The Prognostic Value of Cardiac Biomarkers in Combination with the SOFA Score for the Evaluation of Sepsis-Related Mortality

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Article

The Prognostic Value of Cardiac Biomarkers in Combination with the SOFA Score for the Evaluation of Sepsis-Related Mortality

Vedrana Petrić [1,2,*], Vanja Vlatković [2], Maria Pete [1,2], Dajana Lendak [1,2], Siniša Sević [1,2] and Nadica Kovačević [1,2]

[1] Faculty of Medicine, University of Novi Sad, Serbia

[2] Clinic for Infectious Disease, University Clinical Center of Vojvodina, Novi Sad, Serbia; e mail: borka.milanovic@kcv.rs

* Correspondence: Vedrana Petrić, Clinic for Infectious Disease, Clinical Center of Vojvodina, Hajduk Veljkova 1-7, 21000 Novi Sad, Serbia; Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia. Phone: +381646163916; e-mail: vedrana.petric@mf.uns.ac.rs

Abstract

Background and Objectives: Sepsis is a life-threatening organ dysfunction, and specific biomarkers could improve prognostic assessment in septic patients. The Sequential Organ Failure Assessment (SOFA) score is the standard tool for clinical sepsis monitoring. Recent studies highlight the need for its revision and the identification of rapid, specific, sensitive predictors of sepsis mortality. The aim of this study was to determine the significance of cardiac biomarkers alone or combined with the SOFA score for evaluating sepsis-related mortality. **Materials and Methods:** This is a retrospective, single-center study with a relatively small sample size of 73 septic patients (Sepsis-3 criteria) hospitalized in an intensive care unit (ICU) and intermediate care unit (IMCU). All patients had standard laboratory parameters, cardiac biomarkers, and the SOFA score available upon admission. Statistical analyses included non-parametric Mann–Whitney U test, ROC (Receiver Operating Characteristic) curve analysis, Hanley & McNeil method and Hosmer–Lemeshow goodness-of-fit test. **Results:** Lactate ($p < 0.001$) and SOFA ($p < 0.001$) showed the highest area under the curve (AUC) values, and all cardiac biomarkers had statistically significant AUCs ($p < 0.05$) for sepsis mortality prediction. A comparison of all ROC curves was conducted, but no statistically significant differences were observed. Adding hs-cTn (high-sensitivity cardiac troponin) and lactate to the SOFA score increased its AUC from 0.767 to 0.827 ($p = 0.421$). **Conclusions:** The results highlight the potential role of cardiac biomarkers alone or in combination with the SOFA score as useful clinical tool for predicting sepsis mortality. Further research with a larger sample size is required to validate and generalize the findings.

Keywords: sepsis; septic shock; SOFA score; cardiac biomarkers; mortality

1. Introduction

Sepsis is a clinical syndrome responsible for high rates of mortality and morbidity worldwide. The new 2016 definition (Sepsis-3) describes sepsis as life-threatening organ dysfunction caused by a dysregulated host response, that is, as an infection accompanied by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more [1]. Septic shock is accompanied by circulatory, cellular, and metabolic instability, which increases the risk of fatal outcomes. The diagnosis is established when hypotension is present that requires the use of vasopressors to maintain a mean arterial pressure above 65 mmHg, along with a blood lactate level greater than 2 mmol/L after adequate fluid resuscitation [2]. In 2021, the Surviving Sepsis Campaign (SSC) published updated international guidelines for the treatment of sepsis and septic shock. In addition to the new definition,

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recommendations were provided for clinical monitoring and timely recognition of potentially septic patients through the use of the SOFA (Table A1), quick Sequential Organ Failure Assessment (qSOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores [3]. Recently published studies have focused on identifying reliable, rapid, easily accessible, and cost-effective biomarkers for mortality prediction in sepsis. Currently, among the 200 known biomarkers of sepsis, none is sufficiently sensitive and specific, which clearly indicates that even the new definition is not entirely adequate [4–9].

Septic cardiomyopathy (SCM) is a reversible myocardial dysfunction that occurs in patients with sepsis and septic shock. It results from multifactorial mechanisms. SCM manifests as systolic or diastolic dysfunction of the left or right ventricle, global hypokinesia of the heart, or a localized wall motion abnormality [10–12]. Approximately 50% of patients with severe forms of sepsis and septic shock will develop some form of left ventricular systolic dysfunction [12].

The SOFA score is most commonly used for clinical monitoring of sepsis and assessment of organ dysfunction, while the qSOFA score can be used when a rapid evaluation is needed [13]. In recent years, supplementation and revision of the SOFA score have been considered, since new clinical studies and real-world results indicate its shortcomings, particularly regarding the cardiac component. Efforts are being made to incorporate cardiac markers into the SOFA score. The reason why cardiac biomarkers could be combined with the SOFA score lies in their ability to provide an early and accurate picture of cardiac function, even before blood pressure drops or obvious myocardial dysfunction appears [11,14].

Markers that could improve the sensitivity and specificity of the SOFA score include hs-cTn (high-sensitivity cardiac troponin), N-terminal pro–brain natriuretic peptide (NT-proBNP), Creatine Kinase-MB (CK-MB), and lactate [11,15,16]. Incorporating these parameters into the existing SOFA score may enhance risk stratification and improve the identification of patients at high risk of mortality. This would allow timely initiation of adequate therapy, thereby reducing complications and improving outcomes [11].

Beyond sepsis, cardiac biomarkers may be elevated in a variety of other clinical conditions such as acute coronary syndromes, acute and chronic heart failure, pulmonary embolism, myocarditis, tachyarrhythmias, and hypertensive crises. Elevated concentrations are also reported in patients with chronic kidney disease due to reduced clearance. Therefore, while these biomarkers may have prognostic value in sepsis, their elevation is not disease-specific and should be interpreted within the overall clinical context [17].

The aim of this study was to determine the significance of cardiac biomarkers alone and in combination with the SOFA score for the evaluation of sepsis related mortality.

2. Materials and Methods

2.1. Patient Selection

Septic patients were identified according to the Sepsis-3 criteria. Between January 1, 2024, and December 31, 2024, a total of 160 septic patients hospitalized at the Clinic for Infectious Diseases, University Clinical Center of Vojvodina (UKCV), were included in this single-center retrospective study, which was approved by the Ethics Committee of UKCV (approval number 00-132).

Data were collected retrospectively from electronic healthcare records for all consecutive patients diagnosed with sepsis; consequently, additional informed consent was not required.

The exclusion criteria were designed to minimize confounding factors influencing cardiac biomarker levels and improve the generalizability of the study. Patients younger than 18 years, patients with acute coronary syndrome, patients with recent myocardial infarction (in the last 72 hours) or with active myocarditis and recent cardiac surgery, patients with confirmed pulmonary embolism, end-stage renal disease requiring dialysis, recent cardiac surgery, recent solid organ transplantation (in the last 3-6 months), auto-immune diseases, or malignancies, as well as HIV (Human Immunodeficiency Virus)-positive patients and pregnant patients, were excluded.

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Additionally, patients who didn't need intensive care unit (ICU) admission or intermediate care admission (IMCU) were excluded. Consequently, in our hospital, biomarker testing was not routinely performed and may have preferentially included more severely ill patients. While this reflects real-world clinical practice, it may limit the generalizability of the findings; however, the statistical associations were analyzed within a clearly defined cohort with complete data, thereby preserving the internal validity of the predictive model.

A total of 73 patients were included in the final analysis and were divided into two groups: survivors and non-survivors (Figure 1.).

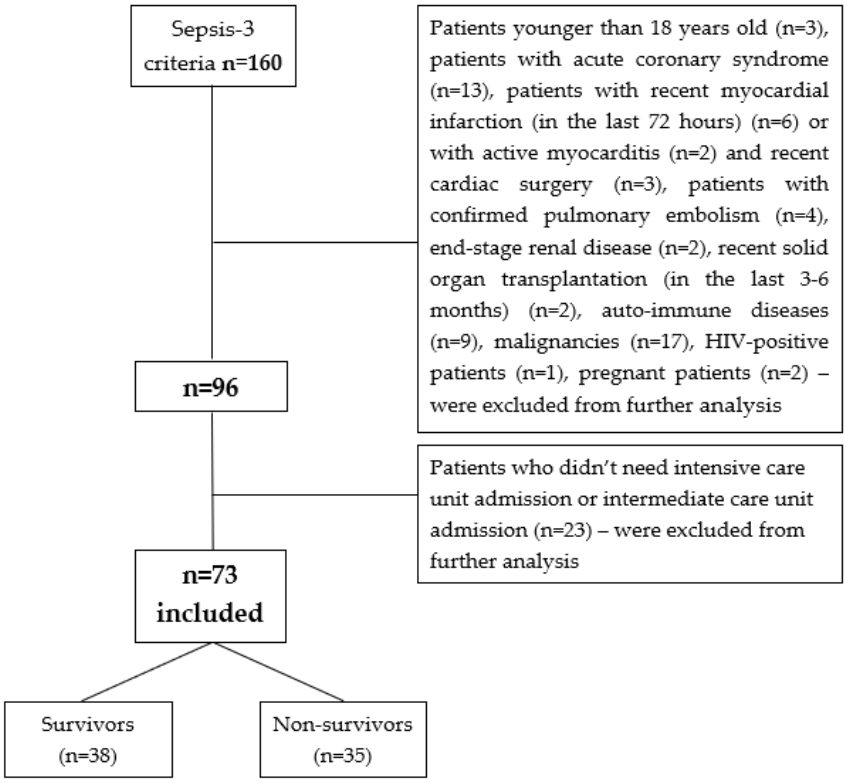

Figure 1. Patient selection flowchart.

2.2. Laboratory Testing

For all patients included in the study, demographic data, clinical characteristics, vital signs at admission, comorbidities, length of stay, source and cause of infection and outcomes were recorded. All patients had following routine laboratory analyses at admission: complete blood count (CBC) with white blood cell count (WBC), neutrophil (Neu), lymphocyte cell count (Limf)), sodium (Na), potassium (K), magnesium (Mg), concentrations of bilirubin; C-reactive protein (CRP), procalcitonin (PCT) and D-dimer, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT).

All patients had serum cardiac biomarkers (hs-cTn, NT-proBNP, and CK-MB), blood gas analysis (lactate, pH (potential of hydrogen), pO_2 (partial pressure of oxygen), pCO_2 (partial pressure of carbon dioxide), bicarbonate and base excess). The neutrophile to lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Mean arterial pressure (MAP) was calculated from measured systolic and diastolic blood pressure values. The SOFA score, qSOFA score and Glasgow Coma Scale (GCS) were recorded.

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2.3. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 21.0. Data with a normal distribution are presented as mean ± standard deviation ($\bar{X}$ ± SD), data with a skewed distribution are presented as median with interquartile range (IQR). Categorical variables were presented numerically and with percentages (N(%)), and comparisons were analyzed using the Chi-square test (χ^2 test). For numerical data, the t-test was used to compare groups when the data followed a normal distribution, and the Mann–Whitney U test was performed for non-normally distributed data.

For all individual biomarkers (hs-cTn, CK-MB, NT-proBNP), the SOFA score, and hematological and biochemical parameters (red blood cell (RBC) count, red cell distribution width (RDW), neutrophils (Neu), lymphocyte cell count (Limf), neutrophil-to-lymphocyte ratio (NLR), platelets (PLT), hemoglobin (Hb), CRP, and lactate), we constructed Receiver Operating Characteristic (ROC) curves and calculated the areas under the curve (AUCs), optimal cut-off values, sensitivity, and specificity.

Univariate analysis was performed to evaluate the predictive value of individual cardiac biomarkers for mortality. Due to the limited sample size, multivariate analysis was not performed, as it would not provide statistically reliable estimates.

The predictive performance of the combined models incorporating the SOFA score and selected cardiospecific biomarkers was assessed using ROC analysis. The biomarkers included in the combined models were those demonstrating the highest area under the curve (AUC) values in the individual ROC analyses. As lactate demonstrated the highest area under the curve (AUC) value, followed by the SOFA score and hs-cTn, a modified SOFA score was constructed by first incorporating hs-cTn and subsequently both hs-cTn and lactate. For hs-cTn and lactate, values within the reference range were assigned a score of 0, whereas values above the reference range were divided into quartiles and assigned scores from 1 to 4, consistent with the scoring structure of the original SOFA components.

The modified scores were then calculated by summing the SOFA and troponin points, and a corresponding ROC curve was generated. Subsequently, a combined score including the SOFA score, hs-cTn, and lactate was constructed, and its ROC curve was analyzed. Calibration of the model was evaluated using the Hosmer–Lemeshow goodness-of-fit test, with a p-value > 0.05 indicating good agreement between predicted and observed outcomes.

The statistical significance of the difference between two ROC curves was assessed using the Hanley & McNeil method implemented in MedCalc software (version 23.2.0).

A p-value < 0.05 was considered statistically significant. The results are presented in tables and figures with textual interpretation.

3. Results

Out of the 73 included patients in this study 37/73 (50.7%) were females and 36/73 (49.3%) were males (Table 1.).

Average age was 72.7 ± 11.14 years (range: 41–93), indicating a predominance of the geriatric population.

The overall mortality was 35/73 (47.9%) (Table 1.).

There was no statistically significant difference between the two groups in terms of age, gender, comorbidities, site of infection, source of infection and length of stay (Table 1.).

Significantly higher values of respiratory rate (RR) was observed in the non-survivor group, and other vital signs did not differ significantly between two groups. MAP was significantly lower in non-survivor group (Table 1.).

There was a statistically significant difference in SOFA and qSOFA scores, and both scores were higher in non-survivors ($p < 0.001$). However, GCS also differed significantly between the groups ($p < 0.001$) (Table 1.).

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Among all patients with sepsis in ICU and IMCU, 20 (27.39%) developed septic shock. There was a significant difference between the groups of patients with septic shock (p<0.001) (Table 1.).

Comparing the levels of all cardiac biomarkers between the groups, significantly higher values were observed in non-survivors group (Table 2.).

There was a statistically significant difference in magnesium levels (p = 0.049), AST (p = 0.006), GGT (p < 0.001) and D dimer (p < 0.001). There was no significant difference in other routine laboratory parameters (Table 2.).

Non-survivors had statistically significantly higher lactate levels (p < 0.001), as well as statistically significantly lower values of pCO_2, bicarbonate, and base excess (p = 0.04, p = 0.048, and p = 0.01, respectively) (Table 2.).

Table 1. Demographic characteristics of the sample, comparation of comorbidity structure, sites of infection, isolated pathogens, hemodynamic parameters between survivors and non-survivors.

VARIABLE	Survivors (N=38)	Non-survivors (N=35)	p
Age (Mean ± SD)	71.50 ± 12.77	73.00 ± 9.20	0.624**
Gender N(%)			
Male	19 (50.0%)	17 (48.6%)	0.903*
Female	19 (50.0%)	18 (51.4%)	
Comorbidity structure N(%)			
Arterial hypertension	27 (71.1%)	29 (82.9%)	0.233*
Diabetes mellitus	13 (35.1%)	18 (51.4%)	0.163*
Chronic obstructive pulmonary disease (COPD)	4 (10.5%)	3 (8.6%)	0.777*
Asthma	2 (5.3%)	2 (5.7%)	0.933*
Sepsis source N(%)			
Lungs	*2 (5.26%)*	*3 (8.57%)*	
Central nervous system infection (CNS)	2 (5.26%)	5 (14.28%)	
Abdomen	4 (10.52%)	3 (8.57%)	0.4927*
Skin	2 (5.26%)	4 (11.42%)	
Not identified	10 (26.32%)	8 (22.86%)	
Microbiologically confirmed bacteria from blood culture N(%)	14 (36.8%)	14 (40.0%)	
Escherichia coli (E. coli)	8 (21.1%)	5 (14.3%)	
Klebsiella pneumoniae (K. pneumoniae)	2 (5.3%)	2 (5.7%)	****
Pseudomonas aeruginosa (P. aeruginosa)	1 (2.6%)	1 (2.9)	
Acinetobacter baumanii	0 (0.0%)	1 (2.9%)	
Vancomycin resistant enterococcus	1 (2.6%)	0 (0.0%)	
Other	2 (2.6%)	5 ((14.3%)	
Vital Signs			
Heart rate (beats per minute - bpm); (Mean ± SD)	95.00 ± 21.35	87.00 ± 26.23	0.728**
Respiratory rate (RR) (Median (IQR))	15 (13-16.5)	18 (15-21)	**0.003****
Body temperature (Median (IQR))	37.00 (36.6-38.7)	37.00 (36.7-38.2)	0.214***
Oxygen saturation (SaO2) (Median (IQR))	96 (94-98)	95.2 (93-98)	0.398***
MAP (Mean ± SD)	86.67 ± 18.85	73.33 ± 21.54	**0.037**
SOFA (Median (IQR))	4 (4-5)	7 (7-9)	**< 0.001**
qSOFA (Median (IQR))	0 (0-1)	1 (1-2)	**< 0.001**
GCS (Median (IQR))	15 (10-15)	9 (6-15)	**< 0.001**
Septic shock N(%)	3 (7.9%)	17 (48.6%)	**<0.001**
Length of stay (Median (IQR))	12 ((10.5-32.5)	2 (2-19)	0.051
χ^2 test*		**Mann–Whitney U test *** **	
T test**			

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P value is not calculated due to small numbers in groups***

Table 2. Differences in standard laboratory parameters, blood gas analysis and cardiac biomarkers between survivors and non-survivors.

VARIABLE	Survivors (N=38)	Non-survivors (N=35)	p
WBC† [x10^9/L]	16.71 (10.6-20.2)	14.87 (10.8-20.9)	0.947
Neu† [%]	88.90 (81.3-91.7)	89.10 (83.3-91.1)	0.847
Limf† [%]	5.60 (3.5-11.1)	6.20 (4.1-12.0)	0.600
NLR†	16.29 (7.38-25.87)	14.15 (6.94-21.78)	0.612
PLT† [x10^9/L]	208.00 (141.75-291.0)	183.00 (128.0-296.0)	0.547
RBC [x10^12/L]	4.09 ± 0.81*	4.32 ± 0.91	0.255*
RDW† [%]	14.40 (13.3-15.97)	14.60 (13.6-16.3)	0.607
Hb [g/L]	121.63 ± 24.98	129.97 ± 31.03	0.208*
Hct† [L/L]	0.35 (0.32-0.40)	0.40 (0.31-0.44)	0.198
CRP [mg/L]	227.08 ± 103.40	221.51 ± 132.04	0.841*
PCT† [ng/mL]	9.20 (3.54-40.04)	14.60 (2.30-79.72)	0.787
Fibrinogen† [g/L]	5.46 (4.32-8.55)	4.64 (3.48-8.13)	0.307
Na† [mmol/L]	137.00 (134.0-141.0)	139.00 (135.0-143.0)	0.226
K† [mmol/L]	3.90 (3.5-4.2)	4.30 (3.4-4.8)	0.114
Mg† [mmol/L]	0.81 (0.66-0.90)	0.89 (0.74-0.96)	**0.049**
Urea† [mmol/L]	14.15 (7.85-22.07)	17.50 (9.90-26.30)	0.140
ALT† [U/L]	29.50 (20.5-44.2)	40.00 (23.0-109.0)	0.139
AST† [U/L]	30.00 (20.75-62.75)	59.00 (40.0-141.0)	**0.006**
GGT† [U/L]	28.50 (19.0-65.75)	51.00 (27.0-113.0)	**0.022**
D dimer† [mg/L] FEU]	2.26 (1.5-3.7)	4.38 (3.5-12.7)	**<0.001**
Hs-cTn† [ng/L]	27.00 (12.6-133.29)	172.20 (27.5-1676.9)	**0.001**
CK-MB† [U/L]	21.00 (13.0-33.0)	36.00 (17.0-79.0)	**0.009**
NT-pro BNP† [pg/mL]	2.603.50 (1526.5-4971.0)	5.024.00 (2516.0-25000.0)	**0.009**
Laktati† [mmol/L]	1.40 (1.07-1.82)	2.70 (1.60-4.60)	**<0.001**
pH†	7.42 (7.35-7.44)	7.38 (7.27-7.45)	0.246
pO_2† [mmHg]	75.00 (66.5-88.0)	79.00 (65.0-103.0)	0.154
pCO_2† [mmHg]	35.00 (32.0-38.0)	33.00 (26.0-36.0)	**0.040**
Bicarbonate† [mmol/L]	21.95 (20.07-25.60)	20.10 (12.60-23.30)	**0.048**
Base excess† [mmol/L]	-0.95 (-4.0 - 0.90)	-5.00 (-9.7 - -0.5)	**0.010**
Mean ± SD			
Median (IQR) †			
Mann-Whitney U test*			

The ROC curves analysis demonstrated that lactate and SOFA score had the greatest area under the curve (AUC) for predicting sepsis mortality. AUC, ROC, cut-off, sensitivity and specificity are shown in Table 3. and Figure 2.

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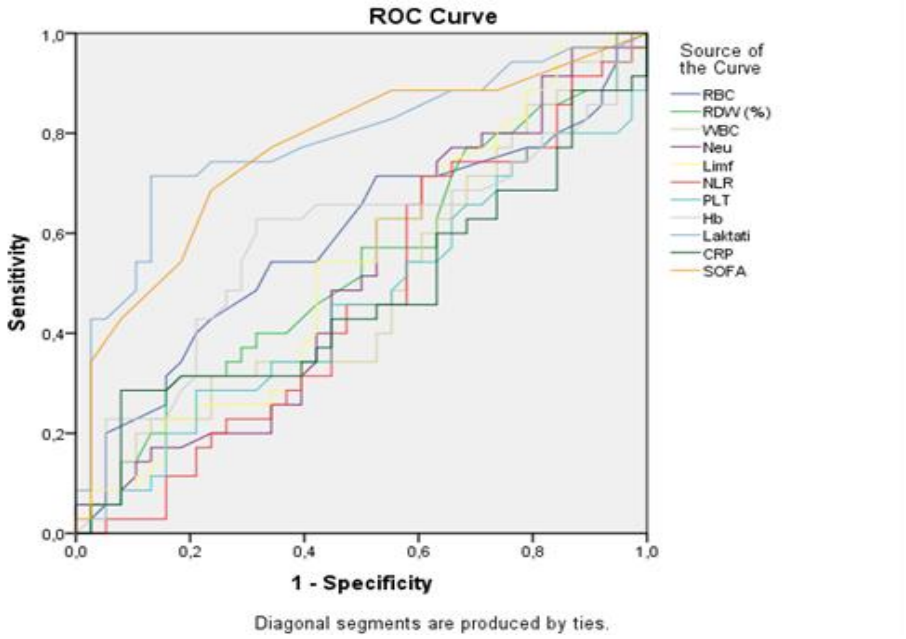

Figure 2. ROC curves for RBC, RDW, WBC, Neu, Limf, NLR, PLT, CRP, Hb, and lactate.

Table 3. Diagnostic value of laboratory parameters and SOFA score in predicting mortality in sepsis.

Variables	AUC (95% confidence interval (CI*))	p	Cut-Off Value	Sensitivity (%)	Specificity (%)
RBC [x10^12/L]	0.588 (0.454-0.721)	0.189	4.2	54.3	65.8
RDW [%]	0.535 (0.401-0.669)	0.608	16.1	31.4	81.6
WBC [x10^9/L]	0.495 (0.361-0.630)	0.947	16.54	65.7	52.6
Neu [%]	0.513 (0.379-0.648)	0.847	91.2	20.0	65.8
Limf [%]	0.536 (0.402-0.669)	0.600	2.8	97.1	15.8
NLR	0.465 (0.332-0.599)	0.612	18.69	68.6	44.7
PLT [10^9/L]	0.459 (0.325-0.593)	0.547	104	20.0	94.7
Hb [g/L]	0.585 (0.449-0.721)	0.212	126	62.9	68.4
Lactate [mmol/L]	**0.785 (0.676-0.895)**	**<0.001**	**2.1**	**71.4**	**86.8**
CRP [mg/L]	0.475 (0.338-0.612)	0.711	333	71.4	7.9
SOFA	**0.767 (0.655-0.879)**	**<0.001**	**5**	**68.6**	**76.3**

CI- Confidence interval*

ROC curve analysis demonstrated that hs-cTn had the highest AUC for predicting mortality. AUC, ROC, cut-off, sensitivity and specificity are shown in Table 4. and Figure 3.

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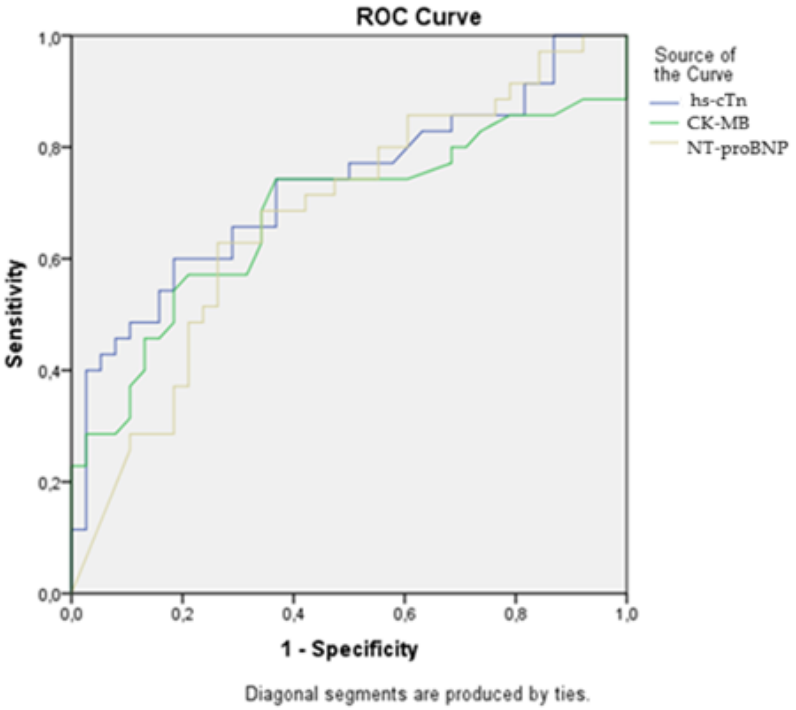

Figure 3. ROC curves for cardiac markers.

Table 4. Diagnostic value of cardiac biomarkers in predicting sepsis mortality.

Variables	AUC (95% CI)	p	Cut-Off Value	Sensitivity (%)	Specificity (%)
hs-cTn [ng/L]	0.729 (0.610-0.847)	**0.001**	146.200	60.0	81.6
CK-MB [U/L]	0.679 (0.550-0.808)	**0.009**	26.50	74.3	63.2
NT-proBNP [pg/mL]	0.677 (0.553-0.801)	**0.009**	4385.00	62.90	73.7

In order to assess whether there is a statistically significant difference in discriminative performance between cardiac biomarkers, SOFA score and lactate, we used comparation of ROC curves (Hanley & McNeil method). However, none of the pairwise comparisons revealed statistically significant differences between AUC values. These findings indicate that although each parameter showed significant individual discriminatory ability, their predictive performance was not statistically distinguishable from one another within the present cohort (Table 5.).

Table 5. Statistical comparison of ROC curves (Hanley & McNeil method).

Comparation between ROC Curves	p	Standard Error	Difference	Z Statistic
Lactate vs SOFA	0.822	0.079	0.018	0.225
Lactate vs hs-cTn	0.495	0.082	0.056	0.682
Lactate vs CK-MB	0.221	0.087	0.106	1.225
Lactate vs NT-proBNP	0.200	0.084	0.108	1.281
SOFA vs hs-cTn	0.646	0.083	0.038	0.459
SOFA vs CK-MB	0.313	0.087	0.088	1.009
SOFA vs NT-proBNP	0.289	0.085	0.090	1.059
hs-cTn vs CK-MB	0.575	0.089	0.050	0.561
hs-cTn vs NT-proBNP	0.550	0.087	0.052	0.598
CK-MB vs NT-proBNP	0.982	0.089	0.002	0.022

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Univariate analysis was performed to identify the impact of cardiac biomarkers and the SOFA score on mortality in patients with sepsis. Due to the highly skewed distribution of some biomarkers (hs-cTn and NT-proBNP), log-transformation was applied prior to analysis to obtain more appropriate and interpretable effect estimates. In this analysis, all variables demonstrated statistical significance (Table 6.).

For the identification of independent predictors of sepsis mortality, multivariable regression analysis was required. Multivariable regression analysis was not conducted because of the limited sample size and small number of events, which would violate the underlying statistical assumptions, particularly with respect to the events-per-variable (EPV) rule and model stability. Therefore, we emphasize that statistical significance was observed primarily in the univariate analysis and the findings should be interpreted as exploratory.

Table 6. Analysis of the individual impact of biomarkers and the SOFA score on mortality in patients with sepsis - results of univariate analysis.

Variables	Univariate			
	P	Odds ratio (OR)	95% CI	
			Lower Limit	Upper Limit
hs-cTn (log10) [ng/L]	**0.001**	**2.766**	**1.518**	**5.041**
CK-MB [U/L]	**0.030**	**1.020**	**1.002**	**1.039**
NT-Pro BNP (log10) [pg/mL]	**0,015**	**2.937**	**1.237**	**6.976**
SOFA	**<0.001**	**1.450**	**1.180**	**1.781**

Given the limited sample size and the inability to perform a multivariable regression analysis, the predictive performance of different combinations of the SOFA score and cardiac biomarkers were evaluated using ROC curve analysis (Figure 4.).

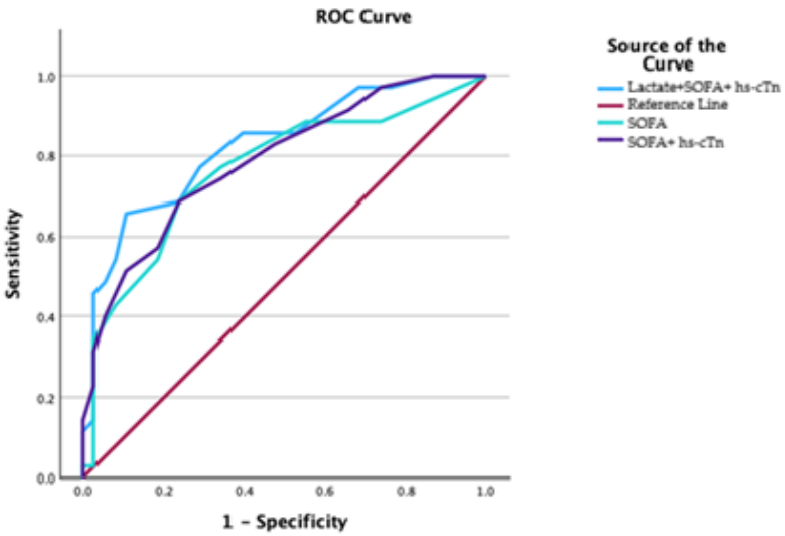

Figure 4. ROC curves for combinations of cardiac biomarkers.

ROC analysis of biomarker combinations for the prediction of mortality did not reach statistical significance. However, the model showed that adding hs-cTn to the SOFA score increased the ROC AUC from 0.767 to 0.789, although the difference between the two AUC values was not statistically significant (p = 0.775) (Table 7.).

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Further addition of lactate to the modified score that already included both the SOFA score and hs-cTn increased the ROC AUC from 0.767 to 0.827; however, this difference also did not reach statistical significance (p = 0.421).

Table 7. ROC analysis of biomarker combinations for prediction of mortality.

Test Variable(s)	AUC (95% CI)	Standard Error	p	Cut-Off	Sensitivity (%)	Specificity (%)
Lactate+SOFA+ hs-cTn	0,827 (0,732-0,922)	0,048	<0.001	8	77	81
SOFA+ hs-cTn	0.789 (0.686-0.892)	0.052	<0.001	7	74	66
SOFA	0.767 (0.655-0.879)	0.057		5	77	66

The calibration of both models was evaluated using the Hosmer–Lemeshow goodness-of-fit test. The SOFA + hs-cTn model demonstrated a p value of 0.908, whereas the Lactate+ SOFA+ hs-cTn model had a p value of 0.327, suggesting good agreement between predicted and observed outcomes for both models.

4. Discussion

The pathophysiological mechanisms of sepsis-induced cardiovascular dysfunction are still not entirely understood, and the presence of cardiovascular dysfunction is associated with a significantly increased mortality rate [11,18], as confirmed by the results of our study (47.9% of the study participants), but the high incidence of mortality observed in our study is inconsistent with the findings from a recent study [7,19]. A potential explanation for this difference may lie in the fact that our study included only patients hospitalized in ICU and IMCU.

According to these data, the timely identification and implementation of potentially highly specific, rapid, useful, low-cost, available, and sensitive biomarkers for predicting mortality in septic patients is of great importance [19]. Many studies have investigated the importance of various biomarkers that are more or less specific to sepsis, as well as combinations of biomarkers, for the early recognition of sepsis severity and their potential role in predicting mortality [20,21]. Therefore, our primary aim was to examine the ability of cardiac biomarkers and the SOFA score, alone or in combination, for the evaluation of sepsis-related mortality in routine clinical practice in middle-income countries.

The results of our study show a predominance of older patients, with an almost equal distribution of males and females. Similar age-related findings have been reported by other authors [11,22]. Almost half of our patients had three or more chronic diseases.

In a previous study conducted in China, the most common comorbidities were hypertension (40.1%), diabetes (21.9%), cerebrovascular diseases (17.2%), and COPD (12.2%), which aligns with the data observed in our study and in other recent studies [11,23].

Vincent JL et al., in their retrospective study, reported that pneumonia was the primary cause of sepsis, with the respiratory tract being the most common site of infection, and the urinary tract was the second most common site [19,24]. Our data show that 41.09% of patients had a urinary tract infection. A possible explanation for these results is the presence of a specialized institution for treating respiratory tract infections in Vojvodina, namely the Institute for Pulmonary Diseases in Sremska Kamenica. The percentage of undetermined sources of infection in our study was significantly higher (26.3%) than in previous studies, exceeding the global average, which ranges between 6% and 21% [25].

A comparison of routinely tested laboratory parameters, inflammatory biomarkers, cardiac markers between survivors and non-survivors showed that all cardiac biomarkers, Mg, AST, D-dimer and lactate had significantly higher values in non-survivors than in survivors. These results indicate

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multisystem derangements, including increased oxidative stress, inflammatory response, and ischemia–reperfusion injury [11,14,26–30]. These findings from our study show that all cardiac biomarkers were significantly elevated in the non-survivor group, suggesting a role in sepsis prognosis and informing the approach to critically ill septic patients with elevated cardiac biomarkers.

The results of our study show that lactate and the SOFA score had better predictive value for sepsis mortality, with higher AUC ROC then cardiac biomarkers. This could be explained by the fact that both SOFA score and lactate are primarily used to asses organ failure.

In an Australian study, lactate was identified as the strongest predictor of mortality in multivariate analysis [31].

Several studies have shown that elevated lactate levels in sepsis are associated with mortality [32,33].

But there are currently controversies regarding the use of the SOFA score in clinical practice. A 2023 study by Moreno et al. suggested that the SOFA score should be updated [34].

But there are currently controversies regarding the use of the SOFA score in clinical practice. A 2023 study by Moreno et al. suggested that the SOFA score should be updated [34]. Since new clinical studies and real-world results indicate its shortcomings, particularly regarding the cardiac component, efforts are being made to incorporate cardiac biomarkers into the SOFA score. The reason why cardiac biomarkers could be combined with the SOFA score lies in their ability to provide an early and accurate picture of cardiac function, even before blood pressure drops or obvious myocardial dysfunction appears [11,14,28]. *Lee* et al. developed a modified CV SOFA score (cardiovascular SOFA), due to changes in vasopressor use. This study was based on data from multiple cohorts. Even this score was not for global use because of multiple limitations, but it could be a good starting point for SOFA score modification and other new research [28]. A 2024 study developed a cardiac–extended SOFA score model by adding hs-cTnT, NT-proBNP, heart rate, and presence of atrial fibrillation. Even this model did not significantly improve the discriminatory ability for 30-days mortality compared to the standard SOFA score; therefore, future studies are needed to investigate this model and the revised cardiovascular component of the SOFA score [29].

Results from our study show that among the cardiac biomarkers, hs-cTn had the highest AUC. It is well known that elevated troponin levels in sepsis are associated with sepsis induced myocardial injury [30,35]. Recent meta-analyses suggest a significant association between troponin elevation and increased mortality in patients with sepsis, emphasizing the need for a better understanding of this relationship [35].

The findings also showed a significant association between cardiac troponin elevation and mortality among septic patients [35].

Although the AUC values in our ROC analysis did not reach statistical significance, the calculated optimal cut-off values may still serve as indicators for identifying patients at higher risk of severe sepsis and support further diagnostic and treatment procedures, as well as clinical decision-making.

Univariate analysis was performed to evaluate the association between the SOFA score, individual biomarkers, and sepsis mortality. In this analysis, all three cardiac markers demonstrated statistical significance; however, these findings should be considered exploratory. To establish an independent prognosticator of mortality, multivariate analysis using binary logistic regression would be needed.

Because of the limited sample size and the inability to perform multivariable regression analysis, we evaluated the predictive performance of different combinations of the SOFA score, serum lactate, and cardiospecific biomarkers using ROC curve analysis; therefore, it was very difficult to compare our results with those of other studies.

This model aimed to show that a combined biomarker approach had better prognostic value than the SOFA score alone in predicting mortality. The calibration of both models was evaluated using the Hosmer–Lemeshow goodness-of-fit test.

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This study further found, through ROC curve analysis, that the combination of the SOFA score and cardiac markers for predicting mortality had a higher AUC than the SOFA score alone, but the difference did not reach statistical significance.

Similarly, the AUC of the combined model integrating the SOFA score, hs-cTn and lactate was superior to that of both the SOFA score alone and the SOFA score plus hs-cTn model, however, no statistically significant differences were observed.

One study showed that the combination of different biomarkers had better prognostic value than SOFA score alone in predicting sepsis mortality [36]. Our results, however, might have been affected by selection bias and the small sample size. Even though we did not identify a statistically significant prognostic combination, the SOFA score combined with hs-cTn and serum lactate could be a useful tool for clinical use.

Many studies have attempted to modify the cardiovascular component of the SOFA score to better reflect cardiac dysfunction and improve its predictive performance (11, 14, 16).

Our study has several limitations. First, to the best of our knowledge, this is the first study in our clinical setting exploring the association between cardiac biomarkers and sepsis mortality. Second, this is a single-center study, including only patients hospitalized in ICU and IMCU unit, and the findings may differ when using records from other centers, limiting the generalizability of our findings to other populations. Third, although we adjusted for as many covariates as possible to diminish their possible influences, owing to the retrospective design of the study, residual confounding may still exist, which needs to be investigated in the future. Fourth, the relatively small number of patients represents an additional limitation for proper statistical analysis; therefore, further multicenter studies with larger sample sizes are needed to identify optimal prognostic cardiac biomarkers.

5. Conclusions

Based on our findings, the SOFA score and lactate showed the best predictive performance for mortality in this cohort.

In the present study, each cardiac biomarker demonstrated statistically significant discriminatory performance for mortality prediction. This finding suggests that it may be possible to determine the cut-off value for each biomarker for predicting mortality in sepsis patients.

In our univariate analysis, all cardiac markers showed association with mortality; however, multivariate analysis is required to confirm this observation.

Although adding lactate and troponin to the SOFA score did not improve the model performance significantly, we would like to highlight the possible role of combined models in the prognosis of sepsis, but this requires further validation in larger, adequately powered prospective studies.

Due to the complex pathophysiology of sepsis, combined biomarkers may represent the future of predicting outcomes among patients.

6. Patents

There are no patents resulting from the work reported in this manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of University Clinical Center of Vojvodina (protocol code 00-132; the approval was granted on 7 March 2025).

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the research.

Data Availability Statement: The data presented in this study are available from the first author upon request.

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Abbreviations

ALT - Alanine aminotransferase
APACHE II - Acute Physiology and Chronic Health Evaluation II
AST - Aspartate aminotransferase
AUC- Area under the curve
CI - Confidence interval
CK-MB - Creatine kinase-MB
CNS - Central nervous system
COPD - Chronic obstructive pulmonary disease
CRP - C-reactive protein
EPV - Events-per-variable
GCS - Glasgow Coma Scale
GGT - Gamma-glutamyl transferase
Hb - Hemoglobin
HCT - Hematocrit
HIV- Human immunodeficiency virus
hs-cTn - High-sensitivity cardiac troponin
ICU - Intensive care unit
IMCU - Intermediate care unit
IQR - Interquartile range
K - Potassium
Limf - Lymphocyte cell count
MAP - Mean arterial pressure
Mg - Magnesium
N - Number of observed parameters
Na - Sodium
Neu - Neutrophil
NLR - Neutrophil to lymphocyte ratio
NT-proBNP - N-terminal pro-brain natriuretic peptide
OR - Odds ratio
pCO_2 - Partial pressure of carbon dioxide
PCT - Procalcitonin
pH - Potential of hydrogen
PLT - Platelets
pO_2 - Partial pressure of oxygen
qSOFA - Quick Sequential Organ Failure Assessment
RBC - Red blood cell count
RDW - Red cell distribution width
ROC - Receiver operating characteristic
RR - Respiratory rate
SaO_2 - Oxygen saturation

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SCM - Septic cardiomyopathy
SD - Standard deviation
SOFA - Sequential Organ Failure Assessment
SSC - Surviving Sepsis Campaign
UKCV - University Clinical Center of Vojvodina
WBC - White blood cell count
χ^2 test - Chi-square test

Appendix A

Table A1. Parameters for calculating the SOFA score.

System	Parameter	0	1	2	3	4
Respiratory	PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200 with mechanical ventilation	<100 with mechanical ventilation
Coagulation	Platelets ($10^9/L$)	≥150	<150	<100	<50	<20
Liver	Bilirubin (mg/dL)	<1,2	1,2-1,9	2-5,9	5-11,9	>12
Cardiovascular	MAP or need for vasopressors	>70	<70	Dopamine <5; ILI dobutamine	Dopamine 5,1-15; ILI epinephrine <0,1; ILI norepinephrine <0,1	Dopamine >15; ILI epinephrine >0,1; ILI norepinephrine >0,1
CNS	Glasgow Coma Scale (GCS)	15	13-14	10-12	6-9	<6
Kidneys	Creatinine (mg/dL) or urine output	<1,2	1,2-1,9	2-3,4	3,5-4,9	>5

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