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Parameters of leukopoiesis and thrombocytopenia in early urosepsis as potential predictors of a lethal outcome in hospitalized patients

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ABSTRACT

Aim. To perform a comparative analysis of leukopoiesis parameters and platelet count in peripheral blood with evaluation of their changes in the first 48 hours from urosepsis (US) verification in hospitalized patients depending on the outcome of the disease.

Materials and methods. A retrospective comparative study included 40 patients with US divided into a group of deceased ($n = 10$) and a group of recovered ($n = 30$) individuals. Along with a full clinical and paraclinical examination, which is a routine practice in the urology clinic in case of suspected (confirmed) sepsis, we performed a differentiated assessment of leukopoiesis and platelet count in peripheral blood at baseline (at the moment of US verification) and 48 hours after US verification. The assessment included determination of the immature granulocyte count, investigation of neutrophil granularity intensity (NEUT-GI) and neutrophil reactivity intensity (NEUT-RI), and measurement of the mean platelet volume (MPV).

Results. The baseline level of organ dysfunction graded by the SOFA (Sequential Organ Failure Assessment) score was significantly higher in deceased patients than in survivors (6 points vs. 3 points, respectively; $p = 0.001$). The group of the deceased was characterized by lower platelet and monocyte levels. The ROC analysis with the calculation of area under the curve (AUC) identified the following potential predictors of a lethal outcome in US: proportion of monocytes from the total leukocyte count at baseline $\leq 5.5\%$ (AUC 0.732, $p = 0.032$), proportion of eosinophils from the total leukocyte count at baseline $\leq 0\%$ (AUC 0.756, $p = 0.011$), absolute eosinophil count at baseline $\leq 0.01 \times 10^9 / l$ (AUC 0.802, $p = 0.009$), absolute basophil count at baseline $\leq 0.03 \times 10^9 / l$ (AUC 0.718, $p = 0.028$), NEUT-GI at baseline ≤ 153.2 scatter intensity (SI) units (AUC 0.754, $p = 0.021$), NEUT-RI at baseline ≤ 59.3 SI units (AUC 0.737, $p = 0.024$) and their increase after 48 hours by > 0.9 SI units (AUC 0.852, $p = 0.001$) or by $> 1.34\%$ (AUC 0.844, $p = 0.003$), platelet count at baseline $\leq 144 \times 10^9 / l$ (AUC 0.762, $p = 0.007$) and after 48 hours $\leq 174 \times 10^9 / l$ (AUC 0.769, $p < 0.007$).

Conclusion. The assessment of the platelet count and leukopoiesis parameters, including the ones characterizing neutrophil maturation (NEUT-RI, NEUT-GI), in the first 48 hours from US verification, can be effective predictors of a lethal outcome in patients with US.

Keywords: urosepsis, lethal outcome, NEUT-GI, NEUT-RI, immature reticulocytes, MPV, lymphopenia, thrombocytopenia, anemia

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Показатели лейкоцитарного роста кроветворения и тромбоцитопения в ранние сроки развития уросепсиса как потенциальные предикторы летального исхода у госпитализированных пациентов

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РЕЗЮМЕ

Цель. Выполнение сравнительного анализа показателей лейкоцитарного роста гемопоэза и уровня тромбоцитов в периферической крови с оценкой характера их изменений в первые 48 ч от момента верификации уросепсиса (УС) у госпитализированных пациентов в зависимости от исхода болезни.

Материалы и методы. Проведено ретроспективное сравнительное исследование 40 пациентов с УС, разделенных на группу умерших ($n = 10$) и выздоровевших ($n = 30$). Наряду с полным клиническим и параклиническим обследованием, принятым в урологической клинике при подозреваемом (подтвержденном) сепсисе, исходно в момент верификации УС и через 48 ч проводилась дифференцированная оценка в периферической крови форменных элементов лейкоцитарного гемопоэтического роста и тромбоцитов, включающая подсчет числа незрелых гранулоцитов, исследование интенсивности нейтрофильной зернистости (NEUT-GI) и реактивности (NEUT-RI) нейтрофилов, а также среднего объема тромбоцитов (MPV).

Результаты. Исходно уровень органной дисфункции, оцененный по шкале SOFA (Sequential Organ Failure Assessment), у умерших пациентов был значимо выше, чем у выживших (6 баллов vs 3 балла соответственно; $p = 0,001$). Группа умерших отличалась более низкими уровнем тромбоцитов и моноцитов. ROC-анализ с расчетом AUC (площадь под кривой) позволил выявить следующие потенциальные предикторы летального исхода при УС: доля моноцитов от общего числа лейкоцитов исходно $\leq 5,5\%$ (AUC 0,732; $p = 0,032$), доля эозинофилов от общего числа лейкоцитов исходно $\leq 0\%$ (AUC 0,756; $p = 0,011$) и абсолютное число эозинофилов исходно $\leq 0,01 \times 10^9/\text{л}$ (AUC 0,802; $p = 0,009$), абсолютное число базофилов исходно $\leq 0,03 \times 10^9/\text{л}$ (AUC 0,718; $p = 0,028$), NEUT-GI исходно $\leq 153,2$ единицы интенсивности флуоресценции (ИФ) (AUC 0,754; $p = 0,021$), NEUT-RI исходно $\leq 59,3$ ИФ (AUC 0,737; $p = 0,024$) и их увеличение через 48 ч на более чем 0,9 ИФ (AUC 0,852; $p = 0,001$) или на более чем 1,34% (AUC 0,844; $p = 0,003$), уровень тромбоцитов исходно $\leq 144 \times 10^9/\text{л}$ (AUC 0,762; $p = 0,007$) и через 48 ч $\leq 174 \times 10^9/\text{л}$ (AUC 0,769; $p < 0,007$).

Заключение. Оценка уровня тромбоцитов, а также показателей лейкоцитарного роста гемопоэза, включая параметры, характеризующие активацию нейтрофилов (NEUT-RI, NEUT-GI), в первые 48 ч от момента диагностики септического состояния может быть полезной при прогнозировании летального исхода у пациентов с УС.

Ключевые слова: уросепсис, летальный исход, NEUT-GI, NEUT-RI, незрелые ретикулоциты, MPV, лимфопения, тромбоцитопения, анемия

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Urosepsis (urogenic sepsis, US) is characterized by clinical manifestations of urinary tract infection (UTI) and / or male genital tract infection, which are complicated by the development of acute systemic organ dysfunction. The prevalence of US among all sepsis cases varies significantly and ranges from 9 to 31% [1].

Regardless of the lesion intensity, urinary tract obstruction is the main risk factor for US development. According to the retrospective study by R.S. Hotchkiss et al. (2003), this risk factor was associated with the development of US in men in 78% and in women – in 54% of cases [2]. At the same time, this complication most often develops in women (approximately in 2/3 of cases) [3, 4].

In addition to high prevalence, the problem of US is also relevant due to high mortality of patients which can be as high as 30–49% [5].

The diagnosis of US is based on the detection of UTI and / or male genital tract infection in combination with acute organ dysfunction, as determined by the Sequential Organ Failure Assessment (SOFA) score. The SOFA score is an important tool for assessing the risk of death and predicting the duration of hospitalization and stay in the intensive care unit (ICU) [6]. Thus, the SOFA score ≥ 2 is associated with a mortality risk of $> 10\%$ [4]. However, in real clinical practice, the search for reliable biomarkers and criteria for a dynamic assessment of the patient's condition at an early stage (e.g., in the first 24–48 hours) of US development remains relevant. It will allow to more accurately identify patients at high risk of a lethal outcome and timely adjust the pharmacotherapeutic approach to their treatment.

The **aim of the study** was to perform a comparative analysis of leukopoiesis parameters and platelet count in peripheral blood with evaluation of their changes in the first 48 hours from urosepsis (US) verification in hospitalized patients depending on the outcome of the disease.

MATERIALS AND METHODS

Based on the study protocol approved by the local Ethics Committee at Siberian State Medical University (Protocol No. 8616/1 of 29.03.2021.), a retrospective comparative study was performed that included data of 40 patients with US hospitalized to Siberian State Medical University clinics via the ICU with acute infection or via planned admission to the urology unit with subsequent development of infectious complications from 01.01.2019 to 30.04.2023 (continuous sampling). Within the study, two comparison groups were formed depending on the outcome of hospitalization (discharge from the hospital or a fatal outcome) for a dynamic assessment of clinical, anamnestic, and laboratory parameters in early US (first 48 hours) in order to determine their relationship with the outcome of the disease.

The study included data obtained from patients with confirmed bacterial UTI and the quick SOFA (qSOFA) score of at least 2, as well as with the presence of comprehensive information about the disease and the clinical and laboratory parameters of interest, as stated in the medical record of the inpatient and in the medical information system used by the medical institution.

Data on the nature, timing, and outcome of hospitalization, as well as anthropometric data were analyzed. The qSOFA and SOFA scores, duration of US, and data on the patient's stay in the ICU were recorded for all patients. We performed a dynamic assessment (at the moment of US verification and after 48 hours) of standard leukopoiesis parameters and platelet count in peripheral blood, including the differential assessment of blood cell count and the neutrophil-to-lymphocyte ratio (NLR). The use of the extended version of the Sysmex XN-1000 hematology analyzer software (Sysmex, Germany) allowed to additionally evaluate such parameters as immature granulocyte (IG) count, neutrophil granularity intensity (NEUT-GI), neutrophil reactivity intensity (NEUT-RI), mean platelet volume (MPV), platelet crit (PCT), and the

proportion of reactive lymphocytes (RE-LYMP) and antibody-synthesizing lymphocytes (AS-LYMP).

Statistical analysis was performed using the StatSoft STATISTICA 12.5 program. Quantitative variables were presented as the median and the interquartile range ($Me (Q_1; Q_3)$). Qualitative variables were presented as absolute and relative frequencies ($n (%)$). Quantitative and qualitative variables in independent samples were compared using the Mann – Whitney U -test and the Fisher's exact test. Quantitative variables in dependent samples were compared using the Wilcoxon test. The ROC analysis was performed using the MedCalc software package, Version 18.9.1. The area under the curve (AUC) with 95% confidence interval (CI), the cut-point according to the Youden's index, as well as sensitivity and specificity for this point were evaluated. The results were considered statistically significant at $p < 0.05$.

RESULTS

Clinical and anamnestic characteristics of the comparison groups

In accordance with the protocol, 40 patients of both sexes were included in the study: 21 (53.0%) women and 19 (47.0%) men. Depending on the outcome of the disease (discharge from the hospital or a fatal outcome), two comparison groups were formed: group 1 ($n = 30$) included hospitalized patients with a favorable outcome (survivors), group 2 ($n = 10$) encompassed hospitalized patients with a fatal outcome (deceased).

The majority of the patients ($n = 38$, 95.0%) included in the study were hospitalized in the urology unit of Siberian State Medical University clinics via the ICU. Two patients (5.0%) were hospitalized following planned admission for surgical treatment of urolithiasis and benign prostatic hyperplasia, but subsequently developed infection complicated by US.

The age of the patients was 64.5 (48.0; 75.0) years. It was noted that the patients in the deceased group belonged to an older age group (77 (65; 83) years) than the patients discharged from the hospital with a favorable outcome (60 (34; 75) years, $p = 0.026$).

The groups of patients did not differ in the time of US detection, which was 3.0 (1.0; 6.0) days in the group of survivors and 2.5 (1.0; 6.0) days in the group of deceased patients ($p = 0.775$). Twenty patients (50% of the total number) required transfer to the ICU, of whom 50% of patients died ($n = 10$).

Analyzing the causes of US development, we found that 24 patients had acute nonobstructive ($n = 17$) or obstructive ($n = 8$) pyelonephritis, 7 patients had renal carbuncle, 3 patients were followed up for chronic bilateral pyelonephritis, 2 patients were hospitalized with a renal abscess, and 1 patient was hospitalized with a renal and related retroperitoneal abscess. Surgery was performed in 30 (75%) patients, with 9 patients out of 10 (90%) in the group of deceased patients undergoing surgery. The data analysis identified 5 patients with infection directly caused by medical manipulations. Thus, catheter-associated UTI was verified in 3 patients, and UTI caused by surgical interventions was verified in 2 patients.

When taking a history, the presence of comorbidity was recorded. Ischemic heart disease was registered in 12 (30%) patients, history of acute myocardial infarction – in 6 (15%) patients, history of stroke – in 6 (15%) cases, diabetes mellitus – in 7 (17.5%) patients, stage 2–3 chronic heart failure – in 9 (22.5%) patients, bronchial asthma – in 2 (5%) cases, chronic obstructive pulmonary disease – in 3 (7.5%) patients. HIV infection was observed in 2 (5%) patients, chronic kidney disease – in 8 (20%) patients, intravenous drug abuse – in 1 (2.5%) patient, and alcohol abuse – in 2 (5%) patients. Also, 7 (17.5%) patients included in the study had active cancer. The groups differed significantly only in the presence of hypertension, which was registered in 15 (50%) survivors and in 9 (90%) deceased patients ($p = 0.032$).

Chest radiography revealed that infiltrative changes in the lung parenchyma during hospitalization emerged in 7 (23.3%) hospitalized patients with a favorable outcome and in 2 (20%) hospitalized patients who died. These radiographic changes with corresponding clinical manifestations were registered ≥ 48 hours from the moment of hospitalization. Therefore, hospital-acquired pneumonia was diagnosed, the development of which was associated with the progressive course of the underlying disease and / or invasive mechanical ventilation [7].

Progression of UTI was characterized by leukocyturia and bacteriuria according to urinalysis in 100% of patients. At the time of US verification, all patients underwent bacteria culture tests of blood and urine. It was found that UTI in all examined patients was caused by one pathogen, most often

from the *Enterobacteriaceae* family. The dominant pathogen was *Escherichia coli* (in 73% of patients) and *Enterococcus faecium* (in 13% of cases); much less frequently (not more than in 1 case), the infection was caused by *Klebsiella pneumoniae*, *Acinetobacter baumannii*, etc. Positive blood culture test was obtained in 3 (7.5%) patients: *Klebsiella pneumoniae* was identified in 1 patient, *Escherichia coli* – in 1 patient, and *Enterococcus faecium* – in 1 patient.

The comparison groups did not differ significantly in the choice of drugs for initial antibiotic therapy (ABT), which was based on the stratification of patients by the presence of antibiotic resistance and complied with current clinical guidelines [8]. Thus, amoxicillin + clavulanic acid was received by 5 (12.5%) patients, cefuroxime – by 1 (2.5%) patient, cefotaxime – by 12 (30%) patients, ceftriaxone – by 3 (7.5%) patients, cefepime – by 1 (2.5%) patient, cefoperazone + sulbactam – by 1 (2.5%) patient, ciprofloxacin – by 6 (15%) patients, levofloxacin – by 6 (15%) patients, ertapenem – by 3 (7.5%) patients, and meropenem – by 2 (5%) patients. In 33 (82.5%) patients, 1 (1; 2) substitution of the anti-infective drug / modification of ABT regimen was required due to aggravation of the clinical course of the disease (in 15 (37.5%) patients) or following the results of the microbiological examination and

antibiotic sensitivity test in case of doubtful efficacy of initial therapy – in 18 (45%) patients.

At the time of US verification in patients with a lethal outcome, the SOFA score was 6 (4; 7) points, while in the survivors, it was significantly lower – 3 (1; 5) points ($p = 0.001$).

Results of blood tests

The detailed analysis of the hemogram did not reveal significant differences in most of the studied parameters. In contrast to the recovered patients, the group of fatal patients differed in thrombocytopenia at both time points: $235 (178; 392) \times 10^9 / l$ vs. $105 (82; 194) \times 10^9 / l$, respectively, at baseline ($p = 0.019$) and $262 (203; 358) \times 10^9 / l$ vs. $101 (97; 174) \times 10^9 / l$, respectively, after 48 hours ($p = 0.058$). At the same time, the comparison groups did not differ significantly in MPV and platelet distribution width (PDW).

Changes in the most significant leukopoiesis parameters of peripheral blood are presented in the Table. The comparison groups were characterized by a steady increase in the neutrophil count in the first 48 hours from the moment of US verification without significant differences in the number of mature and immature granulocytes, lymphocytes, and NLR value (Table).

Table

Changes in the leukopoiesis parameters of peripheral blood in the first 48 hours after US verification, Me (Q_1 ; Q_3)			
Parameter	Group 1 – hospitalized patients with a favorable outcome	Group 2 – hospitalized patients with a lethal outcome	P_{1-2}
Leukocytes, $10^9 / l$, at baseline	11.74 (8.15; 21.60)	10.27 (5.90; 17.80)	0.391
Leukocytes, $10^9 / l$, after 48 hours	10.86 (6.14; 15.63)	12.17 (10.10; 12.70)	0.942
Neutrophils, %, at baseline	85.4 (75.2; 88.9)	88.0 (69.7; 93.2)	0.571
Neutrophils, %, after 48 hours	79.7 (71.3; 85.1)	85.2 (84.2; 89.3)	0.215
Neutrophils, $10^9 / l$, at baseline	9.27 (5.40; 18.96)	8.94 (5.20; 9.57)	0.524
Neutrophils, $10^9 / l$, after 48 hours	7.91 (4.61; 13.45)	11.06 (10.25; 12.12)	0.616
NEUT-GI, SI, at baseline	158.6 (154.1; 161.2)	152.9 (148.2; 159.2)	0.065
NEUT-GI, SI, after 48 hours	157.3 (151.3; 160.1)	148.4 (144.4; 154.9)	0.160
NEUT-RI, SI, at baseline	59.2 (49.1; 62.6)	48.3 (46.9; 56.8)	0.086
NEUT-RI, SI, after 48 hours	56.9 (50.8; 60.5)	54.8 (47.8; 61.7)	0.670
Changes in NEUT-RI (T2–T1), SI units	–1.65 (–3.85; 0.35)	4.15 (–0.20; 9.70)	0.033
Changes in NEUT-RI (T2–T1), SI, %	–3.24 (–6.92; 0.69)	7.44 (–0.49; 19.24)	0.038
Lymphocytes, %, at baseline	7.3 (4.7; 16.3)	7.4 (5.5; 13.1)	0.941
Lymphocytes, %, after 48 hours	12.4 (8.2; 16.6)	8.4 (4.7; 9.0)	0.197
Lymphocytes, $10^9 / l$, at baseline	1.12 (0.76; 1.64)	0.65 (0.60; 1.06)	0.058
Lymphocytes, $10^9 / l$, after 48 hours	1.42 (0.81; 2.01)	0.80 (0.51; 1.02)	0.175
NLR	12.84 (4.52; 21.46)	14.54 (7.39; 19.86)	0.658
NLR	6.91 (4.49; 11.62)	15.87 (5.34; 65.93)	0.345
Monocytes, %, at baseline	6.0 (4.5; 7.7)	4.4 (3.1; 5.2)	0.038
Monocytes, %, after 48 hours	6.4 (4.7; 9.0)	4.3 (3.6; 6.7)	0.185
Monocytes, $10^9 / l$, at baseline	0.80 (0.41; 1.12)	0.55 (0.21; 0.59)	0.132

Table (continued)

Parameter	Group 1 – hospitalized patients with a favorable outcome	Group 2 – hospitalized patients with a lethal outcome	p_{1-2}
Monocytes, $10^9 / l$, after 48 hours	0.69 (0.37; 0.88)	0.44 (0.44; 0.46)	0.161
Eosinophils, %, at baseline	0.4 (0.1; 1.4)	0.0 (0.0; 0.2)	0.021
Eosinophils, %, after 48 hours	0.7 (0.3; 1.6)	0.0 (0.0; 0.0)	0.062
Eosinophils, $10^9 / l$, at baseline	0.065 (0.030; 0.125)	0.010 (0.010; 0.040)	0.055
Eosinophils, $10^9 / l$, after 48 hours	0.085 (0.050; 0.155)	0.105 (0.090; 0.120)	0.531
Basophils, %, at baseline	0.3 (0.2; 0.5)	0.2 (0.1; 0.2)	0.067
Basophils, %, after 48 hours	0.3 (0.2; 0.4)	0.6 (0.3; 0.7)	0.236
Basophils, $10^9 / l$, at baseline	0.040 (0.020; 0.070)	0.025 (0.015; 0.030)	0.062
Basophils, $10^9 / l$, after 48 hours	0.030 (0.020; 0.040)	0.040 (0.010; 0.090)	0.716
IG, %, at baseline	0.90 (0.50; 2.65)	1.70 (0.50; 2.70)	0.562
IG, %, after 48 hours	0.75 (0.40; 2.55)	0.50 (0.15; 4.10)	0.509
IG, $10^9 / l$, at baseline	0.11 (0.04; 0.60)	0.49 (0.08; 0.77)	0.349
IG, $10^9 / l$, after 48 hours	0.08 (0.03; 0.25)	0.17 (0.06; 0.57)	0.693

Note. SI – scatter intensity.

It should be noted that the group of patients with a lethal outcome was characterized by smaller relative monocyte and eosinophil counts in the blood at baseline. At the same time, the eosinophil count in this group at the time of US verification was actually close to zero, amounting to $10 \text{ kl} / \mu\text{l}$ (Table).

Despite the fact that NEUT-RI in the comparison groups did not differ significantly at baseline and 48 hours after US verification, the nature of changes in this parameter in the groups in the first two days was multidirectional ($p < 0.05$). In the group of patients with a lethal outcome, NEUT-RI increased by almost 7.5%, while in the group with a favorable outcome, it decreased by more than 3% (Table).

Verification of potential early predictors of mortality in US by the ROC analysis

Predictors of an unfavorable outcome in US can be:

– proportion of monocytes from the total leukocyte count at baseline $\leq 5.5\%$ with the sensitivity of 88.9% and specificity of 57.1% (AUC 0.732, 95% CI (0.561; 0.864), $p = 0.032$);

– proportion of eosinophils from the total leukocyte count at baseline $\leq 0\%$ with the sensitivity of 66.67% and specificity of 82.14% (AUC 0.756, 95% CI (0.587; 0.882), $p = 0.011$) and absolute eosinophil count $\leq 0.01 \times 10^9 / l$ with the sensitivity of 75.0% and specificity of 83.3% (AUC 0.802, 95% CI (0.609; 0.927), $p = 0.009$);

– absolute basophil count at baseline $\leq 0.03 \times 10^9 / l$ with the sensitivity of 87.5% and specificity of 66.7% (AUC 0.718, 95% CI (0.540; 0.856), $p = 0.028$);

– NEUT-GI at baseline ≤ 153.2 SI units with the

sensitivity of 66.7% and specificity of 79.0% (AUC 0.754, 95% CI (0.543; 0.903), $p = 0.021$);

– NEUT-RI at baseline ≤ 59.3 SI units with the sensitivity of 100.0% and specificity of 47.4% (AUC 0.737, 95% CI (0.524; 0.891), $p = 0.024$) and an increase in this index after 48 hours by > 0.9 SI units with the sensitivity of 75.0% and specificity of 87.5% (AUC 0.852, 95% CI (0.623; 0.969), $p = 0.001$) or by $> 1.34\%$ with the sensitivity of 75.0% and specificity of 87.5% (AUC 0.844, 95% CI (0.614; 0.965), $p = 0.003$);

– platelet count at baseline $\leq 144 \times 10^9 / l$ with the sensitivity of 66.7% and specificity of 82.8% (AUC 0.762, 95% CI (0.597; 0.885), $p = 0.007$) and after 48 hours $\leq 174 \times 10^9 / l$ with the sensitivity of 80.00% and specificity of 75.86% (AUC 0.769, 95% CI (0.593; 0.896), $p < 0.007$). The identified critical values of factors that increase the probability of a lethal outcome are presented in the Figure.

DISCUSSION

Regardless of the localization of the source of infection, sepsis is a life-threatening condition characterized by systemic inflammation with the development of dysfunction of various organs, hemodynamic disorders, systemic hypotension, and tissue hypoxia. The mechanisms of sepsis cannot but affect the blood system, which is most often associated with the development of coagulation disorders and thrombocytopenia, as well as multidirectional changes in the leukocyte formula [9].

In sepsis, low platelet count is a well-known biomarker of disease severity. Recently, researchers

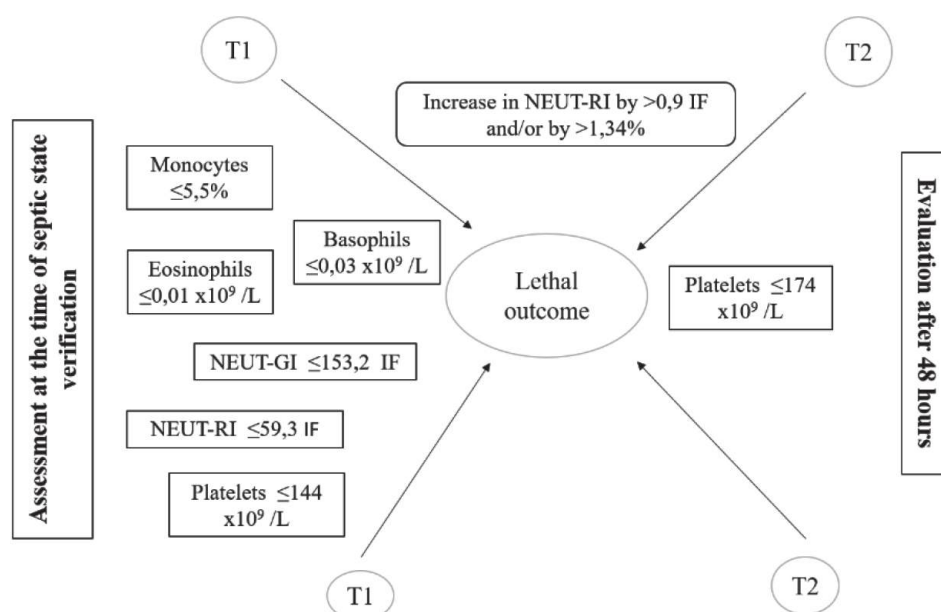


Figure. Factors associated with mortality in urosepsis: T1 – baseline value; T2 – evaluation after 48 hours

have focused on the role of platelets in the pathogenesis of multiorgan failure and have considered them as a potential therapeutic target in sepsis [10]. It is assumed that the predominant processes here include peripheral platelet consumption, determined by platelet activation, chemotaxis, and isolation in the microcirculation. Immune destruction and disseminated intravascular coagulation are also discussed [11]. In the present study, the group of deceased patients was characterized by decreased platelet counts at both time points. It is worth noting that the platelet counts at the time of US verification and after 48 hours were $\leq 144 \times 10^9 / l$ and ≤ 174 , respectively, and were associated with a lethal outcome.

In sepsis, infection is known to trigger a complex and prolonged host response involving both innate and adaptive immunity. An imbalance in the production of pro- and anti-inflammatory immunoregulatory molecules and inadequate involvement of effector cells impair the host response to infectious agents and cause tissue damage. Recent studies including patients with US have confirmed that significant depletion of circulating CD4+ and CD8+ lymphocytes was associated with a lethal outcome in this group of patients [12].

In our study, a significant increase in the absolute neutrophil count was recorded in the first 48 hours in both groups. In the group of patients with an

unfavorable outcome of US treatment, a trend toward absolute lymphocytopenia ($< 1.0 \times 10^9 / l$) with lower baseline monocyte counts was noted. The eosinophil count in this group of patients approached zero.

Eosinopenia is often observed in severe non-parasitic infections characterized by a shift in hematopoiesis toward an increase in the number of neutrophil granulocytes in peripheral blood. According to H. Shaaban et al. (2010), eosinophil count < 50 cells / μl with the sensitivity of 81% and specificity of 65% was associated with the presence of sepsis in adults [13]. A systematic literature review noted that of 39 analyzed studies on the role of eosinophils in sepsis, 11 studies demonstrated an association between eosinopenia and sepsis, and 8 studies found persistent eosinopenia > 48 hours after admission to the ICU. The authors concluded that persistent peripheral eosinopenia was a marker of bacterial sepsis and was independently associated with adverse outcomes, such as death or re-hospitalization [14].

In our study, the baseline eosinophil count (values at the time of US verification) of 0% and monocyte count of $\leq 5.5\%$ in the leukocyte formula, as well as the absolute eosinophil count of ≤ 10 cells / μl and the absolute basophil count ≤ 30 cells / μl were registered as predictors of a lethal outcome. The obtained data regarding the prognostic value of the basophil count in peripheral blood in US patients

correlate with the data obtained by X. Chen et al. (2023), who found that the absence of basophils in blood in patients with sepsis in ICU was associated with critical progression of the disease, positively correlated with 28-day mortality, and served as an independent predictor of an unfavorable outcome for this group of patients (odds ratio (OR) 3.425, 95% CI (3.717–3.165), $p < 0.001$) [15].

Monocytes play an important role in the development of sepsis. However, the diagnostic and prognostic value of changes in the monocyte count is controversial. Some authors report an increase in the number of monocytes in peripheral blood, while others describe monocytopenia associated with increased mortality [16, 17].

Modern capabilities of hematology analyzers allow to additionally assess such parameters as NEUT-GI and NEUT-RI, which, in our opinion, have a prognostic potential in US. These parameters characterize the innate immune response: an increase in NEUT-GI reflects intensification of the inflammatory process, and NEUT-RI reflects the metabolic activity of the neutrophil population [18]. NEUT-RI can potentially correlate with the development of sepsis [19]. Thus, NEUT-RI can predict the emergence of IGs in the peripheral blood, thereby acting as an early marker of bacterial infection. At the same time, an increase in the NEUT-RI levels correlated with an increase in the concentration of immunoglobulins in peripheral blood within 72 h from the development of infection [20]. Similarly, in the study by R.J. Dinsdale et al. (2017), the NEUT-RI value was significantly greater in patients with sepsis after burn injury compared to patients without sepsis, indicating the possibility of early diagnosis of sepsis [18]. The study by E. Mantovani et al. (2023) demonstrated that NEUT-RI showed AUC > 0.80 and better prognostic value of a negative result than procalcitonin and C-reactive protein in patients in ICU for the diagnosis of US (87.4 vs. 83.9% and 86.6%, $p = 0.038$) [20].

Despite the fact that in our study, the comparison groups with US did not differ significantly in the NEUT-RI value at baseline and after 48 hours, the nature of changes in this parameter in the first two days in the groups was multidirectional ($p < 0.05$). Thus, in the group of patients with a lethal outcome, the NEUT-RI value continued to grow from lower values, while in the group with a favorable outcome,

a trend toward a decrease in this parameter was noted. The ROC analysis revealed that the baseline value of NEUT-RI ≤ 59.3 SI units and the increase in this parameter by > 0.9 SI units after 48 hours predicted the onset of a lethal outcome. It is worth noting that baseline NEUT-GI ≤ 153.2 SI units was also associated with a lethal outcome in US patients. It is possible that delayed activation of neutrophils with relatively low baseline granularity in US reflects a delayed and inadequate response to infection, which may be associated with an increased risk of a lethal outcome in US.

CONCLUSION

The results of the study showed that certain blood parameters can serve as predictors of a lethal outcome in US. For example, it was found that the low platelet counts at the time of US verification and after 48 hours, as well as changes in the values of some parameters in the leukocyte formula may be associated with a lethal outcome.

Such parameters as NEUT-GI and NEUT-RI may also play an essential role in predicting the outcome of sepsis. Their changes in the first days of the disease can be evidence of the disease severity and indicate an inadequate immune response to infection.

Therefore, the hematologic parameters analyzed in this study may be effective for assessing the risk of a lethal outcome in US and may be used as predictors of its development. Further studies and clinical observations may help to clarify their role in prognosis and treatment of this group of patients.

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Authors' contribution

Fedosenko S.V. – conception and design, coordination of the study, drafting of the article, review of literature, final approval of the manuscript for publication. Rodionova Yu.O. – compilation of the database, acquisition and interpretation of clinical data. Ivanova A.I. – statistical processing of the data, interpretation of the data, drafting of the article. Arzhanik M.B. – conception and design, statistical processing of the data, interpretation of the data, critical revision of the manuscript for important intellectual content. Semenova O.L. – statistical processing of the data. Nesterovich S.V. – coordination of the study, critical revision of the manuscript for important intellectual content. Starovoitova E.A. – critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Zima A.P. – interpretation of the laboratory data, critical revision of the manuscript for important intellectual content. Vinokurova D.A., Kamaltynova E.M. – critical revision of the manuscript for important intellectual content, drafting of the manuscript. Kalyuzhin V.V. – review of literature, interpretation of the data, final approval of the manuscript for publication.

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