https://doi.org/10.15360/1813-9779-2026-3-2698

Prognostic Index for Compensation of Reduced Heart and Lung Functions in Patients with Sepsis

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For citation: *Sergey A. Andreychenko, Dmitry O. Ovcharov, Konstantin V. Yatskov, Georgy N. Arbolishvili, Maxim A. Rakhmanov, Tatyana V. Klypa.* Prognostic Index for Compensation of Reduced Heart and Lung Functions in Patients with Sepsis.*Obshchaya Reanimatologiya = General Reanimatology.* 2026; 22 (3): 4–12. https://doi.org/10.15360/1813-9779-2026-3-2698 [In Russ. and Engl.]

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Summary

Magnitude of heart rate (HR) fluctuation during sepsis and septic shock can significantly impact tissue perfusion and organ dysfunction.

The aim of the study is to examine and compare the predictive characteristics of a composite index based on clinical parameters and demographic variables for early risk stratification of mortality in patients with sepsis.

Materials and Methods. In a multicenter retrospective cohort study, data from 257 patients with sepsis or septic shock were analyzed, including age, sex, height, weight, severity of illness, comorbidities, bedside hemodynamic and respiratory monitoring parameters upon admission to the ICU, and 3 hours after the initiation of intensive therapy, as well as treatment outcomes. Statistical characteristics of the generated Prognostic Index for Compensation of Reduced Cardiorespiratory Function (PICRCF) were assessed, calculated as the ratio of the product obtained by multiplying heart rate by respiratory rate and by age to the product obtained by multiplying of diastolic blood pressure by body surface area (BSA). To identify clinical and laboratory predictors of fatal outcomes, all patients were divided into two groups: survivors and those who died during treatment.

Results. The hospital mortality rate in the analyzed patient sample was 48%. Differences were found between those who died and those who survived in terms of age, scores on the Glasgow (RR), heart rate (HR), and blood pressure (BP), as well as PICRCF values both upon admission ((PICRCF 0) and after 3 hours of intensive care ((PICRCF 3). Notably, (PICRCF 3 demonstrated the highest discriminative performance among all studied predictors (AUC 0.800; 95% CI 0.744–0.855) with a cutoff value of 1.1 (sensitivity 69%, specificity 85%). In the Cox proportional hazards model, (PICRCF 3 was the only independent predictor of mortality (OR 1.313 (95% CI 1.062–1.623), $p = 0.012$). Additionally, PICRCF values were associated with the number of days without organ replacement support.

Conclusion. The indicators reflecting the state of the cardiovascular and respiratory systems, indexed according to anthropometric and age characteristics, have several advantages over standard prognostic scales in the early risk stratification of patients with sepsis. The simplicity, accessibility, and rapid measuring of the components for calculating PICRCF allow for dynamic assessment of the patient's condition from the first minutes of admission to the ICU.

Keywords: predictive compensation index; reduced heart and lung function; mortality prediction in sepsis; sepsis; ICU

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Sepsis and septic shock are life-threatening complications, and intensive care for these conditions is aimed at restoring and maintaining adequate tissue perfusion [1]. The substrate for the deterioration of patient's condition is usually a combination of hemodynamic disturbances, the primary one being a decrease in vasomotor tone. In this context, vasoplegia has the most pronounced effect on diastolic blood pressure (DBP) compared to systolic blood pressure (SBP) or mean arterial pressure (MAP) [2].

However, DBP should not be assessed in isolation from heart rate (HR). A generalized infection activates the sympathetic nervous system, leading to the release of endogenous catecholamines and tachycardia. This biological mechanism is aimed at compensatory maintenance of cardiac output and vascular tone [3]. Nevertheless, persistent tachycardia contributes to increased myocardial oxygen consumption and may exacerbate coronary hypoperfusion [4]. Furthermore, prolonged sympathetic activation promotes the development of autonomic nervous system dysfunction [5].

The degree of changes in the combination of increased HR and decreased DBP can be assessed using the diastolic shock index (DSI). Several studies have demonstrated that opposing pathophysiological deviations in DBP and HR may indicate severe cardiovascular dysfunction, where increasing tachycardia is unable to compensate for diastolic hypotension. This allows the DSI to be used as a clinically significant predictor of adverse outcomes in a wide range of critical conditions [6–8].

In addition to arterial hypotension, tachycardia is associated with a number of clinical and demographic parameters. Although there is no evidence of a direct correlation, there is likely a certain inverse relationship between HR and body surface area (BSA) [9]. In turn, BSA, in addition to its wide clinical application as a biometric unit for standardizing physiological parameters, can also be directly applied for prognostic purposes. The predictive value of BSA has been confirmed in patients with acute kidney injury, congestive heart failure, and sepsis [10–12].

During cardiorespiratory testing, which allows for an objective assessment of exercise tolerance, maximum HR is of particular clinical significance, as it decreases proportionally with the patient's age [13]. Thus, the prognostic significance of HR varies across different age groups [14].

Respiratory rate (RR) is a well-known parameter for assessing the condition not only of the respiratory system but also of the entire body as a whole. RR is associated with clinical deterioration and mortality in various patient cohorts [15]. At the same time, RR and HR are also interrelated in a certain way and can be used to predict mortality in critically ill patients [16].

We hypothesized that the combination of the listed clinical and demographic parameters could serve as a simplified equivalent of the functional status of the cardiovascular and respiratory systems in patients in the intensive care unit (ICU).

The aim of the study is to investigate and compare the predictive characteristics of a composite index based on clinical and demographic paramters for early risk stratification of mortality in patients with sepsis.

Materials and Methods

A multicenter retrospective cohort study was conducted at the ICU of the Central Clinical Hospital of Russian Railways-Medicine, the ICU of the Federal Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia (FSCC FMBA), and ICU No. 8 of the Moscow Clinical Research Center of Hospital No. 52 of the Moscow City Health Department. The study included all patients with sepsis and/or septic shock hospitalized between January 2023 and December 2024. The criteria for «sepsis» and «septic shock» were defined in accordance with the Third International Consensus (Sepsis-3) [17]. The study was approved by the local ethics committee of the Federal Scientific and Clinical Center of the Federal Medical Biological Agency (Protocol No. 8_2023 dated September 12, 2023).

Patients who did not undergo invasive blood pressure monitoring, who were readmitted to the ICU, or who died within the first 3 hours after sepsis verification were excluded.

For analysis, data from electronic and/or paper medical records, including clinical and demographic characteristics of patients (age, sex, height, weight), assessment of severity of condition and comorbidities upon admission to the ICU (Glasgow Coma Scale (GCS), SOFA, APACHE II, Charlson Comorbidity Index), types of therapeutic modalities utilized (respiratory support and rate of mechanical ventilation (MV), vasopressor support, renal replacement therapy (RRT), as well as duration of treatment in the ICU, and outcome). Assessment of bedside vital signs was performed in two stages: the first upon the patient's admission to the ICU (BP_0, HR_0, RR_0); the second — 3 hours after initiation of intensive care (BP_3, HR_3, RR_3).

When processing missing readings median values were imputed, as their maximum proportion for each variable was less than 5%.

The Dubois formula was used to calculate BSA. DSI was calculated as the ratio of HR to DBP. We also assessed the statistical characteristics of a new indicator, named the prognostic index of compensation for reduced cardiorespiratory function (acronym «PICRCF»), calculated using the formula: PICRCF = (HR × RR × age / DBP × BSA) / 1000. For patients on mechanical ventilation, the default RR was set to 50. This figure was chosen based on the maximum rank value for RR in the APACHE II scale.

The hypothesis was that the predictive value of the composite PICRCF index would be higher than the predictive values of its components when used individually.

To identify clinical and laboratory predictors of mortality, all patients were divided into groups of survivors and those who died during treatment.

Statistical analysis of the data was performed using IBM SPSS Statistics 31.0.0.0 (IBM Corporation, USA). Continuous variables were expressed as the median and quartiles (*Me* [*Q1*; *Q3*]) and analyzed using the Mann–Whitney *U* test. Categorical variables were presented as absolute numbers and percentages and analyzed using Pearson's χ^2 test or Fisher's exact test. Cox univariate regression was used to assess the association between mortality and indicators differing between groups. Variables with a *p-value*<0.1 were included in a Cox proportional hazards multivariate regression model to identify independent predictors of in-hospital mortality. The assumption of proportional hazards for each predictor was assessed using log-log survival plots and analysis of partial (Schoenfeld) residuals over follow-up time. ROC analysis was performed to determine the cutoff point for the identified predictors. The optimal cutoff value, providing the best balance between sensitivity and specificity, was determined using the Youden index. The strength of the relationship between variables was assessed using Spearman's rank correlation coefficient. Two-sided *p-value*$<.05$ were considered statistically significant.

Sample adequacy was determined based on the «10 events per variable» (EPV) rule for Cox multivariate regression. Based on the estimated hospital mortality rate for sepsis in low- and middle-income countries of 40% [18], the minimum cohort size was 175 individuals. To account for an expected 20% rate of missing data (a conservative estimate based on a preliminary analysis of the local database), the target number of observations was increased to 219.

Results

The final study model included 257 patients (exceeding the minimum calculated sample size, $n=219$; Fig. 1).

In-hospital mortality was 48% (Table 1).

A comparison of parameters between surviving and deceased patients revealed significant differences in age, GCS, SOFA, APACHE II scores, and the Charlson Comorbidity Index ($p<0.001$). Deceased patients also had lower BSA values and were more frequently diagnosed with AF upon admission to the ICU. No differences in gender distribution were observed. When comparing bedside monitoring, baseline HR_0 and RR_0 were higher in the group of deceased patients, while SBP_0 and MAP_0 were higher in the group of survivors. After 3 hours of intensive care, differences between the groups in hemodynamic and respiratory parameters persisted and became apparent, including in SBP3 levels. Baseline values of combined calculated indices (DSI_0 and $PICRCF_0$) also differed and were higher in the group of deceased patients ($p<0.001$). After 3 hours of targeted intensive care, a similar trend persisted for DSI_3 and $PICRCF_3$.

The need for vasopressor support, MV, and RRT was higher in the group of deceased patients ($p<0.001$).

After testing for multicollinearity among the clinically significant parameters differing between surviving and deceased patients, a univariate Cox regression analysis was performed (Table 2). Of the 7 variables included in the Cox proportional hazards multivariate model, only $PICRCF_3$ was statistically significantly associated with the risk of death in patients with sepsis (OR 1.313 (95% CI 1.062–1.623), $p=0.012$).

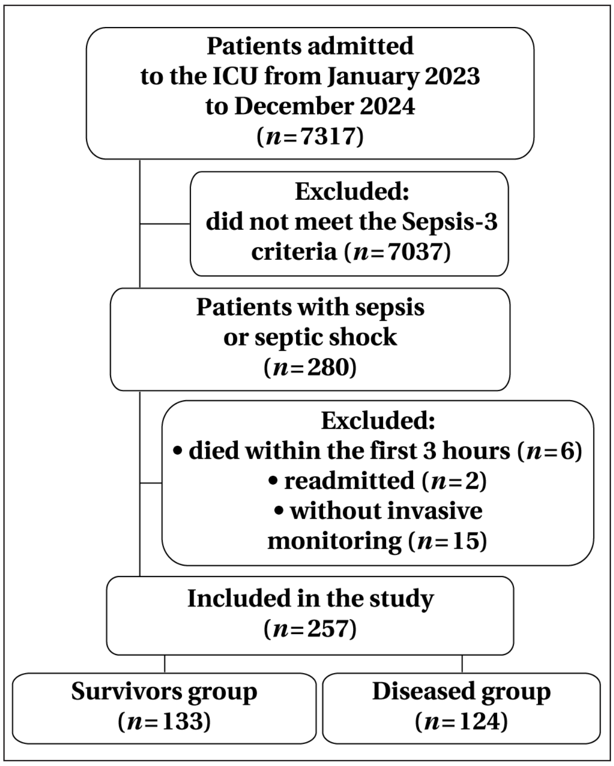

Fig. 1. Flowchart of patient selection for the study.

Among the early predictors of mortality studied, $PICRCF_3$ had the highest discriminatory power with an AUC of 0.800 (95% CI 0.744–0.855), a cutoff value of 1.1, with a sensitivity of 69% (95% CI 60–77%) and a specificity of 85% (95% CI 78–91%). The positive predictive value was 81% (95% CI 72–88%), and the negative predictive value was 74% (95% CI 67–81%). Furthermore, the predictive value of $PICRCF_3$ exceeded that of $PICRCF_0$ (Fig. 2, *b*).

In the correlation analysis, $PICRCF_3$ was also associated with the number of vasopressor-free days (*rho*=–0.5), ventilator-free days (*rho*=–0.5), and RRT-free days (*rho*=–0.3) (all $p<0.001$).

Discussion

A hyperdynamic circulatory pattern with increased cardiac output and low systemic vascular resistance is the most typical course of sepsis and septic shock. However, prolonged sympathetic hyperactivation can lead to myocardial dysfunction characterized by a significant deterioration in hemodynamics in the context of tachycardia [19]. This relationship between heart rate and mortality can be described by a *U*-shaped curve. Thus, during sepsis, both very low and very high heart rates increase the risk of death [20]. However, international

Table 1. Clinical, demographic, laboratory, and diagnostic parameters of deceased and surviving patients with sepsis ($n=257$).

Parameters	Parameter values in the groups		p
	Survivors, $n=133$	Diseased, $n=124$	
Age, years	64 [54–72]	71 [58–77]	<0.001
Male, n (%)	71 (53.4)	73 (58.9)	0.376
BMI, kg/m^2	27.0 [24.1–31.6]	25.1 [22.5–29.4]	0.006
BSA, m^2	1.91 [1.79–2.07]	1.82 [1.69–1.97]	0.001
GCS, scores	15 [15–15]	15 [12–15]	<0.001
SOFA, scores	6 [4–8]	8 [6–11]	<0.001
APACHE II, scores	19 [16–24]	24 [20–29]	<0.001
Charlson Index, scores	6 [4–9]	9 [6–12]	<0.001
Prevalence of AF on admission to the ICU, n (%)	17 (12.8)	34 (27.4)	0.003
CVP, cm H_2O.	4 [1–8]	5 [2–7]	0.487
Treatment results			
HR$_0$, beats per minute	95 [80–110]	101 [86–119]	0.002
HR$_3$, beats per minute	90 [78–102]	100 [86–117]	<0.001
Respiratory rate 0, breaths per minute	18 [17–20]	19 [18–22]	0.002
RR$_3$, breaths per minute	18 [16–20]	18 [17–21]	0.006
SBP$_0$, mm Hg	117 [98–130]	105 [90–128]	0.062
SBP$_3$, mm Hg	120 [102–130]	110 [95–125]	0.003
DBP$_0$, mm Hg	66 [56–75]	60 [51–70]	0.004
DBP$_3$, mm Hg	65 [59–73]	60 [54–69]	<0.001
MAP$_0$, mm Hg	83 [71–93]	75 [65–87]	0.007
MAP$_3$, mm Hg	83 [73–92]	76 [68–87]	<0.001
DSI$_0$	1.4 [1.2–1.7]	1.7 [1.3–2.1]	<0.001
DSI$_3$	1.4 [1.1–1.6]	1.7 [1.4–2.0]	<0.001
PICRCF$_0$	0.9 [0.7–1.1]	1.3 [0.9–1.9]	<0.001
PICRCF$_3$	0.8 [0.6–1.0]	1.4 [1.0–1.9]	<0.001
Length of treatment in the ICU, days	6 [3–11]	7 [2–15]	0.546
MV rate, n (%)	39 (29.3)	124 (100)	<0.001
RRT rate, n (%)	40 (30.1)	93 (75.0)	<0.001
Frequency of vasopressor support, n (%)	94 (70.7)	124 (100)	<0.001

Note. BMI — body mass index; BSA — body surface area; GCS — Glasgow Coma Scale; AF — atrial fibrillation; CVP — central venous pressure; ICU — intensive care unit; MV — mechanical ventilation; RRT — renal replacement therapy; HR, RR — heart rate, respiratory rate; SBP, DBP, MAP — systolic blood pressure, diastolic blood pressure, mean arterial pressure; DSI — diastolic shock index; PICRCF — prognostic index of compensation for reduced heart and lung function; subscript indices: 0 — on admission, 3 — after 3 hours of intensive care. SOFA — Severe Organ Failure Assessment; APACHE II — acute physiology and chronic health evaluation.

Table 2. Cox regression analysis accounting for variables associated with in-hospital mortality.

Variable	Univariate Cox regression		Multivariate Cox regression	
	OR (95% CI)	p	OR (95% CI)	p
BMI	0.974 (0.949–1.000)	0.054	0.991 (0.963–1.020)	0.549
GCS	0.964 (0.915–1.016)	0.172		
SOFA	1.025 (0.969–1.085)	0.392		
APACHE II	1.044 (1.018–1.071)	<0.001	1.016 (0.982–1.050)	0.373
Charlson M.index	1.049 (1.006–1.093)	0.024	1.030 (0.984–1.078)	0.206
AF on admission	1.336 (0.898–1.987)	0.153		
HR$_0$	1.007 (1.000–1.015)	0.062	1.002 (0.992–1.013)	0.660
RR$_3$	0.990 (0.939–1.045)	0.725		
DBP$_0$	0.994 (0.982–1.005)	0.286		
MAP$_3$	0.982 (0.968–0.996)	0.010	0.993 (0.973–1.013)	0.496
DSI$_3$	1.669 (1.250–2.230)	<0.001	1.105 (0.642–1.902)	0.719
PICRCF$_3$	1.522 (1.291–1.795)	<0.001	1.313 (1.062–1.623)	0.012

Note. See the notes for Table 1 for an explanation of abbreviations.

guidelines for the intensive care of sepsis specify a particular level of MAP to guide treatment strategy, without indicating target HR values [21]. This approach is likely flawed and requires revision in light of the body of evidence from recent clinical trials.

The shock index, first proposed more than half a century ago! and calculated as the ratio of HR to MAP, is a simple and informative hemodynamic parameter for the early diagnosis of shock and hypoperfusion [22]. Numerous studies have demonstrated its prognostic value, including in patients with sepsis [23]. Subsequently, several variations of the index were proposed to expand the capabilities of assessing hemodynamic status — the so-called modified shock index (ratio of HR to MAP), as well as the diastolic and age-adjusted shock indices (the product of age and the ratio of HR to SBP). All of these modifications have also been validated for identifying patients with sepsis and an increased risk of death [24, 25, 6]. Furthermore, when comparing the variations of the indices with one another, the age-adjusted shock index demonstrated the highest prognostic accuracy [26]. Thus, it can be concluded that adding an age component improves the discriminatory characteristics of hemodynamic predictors of mortality in sepsis.

In the mammalian phylogenetic series, an allometric relationship is observed between an increase in body size and a decrease in heart rate. Within the human population, this relationship is nonlinear and varies depending on lifestyle, constitutional characteristics, and the state of autonomic regulation [27]. Nevertheless, several studies have demonstrated an association between stroke volume and BSA [28], as well as an inverse correlation between height and resting HR in healthy volunteers [29]. Furthermore, the increase in survival with increased BSA in patients with sepsis can also be explained by the «obesity paradox». Patients with larger BSA (and, as a rule, with increased body weight) have greater reserves of fat and muscle mass, which serve as reservoirs of energy and amino acids [30]. Thus, high BMI values serve, to a certain extent, as markers of the body's greater physiological reserves.

We developed the PICRCF formula based on literature data regarding the association of HR, age, RR, diastolic BP, and BSA with mortality. The direction of these associations determined the distribution of components between the numerator and denominator: factors associated with an increased risk of mortality were placed in the numerator, and those associated with a reduced risk — in the denominator. Thus, PICRCF represents a modification of the age-adjusted DSI, adjusted for RR and BSA. This indexing allowed for further improvement of the predictive characteristics of the developed indicator with minimal complication of the calculation formula.

The combination of clinical-demographic, respiratory, and hemodynamic data from bedside monitoring associated with HR, as presented in this study, allows for the effective prediction of an adverse treatment outcome in patients with sepsis upon admission to the ICU. Furthermore, the results indicate that the discriminatory ability of the prognostic index calculated based on these indicators increases when they are reassessed after the completion of the initial phase of intensive care, which is consistent with published data [31].

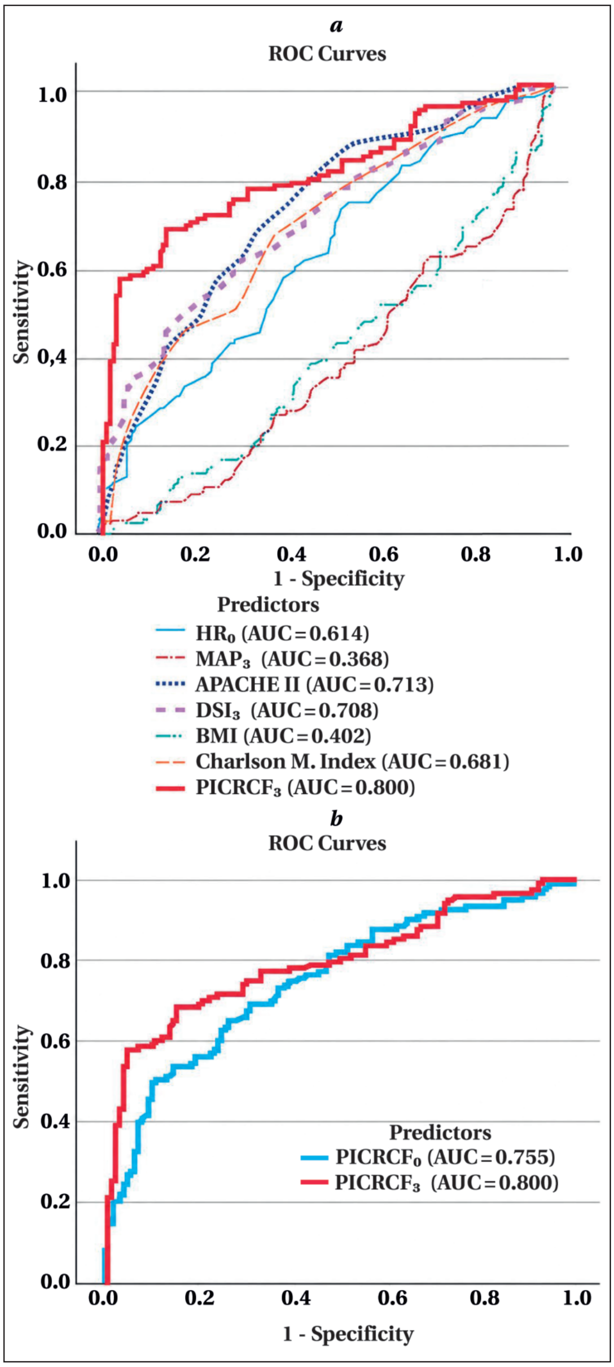

Fig. 2. ROC curves for predictors of in-hospital mortality in patients with sepsis (a) and the PICRCF score before and after 3 hours of intensive care (b).

Note. PICRCF indices: 0 –on admission; 3 – after 3 hours of intensive care. For a, b – all p<0.05.

From a practical standpoint, this allows for rapid bedside stratification of patients based on readily available clinical parameters. For example, during sepsis, a decrease in diastolic BP from 60 to 40 mm Hg accompanied by an increase in HR from 90 to 125 beats per minute and RR from 20 to 24 breaths per minute in an average 40-year-old patient who is 170 cm tall and weighs 69 kg is associated with a 31% increase in the risk of in-hospital mortality. However, for an 80-year-old patient with identical anthropometric characteristics, such changes in hemodynamic and respiratory parameters and the need for only mechanical ventilation will increase the risk of an adverse outcome by 62%. Thus, the predictive value of PICRCF, in addition to statistical characteristics that exceed standard prognostic scales, lies in the ability to identify high-risk patients early, optimize resource allocation, and individualize intensive care.

The study's limitations should be noted. First, due to the retrospective nature of the analysis, data on the types and doses of vasopressors were not taken into account. Nevertheless, a study by Y. Shen et al. [20] demonstrated that in patients with sepsis, mortality is associated with tachycardia regardless of norepinephrine use. Second, the exclusion of patients in an agonal state, as well as those readmitted to the ICU, may have limited the diagnostic value of the results obtained due to selection bias. Nevertheless, the deterioration in vital signs among patients with sepsis — resulting from decompensated multiple organ failure following delayed transfer to the ICU and subsequent death — could also have significantly skewed the results. Third, the current study did not analyze parameters of advanced hemodynamic and laboratory monitoring. However, there is evidence of a variable effect of tachycardia on in-hospital mortality depending on the cardiac index [32] or serum lactate concentration [33]. Fourth, patients with cardiac arrhythmias were not excluded from the study. AF was recorded in 20% of patients upon admission to the ICU. In the tachysystolic variant of AF, PICRCF index values may have been overestimated, thereby distorting the true assessment of disease severity. Fifth, the PICRCF index was assessed at limited time points — upon admission and after 3 hours — which allows for characterization primarily of the early stage of sepsis. The absence of follow-up measurements makes it impossible to assess the prognostic significance of the index at later time points and its dynamics against the backdrop of ongoing intensive care, which requires further prospective studies. Sixth, a fixed RR value was used to calculate PICRCF in patients on mechanical ventilation, which may have limited the accuracy of assessing the respiratory component's contribution to the index value. However, the need for mechanical ventilation in sepsis is an independent predictor of poor outcome, as it reflects the severity of multiple organ failure [34]. Since critical deviations in RR (both tachypnea and bradypnea) in patients with sepsis are an indication for mechanical ventilation, the actual RR in patients on mechanical ventilation loses its independent prognostic value. Similarly to the widely accepted and validated APACHE II scale, where the maximum score for RR is assigned upon reaching the threshold of respiratory decompensation (⩾50 per minute) and does not increase further, reflecting a «ceiling effect» of risk, the continuous value of RR in patients on MV in the PICRCF index serves as a standardized marker of disease severity. This approach, which treats RR as a continuous variable (rather than introducing the dichotomous variable «mechanical ventilation» into the model), allowed us to include in the analysis patients who were on mechanical ventilation from the very first hours of treatment in the ICU, highlighting the severity of their condition without reducing the index's discriminatory power or complicating the calculation formula. An additional physiological rationale is the proven nonlinear (J-shaped) relationship between in-hospital mortality and RR in critically ill patients [35], which confirms the appropriateness of a threshold-based, rather than a linear interpretation of extreme RR values. Finally, the PICRCF formula was developed using the a priori method, without internal validation. Thus, despite the multicenter nature of the study, external validation of the PICRCF index on an independent cohort of patients is necessary prior to its clinical implementation.

The body of data presented allows us to conclude that vital signs reflecting the state of the cardiovascular and respiratory systems, indexed to account for anthropometric and age-related characteristics, offer a number of advantages in early risk stratification in patients with sepsis. Unlike dichotomous and rating scales, the index-based approach allows for continuous bedside assessment of parameters, making it possible to account for even minor changes in physiological parameters. Recording a set of minimal deviations in the functioning of the respiratory and cardiovascular systems in patients with sepsis may be clinically significant, indicating the onset of decompensated organ dysfunction. Furthermore, the numerical scoring format of the calculated index is not subject to subjectivity, unlike assessments of skin mottling (livedo reticularis) or capillary refill time. The simplicity, accessibility, and speed of measuring the components used to calculate PICRCF enable dynamic assessment of patient's condition from the very first minutes of admission to the ICU, which is crucial for the timely identification of the severity of sepsis.

Conclusion

The PICRCF index, based on a combination of cardiovascular and respiratory parameters, as well as demographic and anthropometric characteristics, offers advantages over standard prognostic scales in patients with sepsis. The predictive value of this index 3 hours after the start of intensive care was the highest among the early predictors of mortality studied in this research, with an AUC of 0.800 (95% CI 0.744–0.855), a cutoff value of 1.1, with a sensitivity of 69% and a specificity of 85%. In addition, PICRCF index values were associated with the number of days without organ replacement support.

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Received 21.03.2026
Accepted 13.05.2026
Online First 08.06.2026