emergency Center (EC) at the University Clinical Center of Serbia (UCCS) in Belgrade. Consecutive septic patients, according to the Sepsis-3 definition, with or without shock, presented to the ETR and then hospitalized in Intensive Care Units were included in the study. Mortality data within 24 h and on the 28<sup>th</sup> day were extracted from the Hospital information system or the National mortality database. Scoring systems including sequential organ failure assessment (SOFA), quick sequential organ failure assessment (qSOFA), systemic inflammatory response syndrome (SIRS), National early warning score (NEWS), sepsis patient evaluation in the emergency department (SPEED), and mortality in emergency department sepsis (MEDS) were analyzed for all patients utilizing the available data. The primary outcome of this study was death within 24 hours of triage. Receiver operating characteristic (ROC) analysis was used to determine the most effective scoring system. Lactate was then added to this system to enhance its predictive accuracy.

**RESULTS:** Nineteen out of 120 patients included in the study (15.8%) experienced death within 24 hours of triage. The twenty-eight-day mortality rate was 55%. SOFA score demonstrated the highest predictive value for 24-hour mortality but was only moderately predictive overall, with an area under the receiver operat-

ing curve (AUC) of 0.755 (95% CI 0.625-0.885). SPEED, MEDS, and NEVS exhibited modest discriminatory power [0.673 (95% CI 0.543-0.803), 0.665 (95% CI 0.536-0.794), 0.630 (95% CI 0.528-0.724)], while SIRS and qSOFA remained insignificant in predicting 24-hour mortality. The predictive value of the SOFA score was increased by the addition of lactate (AUC 0.865, 95% CI 0.736-0.995;  $p=0.0081$ ). All scores demonstrated better and satisfactory predictive power for 28-day mortality.

**CONCLUSIONS:** SOFA, with the addition of lactate, is a complex but reliable tool for the early stratification of septic patients who are presenting at an emergency department.

*Key Words:*

Sepsis, Scoring system, Emergency department, Lactate.

## Introduction

Sepsis is a life-threatening medical emergency caused by a dysregulated host's response to infection<sup>1</sup>. It implies organ dysfunction and can be complicated by septic shock<sup>2</sup>. Septic patients require admission to the intensive care unit and have a high risk of death<sup>3</sup>. Therefore, understanding the predictive mortality factors in these patients helps in the quick identification of the critically ill and the timely initiation of therapy.

The initial phase of resuscitation, which consists of fluid administration, vasopressor initiation, and antimicrobial therapy in these patients, should be started immediately<sup>1</sup>. Crystalloids should be administered promptly to correct tissue hypoperfusion in septic patients. However, three questions arise: which crystalloids, how many

crystalloids, and how to monitor the response to crystalloids? According to the Surviving Sepsis Campaign (SSC)<sup>1</sup>, balanced crystalloids have an advantage because they are associated with a smaller number of cases of acute kidney injury<sup>4</sup> and decreased mortality with their use<sup>5</sup>, but the BaSICS study<sup>6</sup> did not confirm this. Additionally, the SSC states that 30 ml/kg should be administered in the first three hours as a bolus, but it is unclear how to proceed with fluid resuscitation. Regardless of the type of crystalloids used, it is clear that fluid administration should be optimized to avoid over- or under-resuscitation, as both conditions make it impossible to maintain adequate tissue perfusion. Considering the fact that one-third of patients are unresponsive to fluid administration, fluid resuscitation should be individualized in the optimization phase in accordance with the patient's responsiveness<sup>7</sup>.

Static parameters such as systolic pressure, heart rate, mean arterial pressure, diuresis, and skin mottling are widely used in emergency departments (ED), but their prognostic value for fluid responsiveness is unreliable. Bedside echocardiography can rapidly provide information about hemodynamic status, especially regarding cardiac output, and it is suitable when the source of hemodynamic disorder is unknown<sup>7</sup>. Lactate levels are suggested by the SSC for this assessment, as well as capillary refill time<sup>1</sup>. Dynamic parameters such as central venous oxygen saturation or mixed venous oxygen saturation provide much more data than static indices<sup>7</sup>. Pulse pressure variation, stroke volume variation, and systolic pressure variation are more accurate in predicting fluid responsiveness, especially in mechanically ventilated patients with regular cardiac rhythm<sup>8</sup>. Understanding these parameters, especially the dynamic ones, their advantages, and limitations allows for better management of fluid resuscitation along the thin line between over- and under-resuscitation of septic patients.

Timely initiation of vasopressors is the next crucial step in the initial management of septic patients. Although it may seem logical to initiate vasopressors after full-volume resuscitation, recent studies<sup>9,10</sup> have shown that early initiation is safe and associated with lower mortality. A diastolic blood pressure (DAP)  $\leq 45$  mmHg and a diastolic shock index (DSI), which represents the ratio between heart rate and DAP  $\geq 2$ , suggest severe vasodilatation, indicating the need for vasopressor initiation<sup>11</sup>. Additionally, the combination of lactate levels and DSI serves as a useful

tool for guiding the initiation of vasopressors<sup>12</sup>. It is well-established that the first vasopressor suggested by the Surviving Sepsis Campaign (SSC) is norepinephrine, followed by vasopressin<sup>1</sup>.

Finally, the administration of broad-spectrum antibiotics is recommended by SSC, ideally within the first hour of recognition in patients with possible septic shock and within the first 3 hours in patients with sepsis without shock<sup>1</sup>. Any delay in antimicrobials therapy is associated with an increased risk of death<sup>13,14</sup>. Thus, antibiotics should be given as early as possible. Nevertheless, only the appropriate antibiotic reduces mortality<sup>15</sup>, and the experience of the doctor and their knowledge of the epidemiological landscape at the given moment, as well as the organization of the hospital and the availability of certain antibiotics in the emergency department, play a crucial role in the initial care of septic patients.

The scoring system usage contributes to the faster identification of septic patients, especially those at a high risk of a fatal outcome. SOFA score became a part of the Sepsis-3 definition<sup>16</sup>, according to which acute change by 2 or more points suggests organ dysfunction and is associated with a 10% increase in in-hospital mortality. Due to its complexity, we have less utility of SOFA score in busy emergency departments compared to the intensive care units. Also, the comorbidities in septic patients elevated initial SOFA score and thus complicate the interpretation of the findings. On the other hand, initial higher SOFA score values suggest higher 28-day mortality with better prognostic accuracy than qSOFA and SIRS<sup>17</sup>. Quick SOFA was derived from The Third International Sepsis Consensus in 2016<sup>16</sup> and was validated by Seymour et al<sup>18</sup>. Compared to SIRS, qSOFA is less reliable for screening septic patients<sup>19</sup>. Therefore, current recommendations<sup>1</sup> of the Surviving Sepsis Campaign (SSC) are against using qSOFA as a single-screening tool for sepsis or septic shock. Nevertheless, qSOFA has better mortality prediction than SIRS<sup>19</sup>.

Diagnostic scoring systems for sepsis, such as SIRS and NEWS, aim to quickly "rule in/rule out" sepsis among patients in the emergency department<sup>20-22</sup>. However, SIRS score is not a part of the Sepsis-3 definition because it is too sensitive and nonspecific<sup>20</sup> while NEWS is part of the current SSC recommendations<sup>1</sup>.

Developed for use in the emergency departments, prognostic scoring systems, SPEED and MEDS have shown moderate to good accuracy in predicting mortality in septic patients in pre-

vious studies<sup>23-25</sup>. Band proportion is a part of the MEDS score, and it is often difficult to obtain in the emergency department which is why "abbreviated MEDS" is mostly used with similar accuracy<sup>25</sup>. Abbreviated MEDS was also used in this research.

Therefore, the best scoring system does not exist, so the search for the optimal is always current. To the best of our knowledge, there are only a few papers dealing with 24-hour outcomes of septic patients. Also, there have been a few studies comparing the effectiveness of established scoring systems in predicting early death, namely death within 24 h of triage. In light of this, the goal of this study is to estimate the prognostic value of six scoring systems in predicting 24-hour mortality among septic patients presenting at an internal and surgery emergency department.

## Patients and Methods

An observational retrospective study was conducted in the Emergency Triage Room (ETR) of the Emergency Center (EC) at the University Clinical Center of Serbia (UCCS) in Belgrade. It is the tertiary and largest Emergency Center in Serbia, with approximately 190,000 annual visits. ETR is the youngest department in EC, established two years ago, where emergency physicians are employed. Surviving Sepsis Campaign (SSC) Recommendations<sup>1</sup> are followed in the initial management of septic patients, but scoring systems for early patients' stratification are not used. A total of 120 consecutive patients with sepsis, according to the Sepsis-3 definition<sup>16</sup>, with or without shock, were included in the study from January 1<sup>st</sup>, 2023, to June 30<sup>th</sup>, 2023. All patients were initially admitted to the ETR and then hospitalized in one of the Intensive Care Units of the EC. Exclusion criteria were age under 18, pregnant women, and patients transferred from other hospitals where they had been treated for infection or sepsis. All demographic and clinical characteristics, as well as vital parameter values, for the patients included in the study, were retrieved from the Hospital information system (HIS). Mortality data within 24 h and on the 28<sup>th</sup> day were also extracted from the Hospital information system or from the National Mortality Database (electronic National Mortality Database - eNMD).

The primary outcome of this study was 24-hour mortality. Data were gathered from the HIS and eNMD and converted into numerical codes, or-

ganized in tables, and then checked for errors. The following data were collected: age, gender, presence of shock, fever, entering site of infections, white blood cell (WBC) count, hemoglobin (Hgb), platelets (PLT), serum glucose (Gly), serum urea (sUr), serum creatinine (sCr), sodium (Na), potassium (K), aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), procalcitonin (PCT), oxygen saturation (sO<sub>2</sub>), mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), partial pressure of oxygen (pO<sub>2</sub>), lactate level (Lac), bicarbonate level (HCO<sub>3</sub>), Glasgow Coma Scale (GCS), time to admission (TTA), use of vasopressors, respiratory deterioration (RespD), mental deterioration (MentD).

## Statistical Analysis

The scoring systems, including SOFA, qSOFA, SIRS, NEWS, SPEED, and MEDS, were manually computed for all patients utilizing the available data. Descriptive statistics were employed to characterize the data, with mean, median, standard deviation, and interquartile range used for continuous data, and frequencies and percentages used for categorical data.

A comparative analysis was undertaken to evaluate the difference in mean/median values of various laboratory and clinical parameters between individuals who experienced mortality within the first 24 hours and those who did not. To account for the assumption of normality, both the *t*-test and Mann-Whitney test were employed for continuous data, and the Chi-square test was utilized for categorical data.

Receiver Operating Characteristic (ROC) curve analysis was conducted to determine the most effective scoring systems for predicting 24-hour mortality. Following the identification of the optimal system, lactate was integrated into the model to assess its potential to improve prognostic accuracy. The threshold for statistical significance was set at 0.05 ( $p < 0.05$ ). Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) and MedCalc v19.6.3 (MedCalc Software, Mariakerke, Belgium).

## Results

The mean age of the patients was 70.48±13.33, with 64 (53.3%) of them being male. Two thirds of patients were older than 65 (66.67%) and those older than 85 were 12.5%. Also, less than 11% of

participants were under the age of 55. Of all 120 participants, 15.8% experienced death within 24 h, and 55% of patients died by the 28<sup>th</sup> day. The baseline characteristics of the study group are summarized in Table I.

The comparative analysis showed that patients who experienced death within both 24 hours and 28 days commonly had lower MAP, pH, and HCO<sub>3</sub> levels. Patients who died in the first 24 hours also had higher Lac (6.784±3.6734 vs.

**Table I.** Baseline characteristics of patients.

Variable	Mean±SD (median, IQR) or n (%)
Age	70.48±13.33 (71.00, 19.00)
Gender	
Male	64 (53.3%)
Shock	45 (37.5%)
Fever	
No fever	91 (75.8%)
Subfebrile	17 (14.2%)
Febrile	12 (10.0%)
Entering site of infection	
Urinary tract	32 (38.1%)
Respiratory tract	18 (21.4%)
Gastrointestinal tract	21 (25.0%)
Skin	11 (13.1%)
Other	2 (2.4%)
AVPU	
A	85 (70.8%)
V	21 (17.5%)
P	14 (11.7%)
U	0 (0%)
WBC	18.708±12.3155 (15.95, 13.80)
Hgb	113.71±29.930 (113.00, 40.00)
Plt	194.57±132.534 (170.00, 138.00)
Gly	9.46±7.5225 (7.20, 4.90)
sUr	113.71±29.930 (113.00, 40.00)
sCr	306.9667±258.60690 (249.00, 286.25)
Na	137.21±7.359 (137.00, 7.00)
K	5.850±12.2384 (4.200, 1.5)
AST	201.63±740.068 (45.00, 64)
ALT	137.38±521.716 (25.00, 35)
CRP	253.738±121.6749 (252.000, 179.6)
PCT	36.1895±60.03667 (12.6800, 40.84)
sO <sub>2</sub>	91.58±8.132 (94.50, 7.00)
MAP	75.30±22.018 (71.50, 33.00)
HR	100.58±22.655 (100.00, 24.00)
RR	22.96±3.973 (22.00, 6.00)
pH	7.3248±0.18176 (7.3850, 0.24)
pO <sub>2</sub>	10.4050±8.87143 (8.5950, 3.69)
Lac	4.141±3.0648 (3.400, 3.4)
HCO <sub>3</sub>	18.845±6.4457 (20.000, 9.0)
GCS	13.47±2.226 (15.00, 3)
TTA	5.616±4.3691 (4.250, 4.3)
Vasopressor	46 (38.3%)
RespD	62 (52.1%)
MentD	64 (53.8%)
Death 24 h	19 (15.8%)
Death 28 d	66 (55.0%)

AVPU – AVPU scale; A – awake; V – reacts to voice; P – reacts to pain; U – unresponsive; WBC – white blood cells; Hgb – hemoglobin; PLT – platelets; Gly – serum glucose; sUr – serum urea; sCr – serum creatinine; Na – sodium; K – potassium; AST – aspartate aminotransferase; ALT – alanine aminotransferase; CRP – C-reactive protein; PCT – procalcitonin; sO<sub>2</sub> – oxygen saturation; MAP – mean arterial pressure; HR – heart rate; RR – respiratory rate; pO<sub>2</sub> – partial pressure of oxygen; Lac – lactate level; HCO<sub>3</sub> – bicarbonate level; GSC – Glasgow coma scale; TTA – time to admission; RespD – respiratory deterioration; MentD – mental deterioration.

3.644±2.6780) prolonged TTA (5.975±4.4731 vs. 3.565±3.0838), and more frequently experienced shock (57.9% vs. 33.7%). For patients who died within 28 days, increased age (73.26±11.307 vs. 67.02±14.884), sUr, sCr, RR, and lower GCS were observed. These patients were also more likely to have respiratory tract infections (34.9% vs. 7.3%). The variables that demonstrated statistically significant differences between the two groups are presented in detail in **Supplementary Table I**.

The SOFA score showed the best discriminatory power. SPEED, MEDS, and NEWS scores had moderate to modest predictive value, while SIRS and the qSOFA scores remained insignificant in predicting 24-hour mortality (Figure 1 and Table II).

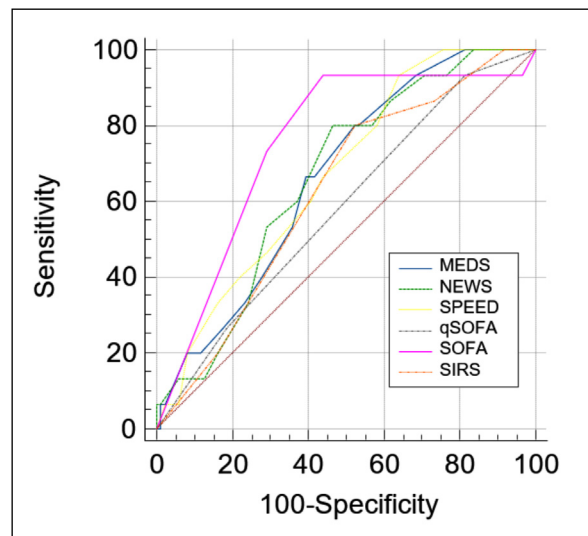
The Youden criterion for lactate is set at 3.8 mmol/l, as determined through ROC curve analysis. A composite variable named SOFA+LAC was created to analyze improvement with the addition of lactate to the SOFA score. In the construction of SOFA+LAC, the lactate variable was transformed to zero for values below 3.8 mmol/l and to one for values equal to or higher than 3.8 mmol/l. Furthermore, the SOFA score was categorized into six groups, as illustrated in Table III.

The addition of lactate significantly improves the ability of the SOFA score to predict 24-hour mortality (Figure 2 and Table IV).

Regarding 28-day mortality, the scoring systems showed sensitivities and specificities, as shown in Figure 3.

All scores demonstrated satisfactory predictive power for 28-day mortality. The best predictive value is the SOFA score (Table V).

The Youden criterion for lactate is set at 3.2 mmol/l, as determined through ROC curve analysis. The composite variable was created as in the 24 h mortality prediction analysis.



**Figure 1.** ROC curve 24 h mortality. SIRS – systemic inflammatory response syndrome; qSOFA – quick sequential organ failure assessment; SOFA – sequential organ failure assessment; NEWS – National early warning score; SPEED – sepsis patient evaluation in the emergency department; meds – mortality in emergency department sepsis.

**Table II.** AUC of scoring systems in the prediction of 24-hour mortality.

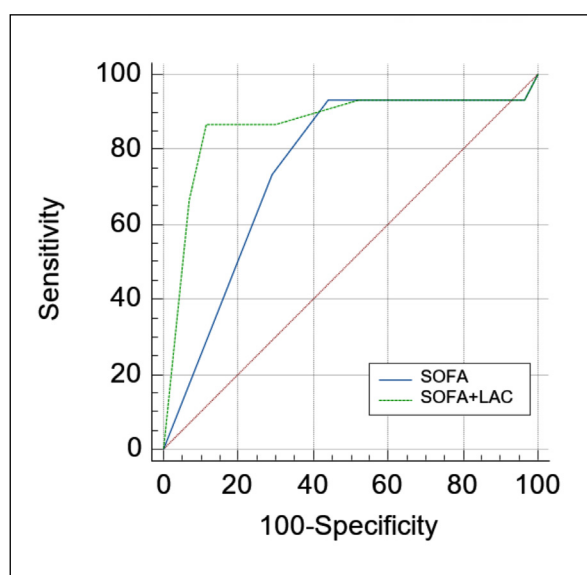
	AUC (95% CI)	Sig.
SIRS	0.626 (0.487-0.765)	.121
qSOFA	0.583 (0.433-0.733)	.307
SOFA	0.755 (0.625-0.885)	.000
NEWS	0.630 (0.528-0.724)	.043
SPEED	0.673 (0.543-0.803)	.033
MEDS	0.665 (0.536-0.794)	.042

SIRS – systemic inflammatory response syndrome; qSOFA – quick sequential organ failure assessment; SOFA – sequential organ failure assessment; NEWS – National early warning score; SPEED – sepsis patient evaluation in the emergency department; meds – mortality in emergency department sepsis.

**Table III.** Improvement in specificity of SOFA when lactate ≥3.8 mmol/l.

	SOFA		SOFA+LAC	
	Sensitivity	Specificity	Sensitivity	Specificity
0-1	100.0	0.0		
2-3	93.3	3.5		
4-5	93.3	14.0	86.7	69.8
6-7	93.3	27.9	86.7	74.4
8-9	93.3	39.5	86.7	80.2
10-11	93.3	55.8	86.7	88.4
12+	73.3	70.9	66.7	93.0

SOFA – sequential organ failure assessment; LAC – lactate.

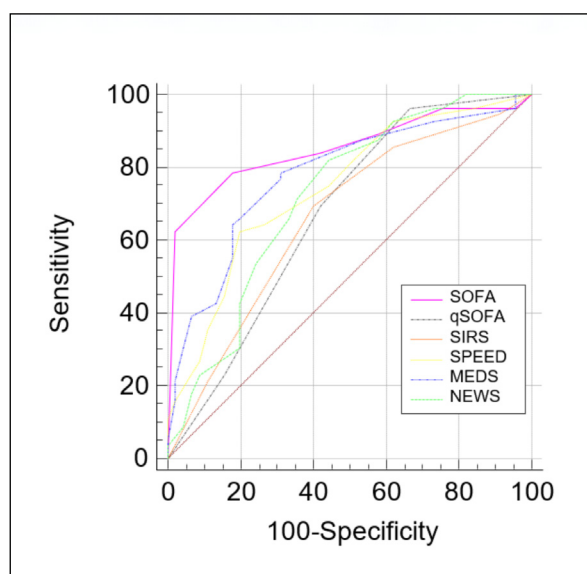


**Figure 2.** ROC curve 24-h mortality SOFA and SOFA+LAC. SOFA – sequential organ failure assessment; LAC – lactate.

**Table IV.** AUC of SOFA and SOFA+LAC in predicting 24-h mortality.

	95% CI	Sig.
SOFA	0.755 (0.625-0.885)	0.002
SOFA+LAC	0.865 (0.736-0.995)	0.000
Difference between areas 0.110, $p=0.0081$ .		

SOFA – sequential organ failure assessment; LAC – Lactate.



**Figure 3.** ROC curve 28-day mortality.

**Table V.** AUC of scoring systems in the prediction of 28-day mortality.

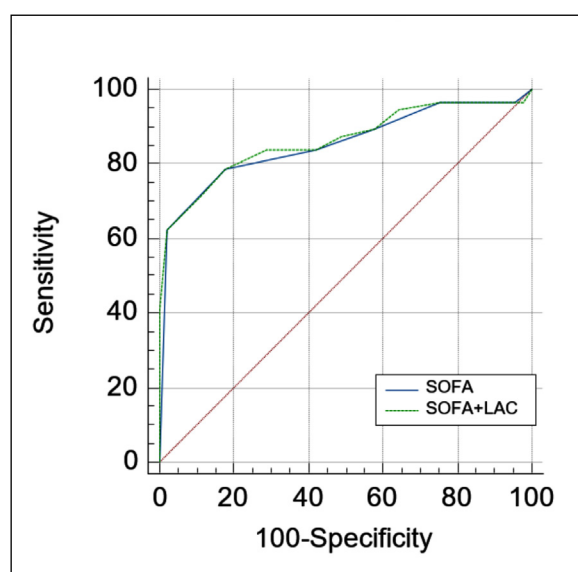
Variable	AUC (95% CI)	Sig.
SOFA	0.852 (0.767-0.915)	0.000
qSOFA	0.672 (0.572-0.762)	0.003
SIRS	0.663 (0.562-0.754)	0.005
SPEED	0.745 (0.648-0.826)	0.000
MEDS	0.779 (0.685-0.855)	0.000
NEWS	0.721 (0.619-0.824)	0.000

SIRS – systemic inflammatory response syndrome; qSOFA – quick sequential organ failure assessment; SOFA – sequential organ failure assessment; NEWS – National early warning score; SPEED – sepsis patient evaluation in the emergency department; meds – mortality in emergency department sepsis.

The predictive value of the composite variable SOFA+LAC is not significantly higher than the SOFA score itself in terms of 28-day mortality (Figure 4).

### Discussion

Our study confirmed that scoring systems, particularly the SOFA score, are powerful tools in predicting 24-hour mortality in septic patients presenting in the emergency department. Additionally, the inclusion of lactate further enhanced the predictive value of the SOFA score. Furthermore, all six scores demonstrated satisfactory predictive power for 28-day mortality.



**Figure 4.** ROC curve 28-day mortality SOFA and SOFA+LAC. SOFA – sequential organ failure assessment; LAC – Lactate.

In this study, 24 h mortality was 15.8%, which is in line with the 9-18% range reported in a previous study<sup>26</sup> although notably higher than in Javed et al<sup>27</sup>'s study, which reported 4.9%.

This discrepancy could be explained by the significantly younger population in their study. In our study, less than 11% of participants were under the age of 55, compared to 34% in their study. Mortality rates tend to increase with age, with individuals over 85 facing a mortality rate five times higher than those aged 65-74<sup>28</sup>. Additionally, our study noted a high proportion (57.9%) of patients in septic shock among those who died within 24 hours. The mortality rate for this subgroup reached up to 60% in the study by Vincent et al<sup>29</sup>.

Furthermore, the 28-day mortality in our study is notably high and stands at 55%. A systematic review and meta-analysis<sup>30</sup>, which included, among others, 19,343 participants from Europe, has shown a mortality rate of 23.58%, which is significantly lower compared to our study. One potential explanation for this discrepancy could be the disparity in healthcare expenditure. According to the World Bank<sup>31</sup>, the estimated healthcare expenditure per capita in Serbia in 2020 was \$672, a figure significantly lower than that of developed European countries. This is consistent with findings from a study by Shrestha et al<sup>32</sup>, which demonstrated that low-income countries tend to have significantly higher mortality rates, with some reaching up to 80% compared to high-income countries.

Finally, TTA was longer for non-survivors: 6 hours (24-hour group) and 6.7 hours (28-day group) vs. 3.6 and 4.6 hours for survivors, respectively. These exceed the SSC recommendations. As the study by Pruinelli et al<sup>33</sup> shows, even a small delay in initial management could have significant survival implications. Early empirical administration of antibiotics has a favorable effect on patient outcomes<sup>13,14</sup>. However, our study did not evaluate the selection of antimicrobial therapy. It is worth noting that inadequate empirical antibiotic therapy due to multi-resistant bacteria increases the risk of death<sup>15</sup>.

SIRS and qSOFA are the simplest scoring systems because they use a few parameters for calculating. In a meta-analysis by Serafim et al<sup>19</sup>, SIRS was significantly superior for sepsis screening and qSOFA was better in predicting hospital mortality<sup>7</sup>. In our study, both scoring systems remained insignificant in predicting 24-hour mortality. We investigated the most severe and most

urgent group of patients who died within 24 h. Their clinical presentation at admission can be different, from non-specific to complex, because sepsis is a clinically heterogeneous syndrome, not only one uniform disease. It is expected that a small number of parameters for calculating the scores (only 3 parameters for qSOFA score) cannot represent this subgroup well enough and cannot give good predictive value in these patients. Also, in SIRS, one parameter is fever, which is a proven protective sign in septic patients<sup>34</sup>. In our study, 75.8% of patients were not febrile. The most urgent septic patients are often anergic and afebrile. Thus, SIRS is not a good tool for this group of patients. While qSOFA has been validated as a predictor of distant mortality, its predictive efficacy diminishes slightly when the prediction window is shorter compared to the findings of Brink et al<sup>35</sup>. In their study, the qSOFA score was less effective than NEWS in predicting 10-day mortality. It is not surprising that qSOFA remains insignificant in the assessment of 1-day mortality, as in our study. It should be emphasized that our study was conducted with a small number of patients and other research with a large volume is needed to confirm this.

On the contrary, the most complex score, the SOFA score, which has less utility in emergency departments, showed the best predictive value of 24-hour mortality in our study but a moderate discriminatory value in general (AUC 0.75 CI 95% 0.625-0.885). Compared to other scores, the SOFA score was significantly better in predicting 24-hour mortality than qSOFA. The initial high value of SOFA score, above 9 (Youden criterion) in this study, categorizes the most severe group of patients at high risk of early death. Javed et al<sup>27</sup> also analyzed SOFA score and reported that modified SOFA is an independent predictor of early 24 h death. Modified SOFA is an adjusted SOFA score excluding the Glasgow coma scale from the calculation.

The discriminatory power of the SOFA score in our study is good to moderate, and in order to improve it, we added an initial lactate level to it. Lactate level at presentation, as well as clearance of lactate, is a predictor of in-hospital mortality<sup>27</sup>. Also, lactate is used routinely in ETR. Following that, a composite variable named SOFA+LAC was used. Improvement of SOFA score with the addition of lactate is significant (AUC SOFA+LAC 0.865; the difference between areas  $p=0.0081$ ). It means that a SOFA score above nine and an initial lactate level above 3.8 mmol/l accurately

identify patients at high risk of early death. Overall, the SOFA score is complex and robust for use in emergency departments, but it has significant prognostic power and can be applied in the ETR in the future without large investments. Also, SOFA+LAC could be a tool for early recognition of the most severe group of septic patients with a high risk of 24-hour death.

Regarding the 28-day mortality, all of the six scoring systems have shown satisfactory predictive value. SOFA score had the best prediction of 28-day mortality (AUC 0.852,  $p=0.00$ ), followed by MEDS, SPEED, and NEWS (AUC 0.779,  $p=0.00$ ; 0.745  $p=0.00$ ; 0.721  $p=0.00$ ). In addition, the SOFA score was significantly better than other scores, except MEDS, in pairwise comparison. Similar results were obtained by Raiht et al<sup>17</sup>, where SOFA had better discriminatory power than SIRS and qSOFA (SOFA AUC 0.75; SIRS AUC 0.58; qSOFA AUC 0.60). SOFA score should be repeated every 24 h, and acute change by two or more points of scores is associated with an increase in mortality. Also, changes in delta SOFA, the difference between the first calculated SOFA and after 24 h or 48 h, correlate with changes in the patient's condition<sup>36</sup>. Repeated calculations of SOFA score are performed after hospitalization in intensive care units. Nevertheless, a high initial SOFA score value reliably represents the severity of the disease of septic patients at presentation. Also, the initial SOFA score is still important in the emergency department and crucial for emergency physicians when recognizing patients with a high risk of death. In support of that, the SOFA score was not improved by the addition of lactate when observing 28-day mortality. That means a good prediction of the SOFA score itself.

Other scores, NEWS, SPEED, and MEDS, showed modest predictive value in predicting 24-hour mortality, with AUC 0.63, 0.673, and 0.0665, respectively. SPEED is more sensitive, followed by MEDS and NEWS, while NEWS is more specific compared to others. Our result is consistent with the study by Innocenti et al<sup>36</sup>, whose estimation of the MEDS score in predicting 24-hour mortality is slightly better but still modest (AUC 0.674, 95% CI 0.633-0.715).

All three scores (NEWS, SPEED, and MEDS) have shown better prediction of 28-day mortality compared to the 24-hour prediction (AUC NEWS 0.721; SPEED 0.745; MEDS 0.779). The MEDS score, in particular, stood out in compar-

ison to the other two. Shankar et al<sup>23</sup> have shown much better discriminatory power of SPEED and MEDS in predicting 28-day mortality than the results in our study [SPEED AUC 0.899 (95% CI 0.847-0.951); MEDS AUC 0.857 (95% CI 0.793-0.92)]. MEDS score is more accurate in predicting the group of patients with a low risk of death<sup>24</sup>. All of our patients were hospitalized in intensive care units with a high mortality percentage, which reflects the severity of the study group. This may partly explain the difference in the predictive value of MEDS but not the difference in SPEED score. Our study is retrospective, and we plan to perform a prospective study with the same six scoring systems in order to have more comparable results.

### Limitations

This study has limitations. First, it was conducted in a single medical center. Second, it has a retrospective design, and bias is possible. Third, the examined group is not large, and further prospective research with a large number of patients is necessary.

### Conclusions

The results of this research show that the SOFA score is the most accurate for assessing 24-hour and 28-day mortality of all scores. By adding lactate levels, the prediction of early death of the SOFA score is significantly enhanced. Other scoring systems investigated in this research (SPEED, MEDS, NEWS) showed modest to moderate prediction of 24-hour and 28-day mortality. SIRS and quick SOFA remained insignificant in this research, especially in predicting 24-hour mortality. A prospective study evaluating these six scoring systems is needed in the future.

### Ethics Approval

The study was approved by the Ethical Committee of the Faculty of Medicine of the University of Belgrade No. 04: 21-UIM-19 on May 05, 2023.

### Informed Consent

All patients admitted to the hospital gave their consent for treatment procedures and the use of their medical data. Data usage from the hospital database was approved by the Institutional Review Board.



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### Availability of Data and Materials

The data and material supporting this study's findings are available upon request to the corresponding author.

### Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

### Authors' Contributions

Each of the authors contributed uniquely and significantly to the conception and design of the study. Djikic Marina, Milenkovic Marija, Stojadinovic Milorad, Miladinovic Tijana, Gujanic Duseca, Milicevic-Nesic Ivana, Uzelac Bojana, Laban Marija helped with the acquisition of data, analysis, and interpretation of data. Markovic Dejan made critical revisions related to the relevant intellectual content of the manuscript, and they supervised the whole process. Markovic Dejan also validated and approved the final version of the article to be published.

## References

- 1) Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, McIntyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belle-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papatthanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med* 2021; 49: e1063-e1143.
- 2) Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M; Sepsis Definitions Task Force. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315: 775-787.
- 3) Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; 395: 200-211.
- 4) Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg* 2012; 256: 18-24.
- 5) Rochwerg B, Alhazzani W, Sindi A, Heels-Andsdell D, Thabane L, Fox-Robichaud A, Mbuagbaw L, Szczeklik W, Alshamsi F, Altayyar S, Ip WC, Li G, Wang M, Wludarczyk A, Zhou Q, Guyatt GH, Cook DJ, Jaeschke R, Annane D; Fluids in Sepsis and Septic Shock Group. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med* 2014; 161: 347-355.
- 6) Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, Lovato WJ, Amêndola CP, Serpa-Neto A, Paranhos JLR, Guedes MAV, Lúcio EA, Oliveira-Júnior LC, Lisboa TC, Lacerda FH, Maia IS, Grion CMC, Assunção MSC, Manoel ALO, Silva-Junior JM, Duarte P, Soares RM, Miranda TA, de Lima LM, Gurgel RM, Paisani DM, Corrêa TD, Azevedo LCP, Kellum JA, Damiani LP, Brandão da Silva N, Cavalcanti AB; BaSICS investigators and the BRICNet members. Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial. *JAMA* 2021; 326: 1-12.
- 7) Suh GJ, Shin TG, Kwon WY, Kim K, Jo YH, Choi SH, Chung SP, Kim WY; Korean Shock Society investigators. Hemodynamic management of septic shock: beyond the Surviving Sepsis Campaign guidelines. *Clin Exp Emerg Med* 2023; 10: 255-264.
- 8) La Via L, Vasile F, Perna F, Zawadka M. Prediction of fluid responsiveness in critical care: Current evidence and future perspective. *Trends in Anaesthesia and Critical Care* 2023; 54: 101316.
- 9) Colon Hidalgo D, Patel J, Masic D, Park D, Rech AM. Delayed vasopressor initiation is associated with increased mortality in patients with septic shock. *J Crit Care* 2020; 55: 145-148.
- 10) Bakker J, Kattan E, Annane D, Castro R, Cecconi M, De Backer D, Dubin A, Evans L, Gong MN, Hamzaoui O, Ince C, Levy B, Monnet X, Ospina Tascón GA, Ostermann M, Pinsky MR, Russell JA, Saugel B, Scheeren TWL, Teboul JL, Vieillard Baron A, Vincent JL, Zampieri FG, Hernandez G. Current practice and evolving concepts in septic shock resuscitation. *Intensive Care Med* 2022; 48: 148-163.
- 11) Ospina-Tascon GA, Teboul JL, Hernandez G, Alvarez I, Sánchez-Ortiz AI, Calderón-Tapia LE,

- Manzano-Nunez R, Quiñones E, Madriñan-Navia HJ, Ruiz JE, Aldana JL, Bakker J. Diastolic shock index and clinical outcomes in patients with septic shock. *Ann Intensive Care* 2020; 10: 41.
- 12) Ammar MA, Ammar AA, Wieruszewski PM, Bissell BD, T Long M, Albert L, Khanna AK, Sacha GL. Timing of vasoactive agents and corticosteroid initiation in septic shock. *Ann Intensive Care* 2022; 12: 47.
  - 13) Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zannotti S, Taiberg L, Gurka D, Kummer A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34: 1589-1596.
  - 14) Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RR, Artigas A, Schorr C, Levy MM. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med* 2014; 42: 1749-1755.
  - 15) Garnacho-Montero J, Ortiz-Leyba C, Herrera-Melero I, Aldabo-Pallas T, Cayuela-Dominguez A, Marquez-Vacaro JA, Carbajal-Guerrero J, Garcia-Garmendia JL. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study. *J Antimicrob Chemother* 2008; 61: 436-441.
  - 16) Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard G, Chiche JD, Cooper-Smith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, Van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315: 801-810.
  - 17) Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, Pilcher DV. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. *JAMA* 2017; 317: 290-300.
  - 18) Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of Clinical Criteria for Sepsis. For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315: 762-774.
  - 19) Serafim R, Gomes JA, Salluh J, Póvoa P. A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of Sepsis and Prediction of Mortality: A Systematic Review and Meta-Analysis. *Chest* 2018; 153: 646-655.
  - 20) Churpek MM, Zdravetz FJ, Winslow C, Howell MD, Edelson DPL. Incidence and Prognostic Value of the Systemic Inflammatory Response Syndrome and Organ Dysfunctions in Ward Patients. *Am J Respir Crit Care Med* 2015; 192: 958-964.
  - 21) Corfield AR, Lees F, Zealley I, Houston G, Dickie S, Ward K, McGuffie C; Scottish Trauma Audit Group Sepsis Steering Group. Utility of a single early warning score in patients with sepsis in the emergency department. *Emerg Med J* 2014; 31: 482-487.
  - 22) Ramdeen S, Ferrell B, Bonk C, Schubel L, Littlejohn R, Capan M, Arnold R, Miller K. The Available Criteria for Different Sepsis Scoring Systems in the Emergency Department—A Retrospective Assessment. *Open Access Emerg Med* 2021; 13: 91-96.
  - 23) Shankar T, Kaeley N, Nagasubramanyam V, Bahurupi Y, Bairwa A, Infimate DJL, Asocan R, Shukla K, Galagali SS. An Evaluation of the Predictive Value of Sepsis Patient Evaluation in the Emergency Department (SPEED) Score in Estimating 28-Day Mortality Among Patients With Sepsis Presenting to the Emergency Department: A Prospective Observational Study. *Cureus* 2022; 14: e22598.
  - 24) Shapiro NI, Howell MD, Talmor D, Donnino M, Ngo L, Bates DW. Mortality in Emergency Department Sepsis (MEDS) score predicts 1-year mortality. *Critical Care Medicine* 2007; 35: 192-198.
  - 25) Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW. Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. *Crit Care Med* 2003; 31: 670-675.
  - 26) Pieroni M, Olier I, Ortega-Martorell S, Johnston B, Welters ID. In-Hospital Mortality of Sepsis Differs Depending on the Origin of Infection: An Investigation of Predisposing Factors. *Front Med (Lausanne)* 2022; 9: 915224.
  - 27) Javed A, Guirgis FW, Sterling SA, Puskarich MA, Bowman J, Robinson T, Jones AE. Clinical predictors of early death from sepsis. *J Crit Care* 2017; 42: 30-34.
  - 28) Kramarow EA. Sepsis-related Mortality Among Adults Aged 65 and Over: United States, 2019. *NCHS Data Brief* 2021; 422: 1-8.
  - 29) Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njimi H, Jimenez E, Sakr Y; ICON investigators. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. *Lancet Respir Med* 2014; 2: 380-386.
  - 30) 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.
  - 31) World Bank. Current health expenditure per capita (current US\$) - Serbia [Internet]. Washington, DC: World Bank; [accessed on Feb 8, 2024].

Available from: <https://data.worldbank.org/indicator/SH.XPD.CHEX.PC.CD?locations=RS>.

- 32) Shrestha GS, Kwizera A, Lundeg G, Baelani JI, Azevedo LCP, Pattnaik R, Haniffa R, Gavrilovic S, Mai NTH, Kissoon N, Lodha R, Misango D, Neto AS, Schultz MJ, Dondorp AM, Thevanayagam J, Dünser MW, Alam AKMS, Mukhtar AM, Hashmi M, Ranjit S, Otu A, Gomersall C, Amito J, Vaeza NN, Nakibuuka J, Mujiyarugamba P, Estenssoro E, Ospina-Tascón GA, Mohanty S, Mer M. International Surviving Sepsis Campaign guidelines 2016: the perspective from low-income and middle-income countries. *Lancet Infect Dis* 2017; 17: 893-895.
- 33) Pruinelli L, Westra BL, Yadav P, Hoff A, Steinbach M, Kumar V, Delaney CW, Simon G. Delay within the 3-hour surviving sepsis campaign guideline on mortality for patients with severe sepsis and septic shock. *Crit Care Med* 2018; 46: 500-505.
- 34) Sozio E, Bertini A, Bertolino G, Sbrana F, Ripoli A, Carfagna F, Giacinta A, Viaggi B, Meini S, Ghiadoni L, Tascini C. Recognition in Emergency Department of Septic Patients at Higher Risk of Death: Beware of Patients without Fever. *Medicina (Kaunas)* 2021; 57: 612.
- 35) Brink A, Alisma J, Verdonshot RJCG, Rood PPM, Zietse R, Lingsma HF, Schuit SCE. Predicting mortality in patients with suspected sepsis at the emergency department: A retrospective cohort study comparing qSOFA, SIRS and national early warning score. *PLoS One* 2019; 14: e0211133.
- 36) Innocenti F, Tozzi C, Donnini C, De Villa E, Conti A, Zanobetti M, Pini R. SOFA score in septic patients: incremental prognostic value over age, comorbidities, and parameters of sepsis severity. *Intern Emerg Med* 2018; 13: 405-412.