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РАННИЕ КЛИНИКО-ЛАБОРАТОРНЫЕ ПРЕДИКТОРЫ ГОСПИТАЛЬНОЙ ЛЕТАЛЬНОСТИ У ПАЦИЕНТОВ С СЕПСИСОМ НА ФОНЕ ПНЕВМОНИИ

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Early Clinical and Laboratory Predictors of Hospital Mortality in Patients with Sepsis Secondary to Pneumonia

Абстракт

Несмотря на значительный прогресс в области профилактики, ранней диагностики и антибактериальной терапии, внебольничная пневмония по-прежнему сохраняет статус не только наиболее распространенного среди острых инфекционных заболеваний, но и является частым источником развития сепсиса, многократно повышающего вероятность летального исхода в данной группе пациентов. **Целью исследования** стало выполнение сравнительного анализа клинико-лабораторных показателей и оценка характера их изменений в первые 48 часов от момента верификации сепсиса, развившегося на фоне пневмонии, у пациентов терапевтического отделения в зависимости от исхода госпитализации. **Клинические группы и методы исследования.** Выполнено ретроспективное сравнительное исследование, включившее методом сплошной выборки пациентов с сепсисом, развившемся на фоне пневмонии у пациентов, госпитализированных в терапевтические клиники ФГБОУ ВО СибГМУ Минздрава России в период с 01.01.2019 г. по 30.04.2023 г. Всего в исследование включены 40 пациентов обоего пола с последующим разделением на две группы сравнения в зависимости от исхода госпитализации (выписка из стационара или наступление летального исхода) для динамической оценки клинико-анамнестических и лабораторных параметров в ранние сроки развития септического состояния (первые 48 часов) с целью определения их связи с исходом госпитализации. **Результаты.** Все пациенты были разделены на 2 группы. Первую группу (n=17, 42,5 %) составили пациенты с благоприятным исходом госпитализации (выздоровление), вторую группу (n=23, 57,5 %) составили пациенты с летальным исходом. На момент верификации сепсиса пациенты с благоприятным исходом имели значимо ниже балл по шкале SOFA (3 (2; 6) балла), чем у пациентов с летальным исходом (6 (5; 7) баллов), p=0,037. Изменение концентрации мочевины в первые 48 часов от момента верификации сепсиса в группе выживших составило -1,3 (-4,4; 1,99) ммоль/л, а в группе умерших 5,5 (-1,5; 12,2) ммоль/л, p=0,020. В группе умерших пациентов 8 человек (34 %) на момент верификации сепсиса имели сочетание гипотонии (<90/60 мм рт. ст.) и содержание лактата в сыворотке крови >5 ммоль/л. В группе выживших гипотония наблюдалась только у 2 человек (11 %), причем показатели уровня лактата у этих пациентов находились в диапазоне 4,5-4,6 ммоль/л. В точке 1 показатели незрелых гранулоцитов статистически значимо не различались у выживших и умерших пациентов (1,2 (0,7; 2,1)% vs 0,8 (0,6; 1,5)%, соответственно, p>0,05). Через 48 часов уровень незрелых гранулоцитов нарастал у выживших паци-

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ентов до 1,5 (1; 3,2)% и наоборот, снижался до 0,65 (0,45; 1,45)% в группе умерших, причем разница этих показателей между группами стала статистически значимой, p <0,05. **Заключение.** У пациентов с сепсисом на фоне тяжелой пневмонии летальность составила 57,5 %. С целью выделения групп высокого риска летального исхода помимо оценки по шкале SOFA следует осуществлять динамический контроль в первые 48 часов от момента верификации септического состояния таких биомаркеров, как уровень мочевины, лактата, уровень незрелых гранулоцитов и ретикулоцитов.

Ключевые слова: *сепсис, летальность, пневмония, предикторы летального исхода*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Despite significant progress in the field of prevention, early diagnosis and antibacterial therapy, community-acquired pneumonia still retains the status of not only the most common among acute infectious diseases, but is also a frequent source of sepsis, which greatly increases the likelihood of death in this group of patients. The purpose of the study was to perform a comparative analysis of clinical and laboratory parameters and assess the nature of their changes in the first 48 hours from the moment of verification of sepsis that developed against the background of pneumonia in patients of the therapeutic department, depending on the outcome of hospitalization. **Clinical groups and research methods.** A retrospective comparative study was carried out, which included, using a continuous sampling method, patients with sepsis that developed against the background of pneumonia in patients hospitalized in therapeutic clinics of the Federal State Budgetary Educational Institution of Higher Education Siberian State Medical University of the Ministry of Health of Russia in the period from 01/01/2019 to 04/30/2023. In total, the study included 40 patients of both gender, followed by division into two comparison groups depending on the outcome of hospitalization (discharge from hospital or death) for the dynamic assessment of clinical, anamnestic and laboratory parameters in the early stages of the development of a septic condition (the first 48 hours) in order to determine their relationship with the outcome of hospitalization. **Results.** All patients were divided into 2 groups. The first group (n=17, 42.5 %) consisted of patients with a favorable outcome of hospitalization (recovery), the second group (n=23, 57.5 %) consisted of patients with a fatal outcome. At the time of verification of sepsis, patients with a favorable outcome had a significantly lower SOFA score (3 (2; 6) points) than patients with a fatal outcome (6 (5; 7) points), p = 0.037. The change in urea concentration in the first 48 hours from the moment of verification of sepsis, which in the group of survivors was -1.3 (-4.4; 1.99) mmol/l, and in the group of deceased 5.5 (-1.5; 12. 2) mmol/l, p=0.020. In the group of deceased patients, 8 people (34 %) at the time of verification of sepsis had a combination of hypotension (<90/60 mm Hg) and serum lactate >5 mmol/l. In the survivor group, hypotension was observed in only 2 people (11 %), and lactate levels in these patients were in the range of 4.5-4.6 mmol/l. At point 1, the indicators of immature granulocytes were not statistically significantly different between surviving and deceased patients (1.2 (0.7; 2.1)% vs 0.8 (0.6; 1.5)%, respectively, p>0. 05). After 48 hours, the level of immature granulocytes increased in surviving patients to 1.5 (1; 3.2)% and, conversely, decreased to 0.65 (0.45; 1.45)% in the group of deceased patients, and the difference in these indicators between groups became statistically significant, p <0.05. **Conclusion.** Thus, in patients with sepsis against the background of severe pneumonia, the mortality rate was 57.5 %. In order to identify groups at high risk of death due to sepsis due to pneumonia, in addition to the SOFA scale, dynamic monitoring of biomarkers such as urea, lactate, immature granulocytes and reticulocytes should be carried out in the first 48 hours from the moment of verification of the septic state.

Key words: *sepsis, mortality, pneumonia, predictors of death*

Conflict of interests

The authors declare no conflict of interests

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Introduction

Pneumonia remains the most common acute infectious diseases and, according to the World Health Organization, it takes the fourth place among causes of death globally [1]. In 2109 in the Russian Federation, the incidence of community-acquired pneumonia among adults was 410 per 100,000 people [2]. In 2018 in Russia, pneumonia mortality was 17.0 per 100,000 people [3]. Severe community-acquired pneumonia, which complications include marked acute respiratory failure

and/or sepsis, is of special interest. According to some authors, the need for intensive care in patients hospitalised with community-acquired pneumonia can be as high as 21 % because of organ dysfunction and sepsis [4]. According to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), setting forth new definitions and diagnostic criteria, sepsis is an "acute, life-threatening organ dysfunction, caused by impaired regulation (dysregulation) of host response to infection" [5, 6]. Since clarification of the source of infection is important for sepsis verification, the criteria for pneumonia-associated sepsis should include the presence of an identified site of infection and acute organ dysfunction, confirmed with assessment results of ≥ 2 points under the SOFA (Sequential Organ Failure Assessment).

According to various authors, mortality caused by pneumonia-associated mortality is relatively high and is 41 % to 50 % in various populations [7, 8]. Despite the developed diagnostic scales used in early diagnosis of a septic condition, the search for predictors to identify patients at a high risk of death is ongoing. According to literature, promising prognostic factors can be age, lactate concentration, body temperature, oxygenation index, bilirubin levels, Glasgow coma scale, hepatic disorders, cancer, organ transplantation, troponin T levels, neutrophil-to-lymphocyte ratio (NLR), and use of vasoconstrictors [9]. The main requirement for these parameters is their ability to change over time and the possibility to accurately forecast disease outcome. Currently, the search for such predictors is ongoing; therefore, it is important to assess the early changes in clinical and laboratory parameters in order to evaluate their prognostic value in hospitalised patients with pneumonia-associated sepsis.

Thus, **the objective of this study** is a comparative analysis of clinical and laboratory parameters and assessment of the nature of their changes during the first 48 hours after verification of pneumonia-associated sepsis in patients, depending on hospitalisation outcome.

Clinical Groups and Study Methods

The study protocol approved by the Local Ethics Committee (LEC) at the Siberian State Medical University of the Ministry of Health of Russia (LEC resolution No. 8616/1 dated 29 March 2021) was used to conduct a retrospective, comparative study of patients with pneumonia-associated sepsis hospitalised to the Clinic of the Siberian State Medical University of the Ministry of Health of Russia during the period from September 1, 2019 to April 20, 2023, who were included in the study under the continuous sampling method. 40 male and female patients were included in the study and divided into two groups, depending on the hospitalisation outcome (discharge or death), for dynamic assessment of their clinical and laboratory parameters at early stages of a septic condition (first 48 hours), in order to establish their relation to hospitalisation outcome.

The study enrolled patients with pneumonia and SOFA score of ≥ 2 points (Sequential Organ Failure Assessment, which includes hypotonia (systolic blood pressure below 100 mm Hg), respiratory distress (respiratory rate at least 22 respirations per minute), as well as altered mental status, assessed using the Glasgow coma scale (< 15 points), where each indicator was assigned 1 point), as well as availability of complete information about the disease and clinical and laboratory parameters, stated in the inpatient medical record and information registration system used by the medical institution.

In this study, the information on the nature, duration and outcome of hospitalisation, anthropometric data (sex, age, height, weight, body mass index (BMI)), presence of comorbidity/underlying pathology (including potential causes and confirmed immunodeficient conditions) were analysed. All patients had their qSOFA and SOFA recorded; also, the following information was documented: duration of the septic condition, information on patient's admission to the intensive care unit (ICU) (duration, artificial pulmonary ventilation, vasoconstrictor support); objective parameters (BP, HR, consciousness, SpO2) were monitored. All patients underwent assessment of the results in accordance with the unified list of laboratory tests during verification (point 1) and 48 hours later (point 2): serum iron, electrolytes, arterial blood gases, C-reactive protein (CRP), lactate, procalcitonin, sodium, potassium, urea, total bilirubin, direct bilirubin, calcium, CBC+DIFF (with calculation of the neutrophil-to-lymphocyte ratio (NLR) and eosinophil count). In this study, we used a differentiated approach to the calculation of reticulocyte count, depending on their maturity, using Sysmex XN-1000 blood analyser (Sysmex, Germany). Reticulocyte measurements were based on the principle of fluorescent flow cytometry with the use of a nucleinic acid colourant oxazine 750, which stains RNA cells. Depending on their maturity, reticulocytes have different fluorescence intensity, thus, they are subdivided into three subtypes: mature reticulocytes with

limited fluorescence are called "low fluorescence reticulocytes" (LFR), intermediately mature reticulocytes are "medium fluorescence reticulocytes" (MFR), while very immature reticulocytes are "high fluorescence reticulocytes" (HFR). Immature reticulocyte fraction (IRF) is the percentage of immature reticulocytes calculated as the sum of MFR and HFR; it represents erythropoietic activity.

Statistical analysis was performed in Statistica 12.0 (IBM SPSS Statistics, USA). Quantitative parameters are described using median (25th; 75th percentiles). Qualitative parameters are described using absolute and relative frequencies, n (%). Quantitative and qualitative parameters in independent samples were compared with the help of Mann–Whitney U test and Pearson's chi-square test or Fisher's exact test. Quantitative parameters in dependent samples were compared using Wilcoxon rank sum test. ROC analysis was performed in MedCalc SW, Version 18.9.1. The area under curve (AUC) with 95 % confidence interval, cutoff point using Youden's index, sensitivity and specificity of this point, were assessed. Results were statistically significant at $p < 0.05$.

Study Results

18 female (45 %) and 22 male (55 %) patients were included in the study. All patients were divided into two groups. Group 1 (n = 17, 42.5 %) were patients with a favourable outcome of hospitalisation (recovery); group 2 (n = 23, 57.5 %) were patients who died. There were no statistically significant differences in age (68 (41; 77) years old and 67 (58; 81) years old, p = 0.373) and BMI (25.45 (20.76; 30.72) and 25.85 (23; 27.68), p = 0.711, respectively) between the groups. In the survivors group, 64.7 % were men and 35.3 % were women, whereas in the other group 47.8 % were men and 52.2 % were women ($p > 0.05$). The most common comorbidities in the group of patients with unfavourable outcome were IHD, hypertensive disease, a history of myocardial infarction, stage 2–3 CHF; however, there were no statistically significant differences in comorbidities between the groups (intergroup p for all conditions was > 0.05) (Table 1).

In this study, in 56 % of patients, sepsis was diagnosed on the first day of hospitalisation. It is interesting to note the trend towards earlier diagnosis of sepsis in the group of patients with lethal outcome (day 1 (1; 4) of hospitalisation) as compared to survivors (day 2 (1; 5) of hospitalisation); however, there were no statistically significant differences, $p > 0.05$.

The qSOFA scale was used as a preliminary sorting tool, because the study enrolled patients with confirmed pneumonia and qSOFA score of ≥ 2 points (Table 2). An analysis of differences using Fisher's exact test demonstrated that, in the group with favourable outcome, 16 (94.12 %) patients had qSOFA score of 2 points and only one patient had a score of 3 points, whereas in the group with lethal outcome, 14 (60.87 %) patients had a score of 2 points and 9 (39.13 %) patients — 3 points (p = 0.018).

At the moment when sepsis was verified on the basis of an assessment of organ dysfunction severity (SOFA), statistically significant differences were observed. At the moment when sepsis was verified, patients with favourable outcome had a significantly lower SOFA score (3 (2; 6) points) as compared to patients who died (6 (5; 7) points), p = 0.037.

Patients who died had spent less time in an inpatient unit because of their unfavourable outcome: 7 (2; 16) days vs 30 (13; 48) days in the group of patients

Table 1. *Presence of concomitant pathology in patients diagnosed with sepsis*

Concomitant pathology	Patients with a favorable outcome, n (%)	Fatal patients, n (%)
Cardiac ischemia	9 (52,9 %)	16 (69,5 %)
Hypertonic disease	10 (58,8 %)	18 (78,7 %)
History of myocardial infarction	3 (17,6 %)	8 (34,7 %)
Chronic heart failure stages 2-3	9 (52,9 %)	12 (52,2 %)
Diabetes mellitus type 2	5 (29,4 %)	5 (21,7 %)
COPD	2 (11,7 %)	3 (13,0 %)
HIV	5 (29,4 %)	2 (8,6 %)
Addiction	5 (29,4 %)	2 (8,6 %)

Note: COPD — chronic obstructive pulmonary disease, HIV — human immunodeficiency virus

Table 2. Clinical characteristics of patients

	1. Patients with a favorable outcome Me (Q1; Q3)	2. Fatal patients Me (Q1; Q3)	P_{1-2}
Number of people, n (%)	17 (42,5 %)	23 (57,5 %)	-
Duration of hospitalization, bed days	30 (13; 48)	7(2; 16)	0,0003
Age, years	68 (41; 77)	67 (58; 81)	0,373
BMI, kg/m^2	25,45 (20,76; 30,72)	25,85 (23; 27,68)	0,711
Number of qSOFA points, point	2 (2; 2)	2 (2; 3)	0,017
Diagnosis of sepsis from the beginning of hospitalization, day	2 (1; 5)	1 (1; 4)	0,678
Duration of hospitalization for sepsis, days	6 (3; 9)	4 (2; 8)	0,236
Assessment of the severity of organ dysfunction according to the SOFA scale, score	3 (2; 6)	6 (5; 7)	0,037
Duration of stay in the ICU, bed days	6 (3; 12)	4 (1; 4)	0,115
Duration of use of vasopressors, days	3,5 (2; 5)	1 (1; 3,5)	0,141
Objective data at the time of diagnosis of septic condition			
Body temperature, °C	38 (37,7; 38,5)	37,8 (36,6; 38)	0,085
Heart rate, beats/min	101 (90; 115)	110 (90; 120)	0,467
NPV, in a minute	25 (24; 28)	26 (24; 30)	0,499
Systolic blood pressure, mm hg art.	100 (97; 120)	100 (90; 120)	0,362
Diastolic blood pressure, mm hg art.	60 (60; 70)	60 (60; 70)	0,156
Pulse blood pressure, mm hg frt.	40 (30; 50)	40 (30; 50)	0,625
SpO_2, %	90 (90; 96)	93 (90; 95)	0,923
Glasgow scale, point	13 (13; 13)	13 (13; 13)	0,086

Note: BMI — body mass index, (q)SOFA — (quick) Sequential Organ Failure Assessment, scale for (quick) assessment of organ failure, ICU — intensive care unit, HR — heart rate per 1 minute, RR — respiratory rate movements per minute, BP — blood pressure, SpO2 — oxygen saturation of peripheral blood

with favourable outcome of sepsis, $p < 0.001$. Duration of ICU admission and number of days on vasoconstrictors and antibiotics in the survivors group were lower in survivors; however, differences were not statistically significant (Table 2). It is worth mentioning that in the survivors group there were only two cases (11.7 %) of artificial pulmonary ventilation and vasoconstrictors, whereas in the other group such interventions were required by 11 patients (47.8 %).

Of note, at the moment when sepsis was diagnosed, such objective parameters as body temperature, HR, RR, arterial and pulse pressure, oxygen saturation and Glasgow coma scale score were not significantly different in the groups of favourable and poor outcomes (Table 2). It proves that it is not possible to forecast disease outcome only on the basis of these parameters.

All patients had their key biochemical and haematological parameters analysed.

Creatinine and Urea As Renal Function Markers

It has been shown that, at the moment when sepsis was verified, 85 % of patients were diagnosed with changes in biochemical parameters, which correspond to kidney injury (increased urea and/or creatinine levels). Urea levels in point 1 were lower in survivors vs. patients who died (10.8 (8.9; 19.8) vs 16.9 (10.7; 28.2) mmol/L; however, there were no statistically significant differences between the groups. Over time (point 2, 48 hours later), urea levels in survivors dropped to 10.4 (5; 19.3) mmol/L (no significant difference vs baseline), whereas in the group of patients with poor outcome, urea rose to 24 (14.8; 32.6) mmol/L (0.020); and 48 hours later, serum urea concentration in this group was considerably higher than in survivors, $p = 0.020$. Changes in urea concentration during the first 48 hours after sepsis verification in survivors was

-1.3 (-4.4; 1.99) mmol/L, while in the other group — 5.5 (-1.5; 12.2) mmol/L, p = 0.020.

A similar pattern was observed for creatinine; however, there were no statistically significant differences between the groups either in point 1 (108 (78; 150) μmol/L vs 139.2 (75.5; 195) μmol/L, respectively, p > 0.05) or in point 2 (48 hours later), despite a trend towards lower creatinine levels in survivors (76 (64; 134) μmol/L) and increased creatinine levels in the other group (148.3 (76; 255) μmol/L).

Lactate As a Marker of Cellular Damage

It is well known that, if serum lactic acid levels rise to the concentration of over 5.0 mmol/L and pH drops below 7.25, metabolic acidosis (lactic acidosis) develops. Lactic acidosis is an acute complication, caused by a sharp increase in blood lactate levels, which can result in death, especially if combined with hypotonia [5]. In this study, baseline lactate levels of over 4.5 mmol/L were recorded in 16 patients (40 %). When blood concentrations of this biomarker were analysed in point 1, it has been shown that in survivors the blood lactic acid levels were considerably lower (3.6 (3.1; 4.5) mmol/L vs the group with poor outcome (5.2 (4; 5.6) mmol/L (p = 0.004). When this parameter was assessed in point 2, there was a common trend towards reduction in both groups; however, there still were statistically significant differences between survivors and those who died (2.75 (2.1; 3.6) mmol/L vs 3.9 (3; 6.5) mmol/L, respectively, p = 0.011).

In the group with poor outcome, at the moment when sepsis was verified, 8 patients (34 %) had hypotonia (< 90/60 mm Hg) and high serum lactate levels (> 5 mmol/L). In survivors, hypotonia was observed only in 2 patients (11 %), with lactate levels being 4.5-4.6 mmol/L.

Blood Count

Recently, literature sources actively describe one parameter of complete blood count — *relative and absolute count of immature granulocytes (IG)*. The term "immature granulocyte" includes promyelocytes, myelocytes, metamyelocytes. Normally, immature granulocyte are not present in peripheral blood and appear only when neoplastic or infectious inflammatory processes begin. Positive correlation of this parameter with WBC and procalcitonin levels in infectious inflammatory processes has been observed [10, 11]. An analysis of relative immature granulocyte count in groups with favourable and poor outcome demonstrated that in point 1 the IG value is not statistically different in both groups (1.2 (0.7; 2.1) % vs 0.8 (0.6; 1.5) %, respectively, p > 0.05). In 48 hours, IG increased in survivors to 1.5 (1; 3.2) %, and vice versa dropped to 0.65 (0.45; 1.45) % in the poor outcome patients, and the difference between groups became statistically significant, p < 0.05. Similar trends were observed for the absolute immature granulocyte count (Table 3). It is important to note that WBC count was higher both at the moment of sepsis verification and after 48 hours in patients with poor outcome of the disease (Table 3).

Reticulocytes. Development of respiratory distress activates compensatory erythropoiesis. The number of immature reticulocytes in peripheral blood represents the erythropoietic activity of the bone marrow. In this study, the relative immature reticulocyte count (IRF%) in point 1 was significantly higher in patients with poor outcome vs survivors (27.5 (16.1; 31.2) % vs 10.9 (7.8; 15.6) %, p = 0.005). In 48 hours, the relative immature reticulocyte count reduced in both groups, but remained high in patients with poor outcome (20.8 (13; 28.7) % vs 7.8 (4.8; 10.1) %), p = 0.024).A similar trend was observed for the relative count of medium reticulocytes (MFR, %) (Table 4).

The relative mature reticulocyte count (LFR, %) was initially higher in patients with favourable outcome (p = 0.004). In point 2, this parameter rose in both groups, and the difference between groups was not statistically significant (Table 4).

In this paper, we conducted ROC analysis of a number of parameters and identified some potential predictors of death.

- Organ dysfunction severity using the SOFA score: AUC 0.692 [95 % CI 0.526; 0.828], p = 0.0281. SOFA > 3 is a factor of poor outcome, where sensitivity and specificity are 82 % and 53 %, respectively.
- Urea levels in point 2 (48 hours after sepsis diagnosis): AUC 0.751 [95 % CI 0.560; 0.890], p = 0.0055. Urea levels of > 14.5 mmol/L are a factor of poor outcome, where sensitivity and specificity are 77 % and 64 %, respectively. Also, an important factor to predict poor outcome is an increase in urea values of > 2.5 mmol/L during the first 48 hours after sepsis diagnosis: AUC 0.751 [95 % CI 0.560; 0.890], p = 0.0072, where sensitivity and specificity are 61 % and 88 %, respectively.
- Lactate levels upon diagnosis (point 1) and in 48 hours (point 2). Lactate levels of > 4.6 mmol/L

in point 1 (AUC 0.810 [95 % CI 0.621; 0.931], p = 0.0003, sensitivity 67 %, specificity 93 %) and lactate levels of > 3.7 mmol/L in point 2 (AUC 0.799 [95 % CI 0.591; 0.931], p = 0.0013, sensitivity 63 %, specificity 86 %) can be prognostic of poor outcome.

- Relative count of immature granulocytes in point 2 (48 hours after sepsis diagnosis) of ≤ 0.9 %: AUC 0.762 [95 % CI 0.556; 0.905], p = 0.0151, sensitivity 75 %, specificity 86 %.
- Absolute count of immature granulocytes in point 2 (48 hours after sepsis diagnosis) of ≤ 0.11*10^9/L: AUC 0.735 [95 % CI 0.527; 0.887], p = 0.0233, sensitivity 66 %, specificity 78 %.
- Absolute reticulocyte count (RET#) in point 2 of > 46.3*10^9/L is a predictor of death: AUC 0.800 [95 % CI 0.539; 0.951], p = 0.0157, sensitivity 80 %, specificity 85 %.
- Relative immature reticulocyte count (IRF, %): a level of > 12.2 % in point 1 (AUC 0.855 [95 % CI 0.640; 0.967], p = 0.0001, sensitivity 100 %, specificity 67 %) and > 10.1 % in point 2 (AUC 0.829 [95 % CI 0.571; 0.964], p = 0.0032, sensitivity 80 %, specificity 85 %) is a predictor.

Table 3. *Biochemical parameters in patients with favorable and unfavorable outcomes*

Index	1. Patients with a favorable outcome Me (Q1; Q3)	2. Fatal patients Me (Q1; Q3)	p_{1-2}
Urea, mmol/l, initially	n=17 10,8 (8,9; 19,8)	n=23 16,9 (10,7; 28,2)	0,077
Urea, mmol/l, after 48 hours	n=17 10,4 (5;19,3)	n=13 24 (14,8; 32,6)	0,020
Change in urea concentration (T2-T1), mmol/l	-1,3 (-4,4; 1,99)	n=13 5,5 (-1,5; 12,2)	0,020
Creatinine, μmol/l, initially	n=17 108 (78; 150)	n=23 139,2 (75,5; 195)	0,373
Creatinine, μmol/l, after 48 hours	n=17 76 (64; 134)	n=13 148,3 (78; 255)	0,068
Change in creatinine concentration (T2-T1), μmol/l	n=17 -16 (-32; 5)	n=13 1,6 (-21; 81,3)	0,121
Serum iron, μmol/l, initially	n=8 5,5 (2,5; 8)	n=10 5 (2; 7)	0,525
Serum iron, μmol/l, after 48 hours	n=8 6 (3; 8)	n=9 5 (3; 6)	0,625
C-reactive protein, mg/l, initially	n=17 185 (32,6; 345)	n=20 200,25 (131; 401)	0,401
C-reactive protein, mg/l, after 48 hours	n=17 120,3 (12,7; 195)	n=14 129,5 (86; 200)	0,382
Change in the concentration of C-reactive protein (T2-T1), mg/l	n=17 -25 (-196; -4)	n=14 -29,6 (-105,3; 72)	0,404
Lactate, mmol/l, initially	n=14 3,6 (3,1; 4,5)	n=15 5,2 (4; 5,6)	0,004
Lactate, mmol/l, after 48 hours	n=14 2,75 (2,1; 3,6)	n=11 3,9 (3; 6,5)	0,011
Change in lactate concentration (T2-T1), mmol/l	n=14 -0,75 (-1,8; -0,1)	n=11 -0,9 (-1,9; 1,4)	0,602
Procalcitonin, ng/ml, initially	n=15 2,9 (0,5; 36,3)	n=19 3,25 (1,29; 12,1)	0,821
Procalcitonin, ng/ml, after 48 hours	n=14 3,795 (0,05; 8,38)	n=11 1,26 (0,5; 27,4)	0,761
Change in procalcitonin concentration (T2-T1), ng/ml	n=13 -1,7 (-16,3; -0,45)	n=11 -0,45 (-1,5; 12,53)	0,077

Note: T — research point: T1 — initial value and T2 — after 48 hours

Table 4. *Hematological parameters in patients with favorable and unfavorable outcomes*

Index	1. Patients with a favorable outcome Me (Q1; Q3)	2. Fatal patients Me (Q1; Q3)	p_{1-2}
IG%, initially	n=14 1,2 (0,7; 2,1)	n=19 0,8 (0,6; 1,5)	0,221
IG%, in 48 hours	n=14 1,5 (1; 3,2)	n=12 0,65 (0,45; 1,45)	0,023
IG#, 10^9/l, initially	n=14 0,08 (0,05; 0,19)	n=19 0,16 (0,07; 0,34)	0,465
IG#, 10^9/l, in 48 hours	n=14 0,165 (0,12; 0,25)	n=12 0,09 (0,035; 0,165)	0,041
Change IG# (T2-T1), 10^9/l	n=12 0,045 (-0,12; 0,19)	n=11 -0,03 (-0,16; 0,02)	0,165
Change IG# (T2-T1) в %	n=12 28,42(-44,44;348,33	n=11 -26,32 (-84,21; 22,22)	0,123
MCHC, g/l, initially	n=16 338 (331; 360,5)	n=20 334 (315,5; 345)	0,082
MCHC, g/l, in 48 hours	n=15 335 (332; 347)	n=13 328 (309; 333)	0,025
Change MCHC (T2-T1), г/л	n=13 -1 (-3; 4)	n=11 -5 (-13; 5)	0,416
% MCHC	n=13 -0,3 (-0,94; 1,2)	n=11 -1,43 (-3,45; 1,6	0,369
RDW-CV, %, initially	n=16 13,95(13,15;15,4)	n=20 15,95 (14,45; 17,55)	0,030
RDW-CV, %, in 48 hours	n=15 13,7 (13,3; 14,9)	n=13 15,9 (15; 17)	0,014
IRF, %, initially	n=9 10,9 (7,8; 15,6)	n=13 27,5 (16,1; 31,2)	0,005
IRF, %, in 48 hours	n=7 7,8 (4,8; 10,1)	n=10 20,8 (13; 28,7)	0,024
LFR, %, initially	n=9 87,8 (84,4; 90,5)	n=13 72,2 (68,8; 83,9)	0,004
LFR, %, in 48 hours	n=7 92,2(89,9;95,2)	n=10 83,6 (67,3; 90,9)	0,050
MFR, %, initially	n=9 9,6(8,1;13,9)	n=13 14,1 (13,1; 15,8)	0,021
MFR, %, in 48 hours	n=7 7,1 (2,5; 7,5)	n=10 11,45 (8; 17,8)	0,004
HFR, %, initially	n=9 1,6 (1,2; 1,7)	n=13 9,5 (2,8; 15,1)	0,029
HFR, %, in 48 hours	n=7 2,2 (0; 3)	n=10 7,7 (2,4; 11,9)	0,087
WBC, 10^9/l, initially	n=17 13,9 (7,33; 21,5)	n=23 17,09 (11,22; 22,33)	0,345
WBC, 10^9/l, in 48 hours	n=17 12,01 (7,77; 17,2)	n=14 14,13 (9,42; 17,5)	0,330
RET, %, initially	n=9 1,05 (0,78;1,41)	n=13 1,78 (1,09; 2,5)	0,052
RET, %, in 48 hours	n=7 0,68 (0,53; 0,82)	n=10 1,405 (0,56; 1,8)	0,063
RET, x10^9/l, initially	n=8 37,75 (26,5; 45,9)	n=13 75,5 (41,9; 83,2)	0,070
RET, x10^9/l, in 48 hours	n=7 22 (21; 46,3)	n=10 60,55 (49,1; 74,5)	0,039
Changing the number RET (T2-T1), x10^9/л,	n=7 -0,3 (-25,9; 2,2)	n=10 -11 (-17,8; 0,8)	0,922
Changing the number RET (T2-T1), %	n=7 -1,79 (-54,99; 5,77)	n=10 -13,37 (-26,61; 4,020)	0,845

Note: T — research point: T1 — initial value and T2 — after 48 hours; IG% — relative number of immature granulocytes in%; IG# — absolute number of immature granulocytes; MCHC — average hemoglobin content in erythrocyte; RDW-CV — erythrocyte distribution index; IRF — immature reticulocytes; LFR — low fluorescent (mature) reticulocytes; MFR — medium fluorescent reticulocytes (at the stage of intermediate maturity); HFR — highly fluorescent (very immature) reticulocytes; WBC — leukocytes; RET — reticulocytes.

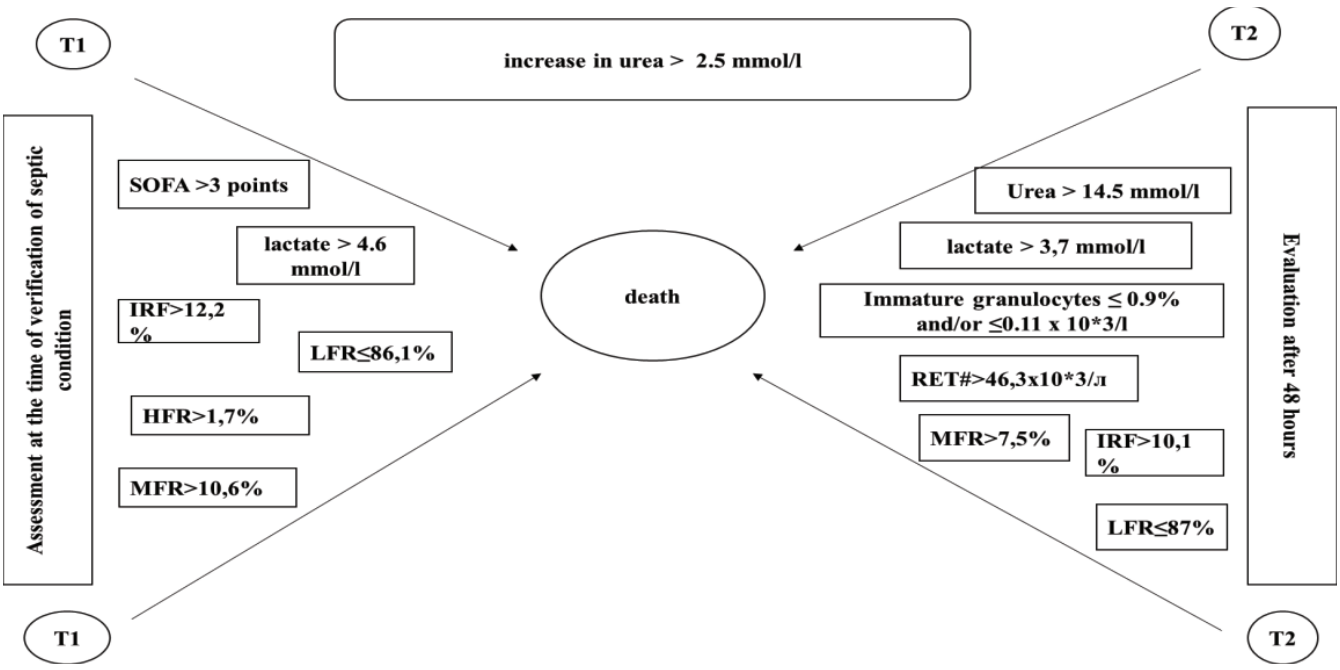

Figure 1. *Factors that increase the likelihood of death in respiratory sepsis*
Note: T1 — initial value and T2 — after 48 hours; SOFA — Sequential Organ Failure Assessment, organ failure rating scale, IRF — immature reticulocytes, LFR — low fluorescent reticulocytes, MFR — medium fluorescent reticulocytes, HFR — highly fluorescent reticulocytes, RET# — reticulocytes

- Relative count of low fluorescence reticulocytes (LFR, %): ≤ 86.1 % in point 1 (AUC 0.863 [95 % CI 0.650; 0.971], p = 0.0001, sensitivity 100 %, specificity 66.7 %) and ≤ 87 % in point 2 (AUC 0.786 [95 % CI 0.524; 0.943], p = 0.0171, sensitivity 70 %, specificity 85.7 %) is a predictor.
- Relative count of medium reticulocytes (MFR, %): > 10.6 % in point 1 (AUC 0.795 [95 % CI 0.571; 0.935], p = 0.0090, sensitivity 100 %, specificity 66.7 %) and > 7.5 % in point 2 (AUC 0.914 [95 % CI 0.676; 0.994], p = < 0.0001, sensitivity 90 %, specificity 85.7 %) is a predictor.
- Relative count of highly immature, high fluorescence reticulocytes (HFR, %): > 1.7 % in point 1 is a predictor (AUC 0.778 [95 % CI 0.552; 0.925], p = 0.0229, sensitivity 92.3 %, specificity 77.7 %.

For a schematic representation of identified critical values of factors, which increase the probability of death, please see Figure 1.

Discussion

Mortality levels in patients with pneumonia and sepsis are very high. A search for early predictors of death is very important. This study demonstrated that the total percentage of patients with pneumonia and sepsis who died was 57.5 %. According to WHO data for 2020, mortality among patients with sepsis, irrespective of the source of infection, was about 27 % in therapeutic wards in 42 % in ICUs [12].

According to a meta-analysis of 13 studies (80,520 subjects) to evaluate the role of gender as an independent prognostic factor of deaths in patients with sepsis admitted to ICUs, female patients had slightly higher all-cause mortality during a 28-day period (OR 1.18, 95 % CI 1.05–1.32) [13]. Despite the fact that in this study, the number of women in the group with poor outcome was slightly higher than men, no statistically significant differences were observed.

According to some authors, prognostic factors include SOFA score, dysfunction of more than two organs, origin of sepsis, lactate and urea levels [14-17]. The obtained results confirmed that the SOFA score of > 3 at diagnosis is a significant factor of poor outcome, with a high AUC value and high sensitivity. Serum lactate levels of > 4.6 mmol/L (baseline) and > 3.8 mmol/L (after 48 hours) have also proven to be predictive of poor outcome in patients with pneumonia-associated sepsis. This study demonstrated that urea concentrations of > 14.5 mmol/L in 48 hours after sepsis verification can be a prognostic marker of death. An increase in urea concentration of > 2.5 mmol/L

during 48 hours after the diagnosis was associated with mortality in the patients.

A brand-new predictor of poor outcome in sepsis can be immature granulocyte (IG) count. It has been proven that their higher count in infectious diseases and sepsis can be a marker of bacterial inflammation [18]. However, currently there are no published studies, where this parameter and its changes are seen as a major predictor of disease severity and poor outcome in patients with sepsis. In this study, immature granulocyte (IG) count of < 0.9 % of the leukocyte count and < $0.11x10^9$/L in peripheral blood 48 hours after sepsis verification was associated with death. The lack of an adequate increase in immature granulocyte levels in the general leukocyte population in patients with pneumonia at early stages of sepsis therapy can be indicative of depleted regenerating capabilities of the immune system as a result of limited proliferative functions of the bone marrow. Therefore, understanding how this biomarker behaves in sepsis can be an objective of future studies of disease outcome forecasting and assessment of drug therapy efficacy.

Also, the results of our study demonstrated the practicability of a dynamic assessment of erythropoiesis activity at early stages of pneumonia-associated sepsis, on the basis of a differential identification of reticulocyte maturity in peripheral blood. An increase in reticulocyte count in peripheral blood represents erythropoiesis activation in the red bone marrow, which is also typical for a number of severe infectious disease and their complications, including sepsis. For example, in a study by Tóth J. et al. (2017), sows with septic shock caused by Escherichia coli infection had a significant increase in blood reticulocytes 2 hours later [19]. A study by Buoro S. et al. (2017) of 62 ICU patients demonstrated that reduction in the relative reticulocyte count (%) was associated with a risk of a septic condition (OR = 0.35, 95 % CI 0.14–0.87) during the following 24 hours [20]. Currently, there is a limited number of published studies involving differential assessment of reticulocyte formation with identification of various reticulocyte maturity forms in sepsis. None of these studies assessed the role of such cells with various degrees of maturity as a potential predictor of deaths un patients with sepsis. In a study by Türkmen D. et al. (2021), a group of critically ill patients with sepsis had a higher immature reticulocyte fraction (IRF) vs healthy volunteers [21]. Therefore, our data are of special interest. A significant increase in immature reticulocyte fraction (IRF, %) in peripheral blood at early stages of sepsis and a reduced fraction of low fluorescence reticulocytes (LFR) can be associated with deaths in patients with sepsis and severe pneumonia. Additional studies are necessary to evaluate the practical significance of a differential assessment of reticulocyte maturity in sepsis. However, given a good availability of blood analysers, this approach can be justified in identification of patients at a high risk of death.

Conclusions

In order to identify groups at a high risk of death among hospitalised patients with pneumonia during the first 48 hours after sepsis diagnosis, such biomarkers as concentrations of urea, lactate, immature granulocytes and reticulocytes should be monitored over time, in addition to an assessment of organ dysfunction using SOFA scale.

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