







## PREDICTION IN INTENSIVE CARE MEDICINE

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### Risk factors for adverse sepsis outcomes in patients with prolonged ICU stay: a real-world clinical practice (retrospective study)

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#### Abstract

**INTRODUCTION:** Sepsis in patients with prolonged and chronic critical illness (PCI/CCI) is frequently characterized by recurrent episodes and a high incidence of severe complications; however, risk factors for adverse sepsis outcomes in this population remain insufficiently studied. **OBJECTIVE:** To identify independent predictors of sepsis unfavorable outcomes in critically ill patients with a prolonged and chronic critical illness. **MATERIALS AND METHODS:** The analysis was based on the Russian Intensive Care Dataset (RICD) v2.0 (FRCRR, 2017–2024). Patients with confirmed sepsis according to Sepsis-3 criteria were included. Demographic characteristics, comorbidities, clinical scores, laboratory values, and vital parameters at the onset of the first sepsis episode were assessed. Independent predictors were determined using multivariable Cox regression. **RESULTS:** A total of 336 patients were analyzed (median age, 64 years; male, 54.8 %). ICU mortality was 14.0 %, and the median intensive care unit (ICU) length of stay was 44 days (30; 62). Septic shock occurred in 55 patients (16.4 %) and was independently associated with the hyperinflammatory sepsis phenotype (hazard ratio [HR] 5.23; 95% confidence interval [CI] 1.61–17.04;  $p = 0.006$ ) and lower diastolic blood pressure at sepsis onset (HR 0.975; 95% CI 0.954–0.996;  $p = 0.019$ ). Recurrent sepsis was observed in 96 patients (28.6 %); the only independent predictor was the hypoinflammatory phenotype (HR 5.23; 95% CI 1.29–13.01;  $p = 0.002$ ). Sepsis-induced coagulopathy occurred in 78 patients (23.2 %) and was independently predicted by a reduced platelet count (HR 0.997; 95% CI 0.994–0.999;  $p = 0.026$ ). **CONCLUSIONS:** This study is the first to identify independent risk factors for complicated sepsis in patients with PCI/CCI. The findings may be applied to risk

## ПРОГНОЗИРОВАНИЕ В ИНТЕНСИВНОЙ ТЕРАПИИ

### Факторы риска неблагоприятного течения сепсиса у длительно находящихся в ОРИТ пациентов: реальная клиническая практика (ретроспективное исследование)

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#### Реферат

**АКТУАЛЬНОСТЬ:** Сепсис у пациентов в продленном и хроническом критическом состоянии (ПКС и ХКС) сопровождается рецидивирующим течением и высокой частотой развития осложнений, однако факторы риска неблагоприятного течения сепсиса у данной категории пациентов остаются малоизученными. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Определить независимые предикторы неблагоприятного течения сепсиса у пациентов в ПКС и ХКС в отделении реанимации. **МАТЕРИАЛЫ И МЕТОДЫ:** Анализ выполнен на основе российской базы данных реанимационных пациентов версии 2.0 (Федеральный научно-клинический центр реаниматологии и реабилитологии [ФНКЦ РР]) в 2017–2024 гг. В исследование включались пациенты с верифицированным сепсисом по критериям Sepsis-3. Рассматривались демографические показатели, сопутствующие заболевания, шкалы, лабораторные данные и витальные параметры на момент начала первого эпизода сепсиса. Для выявления независимых факторов риска использовался многофакторный регрессионный анализ Кокса. **РЕЗУЛЬТАТЫ:** В анализ включено 336 пациентов (медианный возраст — 64 года, мужчин — 54,8 %). Летальность составила 14,0 %, медиана длительности госпитализации в отделениях реанимации и интенсивной терапии (ОРИТ) — 44 (30; 62) дня. Септический шок развился у 55 пациентов (16,4 %) и был независимо связан с гипервоспалительным фенотипом сепсиса (отношение рисков [ОР] 5,23; 95%-й интервал [95% ДИ] 1,61–17,04;  $p = 0,006$ ) и более низким диастолическим артериальным давлением (ОР 0,975; 95% ДИ 0,954–0,996;  $p = 0,019$ ). Повторные эпизоды сепсиса зафиксированы у 96 пациентов (28,6 %); независимым предиктором оказался гиповоспалительный



stratification and the development of dedicated prognostic models in this high-risk ICU population.

**KEYWORDS:** sepsis, critical illness, septic shock, coagulopathy, risk factors

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фенотип сепсиса (ОР 5,23; 95% ДИ 1,29–13,01;  $p = 0,002$ ). Сепсис-индуцированная коагулопатия наблюдалась у 78 пациентов (23,2 %); ее предиктором был сниженный уровень тромбоцитов (ОР 0,997; 95% ДИ 0,994–0,999;  $p = 0,026$ ). **ВЫВОДЫ:** Впервые определены независимые факторы риска осложненного течения сепсиса у пациентов в ПКС и ХКС. Результаты могут быть использованы для стратификации риска и разработки специализированных прогностических моделей в данной популяции пациентов.

**КЛЮЧЕВЫЕ СЛОВА:** сепсис, критически больные пациенты, септический шок, коагулопатия, факторы риска

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## Introduction

Sepsis remains one of the leading causes of adverse outcomes in intensive care units (ICUs), accounting for a substantial proportion of in-hospital mortality and long-term disability among survivors [1–3]. Despite advances in early diagnosis, antimicrobial therapy, fluid resuscitation strategies, and vasoactive support, mortality rates associated with sepsis remain high, reaching 25–50 % according to international registries [4–7].

In recent years, increasing attention has been paid to a subgroup of patients with prolonged and chronic critical illness (PCI/CCI) [8]. This population is characterized by persistent organ dysfunction, extended ICU stay, and a high incidence of nosocomial infections [8, 9]. Notably, a unified

definition of PCI/CCI has not yet been established [10,11]. The clinical course of sepsis in these patients is frequently complicated by a range of adverse events, among which septic shock, recurrent sepsis episodes, and sepsis-induced coagulopathy (SIC) are of particular importance [12–18]. Septic shock is characterized by profound microcirculatory disturbances and persistent arterial hypotension requiring fluid resuscitation combined with vasopressor support and remains one of the principal causes of mortality [19]. Recurrent sepsis episodes in the ICU setting may be associated with prolonged hospitalization and an increased incidence of nosocomial infections [20, 21].

In recent years, sepsis-induced coagulopathy has been increasingly recognized as an early and common manifestation of sepsis-related hemostatic disturbances. According to

published data, laboratory signs of coagulopathy are detected in 20–60 % of patients with sepsis [22]. Sepsis-induced coagulopathy is associated with an elevated risk of thrombotic complications and a significant increase in mortality, which may reach 20–30 % [22, 23].

Widely used severity scoring systems in intensive care (Acute Physiology and Chronic Health Evaluation II [APACHE II], Sequential Organ Failure Assessment [SOFA], Simplified Acute Physiology Score) may be used to predict adverse outcomes in patients with sepsis; however, their discriminative ability with respect to specific complications may be limited [24–26]. This is particularly relevant for patients with prolonged and chronic critical illness, for whom independent risk factors for adverse sepsis course have not been sufficiently studied.

## Objective

The aim of the study was to identify independent predictors of adverse sepsis outcomes in patients with prolonged and chronic critical illness in the intensive care unit.

## Materials and methods

### Data source

Data for the study were obtained from the Russian Intensive Care Dataset (RICD), version 2.0, developed and maintained by the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow, Russia [27, 28]. RICD is a de-identified relational database that includes clinical information on 3,404 ICU patients treated at the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology between December 2017 and September 2024. The RICD contains demographic data, information on comorbidities, laboratory test results, continuously recorded vital parameters, data on therapeutic interventions, severity scores, and hospitalization outcomes and complications occurring during the hospital stay.

### Study design

This real-world clinical practice study included patients who stayed in the ICU for at least 24 hours and had data available for at least one assessment of sepsis according to the Sepsis-3 criteria [29] during hospitalization. Patients who did not develop sepsis during their ICU stay were excluded, as were those with no available data on monitored vital parameters and therapeutic interventions during hospitalization. Episodes of repeated ICU admissions were also excluded.

No formal sample size calculation was performed; all patients meeting the selection criteria during the eight-year observation period were included in the analysis. The study

protocol was approved by the Local Ethics Committee of FRCCICMR (No. 1/24/1 dated April 24, 2024) and was conducted in accordance with recommendations for prognostic factor research and the development of prognostic models [30].

### Data extraction

The analytical cohort was formed on the basis of electronic medical record data using specialized tools for working with relational databases. Primary data extraction and calculation of variables were performed using DB Browser for SQLite (v.3.13.1) and the Python programming language (v.3.12). To ensure reproducibility, the program code has been made publicly available in an open repository (GitHub: <https://github.com/MikhailYadgarov/RICDv2-sql-code>).

The analysis included information on the time of sepsis development, demographic and anthropometric characteristics (age, sex, body mass index), data on comorbidities, and severity scores at the time of the first sepsis episode. Laboratory parameters and vital signs were also analyzed; the values closest to the onset of the first septic episode were selected within  $\pm 24$  hours for laboratory parameters and  $\pm 3$  hours for vital signs.

As hospitalization outcomes, mortality, development of septic shock (patients receiving vasopressors before the onset of the first sepsis episode were excluded from the assessment of septic shock), ICU and hospital length of stay, duration of sepsis episodes, presence of recurrent sepsis episodes and their characteristics, use of vasoactive support and mechanical ventilation during the first sepsis episode, occurrence of nosocomial pneumonia, and development of sepsis-induced coagulopathy and disseminated intravascular coagulation (according to the ISTH SIC and DIC criteria [31, 32]) during the first sepsis episode were evaluated. The completion of a sepsis episode was defined as discontinuation of antibacterial therapy [33, 34].

To assess phenotypic features of sepsis, an approach based on the systemic inflammatory response syndrome (SIRS) criteria was used. A sepsis episode was classified as hyperinflammatory if  $\geq 2$  points according to the SIRS criteria were reached at any time during its course; in other cases, a hypoinflammatory phenotype was recorded. SIRS criteria were calculated retrospectively, while SOFA scores were extracted directly from electronic medical records. Given the retrospective nature of the study and the use of routinely collected clinical data, blinding procedures were not considered necessary.

### Statistical analysis

Before analysis, the distribution of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables are presented as median and interquartile range (IQR), and categorical variables as absolute values and per-

centages. The  $\chi^2$  test or Fisher's exact test was used to compare categorical variables, and the Mann-Whitney U test was used for continuous variables. All statistical tests were two-sided, differences were considered statistically significant at  $p < 0.05$ , and Bonferroni correction was applied for multiple hypothesis testing.

Time-to-event characteristics (survival) were calculated from the onset of the first sepsis episode, which made it possible to exclude immortal time bias. Comparison of survival curves constructed using the Kaplan-Meier method was performed using the log-rank test. To evaluate the prognostic significance of individual risk factors, univariable analysis based on the Cox proportional hazards model was performed. Variables that demonstrated statistical significance were included in multivariable analysis with calculation of adjusted hazard ratios and 95 % confidence intervals. Variables with more than 30 % missing data were not included in multivariable analysis.

When several independent predictors were identified, a prognostic model was constructed based on multivariable Cox regression with assessment of discriminative ability using Harrell's C-index. Missing data were not imputed.

Statistical analysis was performed using IBM SPSS Statistics (version 29.0.1; IBM Corp., USA) and the Python programming language (version 3.12) using specialized libraries (pandas, numpy, lifelines, matplotlib).

## Results

### Patient characteristics

A total of 336 patients with confirmed sepsis were included in the study. The patient selection flowchart is presented in Figure 1.

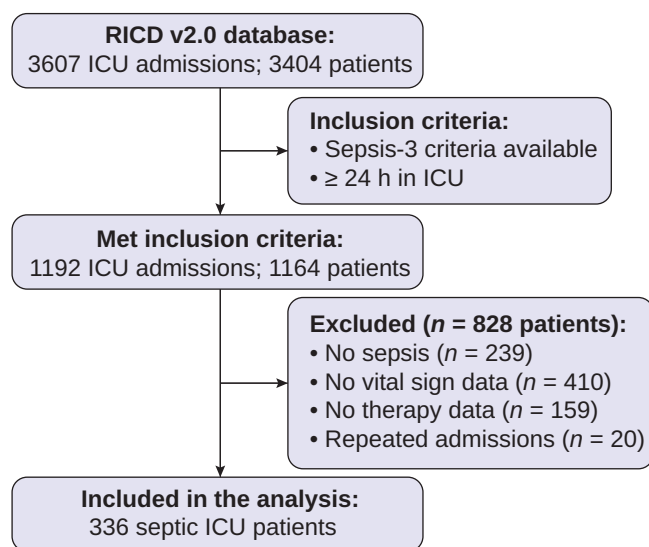


Fig. 1. Flowchart of patient selection into study

The median age of the patients was 64 years (48; 74). The median time from ICU admission to the onset of the first sepsis episode was 10 days (4.0; 17.0), and the median duration of the first episode was 9.7 days (4.3; 16.8). Most patients were in prolonged/chronic critical illness, the median ICU length of stay reached 44 days (30; 62), and more than 98 % of patients were transferred from ICUs of other institutions. The most common comorbidities were arterial hypertension ( $n = 269$ ; 80.1 %) and coronary artery disease ( $n = 209$ ; 62.2 %). Pneumonia was present in more than 70 % of patients at ICU admission.

### Hospital outcomes

ICU mortality was 14.0 % (47 patients), and the median time from the onset of the first sepsis episode to death was 36 days (27; 53). Septic shock during the first sepsis episode developed in 55 patients (16.4 %), with a median time of 13 days (6; 25) from the onset of the episode. The presence of septic shock was associated with a longer duration of the first sepsis episode (median 35 days *vs* 18 days,  $p < 0.001$ ) and a higher incidence of nosocomial pneumonia (100 % *vs* 85.6 %,  $p < 0.001$ ) and was also associated with a higher incidence of sepsis-induced coagulopathy (40.0 % *vs* 14.8 %,  $p < 0.001$ ), Table 1.

DIC criteria were assessed in 21 patients, and disseminated intravascular coagulation was confirmed in 15 cases (71.4 %). The hyperinflammatory sepsis phenotype was recorded in 243 patients (72.3 %) during the first episode. Mechanical ventilation during the first sepsis episode was required in 319 patients (94.9 %). Nosocomial pneumonia developed in 299 patients (89.0 %).

Recurrent sepsis episodes were observed in 96 patients (28.6 %), and the median time from the end of the first sepsis episode to recurrence was 29 days (19; 40). Recurrences of sepsis were associated with a longer ICU length of stay (median 58 days *vs* 38 days,  $p < 0.001$ ) and a longer total hospital length of stay (median 69 days *vs* 55 days,  $p < 0.001$ ), Table 2.

Sepsis-induced coagulopathy was recorded in 78 patients (23.2 %), and the median time from the onset of the sepsis episode to its development was 10 days (3; 22). The presence of sepsis-induced coagulopathy was associated with increased mortality (28.2 % *vs* 7.3 %,  $p < 0.001$ ), as well as with a higher frequency of vasopressor/inotrope use (53.8 % *vs* 21.0 %,  $p < 0.001$ ),

### Predictors of septic shock

In univariable analysis, predictors of septic shock development were the hyperinflammatory sepsis phenotype (HR 6.74,  $p = 0.001$ ), shorter time to sepsis onset (HR 0.998,  $p = 0.011$ ), lower diastolic blood pressure at the onset of the sepsis episode (HR 0.976,  $p = 0.024$ ), and the presence of pneumonia at admission (HR 2.35,  $p = 0.026$ ), Table 4. In multivariable analysis, two independent pre-

**Table 1.** Comparison of baseline characteristics and hospitalization outcomes of ICU patients depending on the development of septic shock during the first sepsis episode

Parameters		No septic shock (n = 243)	Septic shock† (n = 55)	p-value*
Time to first sepsis episode, h		240 (96; 384)	120 (48; 216)	< 0.001 <sup>1</sup>
Time from onset of sepsis episode to development of septic shock, days		—	13 (6; 25)	—
Sepsis phenotype (first episode)	Hyperinflammatory	155; 63.8 %	52; 94.5 %	< 0.001 <sup>3</sup>
	Hypoinflammatory	88; 36.2 %	3; 5.5 %	
Sex	Male	134; 55.1 %	32; 58.2 %	0.7 <sup>2</sup>
	Female	109; 44.9 %	23; 41.8 %	
Age, years		61 (48; 73)	69 (52; 76)	0.1 <sup>1</sup>
BMI, kg/m <sup>2</sup>		n = 205; 24.8 (22.5; 28.9)	n = 51; 26.4 (21.9; 30.9)	0.4 <sup>1</sup>
Transfer from another ICU		240; 98.8 %	53; 96.4 %	0.2 <sup>3</sup>
Pneumonia at admission		169; 69.5 %	47; 85.5 %	0.019 <sup>2</sup>
<b>Scores at the time of the first sepsis episode</b>				
APACHE II, score		n = 15; 15 (12; 17)	n = 6; 20 (15; 27)	0.1 <sup>1</sup>
NUTRIC, score		n = 15; 4 (2; 5)	n = 6; 5 (4; 5)	0.2 <sup>1</sup>
SOFA, score		5 (4; 6)	5 (4; 6)	0.1 <sup>1</sup>
SIRS, score		1 (1; 2)	1 (1; 2)	0.3 <sup>1</sup>
FOUR, score		n = 31; 13 (10; 16)	n = 6; 15 (10; 15)	0.9 <sup>1</sup>
GCS, score		n = 39; 11 (9; 12)	n = 7; 11 (8; 14)	0.7 <sup>1</sup>
CRS-R, score		n = 19; 17 (11; 21)	n = 4; 18 (14; 30)	0.7 <sup>1</sup>
<b>Laboratory parameters at the time of the first sepsis episode</b>				
Hemoglobin, g/L		n = 172; 99 (91; 110)	n = 40; 92 (87; 101)	0.015 <sup>1</sup>
Leukocytes, ×10 <sup>9</sup> /L		n = 164; 8.8 (6.8; 11.2)	n = 37; 9.9 (7.6; 11.4)	0.2 <sup>1</sup>
Neutrophils, ×10 <sup>9</sup> /L		n = 164; 5.9 (4.3; 8.7)	n = 37; 7.0 (5.6; 8.8)	0.08 <sup>1</sup>
Lymphocytes, ×10 <sup>9</sup> /L		n = 165; 1.4 (1.1; 2.0)	n = 37; 1.4 (0.8; 1.9)	0.3 <sup>1</sup>
Eosinophils, ×10 <sup>9</sup> /L		n = 165; 0.2 (0.1; 0.3)	n = 37; 0.1 (0.1; 0.2)	0.07 <sup>1</sup>
Neutrophil-to-lymphocyte ratio		n = 164; 4.2 (2.8; 6.8)	n = 37; 5.3 (3.4; 9.0)	0.08 <sup>1</sup>
Platelets, ×10 <sup>9</sup> /L		n = 165; 277 (209; 367)	n = 37; 259 (185; 334)	0.2 <sup>1</sup>
Lactate, mmol/L		n = 34; 1.3 (0.9; 1.8)	n = 13; 1.0 (0.8; 1.2)	0.1 <sup>1</sup>
Creatinine, μmol/L		n = 160; 72.8 (59.2; 102.6)	n = 36; 84.2 (52.5; 111.3)	0.9 <sup>1</sup>
C-reactive protein, mg/L		n = 150; 49.4 (27.6; 112.3)	n = 38; 65.0 (42.7; 123.8)	0.09 <sup>1</sup>
Albumin, g/L		n = 108; 27.7 (24.0; 30.8)	n = 26; 26.1 (22.9; 29.0)	0.1 <sup>1</sup>
Total protein, g/L		n = 155; 56.4 (51.8; 60.9)	n = 36; 55.9 (51.9; 59.5)	0.5 <sup>1</sup>
Procalcitonin, ng/mL		n = 10; 0.4 (0.2; 25.1)	n = 7; 0.2 (0.1; 0.3)	0.3 <sup>1</sup>
D-dimer, mg/L		n = 8; 2.6 (1.4; 6.2)	n = 1; 7.9 (7.9; 7.9)	0.4 <sup>1</sup>
Arterial blood pH		n = 36; 7.49 (7.46; 7.52)	n = 13; 7.51 (7.48; 7.51)	0.6 <sup>1</sup>

Parameters	No septic shock (n = 243)	Septic shock <sup>†</sup> (n = 55)	p-value*
<b>Vital parameters at the time of the first sepsis episode</b>			
Heart rate, bpm	n = 235; 83 (73; 91)	n = 55; 81 (73; 90)	0.4 <sup>1</sup>
Respiratory rate, per min	n = 168; 17.0 (16.6; 18.0)	n = 38; 17.0 (16.8; 17.5)	0.4 <sup>1</sup>
Body temperature, °C	n = 236; 36.7 (36.5; 36.9)	n = 53; 36.7 (36.6; 37.0)	0.3 <sup>1</sup>
Systolic blood pressure, mmHg	n = 240; 125 (110; 137)	n = 55; 121 (107; 139)	0.6 <sup>1</sup>
Diastolic blood pressure, mmHg	n = 240; 75 (66; 84)	n = 55; 70 (64; 77)	0.009 <sup>1</sup>
Mean arterial pressure, mmHg	n = 171; 97 (86; 108)	n = 43; 92 (80; 102)	0.1 <sup>1</sup>
SpO <sub>2</sub> , %	n = 234; 99 (98; 99)	n = 52; 99 (98; 99)	0.2 <sup>1</sup>
<b>Comorbidities</b>			
Cerebral infarction	109; 44.9 %	26; 47.3 %	0.9 <sup>2</sup>
Hemorrhagic stroke	52; 21.4 %	10; 18.2 %	0.7 <sup>2</sup>
Traumatic brain injury	47; 19.3 %	8; 14.5 %	0.5 <sup>2</sup>
Type 2 diabetes mellitus	38; 15.6 %	8; 14.5 %	0.9 <sup>2</sup>
Chronic kidney disease	27; 11.1 %	10; 18.2 %	0.2 <sup>2</sup>
Chronic obstructive pulmonary disease	10; 4.1 %	1; 1.8 %	0.7 <sup>3</sup>
Coronary artery disease	149; 61.3 %	36; 65.5 %	0.7 <sup>2</sup>
Arterial hypertension	194; 79.8 %	49; 89.1 %	0.2 <sup>2</sup>
Chronic heart failure	46; 18.9 %	12; 21.8 %	0.8 <sup>2</sup>
<b>Outcomes and complications</b>			
Hospital mortality	21; 8.6 %	13; 23.6 %	0.002 <sup>2</sup>
Recurrent sepsis episodes	79; 32.5 %	11; 20.0 %	0.08 <sup>3</sup>
Number of sepsis episodes	1 (1; 2)	1 (1; 1)	0.07 <sup>1</sup>
Duration of first sepsis episode, days	18 (9; 32)	35 (23; 49)	< 0.001 <sup>1</sup>
Duration of all sepsis episodes, days	24 (14; 38)	39 (23; 55)	< 0.001 <sup>1</sup>
ICU length of stay, days	42 (29; 59)	53 (35; 67)	0.038 <sup>1</sup>
ICU length of stay after first sepsis episode, days	31 (21; 47)	44 (25; 61)	0.005 <sup>1</sup>
Total hospital length of stay, days	59 (42; 71)	55 (35; 69)	0.4 <sup>1</sup>
Nosocomial pneumonia <sup>#</sup>	208; 85.6 %	55; 100 %	< 0.001 <sup>3</sup>
Mechanical ventilation <sup>#</sup>	225; 92.6 %	55; 100 %	0.053 <sup>3</sup>
Sepsis-induced coagulopathy (SIC) <sup>#</sup>	36; 14.8 %	22; 40.0 %	< 0.001 <sup>2</sup>
Disseminated intravascular coagulation (DIC) <sup>#</sup>	8; 3.3 %	6; 10.9 %	0.04 <sup>2</sup>
<p><b>Note:</b> APACHE II — Acute Physiology and Chronic Health Evaluation II; CRS-R — Coma Recovery Scale-Revised; FOUR — Full Outline of UnResponsiveness; IQR — interquartile range; NUTRIC — Nutrition Risk in the Critically Ill; SIRS — systemic inflammatory response syndrome; SOFA — Sequential Organ Failure Assessment; BMI — body mass index; ICU — intensive care unit; GCS — Glasgow Coma Scale.</p> <p><sup>1</sup> The Mann—Whitney criterion.</p> <p><sup>2</sup> Criterion <math>\chi^2</math></p> <p><sup>3</sup> Fisher's exact test.</p> <p><sup>#</sup> During the first episode of sepsis.</p> <p>* The critical significance level, taking into account the Bonferroni correction: &lt; 0.001.</p> <p><sup>†</sup> Excluded patients who received vasopressors before the onset of the first episode of sepsis.</p> <p>Continuous variables are presented as the median (Q1; Q3); if there are missing data, the number of patients (n) is indicated.</p>			



**Table 2.** Comparison of baseline characteristics and hospitalization outcomes of ICU patients depending on the development of sepsis recurrence

Parameters		Single sepsis episode (n = 240)	Recurrent sepsis episodes (n = 96)	p-value*
Time to first sepsis episode, h		228 (96; 420)	192 (84; 348)	0.5 <sup>1</sup>
Time from onset of sepsis episode to development of septic shock, days		—	29 (19; 40)	—
Sepsis phenotype (first episode)	Hyperinflammatory	183; 76.3 %	60; 62.5 %	0.016 <sup>2</sup>
	Hypoinflammatory	57; 23.8 %	36; 37.5 %	
Sex	Male	140; 58.3 %	50; 52.1 %	0.3 <sup>2</sup>
	Female	100; 41.7 %	46; 47.9 %	
Age, years		64 (48; 74)	64 (49; 74)	0.8 <sup>1</sup>
BMI, kg/m <sup>2</sup>		n = 203; 24.9 (21.8; 29.1)	n = 81; 24.6 (22.4; 28.7)	0.9 <sup>1</sup>
Transfer from another ICU		237; 98.8 %	93; 96.9 %	0.4 <sup>3</sup>
Pneumonia at admission		175; 72.9 %	68; 70.8 %	0.8 <sup>2</sup>
<b>Scores at the time of the first sepsis episode</b>				
APACHE II, score		n = 19; 16 (13; 21)	n = 5; 15 (15; 16)	0.5 <sup>1</sup>
NUTRIC, score		n = 19; 4 (3; 5)	n = 5; 4 (4; 5)	0.5 <sup>1</sup>
SOFA, score		n = 240; 5 (4; 6)	n = 96; 5 (4; 6)	0.4 <sup>1</sup>
SIRS, score		n = 240; 1 (1; 2)	n = 96; 1 (1; 2)	0.3 <sup>1</sup>
FOUR, score		n = 31; 13 (12; 16)	n = 11; 9 (8; 16)	0.09 <sup>1</sup>
GCS, score		n = 40; 11 (10; 13)	n = 14; 9 (8; 11)	0.034 <sup>1</sup>
CRS-R, score		n = 21; 18 (16; 20)	n = 5; 16 (11; 16)	0.09 <sup>1</sup>
<b>Laboratory parameters at the time of the first sepsis episode</b>				
Hemoglobin, g/L		n = 178; 98 (89; 109)	n = 67; 98 (88; 105)	0.6 <sup>1</sup>
Leukocytes, ×10 <sup>9</sup> /L		n = 172; 9.3 (7.4; 13.4)	n = 61; 8.8 (6.4; 10.8)	0.032 <sup>1</sup>
Neutrophils, ×10 <sup>9</sup> /L		n = 172; 7.1 (5.0; 10.3)	n = 61; 5.9 (4.3; 8.3)	0.08 <sup>1</sup>
Lymphocytes, ×10 <sup>9</sup> /L		n = 173; 1.4 (1.0; 1.9)	n = 61; 1.3 (0.9; 2.0)	0.4 <sup>1</sup>
Eosinophils, ×10 <sup>9</sup> /L		n = 173; 0.12 (0.06; 0.28)	n = 61; 0.13 (0.03; 0.30)	0.9 <sup>1</sup>
Neutrophil-to-lymphocyte ratio		n = 172; 4.8 (2.9; 8.2)	n = 61; 4.3 (3.2; 7.9)	0.8 <sup>1</sup>
Platelets, ×10 <sup>9</sup> /L		n = 173; 282 (209; 377)	n = 61; 262 (185; 333)	0.1 <sup>1</sup>
Lactate, mmol/L		n = 44; 1.2 (0.9; 1.8)	n = 19; 1.0 (0.9; 1.3)	0.2 <sup>1</sup>
Creatinine, μmol/L		n = 166; 76.3 (57.6; 113.9)	n = 62; 73.1 (60.2; 102.4)	0.6 <sup>1</sup>
C-reactive protein, mg/L		n = 154; 71.7 (35.0; 132.6)	n = 64; 45.5 (27.8; 106.7)	0.068 <sup>1</sup>
Albumin, g/L		n = 111; 26.9 (23.0; 30.3)	n = 47; 26.5 (23.1; 30.6)	0.7 <sup>1</sup>
Total protein, g/L		n = 160; 56.0 (51.6; 61.0)	n = 62; 55.0 (50.6; 58.9)	0.4 <sup>1</sup>
Procalcitonin, ng/mL		n = 23; 0.8 (0.2; 3.2)	n = 8; 0.5 (0.2; 4.0)	0.6 <sup>1</sup>
D-dimer, mg/L		n = 9; 3.4 (1.4; 6.5)	n = 1; 1.4 (1.4; 1.4)	0.6 <sup>1</sup>
Arterial blood pH		n = 45; 7.49 (7.47; 7.52)	n = 20; 7.50 (7.46; 7.52)	0.8 <sup>1</sup>

Parameters	Single sepsis episode (n = 240)	Recurrent sepsis episodes (n = 96)	p-value*
<b>Vital parameters at the time of the first sepsis episode</b>			
Heart rate, bpm	n = 235; 84.0 (73.3; 93.0)	n = 93; 81.9 (73.8; 89)	0.1 <sup>1</sup>
Respiratory rate, per min	n = 158; 17.0 (16.5; 18.0)	n = 65; 17.0 (17.0; 17.7)	0.2 <sup>1</sup>
Body temperature, °C	n = 232; 36.7 (36.5; 37.0)	n = 93; 36.7 (36.6; 36.9)	0.9 <sup>1</sup>
Systolic blood pressure, mm Hg	n = 239; 121.6 (107.9; 134.4)	n = 94; 124.7 (112.3; 136.1)	0.2 <sup>1</sup>
Diastolic blood pressure, mm Hg	n = 239; 73.5 (63.2; 82.6)	n = 94; 73.3 (66.3; 83.6)	0.5 <sup>1</sup>
Mean arterial pressure, mm Hg	n = 173; 93.3 (83.7; 104.6)	n = 72; 95.5 (87.3; 109.3)	0.2 <sup>1</sup>
SpO <sub>2</sub> , %	n = 230; 98.9 (97.9; 99.4)	n = 93; 99.0 (97.7; 99.3)	0.9 <sup>1</sup>
<b>Comorbidities</b>			
Cerebral infarction	113; 47.1 %	40; 41.7 %	0.4 <sup>2</sup>
Hemorrhagic stroke	46; 19.2 %	20; 20.8 %	0.8 <sup>2</sup>
Traumatic brain injury	40; 16.7 %	24; 25.0 %	0.1 <sup>2</sup>
Type 2 diabetes mellitus	38; 15.8 %	15; 15.6 %	0.9 <sup>2</sup>
Chronic kidney disease	30; 12.5 %	16; 16.7 %	0.4 <sup>2</sup>
Chronic obstructive pulmonary disease	11; 4.6 %	1; 1.0 %	0.2 <sup>3</sup>
Coronary artery disease	147; 61.3 %	62; 64.6 %	0.7 <sup>2</sup>
Arterial hypertension	192; 80.0 %	77; 80.2 %	0.9 <sup>2</sup>
Chronic heart failure	50; 20.8 %	15; 15.6 %	0.3 <sup>2</sup>
<b>Outcomes and complications</b>			
Hospital mortality	33; 13.8 %	14; 14.6 %	0.9 <sup>2</sup>
Septic shock <sup>†</sup>	44; 18.3 %	11; 11.5 %	0.2 <sup>2</sup>
Number of sepsis episodes	—	2 (2; 2)	—
ICU length of stay, days	38 (28; 55)	58 (44; 76)	< 0.001 <sup>1</sup>
ICU length of stay after the first episode, days	28 (18; 41)	48 (36; 64)	< 0.001 <sup>1</sup>
Total hospital length of stay, days	55 (35; 66)	69 (56; 90)	< 0.001 <sup>1</sup>
Nosocomial pneumonia <sup>#</sup>	216; 90.0 %	83; 86.5 %	0.5 <sup>2</sup>
Mechanical ventilation <sup>#</sup>	229; 95.4 %	89; 92.7 %	0.5 <sup>2</sup>
Vasopressor/inotrope use <sup>#</sup>	76; 31.7 %	17; 17.7 %	0.014 <sup>2</sup>
Sepsis-induced coagulopathy (SIC) <sup>#</sup>	64; 26.7 %	14; 14.6 %	0.026 <sup>2</sup>
Disseminated intravascular coagulation (DIC) <sup>#</sup>	12; 5.0 %	3; 3.1 %	0.6 <sup>3</sup>
<p><b>Note:</b> APACHE II — Acute Physiology and Chronic Health Evaluation II; CRS-R — Coma Recovery Scale-Revised; FOUR — Full Outline of UnResponsiveness; IQR — interquartile range; NUTRIC — Nutrition Risk in the Critically Ill; SIRS — systemic inflammatory response syndrome; SOFA — Sequential Organ Failure Assessment; BMI — body mass index; ICU — intensive care unit; GCS — Glasgow Coma Scale.</p> <p><sup>1</sup> The Mann—Whitney criterion.</p> <p><sup>2</sup> Criterion <math>\chi^2</math></p> <p><sup>3</sup> Fisher's exact test.</p> <p><sup>#</sup> During the first episode of sepsis.</p> <p>* The critical significance level, taking into account the Bonferroni correction: &lt; 0.001.</p> <p><sup>†</sup> Excluded patients who received vasopressors before the onset of the first episode of sepsis.</p> <p>Continuous variables are presented as the median (Q1; Q3); if there are missing data, the number of patients (n) is indicated.</p>			

**Table 3.** Comparison of baseline characteristics and hospitalization outcomes of ICU patients depending on the development of sepsis-induced coagulopathy (SIC) during the first sepsis episode

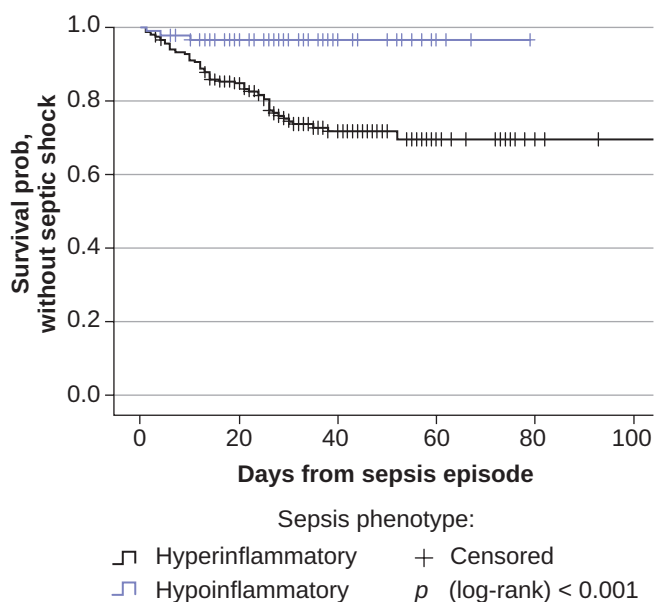
Parameters		No SIC (n = 219)	SIC (n = 78)	p-value*
Time to first sepsis episode, h		240 (120; 408)	144 (72; 288)	0.011 <sup>1</sup>
Time from onset of sepsis episode to development of septic shock, days		—	240 (75; 528); from 22 to 1728	—
Sepsis phenotype (first episode)	Hyperinflammatory	154. 70.3 %	66. 84.6 %	0,02 <sup>2</sup>
	Hypoinflammatory	65. 29.7 %	12. 15.4 %	
Sex	Male	120. 54.8 %	51. 65.4 %	0,4 <sup>2</sup>
	Female	99. 45.2 %	27. 34.6 %	
Age, years		62 (47; 72)	70 (53; 76)	0.013 <sup>1</sup>
BMI, kg/m <sup>2</sup>		n = 185; 25.1 (22.5; 29.8)	n = 68; 24.2 (20.5; 28.4)	0.068
Transfer from another ICU		214; 97.7 %	77; 98.7 %	0.9 <sup>3</sup>
Pneumonia at admission		153; 69.9 %	65; 83.3 %	0.031 <sup>2</sup>
<b>Scores at the time of the first sepsis episode</b>				
APACHE II, score		n = 15; 16 (14; 17)	n = 7; 16 (13; 23)	0.8 <sup>1</sup>
NUTRIC, score		n = 15; 4 (3; 5)	n = 7; 4 (4; 7)	0.4 <sup>1</sup>
SOFA, score		5 (4; 6)	6 (5; 8)	< 0.001 <sup>1</sup>
SIRS, score		1 (1; 2)	1 (1; 2)	< 0.001 <sup>1</sup>
FOUR, score		n = 31; 13 (10; 16)	n = 7; 15 (11; 16)	0.7 <sup>1</sup>
GCS, score		n = 39; 11 (9; 12)	n = 10; 11 (10; 14)	0.9 <sup>1</sup>
CRS-R, score		n = 19; 17 (11; 19)	n = 4; 20 (17; 23)	0.2 <sup>1</sup>
<b>Laboratory parameters at the time of the first sepsis episode</b>				
Hemoglobin, g/L		n = 162; 98.0 (90.0; 109.0)	n = 60; 93.5 (85.5; 105.5)	0.1 <sup>1</sup>
Leukocytes, ×10 <sup>9</sup> /L		n = 156; 9.1 (7.1; 11.4)	n = 56; 10.4 (7.0; 14.1)	0.1 <sup>1</sup>
Neutrophils, ×10 <sup>9</sup> /L		n = 156; 6.7 (4.8; 8.8)	n = 56; 8.3 (4.9; 12.4)	0.051 <sup>1</sup>
Lymphocytes, ×10 <sup>9</sup> /L		n = 156; 1.5 (1.1; 2.0)	n = 56; 1.1 (0.8; 1.5)	0.001 <sup>1</sup>
Eosinophils, ×10 <sup>9</sup> /L		n = 156; 0.2 (0.1; 0.3)	n = 56; 0.1 (0.0; 0.2)	< 0.001 <sup>1</sup>
Neutrophil-to-lymphocyte ratio		n = 156; 4.3 (2.8; 6.9)	n = 56; 6.5 (3.3; 13.9)	0.002 <sup>1</sup>
Platelets, ×10 <sup>9</sup> /L		n = 156; 305.5 (228.0; 378.5)	n = 56; 215.0 (133.0; 293.5)	< 0.001 <sup>1</sup>
Lactate, mmol/L		n = 32; 1.2 (0.9; 1.6)	n = 26; 1.2 (0.8; 1.4)	0.7 <sup>1</sup>
Creatinine, μmol/L		n = 151; 72.3 (55.6; 105.0)	n = 55; 85.8 (64.2; 125.3)	0.03 <sup>1</sup>
C-reactive protein, mg/L		n = 144; 53.5 (28.4; 112.8)	n = 52; 87.0 (51.7; 168.6)	0.001 <sup>1</sup>
Albumin, g/L		n = 108; 27.2 (23.4; 30.6)	n = 38; 25.7 (22.9; 29.8)	0.2 <sup>1</sup>
Total protein, g/L		n = 149; 56.4 (51.8; 61.0)	n = 54; 54.1 (48.8; 57.6)	0.007 <sup>1</sup>
Procalcitonin, ng/mL		n = 14; 0.3 (0.1; 0.5)	n = 14; 1.5 (0.3; 7.5)	0.014 <sup>1</sup>
D-dimer, mg/L		n = 7. 5.9 (1.4; 7.9)	n = 2; 1.4 (1.1; 1.7)	0.3 <sup>1</sup>
Arterial blood pH		n = 32. 7.50 (7.47; 7.52)	n = 27; 7.49 (7.45; 7.53)	0.8 <sup>1</sup>

Parameters	No SIC (n = 219)	SIC (n = 78)	p-value*
<b>Vital parameters at the time of the first sepsis episode</b>			
Heart rate, bpm	n = 213; 83 (73.2; 91)	n = 77; 82.9 (72.5; 93.0)	0.6 <sup>1</sup>
Respiratory rate, per min	n = 148; 17.0 (16.6; 17.7)	n = 48; 17.4 (17.0; 18.1)	0.046 <sup>1</sup>
Body temperature, °C	n = 213; 36.7 (36.5; 36.9)	n = 74; 36.7 (36.6; 37.0)	0.2 <sup>1</sup>
Systolic blood pressure, mm Hg	n = 217; 122.0 (107.9; 135.7)	n = 78; 120.7 (110.1; 137.1)	0.9 <sup>1</sup>
Diastolic blood pressure, mm Hg	n = 217; 73.3 (65.6; 83.0)	n = 78; 71.7 (61.7; 79.2)	0.08 <sup>1</sup>
Mean arterial pressure, mm Hg	n = 160; 94.3 (83.7; 106.1)	n = 59; 94.4 (84.2; 105.1)	0.8 <sup>1</sup>
SpO <sub>2</sub> , %	n = 211; 99.0 (97.9; 99.5)	n = 75; 98.9 (98.0; 99.2)	0.7 <sup>1</sup>
<b>Comorbidities</b>			
Cerebral infarction	106; 48.4 %	35; 44.9 %	0.7 <sup>2</sup>
Hemorrhagic stroke	43; 19.6 %	11; 14.1 %	0.4 <sup>2</sup>
Traumatic brain injury	45; 20.5 %	13; 16.7 %	0.6 <sup>2</sup>
Type 2 diabetes mellitus	37; 16.9 %	9; 11.5 %	0.3 <sup>2</sup>
Chronic kidney disease	27; 12.3 %	15; 19.2 %	0.2 <sup>2</sup>
Chronic obstructive pulmonary disease	10; 4.6 %	2; 2.6 %	0.7 <sup>3</sup>
Coronary artery disease	135; 61.6 %	49; 62.8 %	0.9 <sup>2</sup>
Arterial hypertension	180; 82.2 %	57; 73.1 %	0.1 <sup>2</sup>
Chronic heart failure	38; 17.4 %	21; 26.9 %	0.1 <sup>2</sup>
<b>Outcomes and complications</b>			
Hospital mortality	16; 7.3 %	22; 28.2 %	< 0.001 <sup>2</sup>
Septic shock†	32; 14.6 %	22; 28.2 %	0.012 <sup>2</sup>
Recurrent sepsis episodes	70; 32.0 %	14; 17.9 %	0.027 <sup>2</sup>
Number of sepsis episodes	1 (1; 2)	1 (1; 1)	0.027 <sup>1</sup>
Duration of first sepsis episode, days	21 (11; 34)	28 (15; 38)	0.025 <sup>1</sup>
Duration of all sepsis episodes, days	27 (15; 41)	29 (18; 41)	0.5 <sup>1</sup>
ICU length of stay, days	44 (32; 63)	42 (30; 61)	0.3 <sup>1</sup>
ICU length of stay after the first episode, days	35 (22; 51)	32 (22; 49)	0.5 <sup>1</sup>
Total hospital length of stay, days	60 (44; 76)	51 (35; 64)	0.006 <sup>1</sup>
Nosocomial pneumonia#	190; 86.8 %	76; 97.4 %	0.008 <sup>3</sup>
Mechanical ventilation#	209; 95.4 %	76; 97.4 %	0.7 <sup>3</sup>
Vasopressor/inotrope use#	46; 21.0 %	42; 53.8 %	< 0.001 <sup>2</sup>
Disseminated intravascular coagulation (DIC)#	9; 4.1 %	6; 7.7 %	0.3 <sup>3</sup>
<p><b>Note:</b> APACHE II — Acute Physiology and Chronic Health Evaluation II; CRS-R — Coma Recovery Scale-Revised; FOUR — Full Outline of UnResponsiveness; IQR — interquartile range; NUTRIC — Nutrition Risk in the Critically Ill; SIRS — systemic inflammatory response syndrome; SOFA — Sequential Organ Failure Assessment; BMI — body mass index; ICU — intensive care unit; GCS — Glasgow Coma Scale.</p> <p><sup>1</sup> The Mann—Whitney criterion.</p> <p><sup>2</sup> Criterion <math>\chi^2</math></p> <p><sup>3</sup> Fisher's exact test.</p> <p># During the first episode of sepsis.</p> <p>* The critical significance level, taking into account the Bonferroni correction: &lt; 0.001.</p> <p>† Excluded patients who received vasopressors before the onset of the first episode of sepsis.</p> <p>Continuous variables are presented as the median (Q1; Q3); if there are missing data, the number of patients (n) is indicated.</p>			

**Table 4.** Univariate and multivariable Cox regression analysis (outcome: septic shock)

Parameter	N	Missing, %	Univariable analysis			Univariable analysis		
			HR	95% CI	p-value	aHR	95% CI	p-value
Sepsis phenotype (hyperinflammatory)#	298	0	6.74	2.10; 21.62	0.001	<b>5.23</b>	<b>1.61; 17.04</b>	<b>0.006</b>
Time to first sepsis episode#, h	298	0	0.998	0.997; 0.999	0.011	0.999	0.998; 1.000	0.073
Diastolic blood pressure#, mm Hg	295	1.0	0.976	0.955; 0.997	0.024	<b>0.975</b>	<b>0.954; 0.996</b>	<b>0.019</b>
Pneumonia at admission#	298	0	2.35	1.11; 4.98	0.026	2.10	0.99; 4.47	0.053

**Note:** 95% CI — 95% confidence interval; aHR — adjusted hazard ratio; SOFA — Sequential Organ Failure Assessment. Variables included in the multivariable analysis (< 30 % missing data).  
Equation (prognostic index):  
PI = exp (1.867 × sepsis phenotype (1 = hyperinflammatory, 0 = hypoinflammatory) – 0.023 × diastolic blood pressure (mmHg)).



**Fig. 2.** Kaplan-Meier survival curves: comparison of septic shock-free survival in patients with hyperinflammatory and hypoinflammatory sepsis phenotypes

dictors of septic shock development were identified: the hyperinflammatory sepsis phenotype (adjusted HR 5.23, 95% CI 1.61; 17.04,  $p = 0.006$ ) and lower diastolic blood pressure (adjusted HR 0.975 [risk increase: 1.025], 95% CI 0.954; 0.996,  $p = 0.019$ , Table 4). Survival curves free from septic shock comparing patients with hyperinflammatory and hypoinflammatory sepsis phenotypes are presented in Figure 2.

### Predictors of sepsis recurrence

In univariable analysis, the presence of the hypoinflammatory sepsis phenotype (HR 2.07,  $p = 0.001$ ), lower platelet count (HR 0.998,  $p = 0.024$ ), and a lower SOFA score at the onset of the first sepsis episode (HR 0.49,  $p = 0.034$ )

were associated with a higher risk of sepsis recurrence (Table 5). In contrast, in multivariable analysis, only the hypoinflammatory phenotype remained an independent predictor of recurrence (adjusted HR 5.23, 95% CI 1.29; 13.01,  $p = 0.002$ ).

### Predictors of sepsis-induced coagulopathy

In univariable analysis, the development of sepsis-induced coagulopathy was associated (parameters at the onset of the first sepsis episode) with lower platelet count (HR 0.993,  $p < 0.001$ ), higher SOFA score (HR 1.216,  $p < 0.001$ ), increased neutrophil-to-lymphocyte ratio (HR 1.021,  $p = 0.001$ ), higher absolute neutrophil count (HR 1.057,  $p = 0.002$ ), C-reactive protein level (HR 1.005,  $p = 0.002$ ), SIRS score (HR 1.450,  $p = 0.003$ ), lower total protein level (HR 0.943,  $p = 0.006$ ), decreased absolute lymphocyte count (HR 0.585,  $p = 0.007$ ), higher procalcitonin level (HR 1.032,  $p = 0.009$ ), increased body temperature (HR 1.786,  $p = 0.014$ ), higher leukocyte count (HR 1.046,  $p = 0.016$ ), creatinine level (HR 1.005,  $p = 0.017$ ), as well as the presence of pneumonia at admission (HR 2.006,  $p = 0.022$ ) (Table 6).

In the multivariable model, only platelet count remained an independent predictor (adjusted HR 0.997; 95% CI 0.994; 0.999;  $p = 0.026$ ).

## Discussion

### Main findings

A total of 336 patients with confirmed sepsis from the RICD v2.0 database were included in the study, and ICU mortality was 14.0 %. Septic shock developed in 55 patients (16.4 %); its independent predictor was the hyperinflammatory sepsis phenotype, and septic shock was also characterized by lower diastolic blood pressure at the onset of the episode; the presence of septic

**Table 5.** Univariate and multivariable Cox regression analysis (outcome: sepsis recurrence)

Parameter	N	Missing, %	Univariable analysis			Multivariable analysis		
			HR	95% CI	p-value	aHR	95% CI	p-value
Sepsis phenotype (hypoinflammatory) <sup>#</sup>	336	0	2.07	1.36; 3.14	0.001	<b>5.23</b>	<b>1.29; 13.01</b>	<b>0.002</b>
Platelets, ×10 <sup>9</sup> /L	234	30.4	0.998	0.996; 0.999	0.024	—	—	—
SOFA <sup>#</sup> , score	336	0	0.49	0.26; 0.95	0.034	0.94	0.84; 1.06	0.305

**Note:** 95% CI — 95% confidence interval; aHR — adjusted hazard ratio; SOFA — Sequential Organ Failure Assessment.  
<sup>#</sup> Variables included in the multivariable analysis (< 30 % missing data).

**Table 6.** Univariate and multivariable Cox regression analysis (outcome: sepsis-induced coagulopathy)

Parameter	N	Missing, %	Univariable analysis			Multivariable analysis		
			HR	95% CI	p-value	aHR	95% CI	p-value
Platelets <sup>#</sup> , ×10 <sup>9</sup> /L	212	28.62	0.993	0.990; 0.996	< 0.001	<b>0.997</b>	<b>0.994; 0.999</b>	<b>0.026</b>
SOFA <sup>#</sup> , score	297	0	1.216	1.123; 1.316	< 0.001	0.878	0.759; 1.017	0.082
Neutrophil-to-lymphocyte ratio <sup>#</sup>	212	28.62	1.021	1.009; 1.034	0.001	0.971	0.905; 1.041	0.406
Neutrophils <sup>†</sup> , ×10 <sup>9</sup> /L	212	28.62	1.057	1.020; 1.095	0.002	—	—	—
C-reactive protein, mg/L	196	34.01	1.005	1.002; 1.008	0.002	—	—	—
#SIRS, score	297	0	1.450	1.136; 1.851	0.003	0.915	0.643; 1.301	0.621
Total protein, g/L	203	31.65	0.943	0.905; 0.983	0.006	—	—	—
Lymphocytes <sup>†</sup> , ×10 <sup>9</sup> /L	212	28.62	0.585	0.395; 0.866	0.007	—	—	—
Procalcitonin, ng/mL	28	90.57	1.032	1.008; 1.057	0.009	—	—	—
Body temperature <sup>#</sup> , °C	287	3.37	1.786	1.127; 2.832	0.014	1.215	0.751; 1.965	0.428
Leukocytes <sup>#</sup> , ×10 <sup>9</sup> /L	212	28.62	1.046	1.009; 1.086	0.016	1.013	0.933; 1.099	0.762
Creatinine, μmol/L	206	30.64	1.005	1.001; 1.009	0.017	—	—	—
Pneumonia at admission <sup>#</sup>	297	0	2.006	1.106; 3.639	0.022	0.890	0.457; 1.735	0.733

**Note:** 95% CI — 95% confidence interval; aHR — adjusted hazard ratio; SIRS — systemic inflammatory response syndrome; SOFA — Sequential Organ Failure Assessment score.  
<sup>#</sup> Variables included in the multivariable analysis (< 30 % missing data).  
<sup>†</sup> Not included in the multivariable model due to strong collinearity with WBC and the neutrophil-to-lymphocyte ratio.

shock was associated with a longer duration of the sepsis episode and a higher incidence of nosocomial pneumonia and sepsis-induced coagulopathy. Recurrent sepsis episodes were observed in 96 patients (28.6 %); the hypoinflammatory phenotype was an independent predictor; sepsis recurrences were also associated with longer ICU stay and longer total hospital length of stay. Sepsis-induced coagulopathy was recorded in 78 patients (23.2 %); its independent predictor was a reduced platelet count; the development of coagulopathy was associated with increased mortality and more frequent use of vasoactive support.

### Comparison with previous studies

To our knowledge, this is the first study to identify risk factors for adverse sepsis outcomes in patients with prolonged ICU stay. The results obtained are generally consistent with previously published data. The hyperinflammatory sepsis phenotype has previously been described as a significant risk factor for adverse outcomes, including the development of septic shock [35]. Low diastolic blood pressure also demonstrated a statistically significant association with the risk of septic shock, which is supported by literature data suggesting its potential use as an indicator of early decompensation and as a rationale for timely initiation of

vasoactive support [34]. Moreover, low values of both systolic and diastolic blood pressure are associated with an increased risk of death in patients with septic shock [36].

Particular attention should be paid to the fact that a number of clinical and laboratory parameters traditionally considered predictors of adverse outcomes in sepsis did not demonstrate statistically significant independent associations in our cohort. These include age, presence of comorbidities, and markers of systemic inflammation and organ dysfunction (leukocytosis, lactate level, creatinine, C-reactive protein, procalcitonin, etc.). On the one hand, the absence of independent associations between these parameters and the studied outcomes may reflect the high degree of homogeneity of the included population: most patients had prolonged ICU stays, had a pronounced comorbid background, and relatively high severity scores, which limits variability in both baseline scores and laboratory parameters and reduces their discriminative ability. On the other hand, a strict level of statistical significance was applied due to the use of Bonferroni correction, which may have led to attenuation of small effect sizes in a relatively limited sample.

From a practical perspective, the findings emphasize that in patients with prolonged and chronic critical illness, conventional severity scores and individual laboratory markers may be less informative for predicting complicated sepsis than characteristics reflecting the immuno-inflammatory phenotype and hemostatic status.

It should be noted that in the present study, the median time from the onset of the septic episode to the development of shock was 13 days, which substantially exceeds the time frames typical of standard ICU cohorts (mean time to shock development — within the first two days) [37]. This time gap likely reflects the characteristics of the included population, namely the predominance of patients with prolonged and chronic critical illness, which is characterized by pronounced immunosuppression and reduced inflammatory reactivity [9]. In our study, the development of septic shock was associated with a higher incidence of sepsis-induced coagulopathy, which is consistent with data from Tanaka et al. (2021), who reported more frequent detection of coagulopathy in patients with shock (66.4 % vs 42.2 %) [38].

In the study by van Vught L.A. et al. (2016), it was shown that some ICU patients with sepsis develop recurrent episodes of organ dysfunction during a single hospitalization associated with new infections, which is accompanied by an increased risk of death [39]. In a large multicenter study by Xu Z. et al. (2022), which included more than 20,000 patients, four sepsis subphenotypes were identified based on SOFA score trajectories during the first 72 hours after ICU admission: Rapidly Improving, Delayed Improving, Delayed Worsening, and Rapidly Worsening [40]. The authors demonstrated that unstable clinical course and recurrent episodes of organ dysfunction were associated with increased mortality. In our study, recurrent

sepsis episodes were associated with prolonged ICU stay, and the only independent predictor of recurrence was the hypoinflammatory phenotype. A possible explanation is competing risk: patients with the hyperinflammatory phenotype more often died before a recurrent sepsis episode could develop. In addition, recurrences in patients with the hypoinflammatory phenotype may be related to pronounced immunosuppression, which is characteristic of chronic critical illness [9].

In our study, the development of sepsis-induced coagulopathy was associated with increased mortality and more frequent use of vasoactive agents, which is consistent with previously published data [38]. Among the multiple risk factors identified in univariable analysis, only a low platelet count at the onset of the septic episode remained an independent predictor of coagulopathy. In a multicenter retrospective study by Kasugai et al. (2021), both a relative decrease in platelet count  $\geq 11$  % and an absolute platelet count  $\leq 100 \times 10^9/L$  on the second day of hospitalization were significantly associated with the development of sepsis-associated coagulopathies [41]. Furthermore, in a study by Cheng et al. (2024), which included patients with sepsis-induced coagulopathy between 2014 and 2022, the development of thrombocytopenia was significantly associated with increased in-hospital mortality [42].

It should be noted that most existing studies are based on parameters obtained at the time of ICU admission, whereas in our study the analysis was performed at the onset of the septic episode. This approach may improve prognostic accuracy; however, direct comparison of results is limited due to the lack of studies conducted in patients with comparable ICU length of stay.

### Clinical implications

The study identified independent risk factors for septic shock, sepsis recurrence, and sepsis-induced coagulopathy and demonstrated their association with adverse outcomes. These predictors may be used both for the development of specialized prognostic models in patients with prolonged and chronic critical illness and for direct risk stratification at the onset of the septic episode, thereby providing a basis for more accurate prognostication and optimization of clinical decision-making in the ICU.

### Strengths and limitations

The present study has several strengths. First, it is based on real-world clinical data collected over an eight-year observation period, which ensures a high representativeness of the patient cohort. Second, the use of real-world treatment data provides high external validity. In addition, the analysis of predictors and outcomes in the subgroup of patients with prolonged and chronic critical illness enhances internal validity by reducing heterogeneity of the study population.

At the same time, several limitations should be considered when interpreting the results. First, the RICD database is single-center, which limits the generalizability of the findings. Second, no external validation was performed. Third, the analysis was limited to the first sepsis episode: septic shock and sepsis-induced coagulopathy were assessed within a single episode. Moreover, the retrospective design does not allow definitive conclusions regarding causality of the identified associations. It should also be considered that the retrospective study design and the exclusion of patients with incomplete data may have introduced selection bias.

### Future research directions

The findings define several directions for future research. First, the development and dissemination of specialized databases of patients with prolonged and chronic critical illness are needed to enable external validation of study results. In addition, prospective multicenter studies

are required to confirm the reproducibility and clinical relevance of the identified risk factors. Finally, the absence of unified criteria for defining prolonged and chronic critical illness remains a significant obstacle to comparison of results across studies and necessitates the development of a standardized approach.

### Conclusion

The conducted study made it possible to identify independent risk factors for septic shock, recurrent sepsis episodes, and sepsis-induced coagulopathy in patients with sepsis in the setting of prolonged and chronic critical illness. These findings emphasize the importance of analyzing sepsis phenotypic characteristics and laboratory parameters when assessing prognosis and provide a basis for the development of specialized risk stratification tools in this patient population.

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**Author contribution.** All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

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