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Composite bioscore is superior to routine biomarkers and established scoring systems in predicting mortality in adult critically ill patients with secondary sepsis

Kombinovani bioskor je superiorniji u odnosu na rutinske biomarkere i skorove u predviđanju mortaliteta kod odraslih kritično obolelih bolesnika sa sekundarnom sepsom

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Abstract

Background/Aim. Sepsis represents a significant global burden, with an estimated 48.9 million cases and 11.0 million sepsis-related deaths recently recorded worldwide. The aim of this observational study was to assess a prognostic value of some readily available routine biomarkers: presepsin, procalcitonin, C-reactive protein (CRP), white blood cell (WBC) count, platelet count, mean platelet volume (MPV), and lactate, as well as their combination regarding the outcome in a cohort of critically ill adult patients with secondary sepsis. **Methods.** A total of 86 critically ill patients with secondary sepsis due to peritonitis, pancreatitis, and severe trauma, admitted to the surgical intensive care unit, were enrolled in this prospective study. Blood samples for biomarker analysis were collected in three time points: on admission (the 1st day) and on the 3rd, and 5th day after admission. The Sequential Organ Failure Assessment (SOFA) score, the Simplified Acute Physiology Score (SAPS) II, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were calculated and recorded within the first 24 hours after admission (1st day). SOFA and SAPS II scores were recorded daily. The primary endpoint was hospital mortality. **Results.** Values of each applied score were expectedly significantly higher in non-survivors in all time points. Regarding investigated parameters, only presepsin levels were significantly higher in non-survivors in all time points; MPV levels on the 3rd and 5th day; serum lactate levels on the 3rd day; CRP levels and WBC count on the 5th day. Clinical accuracy of parameters in predicting lethal outcomes was investigated in all time points. On the 1st day, apart from all three scores, only presepsin demonstrated statistically significant discriminative power regarding outcome (AUC of 0.670). Apart from SAPS II and SOFA score, on the 3rd day presepsin, MPV, and lactate (AUCs of 0.716, 0.667, and 0.642, respectively) and on the 5th day presepsin, MPV, CRP, and WBC count (AUCs of 0.790, 0.681, 0.643 and 0.654, respectively) were good predictors of the lethal outcome. Composite bioscore (presepsin, MVP, and lactate) on the 3rd day had the highest AUC of 0.820 in comparison with individual scores and parameters. The independent predictor of the lethal outcome on the 1st day was presepsin ($p < 0.05$) and on the 3rd day MPV ($p < 0.01$). **Conclusion.** Composite bioscore is superior to routine biomarkers and established scoring systems in predicting mortality in adult critically ill patients with secondary sepsis.

Key words:
biomarkers; critical illness; intensive care units; mortality; sepsis; severity of illness index; prognosis.

Apstrakt

Uvod/Cilj. Sepsa predstavlja značajno globalno opterećenje, sa procenjenih 48,9 miliona slučajeva i 11 miliona smrtnih slučajeva povezanih sa sepsom godišnje širom sveta. Cilj prospektivne, opservacione studije bio je da se proceni prognostička vrednost nekih lako dostupnih, rutinskih biomarkera kao što su: presepsin, prokalcitonin, C-reaktivni

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protein (CRP), broj leukocita, srednji volumen trombocita (MPV) i laktati kao i njihove kombinacije, u smislu predviđanja ishoda sekundarne sepse kod odraslih kritično obolelih bolesnika. **Metode.** Prospektivnim istraživanjem obuhvaćeno je ukupno 86 kritično obolelih bolesnika sa sekundarnom sepsom kao komplikacijom peritonitisa, pankreatitisa i teške traume, koji su bili primljeni u hiruršku jedinicu intenzivne terapije. Uzorci krvi za određivanje biomarkera uzimani su u tri vremena: na dan prijema – prvi dan, zatim trećeg i petog dana. Prvog dana izračunati su i zabeleženi sledeći skorovi: *Sequential Organ Failure Assessment* (SOFA) skor, *Simplified Acute Physiology Score* (SAPS) II i *Acute Physiology and Chronic Health Evaluation* (APACHE) II skor. SOFA i SAPS II skorovi su izračunavani i beleženi svakodnevno. Primarni ishod bio je bolnički mortalitet. **Rezultati.** Vrednosti svih primenjenih skorova u sva tri vremena su, očekivano, bile značajno veće kod obolelih sa smrtnim ishodom. Od svih ispitivanih parametara, samo su vrednosti presepsina u sva tri vremena bile značajno veće kod umrlih; vrednosti MPV trećeg i petog dana; vrednosti laktata trećeg dana; vrednosti CRP-a i broj leukocita petog dana. U svim vremenima ispitivana je preciznost parametra u smislu predviđanja smrtnog ishoda. Prvog dana, osim sva tri skora, samo je presepsin bio statistički značajan prediktor ishoda (AUC 0.670). Osim SAPS II i SOFA skora, trećeg dana statistički značajni prediktori ishoda bili su presepsin (AUC 0.716), MPV (AUC 0.667) i laktati (AUC 0.642), a petog dana presepsin (AUC 0.790), MPV (AUC 0.681), CRP (AUC 0.643) i broj leukocita (AUC 0.654). Kombinovani bioskor (presepsin, MPV i laktati) je trećeg dana bio najbolji prediktor ishoda (AUC 0.820) u poređenju sa individualnim skorovima i parametrima. Nezavisni prediktor smrtnog ishoda prvog dana bio je presepsin ($p < 0.05$), a trećeg dana MPV ($p < 0.01$). **Zaključak.** Kombinovani bioskor je superiorniji od rutinskih biomarkera i skorova u predviđanju mortaliteta kod odraslih kritično obolelih bolesnika sa sekundarnom sepsom.

Ključne reči:
biomarkeri; kritična stanja; intenzivna nega, odeljenja; mortalitet; sepsa; bolest, indeks težine; prognoza.

Introduction

Sepsis represents a significant global burden, with an estimated 48.9 million cases and 11.0 million sepsis-related deaths recorded worldwide in 2017. The latest analysis for the global burden of disease study revealed that recorded death toll represented 19.7% of all global deaths [1]. It is evident that this life-threatening organ dysfunction, resulting from uncontrolled host response to infection, is responsible for one-fifth of all deaths despite all the latest technology and newer antibiotics. Bearing in mind the importance of mortality prediction in critically ill septic patients, over the years, investigators focused their attention on various potential biomarkers in this regard [2, 3]. So far, no specific biomarkers for mortality prediction in this patient population have been identified. Without a specific biomarker, it is difficult for clinicians to determine which patients are likely to improve and which will have a poor outcome. Interesting biomarkers in this regard encompass procalcitonin and a rather novel biomarker presepsin. Presepsin, which is a 13-kDa peptide, is another name for the soluble cluster of differentiation (CD)14 subtype (sCD14-ST). Membrane CD14 is a coreceptor for endotoxin, and during the systemic immunoinflammatory response, its soluble form is cleaved from immunocompetent cells like monocytes/macrophages [4]. Procalcitonin is a 116-amino acid polypeptide precursor of calcitonin released by the C cells of the thyroid gland [5].

The aim of this prospective, observational study was to assess the prognostic value of some readily available routine biomarkers: presepsin, procalcitonin (PCT), C-reactive protein (CRP), white blood cell count (WBC), platelet count, mean platelet (MPV) volume, and lactate regarding the outcome in a cohort of critically ill adult patients with secondary sepsis. In addition, the aim was to evaluate the combination of these biomarkers in the same regard and compare their ability to predict mortality with the use of clinical tools like established scoring systems.

Methods

Patients

A total of 86 critically ill patients with secondary sepsis due to peritonitis, pancreatitis, and severe trauma, admitted to surgical intensive care unit (SICU), were enrolled in a prospective study conducted in a tertiary university hospital (Military Medical Academy, Belgrade, Serbia). Approval in concordance with the Declaration of Helsinki was obtained from the local Ethics Committee and informed consent from the patients or first-degree relatives. Sepsis patients were enrolled if they had fulfilled current sepsis – 3 diagnostic criteria for sepsis (formerly severe sepsis) and/or septic shock [acute change in total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points and vasopressors required to maintain mean arterial pressure (MAP) ≥ 65 mmHg and serum lactate level > 2 mmol/L despite adequate volume resuscitation] [6]. The study lasted 3 years and 1 month. The diagnostic criteria encompass any of the following variables thought to be a result of the infection: sepsis-induced hypotension, lactate levels greater than 2 mmol/L, urine output less than 0.5 mL/kg/hr for more than two hours despite adequate fluid resuscitation, acute lung injury with PaO_2/FiO_2 less than 250, blood creatinine level higher than 2.0 mg/dL (176.8 μmol/L), bilirubin greater than 2.0 mg/dL (34.2 μmol/L), platelet count less than 100,000 and coagulopathy (international normalized ratio – INR) greater than 1.5. Critically ill surgical patients with severe trauma [Injury Severity Score – ISS (determined using Abbreviated Injury Scale – AIS) > 25 points] were enrolled after they developed secondary sepsis. The exclusion criteria were as follows: secondary sepsis and/or septic shock with an underlying cause other than severe peritonitis, pancreatitis or trauma, and malignant disease of any origin. Out of 260 patients initially considered for enrolment, 174 were excluded.

Blood samples for biomarker analysis were collected in three time points: on admission (1st day) and on the 3rd, and 5th day after admission. Additionally, samples of blood were

simultaneously drawn for a blood culture. SOFA score, the Simplified Acute Physiology Score (SAPS) II, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were calculated and recorded within the first 24 hours after admission to the SICU (1st day) [7–9]. SOFA and SAPS II scores were recorded daily during SICU stay to assess the severity of organ dysfunction in secondary sepsis.

The use of antibiotics, circulatory volume replacement, vasoactive support, and source controlled were performed according to guidelines [10]. Various modes of mechanical ventilation and surgical procedures were performed if and when necessary in all patients. The outcome measure was hospital mortality; patients were followed until hospital discharge (survivors) or hospital death (non-survivors).

Sampling and analysis

The patient's venous blood was drawn by trained, qualified phlebotomists. The blood samples were taken into BD Vacutainer K_2 EDTA tubes and analyzed within 2 hours from venepuncture. A complete blood count was determined by Siemens Advia 120 hematology system, Siemens Healthineers Germany, which is a flow cytometry-based system. Differentiation of white blood cells is done by the peroxidase and basophil channel. On the Advia 120, the peroxidase method is a primary differential method. Advia 120 analyzer method of counting platelets is based on two-dimensional laser light scatter. The laser optics low angle and high angle scatter was used to determine the platelet count simultaneously with the red blood cells. MPV was a calculated parameter from the platelet volume histogram. For CRP determination ADVIA 1800, Siemens Healthineers Germany, was used and for procalcitonin measurement, CENTAUR Advia XP, Siemens Healthineers Germany, was used. Arterial lactate values were measured by blood gas analyzer GEM3000 Premier, Instrumentation Laboratory Werden Company Spain. For presepsin determination, Patfast compact immunoassay analyzer, Mitsubishi Chemical Europe Germany, was used. Normal ranges for these cells and biomarkers are as follows: leukocytes, 4–11.0 × 10^9/L; platelets, 130.0–400.0 × 10^9/L; CRP, 0.00–4.00 mg/L; procalcitonin, < 0.10 ng/mL; presepsin, < 360 pg/mL (reference values from our laboratory).

Statistical analysis

Complete statistical analysis of data was done with the statistical software package, SPSS Statistics 18. In the case of continuous data, variables were presented as mean value ± standard deviation (SD), median, minimal, and maximal values. Kolmogorov-Smirnov test was used for evaluating the distribution of continual data. Statistical significance between groups was tested by the Mann-Whitney or Friedman test. The Spearman's Rank Correlation analysis was used to establish the relationship between parameters. Receiving Operating Characteristics (ROC) curves were constructed and analyzed to determine the sensitivity and specificity of variables for predicting lethal outcomes (Youden index was used in all cases). Calculations of odds ratios (OR) and their 95% confidence intervals (CI) were done to determine the strength of the association between variables and outcomes. For that purpose, the most promising independent variables as single or combined risk factors were incorporated into binary logistic regression analyses. Mantel-Cox log-rank to analyze survival time between each tertile of presepsin concentration as well as Kaplan-Meier survival curve to analyze the probability of death between each tertile, were performed.

All the analyses were estimated at a $p < 0.05$ level of statistical significance.

Sample size calculation

The sample size of the study was calculated based on a 30% difference in presepsin levels between survivors and non-survivors and a 37% of mortality rate. The effect size was 0.535 and the allocation rate was 0.6. With a test power of 0.8 (80%) and a type I (alpha) error of 0.05, the analysis revealed that the sample size of 86 patients (54 survivors and 32 non-survivors) was sufficient to detect a statistically significant difference between groups. The calculation was performed by GPower 3.1 statistical program, using the Wilcoxon-Mann-Whitney test because of the high data variability.

Results

Baseline characteristics of the study population

During a 3-year period, out of 260 patients initially considered for enrolment, 174 patients were excluded. The remaining 86 patients (average age was 59 years; range 18–

Table 1

Demographic and clinical data of patients with sepsis

Parameter	Values
Patients	86
age (years), mean (range)	59 (18–89)
sex, n (%)	
male	56 (65.1)
female	30 (34.9)
SAPS II score (on the day 1) mean ± SD	37.28 ± 14.56
APACHE II score (on the day 1) mean ± SD	13.15 ± 5.96
SOFA score (on the day 1) mean ± SD	5.81 ± 3.80
Reason for ICU admission, n (%)	
severe sepsis due to:	
peritonitis	40 (46.5)
pancreatitis	18 (20.9)
trauma	28 (32.6)
Blood cultures, n (%)	
Gram-positive	8 (9.3)
Gram-negative	19 (22.1)
polymicrobial	14 (16.3)
negative blood cultures	45 (52.3)
Overall hospital mortality, n (%)	32 (37.2)

SD – standard deviation; SAPS – Simplified Acute Physiology Score; APACHE – Acute Physiology and Chronic Health Evaluation; SOFA – Sequential Organ Failure Assessment; ICU – Intensive Care Unit.

89 years; 30 females) with secondary sepsis and/or septic shock due to peritonitis (40 patients – 46.5%), pancreatitis (18 patients – 20.9%), and trauma (28 patients – 32.6%) as the underlying cause were enrolled. Out of the 86 patients, 8 patients (9.3 %) developed Gram-positive bacteraemia, 19 patients (22.1%) developed Gram-negative bacteraemia, and 14 patients (16.3%) had polymicrobial bacteraemia. In 45 patients (52.3%), no pathogen was isolated from blood culture. Injury Severity Score – ISS (determined using Abbreviated Injury Scale – AIS) was calculated and recorded in all polytrauma patients (mean ± SD): 33.82 ± 3.59. The demographic and clinical data are shown in Table 1.

Baseline laboratory characteristics of patients on the 1st, 3rd, and 5th day according to the outcome are shown in Table 2.

Values of each applied score were, expectedly, significantly higher in non-survivors in all time points. Regarding investigated parameters, only presepsin levels were higher in non-survivors, the difference reached high statistical significance in all time points. The second best were MPV levels. They were significantly higher in non-survivors in two out of three time points: on the 3rd and 5th day. Serum lactate levels were significantly higher in non-survivors on the 3rd day. Finally, CRP levels and WBC count were significantly higher in non-survivors on the 5th day.

Procalcitonin levels and platelet count did not differ significantly between survivors and non-survivors in any of the three time points.

A time course of presepsin according to hospital outcome is presented in Figure 1.

Table 2
Baseline laboratory parameters of patient with sepsis on the 1st, 3rd day, and 5th day according to outcome

Parameter	Survivors (n = 54) mean ± SD; median (min–max)	Non-survivors (n = 32) mean ± SD; median (min–max)	*p*-value
APACHE II score 1st day	11.94 ± 5.22; 11.50 (2–26)	15.19 ± 6.63; 14.50 (5–32)	0.023
SAPS II score			
1st day	34.74 ± 12.68; 35.00 (8–92)	41.56 ± 16.61; 39.50 (6–92)	0.034
3rd day	28.28 ± 12.08; 27.50 (0–58)	38.41 ± 14.34; 37.00 (12–67)	0.003
5th day	25.00 ± 12.03; 23.00 (0–58)	40.18 ± 14.07; 41.00 (0–62)	0.000
SOFA score			
1st day	5.13 ± 3.20; 4.00 (0–15)	6.97 ± 4.46; 6.00 (0–19)	0.040
3rd day	4.56 ± 3.24; 4.00 (0–12)	6.41± 3.68; 5.00 (0–15)	0.017
5th day	3.44 ± 2.90; 3.00 (0–10)	6.59 ± 3.14; 6.00 (0–11)	0.000
Presepsin (pg/mL)			
1st day	1,068.59 ± 1,105.38; 722.50 (101–5315)	1,710.78 ± 1,595.09; 1,160.50 (214.–8,144)	0.008
3rd day	920.98 ± 1,172.52; 530.00 (67.30–5880.00)	1,493.59 ± 1,816.20; 891.00 (425–9,419)	0.002
5th day	683.23 ± 991.49; 473.50 (52.60–7123.00)	1,323.86 ± 1,171.99; 836.00 (345.00–5,142)	0.000
Procalcitonin (ng/mL)			
1st day	5.51 ± 12.00; 0.92 (0.007–61.62)	7.22 ± 15.16; 1.38 (0.19–69.15)	0.281
3rd day	7.73 ± 28.26; 0.91 (0.03–185.57)	14.56 ± 57.68; 1.05 (0.08–259.48)	0.706
5th day	3.12 ± 9.42; 0.51 (0.06–60.36)	1.90 ± 3.27; 0.64 (0.11–11.10)	0.988
C-reactive protein (mg/L)			
1st day	179.65 ± 76.04; 170.37 (10.95–362.87)	174.24 ± 94.75; 175.44 (6.37–396.97)	0.818
3rd day	165.29 ± 80.36; 152.77 (14.97–412.79)	156.69 ± 83.78; 161.71 (10.15–312.08)	0.794
5th day	126.98 ± 70.39; 115.28 (11.16–305.34)	156.72 ± 53.85; 153.63 (46.08–250.38)	0.048
WBC count (10^9/L)			
1st day	14.62 ± 8.33; 13.50 (2.09–34.71)	14.26 ± 6.84; 13.55 (4.55–34.36)	0.993
3rd day	13.08 ± 7.39; 10.76 (3.24–38.45)	13.04 ± 3.87; 13.76 (4.81–23.76)	0.179
5th day	11.26 ± 4.21; 10.85 (3.25–21.90)	14.39 ± 5.63; 13.15 (8.28–30.61)	0.036
Platelet (10^9/L)			
1st day	241.42 ± 142.75; 199.00 (53.20–623.00)	194.87 ± 115.52; 165.50 (25.00–503.00)	0.211
3rd day	255.76 ± 169.12; 210.00 (61.10–735.00)	196.31 ± 87.92; 191.00 (48.00–409.00)	0.302
5th day	281.36 ± 167.18; 238.50 (52.60–724.00)	219.02 ± 107.78; 232.00 (49.10–399.00)	0.200
MPV (fL)			
1st day	9.00 ± 1.37; 8.55 (7.00–12.90)	9.22 ± 1.54; 9.05 (7.10–16.10)	0.437
3rd day	8.85 ± 1.31; 8.55 (6.60–13.00)	9.57 ± 1.49; 9.20 (7.10–14.60)	0.015
5th day	8.86 ± 1.65; 8.50 (6.50–14.30)	9.71 ± 1.77; 9.25 (7.00–15.00)	0.014
Lactate (mmol/L)			
1st day	2.00 ± 1.90; 1.20 (0.50–9.70)	2.03 ± 2.58; 1.20 (0.60–15.00)	0.707
3rd day	1.06 ± 0.66; 0.80 (0.20–4.30)	1.59 ± 1.42; 1.20 (0.30–7.40)	0.038
5th day	0.90 ± 0.26; 0.80 (0.50–1.60)	1.34 ± 0.97; 0.95 (0.20–4.30)	0.164

SD – standard deviation; WBC – white blood count; MPV –mean platelet volume.
For other abbreviations see under Table 1.

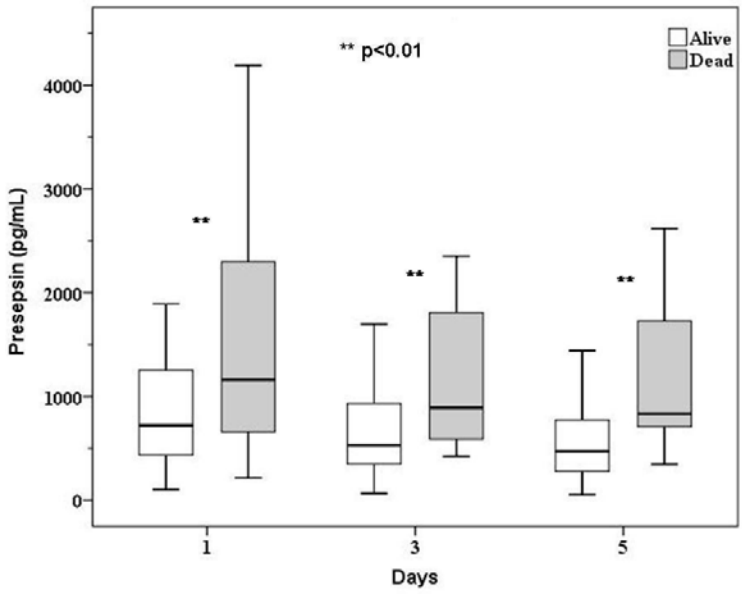

Fig. 1 – Levels of presepsisn in all three-time points according to hospital outcome.

Comparison and correlation of parameters in three time point intervals (1st, 3rd, and 5th day)

Of all measured parameters, only WBC count and MPV did not differ significantly between time point intervals within groups (survivors, non-survivors). Presepsin, PCT, CRP, and serum lactate values differ significantly within survivors; platelet count differs significantly within both survivors and non-survivors. *Post hoc* pairwise comparisons were determined exactly between which time points statistically significant difference in parameter levels occurred (Table 3). Interestingly, except for platelet count, which differed significantly within both survivors and non-survivors in all three time points, all other parameters differ significantly within survivors, but not within non-survivors.

The Spearman's test of correlation between investigated parameters in all three time points was performed. On the 1st day, there was a statistically significant positive correlation between serum lactate and PCT (rho = 0.414; $p = 0.005$) in survivors. Additionally, there was a statistically significant positive correlation between presepsin and PCT in non-survivors (rho = 0.466; $p = 0.014$).

On the 3rd day, there was a statistically significant positive correlation between presepsin and PCT (rho = 0.503; $p = 0.000$) and MPC and lactate (rho = 0.279; $p = 0.041$) in survivors. There were no statistically significant correlations between parameters in non-survivors at this time point.

wOn the 5th day, there was a statistically significant positive correlation between presepsin and PCT (rho = 0.504; $p = 0.000$) as well as between presepsin and WBC count (rho = 0.452; $p = 0.001$) in survivors. On the other hand, in non-survivors, there was a statistically significant positive correlation between presepsin and PCT (rho = 0.465; $p = 0.045$) and lactate and WBC count (rho = 0.662; $p = 0.001$).

In general, regarding all patients, there were several sta-

Table 3

Comparison of presepsin, procalcitonin, C-reactive protein, platelet count, and serum lactate levels between time points within groups

Time point comparison*	Presepsin		Procalcitonin		C-reactive protein		Platelet count		Serum lactates	
	survivors	non-survivors	survivors	non-survivors	survivors	non-survivors	survivors	non-survivors	survivors	non-survivors
All time points z (*p*-value)	23.284 (< 0.01)	0.273 (> 0.05)	9.682 (< 0.01)	3.763 (> 0.05)	19.241 (< 0.01)	1.263 (> 0.05)	19.411 (< 0.01)	6.909 (< 0.05)	28.583 (< 0.01)	1.848 (> 0.05)
3rd vs. 1st day z (*p*-value)	-3.225 (< 0.01)	n.s.	-0.755 (> 0.05)	n.s.	-0.984 (> 0.05)	n.s.	-1.567 (> 0.05)	-0.432 (> 0.05)	-4.591 (< 0.01)	n.s.
5th vs. 1st day z (*p*-value)	-3.687 (< 0.01)	n.s.	-2.210 (< 0.05)	n.s.	-3.684 (< 0.01)	n.s.	-3.200 (< 0.01)	-1.737 (< 0.05)	-4.817 (< 0.01)	n.s.
5th vs. 3rd day z (*p*-value)	-2.734 (< 0.01)	n.s.	-3.496 (< 0.01)	n.s.	-3.799 (< 0.01)	n.s.	-3.723 (< 0.01)	-2.078 (< 0.05)	-1.825 (< 0.05)	n.s.

***Fridman test; n.s. – non significant.**

tistically significant and highly significant positive correlations between some of the investigated parameters. Regardless of statistical significance, most of the correlations were weak (rho below or around 0.5) except for the correlation between lactate and WBC count on the 5th day in non-survivors, which was good (rho = 0.66).

Clinical accuracy of baseline parameters in predicting lethal outcome

Clinical accuracy of baseline parameters in predicting lethal outcome was investigated in all time points. On the 1st day, apart from all three scores, only presepsin demonstrated statistically significant discriminative power regarding the outcome. Levels of all three scores, as well as presepsin higher than cut-off values, were moderate predictors of lethal outcome (Table 4).

On the 3rd day, apart from SAPS II and SOFA score, presepsin, MPV, and lactate demonstrated statistically significant discriminative power regarding the outcome. Levels of two scores, as well as presepsin, MPV, and lactate higher than cut-off values, were good predictors of lethal outcome (Table 5).

On the 5th day, apart from SAPS II and SOFA score, presepsin, MPV, CRP, and WBC count demonstrated statistically significant discriminative power regarding the outcome. Levels of two scores, as well as presepsin, MPV, CRP, and WBC count higher than cut-off values, were very good predictors of lethal outcome (Table 6).

A combination of presepsin, MVP, and lactate into one composite bioscore on the 3rd day was performed in order to determine whether it would increase their discriminative power, which is prognostic ability regarding lethal outcome. Individual values were scored as 1 because they were all above previously determined ROC curve cut-off levels; this composite bioscore ranges from 0 to 3 points.

On the 3rd day, the composite bioscore demonstrated statistically highly significant discriminative power regarding the outcome. Levels higher than cut-off values were very good predictors of lethal outcome (Table 7).

A percentage of non-survivors according to each bioscore point value on the 3rd day is shown in Figure 2.

Table 4

Clinical accuracy of baseline parameters in predicting lethal outcome on the 1st day

Parameter	AUC ROC	*p*-value	95% confidence interval		Cut-off value	Sensitivity (%)	Specificity (%)	Youden index
			lower bound	upper bound				
APACHE II	0.647	0.023	0.524	0.770	15.50	43.8	81.5	0.25
SAPS II	0.637	0.034	0.511	0.764	47.50	34.4	92.6	0.27
SOFA	0.623	0.045	0.498	0.748	5.50	56.3	68.5	0.25
Presepsin	0.670	0.009	0.554	0.786	812.50	71.9	57.4	0.29

AUC ROC – area under the receiver operator characteristic curve.
For other abbreviations see under Table 1.

Table 5

Clinical accuracy of baseline parameters in predicting lethal outcome on the 3rd day

Parameter	AUC ROC	*p*-value	95% confidence interval		Cut-off value	Sensitivity (%)	Specificity (%)	Youden index
			lower bound	upper bound				
SAPS II	0.701	0.003	0.580	0.821	3 0.50	74.1	63.0	0.37
SOFA	0.662	0.018	0.539	0.784	3.50	88.9	64.8	0.35
Presepsin	0.716	0.002	0.606	0.825	539.50	88.9	51.9	0.41
MPV	0.667	0.015	0.546	0.788	8.65	85.2	53.7	0.39
Lactate	0.642	0.039	0.503	0.781	1.15	55.6	70.4	0.26

AUC ROC – area under the receiver operator characteristic curve; MPV – mean platelet volume.
For other abbreviations see under Table 1.

Table 6

Clinical accuracy of baseline parameters in predicting lethal outcome on the 5th day

Parameter	AUC ROC	*p*-value	95% confidence interval		Cut-off value	Sensitivity (%)	Specificity (%)	Youden index
			lower bound	upper bound				
SAPS II	0.813	0.000	0.696	0.929	39.00	68.2	9 0.7	0.59
SOFA	0.761	0.000	0.645	0.876	3.50	9 0.9	55.6	0.46
Presepsin	0.790	0.000	0.688	0.893	639.50	81.8	72.2	0.54
MPV	0.681	0.014	0.557	0.806	8.85	81.8	61.1	0.43
CRP	0.643	0.040	0.518	0.779	118.56	81.0	51.9	0.33
WBC count	0.654	0.036	0.518	0.791	14.90	45.5	85.2	0.31

AUC ROC – area under the receiver operator characteristic curve; MPV – mean platelet volume; CRP – C-reactive protein; WBC – white blood cell.
For other abbreviations see under Table 1.

Table 7

Clinical accuracy of composite bioscore in predicting lethal outcome on the 3rd day

Composite bioscore	AUC ROC	*p*-value	95% confidence interval		Cut-off value	Sensitivity (%)	Specificity (%)	Youden index
			lower bound	upper bound				
	0.820	0.000	0.701	0.895	2.00	75.8	78.0	0.51

AUC ROC – area under the receiver operator characteristic curve.

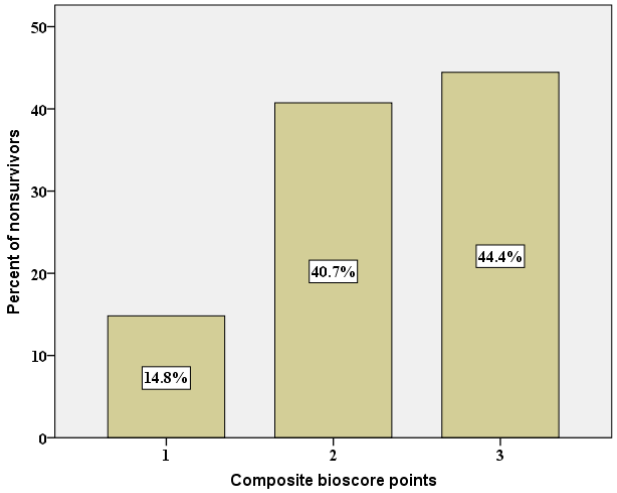

Fig. 2 – Percentage of non-survivors according to each bioscore point value on the 3rd day.

The association of investigated parameters with lethal outcomes was assessed by univariate logistic regression analyses. OR with 95% CI was calculated for each parameter. A forward stepwise multivariate logistic regression model was performed in order to determine the independent predictors of lethal outcome without the effect of possible confounders in each time point. In Table 8 univariate and multivariate logistic regression analyses of parameters for predicting lethal outcome on the 1st, 3rd, and 5th day are shown.

The only independent predictor of lethal outcome by multivariate logistic regression analysis on the 1st day was presepsin.

In the second time point, on the 3rd day, univariate logistic regression analyses of all parameters showed statistical significance only for MPV. This biomarker remained an independent predictor of lethal outcome by multivariate logistic regression analysis on the 3rd day.

In the third time point, on the 5th day, univariate logistic regression analyses of all parameters showed statistical significance only for WBC count and lactate. Both WBC count and lactate lost statistical significance by multivariate logistic regression analysis on the 5th day, therefore, they were not independent predictors of lethal outcome in this time point.

Table 8

Univariate and multivariate logistic regression analyses of parameters for predicting lethal outcome on the 1st, 3rd, and 5th day

Parameter	OR	Univariate logistic regression analysis			OR	Multivariate logistic regression analysis		
		95% CI		*p*-value		95% CI		*p*-value
1st day								
presepsin	1.000	1.000	1.001	0.040	1.000	1.000	1.001	0.035
procalcitonin	1.010	0.974	1.046	0.596				
C-reactive protein	0.999	0.994	1.005	0.771				
WBC count	0.994	0.939	1.052	0.833				
MPV	1.113	0.822	1.507	0.489				
lactate	1.006	0.822	1.231	0.953				
3rd day								
MPV	1.440	1.017	2.039	0.030	1.634	1.110	2.405	0.008
5th day								
WBC count	1.146	1.025	1.280	0.016				
lactate	4.063	1.303	12.666	0.016				

OR – odds ratio; CI – confidence interval; MPV – mean platelet volume; WBC – white blood cell.

Mantel-Cox log-rank to analyze survival time between each tertile of presepsin concentration, as well as Kaplan-Meier survival curve to analyze the probability of death between each tertile, were performed. Analysis of medians of survival in days, in three presepsin concentration tertiles, revealed that for our patient population, day 50 was the critical one. On the 50th day, the estimated mortality was 50%.

Log-rank pairwise comparisons demonstrated that there was a statistically significant difference between tertiles in survival time (shown in Table 9 and Figure 3).

presepsin and PCT in non-survivors on the 1st and 3rd day, yet PCT levels, as well as platelet count, did not differ significantly between survivors and non-survivors in any of three time points. Clinical accuracy of baseline parameters in predicting lethal outcome was investigated in all time points. On the 1st day, apart from all three scores, only presepsin demonstrated statistically significant discriminative power regarding the outcome. Levels of all three scores, as well as presepsin, higher than cut-off values, are moderate predictors of lethal outcome. On the 3rd day, apart from SAPS II and

Table 9

Log rank pairwise comparisons of survival time between presepsin tertiles on the 1st day

	Presepsin tertiles on the 1st day	χ^2	*p*-value
Mantel Cox Log Rank	tertile 1/tertile 2	3.857	0.040
	tertile 1/tertile 3	4.671	0.020

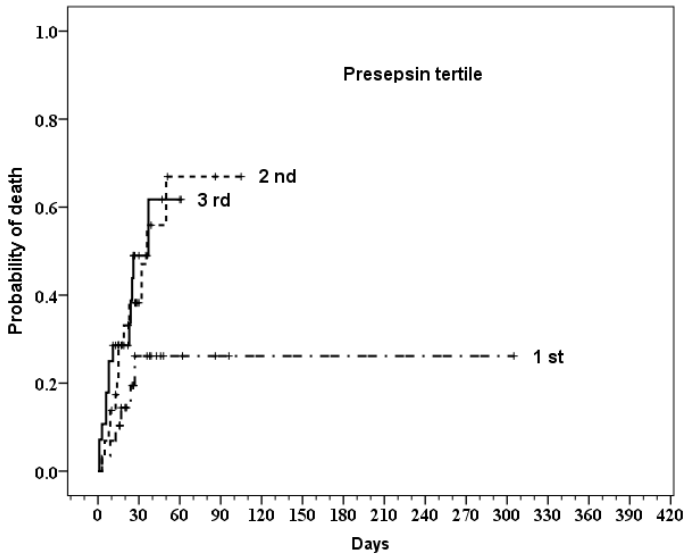

Fig. 3 – Kaplan-Meier survival curves for hospital mortality by tertiles of presepsin concentration on the 1st day.

Discussion

Treating everyone empirically with antibiotics and supportive measures is a difficult endeavor and often non-effective in some cases. Therefore, it is important to identify high-risk patients. Individual biomarkers and/or their various combinations can provide beneficial prognostic information regarding mortality in adult patients with sepsis. Mortality prediction is also an important factor in patient stratification. In our study, only presepsin levels were higher in non-survivors. The difference reached high statistical significance in all time points (on the 1st day – on admission, and then on the 3rd and 5th day after admission). The second best were MPV levels. They were significantly higher in non-survivors in two out of three time points: on the 3rd and 5th day. Serum lactate levels were significantly higher in non-survivors on the 3rd day. Finally, CRP levels and WBC count were significantly higher in non-survivors on the 5th day. There was a statistically significant positive correlation between SOFA score, presepsin, MPV, and lactate demonstrated statistically significant discriminative power regarding the outcome. On the 5th day, apart from SAPS II and SOFA score, presepsin, MPV, CRP, and WBC count demonstrated statistically significant discriminative power regarding the outcome. Levels of two scores, as well as presepsin, MPV, CRP, and WBC count higher than cut-off values, were very good predictors of lethal outcome. The combination of presepsin, MVP, and lactate into one composite bioscore on the 3rd day was performed in order to determine whether it would increase their discriminative power. On the 3rd day, composite bioscore had the highest AUC/ROC of 0.82 and the best combination of sensitivity and specificity, which is obvious from the high Youden index (above 0.5) compared to individual scores and parameters. Only on the 5th day, SAPS II score and presepsin reached the prognostic value of composite bioscore. It should be noted that it happened two days later, which is rather a long period of time when critically ill septic patients are concerned. Finally, the independ-

ent prognostic significance of parameters in predicting lethal outcome was assessed by univariate logistic regression analyses. A forward stepwise multivariate logistic regression model was performed in order to determine the independent predictors of lethal outcome without the effect of possible confounders in each time point. Only presepsin was an independent predictor of lethal outcome on the 1st day and MVP on the 3rd day by multivariate logistic regression analysis.

Our group has been investigating the predictive value of various parameters in critically ill patients for over a decade [11]. It is obvious that, in our study, the best choice of a predictive biomarker in this clinical setting was presepsin. This immuno-biomarker has a complex biological role. Apart from pro-inflammatory properties, it should be noted that sCD14 receptors can prevent cytokine release and facilitate endotoxin transfer to lipoproteins, which are both anti-inflammatory actions, by the virtue of competing with the membrane-bound forms for the free ligand [12]. Presepsin has gained significant attention over the last five years primarily because of the availability of the point-of-care Mitsubishi Pathfast™ compact immunoassay analyzer, with the clinically acceptable turnaround time for obtaining results being less than 20 min. This is important for both diagnostic and therapeutic clinical decisions. Landmark study regarding presepsin as a biomarker in critically ill septic patients is the analysis of data from the multicenter Albumin Italian Outcome Sepsis (ALBIOS) trial [13]. In a multicenter ALBIOS trial, 997 critically ill septic patients were recruited. Presepsin was measured in three time points: on the 1st, 2nd, and 7th day after admission. This timeline was slightly different than ours. Higher presepsin levels on the 1st day were associated with lethal outcome, which is in accordance with our results. Unlike the 90-day mortality rate in the ALBIOS trial, our outcome measure was hospital mortality which is time-consuming but more comprehensive. Levels of presepsin in our study (divided into tertiles) were comparable to those in the ALBIOS trial. ALBIOS investigators reported that presepsin concentration on the 1st day is an independent predictor of lethal outcome by multivariate logistic regression analysis, same as in our study. In the ALBIOS trial, the authors added a clinical model (which included all significant risk factors for mortality) to presepsin concentration on the 1st day in order to improve prognostic accuracy (AUC/ROC). This is a similar approach to our composite bioscore (presepsin, MPV, lactate), which improved AUC/ROC to 0.80 but on the 3rd day, in comparison with presepsin alone on the 1st day with AUC/ROC of 0.67. Interestingly, ALBIOS authors never reported AUC/ROC for presepsin alone, but only for the combination of presepsin and clinical model or clinical model alone. AUC/ROC for presepsin and clinical model was 0.80 in the ALBIOS trial, which is the same as AUC/ROC for composite bioscore in our study. ALBIOS investigators achieved this earlier, on the 1st day; in our study, it was achieved on the 3rd day. However, this is not comparable because, in the ALBIOS trial, investigators used 9 clinical components in the clinical model to add to presepsin. Most of these nine components include the length of stay, duration of infection, time to change in one or another aspect of therapy, etc. Therefore, data can be obtained only after a considerable amount of time and retrospectively. In contrast, we added only two readily available laboratory parameters, MPV and lactate, in our composite bioscore.

Brodska et al. [14] conducted a comparable study regarding diagnostic and prognostic values of presepsin versus established biomarkers in critically ill patients with sepsis (n = 30) and SIRS after cardiac surgery (n = 30). Among other things, they tested the hypothesis that presepsin, as a novel biomarker, can outperform traditional biomarkers as a predictor of 28-day mortality. Similar to our study, they also analyzed procalcitonin, CRP, and lactate in this regard. Opposite to our results, authors reported that all investigated biomarkers were significantly associated with mortality on the 1st day with comparable values of AUC/ROCs. In our study, only presepsin demonstrated statistically significant discriminative power regarding outcome on the 1st day. Moreover, in contrast to our results, they reported that multiple regression analyses showed independent associations of CRP and lactate with mortality. In our study, the independent predictor of lethal outcome was presepsin on the 1st day and MPV on the 3rd day. Lactate showed statistical significance in mortality prediction on the 5th day by univariate logistic regression analysis, yet statistical significance was lost by multivariate logistic regression analysis. Presepsin is a novel biomarker to diagnose sepsis, but its prognostic value has not been comprehensively reviewed until recently. Yang et al. [15] performed a systematic review and meta-analysis of the prognostic value of presepsin in adult septic patients and concluded that the 1st-day presepsin levels had prognostic value to predict mortality in adult patients with sepsis regardless of sepsis severity. However, they noted that further research is warranted for unified clinical information. In accordance with our results are the findings from Behnes et al. [16], who assessed the prognostic utility of presepsin in 116 critically ill septic patients. They reported that presepsin levels on the 1st, 3rd, and 8th day revealed significant prognostic value for 30 days and 6 months all-cause mortality (presepsin: range of AUCs 0.64 to 0.71, $p < 0.02$). Furthermore, just like in our study, in all three-time points, levels of procalcitonin and CRP were not statistically significant predictors of outcome. We had only one exemption, the CRP had an AUC of 0.64 on the 5th day with borderline statistical significance ($p = 0.04$). A similar smaller study was performed by El-Shafie et al. [17]. They enrolled 31 patients and measured presepsin and CRP on admission, on the 2nd and 4th day. The authors reported that all presepsin values were significantly higher in non-survivors while none of the CRP levels were significantly different between survivors and non-survivors. Additionally, ROC analysis was performed and the authors reported slightly higher AUCs in all-time points, compared to ours: 0.75, 0.80, and 0.83, respectively. Recently, another study comparing presepsin with procalcitonin and CRP as predictors of sepsis outcome has been published [18]. Fifty-five patients were enrolled and presepsin, procalcitonin, and CRP were measured on ad-

mission, 24 and 72 hours later. As in our study, the primary outcome was hospital mortality. Our study does not agree with the findings of Mahnod et al. [18], who reported that none of the investigated biomarkers (including presepsin, which was a good predictor of the outcome on admission in our trial) showed predictive ability regarding outcome on admission. Both presepsin and CRP showed good discriminative power at 24 and 72 hours while procalcitonin reached that ability at 72 hours. This is partially in accordance with our data regarding presepsin being a good predictor of mortality on the 3rd day; yet, in contrast to our data were the results regarding CRP and PCT. We found no predictive ability for either one at this time point. The idea of adding biomarkers to improve predictive ability is gaining momentum. An interesting approach to this problem was presented by Kim et al. [19]. In a retrospective study, authors opted to measure several biomarkers (including presepsin and procalcitonin) in leftover blood samples of 157 septic patients; the outcome measure was 30-day mortality. In accordance with our results, their data showed that PCT could not predict 30-day mortality and that AUC for presepsin was 0.68. Their multi-marker panel had an AUC of 0.77, AUC for SOFA score was 0.61. In our study, AUC for composite bioscore was higher, 0.82. A narrative review regarding novel biomarkers for sepsis reiterated the fact that sepsis, as a heterogeneous complex syndrome, is still incompletely understood and that literature regarding many of the established and emerging sepsis biomarkers produced conflicting results so far [20]. Utility, performance and validity of these biomarkers should be extensively tested. Presepsin and PCT are often investigated in their capacity to differentiate between bacterial systemic inflammatory response syndrome and nonbacterial one, which is their usefulness in early infection detecting [21–24]. In a most recent study, the authors enrolled 31 patients who underwent emergency abdominal surgery with abdominal infections. This patient population is comparable to our peritonitis and pancreatitis subgroups. They investigated preoperative levels of presepsin, CRP, and PCT and their correlation with clinical course and 90-day mortality [25]. Moreover, as in our study, they performed a multi-marker approach which is, especially, our composite bioscore. They reported that presepsin had the highest predictive value (AUC of 0.86) for mortality as opposed to previously established blood biomarkers like PCT, which is in accordance with our results. However, opposite to our results, their multi-marker approach, which included presepsin, PCT and interleukin-6, showed no additional predictive value over presepsin alone. The authors noted a very interesting fact that, although presepsin outperformed PCT, the latter is approved in the United States by the Food and Drug Administration (FDA) as a predictive sepsis marker.

Roughly one-third of our patient population was a group of trauma critically ill patients who developed secondary sepsis. In a recent systematic review [26], the prognostic value of serum PCT in critically ill trauma patients was investigated with conflicting results: out of six studies regarding PCT outcome prediction ability, four found significantly higher levels of PCT in non-survivors, which is in contrast to our results, while two demonstrated no association between PCT levels and lethal outcome, which is in accordance with our data. In our present study, CRP levels showed a statistically significant difference between survivors and non-survivors only on the 5th day, which is, from the clinical point of view, a rather late predictor of lethal outcome with an AUC of 0.64. On the 1st and 3rd day, there were no statistically significant differences in CRP levels between survivors and non-survivors, which is in accordance with our previous study demonstrating AUC for this biomarker being < 0.55, thus CRP failed to predict lethal outcome in a similar patient population [27].

Our composite bioscore showed statistically highly significant discriminative power regarding the outcome. Apart from presepsin, MPV and lactate levels were included. We demonstrated, in our previous research, that MPV was an independent predictor of lethal outcome in critically ill and injured patients who developed secondary sepsis [3]. Lactate levels are routinely used to assess circulatory function and tissue perfusion. Higher levels are thought to be associated with circulatory dysfunction and impaired tissue perfusion. Nonetheless, there is no clear-cut relationship and interpretation of results should be performed cautiously. Persistent hyperlactatemia may be the result of decreased clearance, not increased production. Additionally, when adrenalin is administered to the patients, the production of lactate can be increased in the presence of adequate tissue oxygenation. Lactate may be a substrate for metabolism, may be increased in liver dysfunction, and finally, may persist with or without tissue hypoperfusion [28]. In our study, lactate levels were statistically significantly higher in non-survivors on the 3rd day and at that time point demonstrated statistically significant discriminative power regarding outcome; lactate levels higher than cut-off values were good predictors of lethal outcome with an AUC of 0.64. These results are in accordance with other similar studies [29, 30].

Although we calculated study power and complied with the computed sample size, roughly two-thirds of critically ill patients with secondary sepsis had to be excluded primarily because of malignant disease. Therefore, for confirmation of our findings, a larger trial is warranted.

Sepsis continues to be a leading cause of death in hospitalized patients, with nearly 30 million patients worldwide and nearly 6 million deaths due to sepsis each year. Despite exhaustive investigations, there are no specific markers of sepsis yet. Investigators and clinicians alike are working on developing algorithms for early sepsis detection in order to improve survival. A major problem for early sepsis diagnosis, as well as early prognosis of sepsis outcome is highly expressed heterogeneity and significant variability in this patient population. Recently, an interesting study regarding the early prediction of sepsis from clinical data was published [31]. Authors concluded that diverse computational approaches predict the onset of sepsis several hours before clinical recognition, but generalizability to different hospital systems remains a challenge. Currently, more than 175 biomarkers have been studied in sepsis; the majority are inflammatory proteins [32].

Conclusion

Our research demonstrated that composite bioscore (presepsin, MPV, and lactate) is superior to routine biomarkers like PCT and CRP, as well as established scoring systems (APACHE II, SAPS II, SOFA) in predicting mortality in adult critically ill patients with secondary sepsis. Independent predictors of lethal outcome were also components of composite bioscore: presepsin on the 1st day and MPV on the 3rd day. That is clinically relevant because it is early enough to identify high-risk patients in order to improve their survival.

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