REVIEW

Biological markers of sepsis

Lubov V. Radygina#, Larisa V. Mochalova

All-Russian Institute for Scientific and Technical Information of the Russian Academy of Sciences (VINITI RAS), 20 Usievich St., Moscow, 125315 Russia

ABSTRACT

Currently, the issues of early sepsis diagnosis, assessment of the effectiveness of therapies conducted, and disease prognosis are extremely relevant. In the case of sepsis, timely medical assistance is complicated by the ambiguity of symptoms and the absence of a specific diagnostic test. Therefore, the search for sepsis biomarkers with diagnostic, prognostic, and therapeutic potential is underway in medical centers worldwide. This review summarizes research results regarding the diagnostic values of sepsis biomarkers – their sensitivity, specificity, and prognostic value – as presented in scientific publications indexed in international databases.

Keywords: sepsis, biomarkers, diagnosis, disease severity, prognosis

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For correspondence: Lubov Radygina, research scientist, All-Russian Institute for Scientific and Technical Information of the Russian Academy of Sciences, 20 Usievich St., Moscow, 125315 Russia; e-mail: lubaradygina@yandex.ru

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INTRODUCTION

Sepsis is a generalization of infection with a pathogen entering the blood flow. Bacteria (such as Staphylococcus, Streptococcus, Neisseria meningitides, Pseudomonas aeruginosa, etc.) are the most common causative agents of sepsis, while fungal infections (such as candidal sepsis) are much less frequent. In most cases, sepsis is triggered by opportunistic microorganisms (autoflora, or indigenous flora) inhabiting the skin, mucous membranes of the respiratory and digestive tracts, and urinary and reproductive organs. In some cases, two or even three causative microorganisms can be identified. Changes in the causative agent during the disease or the development of antibiotic resistance can also occur [1]. Sepsis is a common disease with a high mortality rate. Such prognostic scales as Sequential Organ Failure Assessment (SOFA), New Early Warning Score (NEWS), and Rapid Emergency Medicine Score (REMS) are used for sepsis risk assessment. In emergency cases, not all scales are suitable, which leads to the application of biomarkers that are potentially more specific and easier to use as an alternative [2]. Biomarkers are used for disease diagnosis, clinical decision-making regarding treatment, and disease prognosis [3]. More than 250 sepsis biomarkers have been identified over the past few decades [4]. At the November 2021 session “Biomarkers: can they really be used in our daily practice?” organized at the conference of the European Shock Society, the progress in the following areas of sepsis biomarkers research was presented: a highly sensitive test for detection of bacteremia, identification of the circulating soluble urokinase plasminogen activator receptor (suPAR), and C-reactive protein (CRP), as well as ferritin and procalcitonin (PCT) as new biomarkers [5].
Biomarkers play a crucial role in screening, early diagnosis, and prediction of a severe course and poor prognosis of various diseases. Different tools using modern technologies have been developed to evaluate their effectiveness, for example, in two-stage case-control studies [6]. The main types of biomarkers, in terms of their role in personalized medicine, are listed in the 2010 European Commission report (Stratification biomarkers in personalized medicine. Summary report. European Commission, DG Research, Brussels, June 10-11, 2010). These biomarkers are used to diagnose a disease (diagnostic), predict the risk of developing pathology (susceptibility/potential risk markers), disease severity (prognostic), as well as to predict response to drug therapy and possible drug toxicity (predictive) [7]. This division is arbitrary since the same biologically active compound can “signal” about one or another pathophysiological status of the organism at different stages of the disease and play the role of a diagnostic, prognostic, or/predictive marker.

The incidence and mortality rates of sepsis are particularly high in newborns. In this case, the problem of early diagnosis is practically unresolved, due to atypical clinical manifestations of neonatal sepsis [8] and the time-consuming nature of blood culture analysis for sepsis, namely inoculation for sterility testing. Thus, the identification of biomarkers for the early diagnosis of neonatal sepsis is a pressing issue [9].

Biomarkers such as CRP, PCT, ferritin, and lactate have long been used to diagnose sepsis in children [10], while CRP and PCT have been proposed as predictors of sepsis [11]. The dynamics of changes in the levels of CRP, PCT, and presepsin is used to assess the effectiveness of sepsis therapy after surgical treatment and to predict the outcome of the disease [12].

SEPSIS BIOMARKERS

Blood cells

Lymphopenia occurs in approximately half of sepsis patients and is associated with an increased risk of mortality. The mechanism of lymphopenia pathogenesis in sepsis remains unclear, although an accelerated apoptosis of lymphocytes has been reported [15].

Lymphocyte dysfunction begins in the early stages of sepsis and is associated with mitochondrial dysfunction. Single-cell mitochondrial mass (SCMM) of T lymphocytes (SCMM-CD4) has been identified as an early sepsis biomarker which is more reliable than the traditionally used PCT. It should be mentioned that the combination of PCT and SCMM-CD4 in the early diagnosis of sepsis has a higher diagnostic potential than SCMM-CD4 alone [14].

Li et al. [15] reported that as sepsis progressed, CD3+, CD4+, and CD4+/CD8+ counts in the blood of patients decreased, while elevated CD4+ and CD4+/CD8+ counts correlated with patient recovery dynamics. Peng et al. [16] found that the CD8+ T lymphocyte/B lymphocyte ratio can help diagnose the progress of sepsis (with sensitivity and specificity of 75.00% and 71.79%, respectively) as well as to assess the effect of the ongoing therapy.

It was found that the level of CD8+ lymphocytes was lower, and the expression of the Programmed Cell Death Ligand 1 (PD-L1) protein was higher in newborns who died from sepsis than in survivors. Based on these results, it was proposed to use the expression of PD-L1 on CD8+ T cells as a biomarker for the prognosis of sepsis in newborns [17].

Evaluating the PD-1 expression on CD8+ T lymphocytes in adults allows for identifying the patients with an unfavorable sepsis outcome [18]. Recently, Wang et al. [19] reported that sepsis severity and disease prognosis correlated with increased PD-1 and CTLA4 (cytotoxic T lymphocyte-associated protein 4) expression on CD4+ T cells and regulatory T lymphocytes (Treg), respectively. Patients with a high expression of PD-1 on CD4+ T cells (>51.25%) and CTLA4 on Treg (>12.64%) had lower survival rates within 28 days. The combination of the SOFA sepsis severity assessment with PD-1 expression on CD4+ T cells and CTLA4 on Treg enhances the predictive value of the analysis.

Increased (as compared to normal) neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte ratios (PLR), as well as decreased lymphocyte-to-monocyte ratios (LMR), are predictors for early sepsis diagnosis that proved to have a high diagnostic significance and economic efficiency. Patients with NLR>2.03, PLR>110.62, and LMR<3.23 should be closely monitored for early detection of postoperative infectious complications [20]. According to Schupp et al. [21], NLR can be considered a reliable diagnostic tool for identifying patients with sepsis. However, this parameter is suitable neither for differential diagnosis of patients with sepsis and septic shock nor for predicting a favorable/unfavorable outcome of the disease. According to the data obtained by Zheng et al. [22] using multivariate logistic regression analysis, the PLR values correlate with a poor prognosis and high in-hospital mortality. Both low and high PLR levels were significantly associated with a higher in-hospital mortality, and an early PLR reduction was associated with an increased risk of in-hospital mortality.

The lymphocyte-to-CRP ratio (LCR) has been suggested as an early sepsis indicator in newborns with suspected sepsis, with a sensitivity of 88% and a specificity of 55%. The sepsis frequency was significantly higher in
the group of newborns with low LCR (<3.94) compared to the group with higher LCR (>3.94) [25].

Thrombocytopenia was associated with an increased risk of death and disease severity in patients with sepsis. The patients in the groups with moderate [(20–50)×10^9/l] and severe (<20×10^9/l) thrombocytopenia showed a higher mortality (28 days) compared to the non-thrombocytopenic group [24]. The blood cell biomarkers of sepsis known to date are summarized in Table 1.

**Procalcitonin (PCT)**

PCT is a protein consisting of 116 amino acids [25]. PCT was first identified by Le Moullec et al. in 1984 [26], but it took nearly a decade before its diagnostic significance was recognized. In 1993, Assicot et al. [27] found elevated levels of PCT in the blood serum of patients with sepsis, but not in cases of viral infections. Furthermore, they demonstrated that the blood serum PCT levels decreased after the appropriate antibiotic therapy [25]. Monitoring PCT blood levels enables adjusting the duration of antibiotic therapy individually for each patient without increasing the likelihood of a lethal outcome [28].

In newborns, elevated PCT is considered a biomarker for late-onset neonatal sepsis. Regarding preterm infants with late neonatal sepsis, PCT has a prognostic significance [29]. PCT is a sensitive biomarker detecting postoperative sepsis in children [30] as well as in risk groups for sepsis morbidity and mortality [31]. PCT levels are used to assess disease severity in different types of sepsis [32]. This marker allows for differentiation between bacterial and non-bacterial sepsis [33]. Comparative studies have shown that serum PCT level is the most diagnostically accurate biomarker for early diagnosis of sepsis caused by bacterial infection and has a greater predictive value than serum ferritin, CRP, or other indicators [34].

It is particularly challenging to diagnose sepsis in cases of burn injuries due to similar symptoms. Elevated PCT levels enable a more reliable diagnosis of sepsis in children with burn injuries compared to CRP [35]. A comparative study conducted by Li et al. [36] demonstrated that PCT has a moderate sensitivity (73%) and specificity (75%) when used as a sepsis biomarker in burn patients. Compared to PCT, CRP showed a higher sensitivity (86%) but lower specificity (54%), while using blood leukocyte levels as a biomarker revealed both low sensitivity (47%) and moderate specificity (65%).

Among individuals with spinal cord injuries and sepsis, 100% showed elevated PCT, 60% had elevated CRP, and 30% had elevated leukocyte counts. A strong positive correlation between PCT and the level of leukocytes was weaker [37]. It has been demonstrated that the PCT to albumin ratio (PAR) is higher during sepsis and correlates with the disease severity in newborns [38]. PAR has been proposed as an independent predictor of sepsis in neonates with pneumonia [39]. In adult patients, a high PAR value was found to be a more diagnostically accurate indicator for predicting septic shock and mortality compared to using only PCT or albumin levels [40]. Liu et al. [41] proposed considering the ratio of PCT concentrations to cortisol as a predictor of disease outcome in patients with abdominal sepsis.

**C-reactive protein (CRP)**

CRP was discovered by Tillet and Francis in 1930 [42]. The name CRP is associated with a protein in the blood serum of patients with acute inflammation, which interacts with the carbohydrate C-antigen of the pneumococcal capsule. CRP is a pentameric protein synthesized by the liver, and its level is elevated in response to inflammation. It is an acute phase protein encoded by the CRP gene whose expression is regulated by interleukin 6 (IL6). Laboratory results for the normal value of CRP vary, which is associated with the use of different methods for its determination. Therefore, the reference interval is not defined, and the control group data is used as a baseline in comparative studies. A CRP concentration of <0.3 mg/dl is generally considered normal, which is typical for most healthy adults. Very high levels of CRP, exceeding 50 mg/dl, are associated with bacterial infections in approximately 90% of cases [43].

The use of diagnostic markers such as CD11b, CD64, IL6, IL8, PCT, and CRP in neonatal sepsis allows for adjustments to antibiotic therapy and even stopping it within 24-48 h. However, discontinuation of antimicrobial therapy solely based on diagnostic biomarkers cannot be considered justified, as none of the existing diagnostic markers are sufficiently sensitive and specific. This should be taken into account when deciding to discontinue antibiotics, and therefore, it is necessary to rely on clinical data [44].

For early diagnosis of sepsis in children, the following indicators can be used: CRP, PCT, amphoterin (High-Mobility Group Protein B1, HMG1), and the CRP/albumin ratio, with their combined use being more effective [45]. At the same time, it has been shown that the CRP measured 6-8 h after delivery is a weak predictor of early-onset neonatal sepsis [46]. Dhudasia et al. [47] reported the limited effectiveness of using CRP for decision-making in cases of early-onset sepsis in infants. Rao et al. [48] found
Table 1. Parameters employed in blood laboratory analyses that are used as biomarkers for sepsis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Clinical specimen / method</th>
<th>Threshold level / normal range</th>
<th>Clinical significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>peripheral blood / complete blood count</td>
<td>Deceased persons: &lt;1×10^9 cells/l; normal range: (1.0–4.8)×10^9 cells/l in adults</td>
<td>Prognostic marker: risk of lethal outcome</td>
<td>[13]</td>
</tr>
<tr>
<td>CD3+, CD4+, CD4+/CD8+</td>
<td>peripheral blood / flow cytometry</td>
<td>Levels are lower than in the control group (62.15±7.21% for CD3+, 37.62±5.87% for CD4+, 1.49±0.58 for CD4+/CD8+)</td>
<td>Diagnostic and prognostic biomarker: diagnosis, disease progression, prognosis</td>
<td>[15]</td>
</tr>
<tr>
<td>CD8+ T lymphocytes / B lymphocytes</td>
<td>peripheral blood / flow cytometry</td>
<td>Normal range: 2.36 (1.66–3.16); in sepsis: 1.26 (0.71–2.55); in septic shock: 4.11 (2.00–10.55)</td>
<td>Prognostic and predictive biomarker: progression of sepsis and assessment of the therapy effectiveness</td>
<td>[16]</td>
</tr>
<tr>
<td>Expression of PD-L1 on CD8+ T cells</td>
<td>peripheral blood / flow cytometry</td>
<td>Healthy babies: 0.94 (0.58–1.6) / 45.0 (26–65.0); sepsis survivors: 0.85 (0.48–7.3) / 62 (50–75); deceased from sepsis: 2.8 (2.5–8.5) / 74 (68.5–79.0)</td>
<td>Prognostic biomarker: survival rate (disease outcome) in newborns</td>
<td>[17]</td>
</tr>
<tr>
<td>Expression of PD-1 on CD8+ T lymphocytes</td>
<td>peripheral blood / flow cytometry</td>
<td>Sepsis survivors: 26.71±3.00%; deceased: 44.77±6.08%</td>
<td>Prognostic biomarker: risk of lethal outcome</td>
<td>[18]</td>
</tr>
<tr>
<td>Expression of PD-1 on CD4+ T cells and CTLA4 on T_{reg}</td>
<td>peripheral blood / flow cytometry</td>
<td>Low 28-day survival: high expression of PD-1 on CD4+ T cells (&gt;51.25%) and CTLA4 on T_{reg} (&gt;12.64%)</td>
<td>Prognostic biomarker: risk of lethal outcome</td>
<td>[19]</td>
</tr>
<tr>
<td>NLR, PLR, LMR</td>
<td>peripheral blood / complete blood count</td>
<td>In patients with sepsis: NLR&gt;2.03 PLR&gt;110.62 LMR&lt;3.23</td>
<td>Diagnostic biomarker: early detection of sepsin</td>
<td>[20, 21]</td>
</tr>
<tr>
<td>PLR</td>
<td>peripheral blood / complete blood count</td>
<td>High in-hospital mortality: low and high PLR values, as well as early decline in PLR</td>
<td>Prognostic biomarker: risk of lethal outcome</td>
<td>[22]</td>
</tr>
<tr>
<td>LCR</td>
<td>peripheral blood / complete blood count and biochemical blood test</td>
<td>The incidence of sepsis was significantly higher in neonates in the low LCR group (&lt;3.94) compared to the higher LCR group (&gt;3.94)</td>
<td>Diagnostic biomarker: an early indicator of neonatal sepsis</td>
<td>[23]</td>
</tr>
<tr>
<td>SCMM-CD4</td>
<td>peripheral blood / flow cytometry</td>
<td>Normal range: 68.25 (35.77–150.21); in sepsis: 343.73 (179.44–576.94)</td>
<td>Diagnostic biomarker: early diagnosis of sepsin</td>
<td>[14]</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>peripheral blood / complete blood count</td>
<td>Increased 28-day mortality: &lt;50×10^9 cells/l</td>
<td>Prognostic biomarker: disease severity and mortality</td>
<td>[24]</td>
</tr>
</tbody>
</table>

^a The combination of SOFA sepsis severity assessment and expression rate of PD-1 on CD4+ T cells and CTLA4 on T_{reg} increases the predictive value of the analysis.

^b In ROC analysis, the NLR threshold value for preoperative/postoperative sepsis was 2.45 with a sensitivity of 87% and a specificity of 31%, with an area under the curve equal to 0.64. The PLR threshold value for postoperative sepsis was 120.25 with a sensitivity of 87.5% and a specificity of 53.2%, with an area under the curve equal to 0.65. The LMR threshold value for postoperative sepsis was 2.88 with a sensitivity of 87.5% and a specificity of 55%, with an area under the curve equal to 0.73.

^c The combination of PCT and SCMM-CD4 in the early diagnosis of sepsis has a higher diagnostic potential than the value of SCMM-CD4 alone.
that 72 and 96 h after extensive non-cardiac surgeries, newborns with sepsis had significantly higher levels of CRP and PCT in their blood serum compared to patients without sepsis. The authors proposed using CRP and PCT as diagnostic markers for sepsis in newborns, considering the response reliably positive for sepsis if both CRP and PCT levels are elevated after 96 h post-surgery (specificity 100%). CRP also exhibits a high sensitivity and specificity for the diagnosis of urinary sepsis [33].

The use of the combination of CRP with the soluble form of sFAS protein, an apoptosis regulator, increased sepsis prediction sensitivity up to 88%. When combining CRP, IL6, and sFAS markers with the soluble form of the adhesion molecule VCAM-1 (sVCAM-1), sensitivity reached 70%, while specificity was 84% [49].

**Lactate**

Lactate is no longer regarded solely as a metabolic product and one of the causes of muscle fatigue. Scientists are investigating the role of lactate in metabolism, perception, and signal transmission in both normal and pathophysiological conditions. The lactate levels in muscles, blood, and other tissues in normal conditions are in the millimolar concentration range, rather than in the nanomolar or picomolar concentration range typical for other myokines. For instance, the concentration of lactate in arterial blood increases from approximately 0.5 mM at rest to more than 20 mM during intense physical exertion. Elevated lactate levels occur due to a metabolic imbalance, i.e., an increase in its production and/or difficulty of its clearance. Depending on the condition, such as at rest, physical exertion, after carbohydrate intake, injury, or pathology, lactate can serve as a myokine or exokine with autocrine-, paracrine-, and endocrine-like functions [50].

When providing emergency care, lactate levels are measured to improve the efficiency of diagnosis and therapy as their increase is associated with a high probability of lethal outcomes in septic shock cases. Currently, elevated blood lactate levels are used to identify patients at a high risk of death before the manifestation of hemodynamic instability, known as the “hidden shock” stage [51]. The concentration of lactic acid in the blood is closely associated with the urosepsis prognosis in patients [33]. Moreover, an association between lactate, PCT, and a lethal outcome was revealed: the highest values of these two markers were recorded in the deceased group of patients [52].

PCT, lactate, and endotoxin testing in children with severe pneumonia complicated by sepsis has been proposed for diagnosis and disease prognosis assessment [53]. Lactate levels, age, and assessment using the SOFA scale effectively predict clinical outcomes in sepsis patients [54].

**Ferritin**

Ferritin is an ubiquitous protein present in most tissues. Its main role is to bind iron ions (Fe^{2+}), oxidize them to Fe^{3+}, and release according to the cell’s needs. Ferritin accumulates iron in a mineralized, non-toxic state, but the iron bound to ferritin cannot be directly used by the cell. For iron to be biologically available, it must be released from ferritin, which happens primarily through proteolytic degradation of the ferritin shell in lysosomes. Ferritin degradation depends on autophagy – a conservative catabolic cellular process, which is responsible for the degradation of cellular proteins and damaged organelles through lysosomes and is a part of a recycling and protection system that maintains cellular homeostasis. Cellular processes involving ferritin include ferritinophagy and ferroptosis. Ferroptosis is associated with various pathological conditions, while ferritinophagy modulates ferroptosis; consequently, the role of these processes in the pathogenesis of neurodegeneration, cancer, and infectious diseases is being intensively studied.

In normal blood serum, ferritin is present at a relatively low concentration: 52±5.1 ng/ml in men and 28.8±3.3 ng/ml in women [55]. Assessing ferritin levels in the blood serum is considered a useful and convenient method to evaluate iron reserves in a routine laboratory test. Many factors, including inflammation, infection, metabolic disorders, and malignancies, can lead to increased ferritin levels in the blood serum [56].

The evaluation of ferritin and monocyte HLA-DR receptor expression allows for identifying sepsis patients and assessing the mortality risk in sepsis cases [57]. It was proposed that a high serum ferritin level is an independent predictor of fatal outcomes in patients with sepsis [58]. Thus, high serum levels of ferritin within five days of the disease onset predicted unfavorable outcomes in critically ill children with severe sepsis [59].

Linarez Ochoa et al. [60] conducted a comparative study of markers in two hospitalized patient groups: those with COVID-19 and with bacterial sepsis. Ferritin was the primary inflammation marker in the COVID-19 patients, while leukocytes, PCT, and D-dimer were primary markers in the patients with sepsis. The predictors of unfavorable outcomes were CRP in COVID-19 patients and leukocytes in those with sepsis.

It is known that hepcidin, a key regulator of iron metabolism in the body, is considered a marker of septic shock and other pathologies associated with acute...
inflammation. Hortová-Kohoutková et al. [61] analyzed hepcidin and ferritin levels as potential biomarkers of inflammation severity. The ferritin levels were elevated more than 4-fold in septic shock cases and 6-fold in COVID-19. This study demonstrated the clinical significance of the hepcidin/ferritin ratio as a predictor of fatal outcomes in septic shock, but not in COVID-19.

In perinatal sepsis, the interpretation of standard diagnostic indicators, such as blood culture results (sterility testing), CRP, and PCT, can be complicated by concomitant factors including gestational age, birth weight, and hypoxia. Therefore, introducing new biomarkers of sepsis into everyday clinical practice is of paramount importance [62].

**Presepsin**

Presepsin is a surface glycoprotein expressed on cells of the myelomonocytic lineage. It is a cleavage product of a high-affinity lipopolysaccharide receptor, CD14, which is a glycoprotein expressed on the surface membranes of monocytes/macrophages. Yaegashi et al. [63] identified its soluble form, sCD14-ST; the level of sCD14-ST is elevated in patients with sepsis. Presepsin is released into the bloodstream as a complex with lipopolysaccharide, peptidoglycan, and other molecules on the surface of the microbial cell. Elevated blood levels of presepsin are caused by the presence of pathogens in the bloodstream and the host's response to the pathogenic microorganism. It is a biomarker that quickly responds to the causative agents of bacterial and fungal infections [64]. Presepsin also plays an important role in the immune system and immune response development and is used as an early marker of sepsis in both adults and children [62].

The presepsin levels are significantly higher in sepsis than in non-infectious organ failure, and significantly higher in patients with septic shock than with sepsis. The levels of presepsin allow for effectively differentiating sepsis from non-infectious organ failure and identifying patients with an unfavorable prognosis of sepsis. Presepsin can be used as an independent risk factor for lethal outcomes in patients with sepsis and septic shock [65]. The determination of presepsin levels can help assess the severity of pneumonia and the development of sepsis in patients undergoing hemodialysis [66].

**Soluble urokinase plasminogen activator receptor (suPAR)**

The suPAR is a soluble form of the urokinase-type plasminogen activator receptor associated with inflammation and immune activation. SuPAR is a three-domain protein formed through alternative splicing of the human PLAUR gene transcript and post-translational processing of the polypeptide chain. It has been shown that suPAR is a systemic mediator of COVID-19 infection associated with lung and kidney dysfunction [67]. SuPAR is known to indicate inflammation, regardless of etiology. Its concentrations increase in infectious diseases, malignant neoplasms, acute coronary syndromes, and other pathological conditions, correlating with the severity of the process [68].

SuPAR is used as a diagnostic biomarker for sepsis in adults and has a potential diagnostic value in neonatal sepsis [8]. Elevated suPAR is associated with mortality in patients with developed sepsis [69]. The HMGB1/suPAR ratio in the blood serum helps diagnose the disease and predict the outcome in patients with sepsis and acute respiratory distress syndrome [70].

**Cytokines**

Cytokines are signaling proteins that play an important role in the initiation, maintenance, and resolution of immune responses [71]. Cytokines play different roles in the induction of the immune response and may even exhibit contrasting effects.

IL6 belongs to pro-inflammatory cytokines and its elevated level indicates the hyperimmune response to harmful stimuli, including infection. Berka et al. [72] studied the dynamics of IL6 levels in preterm infants within 24 h after delivery to assess its possible application as a predictor of early sepsis. Determining IL6 levels can be used to exclude early sepsis within the first 24 h after birth. The possibility of IL6 application as a marker in the diagnostics of early neonatal sepsis in term and preterm infants was evaluated. The range of sensitivity and specificity of IL6 in neonatal patients was 42.1–100% and 45–100%, respectively; the diagnostic accuracy was higher in preterm infants. The earlier the blood samples were collected when sepsis was suspected, the better the sensitivity was. IL6 levels in the umbilical cord blood had a higher diagnostic value compared to the peripheral blood. The combination of IL6 and CRP biomarkers was proved to be highly sensitive but low in specificity. In three studies analyzing the combination of IL6 and CRP, the threshold values ranged from 36 to 100 pg/ml for IL6 and from 10 to 60 mg/l for CRP, with sensitivity ranging from 75% to 100% and specificity from 37% to 74%. It has been proposed to use the level of IL6 in the umbilical cord blood as an early diagnostic marker for sepsis in preterm infants [73].

Increased serum levels of the following cytokines and chemokines have been observed in newborns with...
Sepsis biomarkers

Chemerin, a recently identified adipokine, is a chemotactant with antimicrobial properties involved in immune response. Circulating chemerin increases in the early stages of sepsis, and its dynamics may be of diagnostic and prognostic value in critically ill patients [80].

**Non-coding RNAs**

For decades, RNA molecules were primarily viewed as an “intermediate link” between genes and proteins in the process of expressing genetic information within cells. However, the discovery that eukaryotic genes consist of protein-coding sequences interspersed with large transcribed but not translated regions of DNA paved the way for the identification of non-coding RNAs. Their roles are diverse: they regulate gene transcription and are associated with chromatin-modifying complexes; their patterns vary in different cell types, also changing in the case of diseases. By now, it has become clear that most non-coding RNAs are products of genetic loci called enhancers, which direct common effector proteins to the appropriate site to determine the fate of cells in different “life situations” [81].

**Long non-coding RNAs (lncRNA)**

LncRNAs are involved in processes that occur in sepsis and organ dysfunction related to sepsis (SROF). Experimental studies over the past five years have confirmed that lncRNAs play an important regulatory role in sepsis and SROF. Notably, 94 non-coding RNAs have been evaluated as potential sepsis biomarkers [82], and lncRNAs have been proposed as potential urosepsis biomarkers [33].

The lncRNA associated with urothelial carcinoma 1 (lncRNA UCA1) is involved in inflammation and organ damage processes in various diseases. This lncRNA is overexpressed in patients with sepsis compared with the control group, and its level positively correlates with the levels of TNFα, IL6, IL17, the intercellular adhesion molecule 1 (ICAM1), and the vascular cell adhesion molecule 1 (VCAM1). Furthermore, an elevated level of lncRNA UCA1 was associated with an increased mortality risk from sepsis within 28 days [83].

The lncRNA cancer susceptibility candidate gene 2 (CASC2) inhibits inflammation and multiple organ dysfunction. The expression of lncRNA CASC2 is reduced in patients with sepsis compared with the control group of healthy patients. Its expression was also reduced in patients who died from sepsis compared with sepsis survivors [84].

**MicroRNA (miRNA)**

MiRNAs do not encode proteins, but they regulate gene expression by inhibiting the translation or transcription of their mRNA targets. In adult patients, miRNAs are released into the bloodstream, and their pattern changes

Adipokines

The discovery of leptin in the 1990s led to a reevaluation of the role of adipose tissue (AT) as not only a storage for fatty acids but also an endocrine tissue. White AT secretes biologically active molecules called adipokines and brown AT secretes batokines. Adipokines and batokines interact with internal organs, particularly with the brain, heart, liver, pancreas, and vascular system. Adipokines exhibit both pro- and anti-inflammatory activity. A balance between these two effects of adipokines ensures the homeostasis of many tissues and organs [79].

Chemerin, a recently identified adipokine, is a chemotactant with antimicrobial properties involved in immune response. Circulating chemerin increases in the early stages of sepsis, and its dynamics may be of...
in various pathological conditions, such as inflammation, infection, sepsis, and others. The potential of using miRNAs as markers in the diagnosis and determination of the neonatal sepsis stage has been demonstrated and the adequacy of using some of them – miR-16a, miR-16, miR-96-5p, miR-141, miR-181a, and miR-1184 – was proved (see review by Jouza et al. [85]).

**Pancreatic stone protein (PSP)**

The PSP is a C-type lectin protein with a molecular mass of 16 kDa. It is primarily produced by the pancreas and intestine. Initially, PSP was described in 1990 as a protein secreted by acinar cells of the pancreas to inhibit the formation of calcium carbonate crystals in the pancreatic ducts. Subsequent preclinical studies have shown that, in a sepsis response, PSP plays a role of damage-associated molecular pattern (DAMP) [86]. PSP has recently been studied as a potential biomarker for sepsis. It has been found to have an additional prognostic value and a higher diagnostic significance for identifying this infection compared to commonly used readily available biomarkers [87].

PSP together with apolipoprotein A-V and copeptin are acute-phase proteins that have a diagnostic value in the assessment of seriously ill children with sepsis. PSP and copeptin can be used to predict survival in sepsis [88].

**Neutrophil gelatinase-associated lipocalin (NGAL)**

The human lipocalin associated with neutrophil gelatinase (neutrophil gelatinase-associated lipocalin, NGAL) is a secretory protein released by neutrophils that can be detected in both blood plasma and urine [89]. The NGAL as a biomarker can be used in the early diagnosis of bacterial sepsis [90]. NGAL levels in the blood serum can indicate the severity of sepsis. The levels of NGAL and lactate in the blood serum can be independent mortality risk factors in sepsis patients [91].

Elevated NGAL levels are observed in neonates with sepsis, making it a promising biomarker for detecting neonatal sepsis. High NGAL concentrations were detected in neonates who died from sepsis [9]. The level of this biomarker was found to be statistically significantly higher in the sepsis patient group compared to the control group (1,428 versus 239 pg/ml). After 96 h from the appearance of clinical signs of sepsis, the NGAL blood concentrations were significantly higher in non-surviving newborns (averaging 3,000 pg/ml) compared to survivors (600 pg/ml). The combination of NGAL with fetuin A has shown a high effectiveness in predicting mortality in sepsis patients [92].

**Troponin**

Cardiac troponin is a protein complex located on a sarco-mere that regulates the interaction of myosin with actin filaments [93]. The high-sensitivity cardiac troponin T (cTnT) level is a highly effective prognostic marker for lethality in patients with sepsis [94]. It is also associated with 30-365-day mortality in survivors after the sepsis onset [95]. The combination of serum markers – lactate, cTnT, and 5-hydroxytryptophan – has a high prognostic value for assessing the sepsis condition and the course of the disease. Clinical monitoring of these indicators allows for optimization of the therapy regimen [96].

**Bio-adrenomedullin and proenkephalin**

Biologically active adrenomedullin (bio-ADM) is a peptide hormone involved in blood vessel regulation, and it is considered a promising biomarker for evaluating stasis phenomena in decompensated heart failure [97]. Pro-enkephalin A 119–159 (penKid) is a 5 kDa peptide identical to the met-enkephalin and leu-enkephalin precursors; it is considered an alternative marker for endogenous opioid peptides - enkephalins. Enkephalins participate in various physiological processes by binding to opioid receptors [98].

Bio-ADM and penKid play a key role in the development of organ dysfunctions caused by sepsis. Based on the elevated levels of bio-ADM and penKid in patients, mortality could be predicted in sepsis cases. These two biomarkers may be more effective when integrated with clinical risk indicators [2].

**Brain natriuretic peptides (NPs)**

Natriuretic peptides (NPs) are cardioprotective hormones released by cardiomyocytes in response to elevated pressure or volume overload. The role of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the diagnosis and risk stratification of heart failure has been described [99]. The serum levels of PCT and brain NP are elevated in sepsis patients and correlate positively with the disease severity. Therefore, they can be used as indicators of an unfavorable prognosis in sepsis patients [100]. Additionally, NT-proBNP is an independent risk factor for mortality in burn patients with sepsis [101]. Combining NT-proBNP with patients’ clinical risk indicators enhances its prognostic significance [102].

**Triiodothyronine**

Triiodothyronine, or T3, is an active form of the thyroid hormone that is formed by the peripheral deiodination...
of thyroxine (tetraiodothyronine, T4) [103]. Physical stress during sepsis can disrupt endocrine function and affect the clinical course and prognosis of the disease. The concentration of T3 in the blood serum significantly decreases in children with sepsis. The low T3 syndrome serves as a prognostic indicator of unfavorable disease outcomes [104].

**Brain-derived neurotrophic factor (BDNF)**

The BDNF is a neuropeptide that mediates synaptic development and contributes to the plasticity of the nervous system [105]. BDNF is a myokine produced by immune cells and skeletal muscles. It was shown that preoperative serum BDNF, which reflects the systemic condition, including the nutritional status, liver function, and immune system status, can be a predictive biomarker of sepsis after liver transplantation from a living donor [106].

**P-calprotectin**

Calprotectin, a member of the S100 protein family, plays a key role in the activation of the innate immune system [107]. Blood plasma calprotectin (p-calprotectin) is considered a promising marker for determining the severity of sepsis in the intensive care unit (ICU). P-calprotectin outperforms traditional biomarkers (PCT and NLR) in predicting the need to transfer patients to the ICU [108].

**H3K18la**

Histone lactylation has recently been described as a novel post-translational histone modification linking cellular metabolism to epigenetic regulation. H3K18la serves as a marker not only for active promoters but also for tissue-specific active enhancers [109]. The degree of histone H3 lysine 18 lactylation (H3K18la) and its role in patients with septic shock have been investigated. H3K18la may reflect the severity of the critical condition and the presence of infection [110].

**Carboxyhemoglobin (COHb)**

COHb disrupts cellular processes acting as a direct toxin. It inhibits aerobic metabolism, triggering an inflammatory cascade that leads to central nervous system damage [111]. Researchers found an increase in the COHb levels at the disease onset and a decrease in response to antibiotic therapy during late-onset sepsis in preterm newborns. When used in combination with other sepsis biomarkers, changes in COHb levels can be considered a diagnostic marker of late-onset sepsis in preterm infants [112].

**Metabolites**

Using the metabolomic analysis, the significance of nine different metabolites has been evaluated for sepsis diagnosis, including differential diagnosis. These metabolites include 3-phenyllactic acid, N-phenylacetylglutamine, phenylethylamine, traumatin, xanthine, methyl jasmonate, indole, L-tryptophan, and the compound 1107116. It has been shown that these metabolites can be used as potential biomarkers for sepsis diagnosis [113].

Here, we have analyzed the use of compounds described above as sepsis biomarkers; the results are presented in Table 2. It is worth noting that comparing the numerical values across different studies for the same parameter is often not possible for two reasons: variations in the methods used by authors and differences in the patient populations.

**CONCLUSION**

Despite significant advances in the treatment of patients with sepsis, this disease is still associated with high mortality rates. A pronounced individual variability of symptoms in patients with sepsis complicates its diagnosis and treatment. Extensive research is underway to identify biomarkers to improve sepsis diagnostics and enable early intervention, reducing the risk of death. Biomarkers are crucial not only for an early sepsis diagnosis but also for predicting disease outcomes and optimizing treatment strategies. In addition to the well-established markers such as suPAR, CRP, lactate, presepsin, ferritin, and PCT, a highly sensitive panel has been developed for non-invasive monitoring of several metabolites. The ratios of these metabolites allow for assessing disease severity and predicting its outcome [5]. With the current level of biomedical research, clinicians now can receive laboratory data practically immediately. Through a proper interpretation of these data, they can select the most effective treatment in each specific case, thus implementing a personalized approach to patients with such a severe condition as sepsis. Therefore, it is necessary to have a clear understanding of the biomarkers and their combinations that serve as signals for the development of various pathological processes.
Table 2. Clinical significance of sepsis biomarkers

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients</th>
<th>Threshold</th>
<th>Clinical significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>Premature babies (less than 32 weeks gestational age) with late-onset neonatal sepsis</td>
<td>&gt;8.92 μg/l</td>
<td>Prognostic marker: risk of lethal outcome (60-day mortality)</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td>Patients with postoperative trauma older than 2 weeks</td>
<td>The highest level of PCT 48-72 h after surgery</td>
<td>Diagnostic and prognostic biomarker</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>Children aged 0 to 14 years with sepsis and bacterial meningitis</td>
<td>≥19.6 ng/ml on admission (short-term complications); &gt;19.6 ng/ml on admission and ≥41.9 ng/ml 24 h later (long-term complications); ≥18.9 ng/ml on admission and ≥62.4 ng/ml 24 h later (lethal outcome).</td>
<td>Diagnostics, prognosis of the disease course and outcome</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Sepsis in children with burn injuries</td>
<td>≥0.95 ng/ml</td>
<td>Diagnostic biomarker</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>Adult patients with sepsis</td>
<td>≥0.5 ng/ml</td>
<td>Diagnostic biomarker: early diagnostics</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Patients with bacterial sepsis and patients with viral sepsis</td>
<td>&gt;1.49 ng/ml (bacterial sepsis)</td>
<td>Diagnostic biomarker: differential diagnostics of viral and bacterial sepsis, sepsis severity indicator</td>
<td>[32, 33]</td>
</tr>
<tr>
<td>CRP</td>
<td>Children with sepsis</td>
<td>55.39±46.46 mg/l (sepsis); 7.57±8.14 mg/l (infection without sepsis)</td>
<td>Diagnostic biomarker: early diagnostics</td>
<td>[45]</td>
</tr>
<tr>
<td></td>
<td>Postoperative sepsis in neonates undergoing major non-cardiac surgery</td>
<td>≥74.16 mg/l (Yudin index) 96 h after surgery (sepsis)</td>
<td>Diagnostic biomarker</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>Children with sepsis</td>
<td>≥69.9 mg/l (sepsis prognosis)</td>
<td>Prognostic biomarker</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>Urosepsis</td>
<td>≥8.7 mg/dl (sepsis)</td>
<td>Diagnostic biomarker</td>
<td>[33]</td>
</tr>
<tr>
<td>Lactate</td>
<td>Patients with sepsis</td>
<td>&gt;2 mmol/l (severe course, septic shock, risk of lethal outcome)</td>
<td>Prognosis of the sepsis course severity, septic shock diagnostics</td>
<td>[51, 52]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~1.5 mmol/l (sepsis) / ~1.25 mmol/l (without sepsis)</td>
<td>Prognosis of 28-day mortality</td>
<td>[54]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Predictor of 28-day mortality risk on the first day: 2.34 mmol/l (non-survivors) / 1.3 mmol/l (survivors); on the 7th day: 2.65 mmol/l (non-survivors) / 1.4 mmol/l (survivors)</td>
<td>Prognosis of 28-day mortality</td>
<td>[79]</td>
</tr>
<tr>
<td></td>
<td>Children with severe pneumonia complicated by sepsis</td>
<td>Serum lactate levels significantly negatively correlated with PCIS clinical disease scores ($r=-0.6384$) 24 h after admission ([lactate], mM/PCIS scores): extremely critical group (8.78±1.22 / 0–70), critical group (6.78±1.21 / 71–80), non-critical group (4.22±0.87 / &gt;80)</td>
<td>Diagnostic and prognostic biomarker</td>
<td>[53]</td>
</tr>
</tbody>
</table>
### Sepsis biomarkers

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients</th>
<th>Threshold</th>
<th>Clinical significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>Patients with sepsis</td>
<td>&gt;4420 ng/ml (high risk of death) (normal serum ferritin concentration range is 30-400 ng/ml for men and 15-150 ng/ml for women)</td>
<td>Predictor of lethal outcome</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;591.5 ng/ml (increased risk of in-hospital mortality)</td>
<td>Predictor of lethal outcome</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td>Children with sepsis</td>
<td>-1369 ng/ml (non-survivors) / -282 ng/ml (survivors)</td>
<td>Predictor of lethal outcome</td>
<td>[59]</td>
</tr>
<tr>
<td></td>
<td>Patients with septic shock</td>
<td>~708.73 ng/ml (septic shock) / ~20.46 ng/ml (norm)</td>
<td>Diagnostics of septic shock</td>
<td>[61]</td>
</tr>
<tr>
<td>Presepsin</td>
<td>Patients with sepsis</td>
<td>&gt;582 pg/ml (sepsis); &gt;1285 pg/ml (septic shock); &gt;821 pg/ml (increased risk of mortality)</td>
<td>Diagnostic and prognostic biomarker: differential diagnostics, prognosis of the disease course</td>
<td>[65]</td>
</tr>
<tr>
<td></td>
<td>Patients with pneumogenic sepsis on hemodialysis</td>
<td>6951.1±820.46 pg/ml (pneumogenic sepsis); 1693.0±248.24 pg/ml (chronic glomerulonephritis, nephropathy)</td>
<td>Diagnostic biomarker: differential diagnostics</td>
<td>[66]</td>
</tr>
<tr>
<td>suPAR</td>
<td>Sepsis in newborns</td>
<td>4.79-15.63 ng/ml (sepsis); 3.7-10.8 ng/ml (norm)</td>
<td>Diagnostic biomarker</td>
<td>[8]</td>
</tr>
<tr>
<td></td>
<td>Patients with sepsis</td>
<td>&gt;8.0 ng/ml (high risk of lethal outcome)</td>
<td>Prognostic biomarker</td>
<td>[69]</td>
</tr>
<tr>
<td>Additional biomarkers</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PAR (procalcitonin / albumin)</td>
<td>Newborns with sepsis</td>
<td>&gt;0.065 (neonatal sepsis) &gt;0.070 (severe sepsis)</td>
<td>Diagnostics and severity of sepsis</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>Newborns with pneumonia</td>
<td>According to the results of the ROC analysis of the PAR parameter for the detection of sepsis in this category of patients AUC=0.72 (95% CI 0.68-0.75)</td>
<td>Diagnostics of sepsis in newborns</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td>Adult patients with sepsis</td>
<td>&gt;0.87 (predicted septic shock); &gt;0.83 (predicted 28-day mortality)</td>
<td>Prognosis of septic shock and mortality</td>
<td>[40]</td>
</tr>
<tr>
<td>Procalcitonin / cortisone</td>
<td>Postoperative patients aged 18 to 90 years with sepsis of abdominal origin</td>
<td>&gt;0.2 (85% survival rate after 28 days)</td>
<td>Prognosis of sepsis severity and survival rate</td>
<td>[41]</td>
</tr>
<tr>
<td>CRP / albumin</td>
<td>Children with sepsis</td>
<td>1.38-1.49 (sepsis) 0.18-0.19 (infection without sepsis)</td>
<td>Diagnostic biomarker: early diagnostics</td>
<td>[45]</td>
</tr>
<tr>
<td>CRP, procalcitonin, IL6</td>
<td>Sepsis in children</td>
<td>The combination of any two biomarkers increased diagnostic sensitivity to &gt;92.54% and specificity to 100.00%; the combination of these three biomarkers increased diagnostic sensitivity to 96.55% and specificity to 94.03%</td>
<td>Diagnostic biomarker</td>
<td>[75]</td>
</tr>
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</table>
### Sepsis biomarkers

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients</th>
<th>Threshold</th>
<th>Clinical significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL6</td>
<td>Premature newborns</td>
<td>&gt;200 ng/l (early-onset sepsis)</td>
<td>Diagnostic biomarker: diagnostics of early sepsis</td>
<td>[72]</td>
</tr>
<tr>
<td></td>
<td>Newborns</td>
<td>For cord blood samples, sensitivity and specificity are higher than for peripheral blood (83 vs. 71% and 85 vs. 77%, respectively)</td>
<td>Diagnostic biomarker</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td>Patients with sepsis</td>
<td>~321.78 pg/ml (sepsis) / -6.04 pg/ml (norm)</td>
<td>Diagnostic biomarker</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;52.60 pg/ml (sepsis); &gt;548.92 pg/ml (septic shock); &gt;548.92 pg/ml (28-day mortality)</td>
<td>Diagnostic and prognostic biomarker: diagnostics, differential diagnostics, prognosis of 28-day mortality</td>
<td>[54]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Predictor of 28-day mortality risk on the first day:</td>
<td>Prognosis of 28-day mortality</td>
<td>[77]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>239.03 pg/ml (non-survivors) / 107.95 pg/ml (survivors); on the 7th day:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>93.44 pg/ml (non-survivors) / 40.16 pg/ml (survivors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL2R</td>
<td>Patients with sepsis</td>
<td>1407.47±1102.19 pg/ml (sepsis) / 419.58±152.00 pg/ml (norm)</td>
<td>Diagnostic biomarker</td>
<td>[78]</td>
</tr>
<tr>
<td>IL10</td>
<td>Patients with sepsis</td>
<td>20.76±27.30 pg/ml (sepsis) / 6.87±1.59 pg/ml (norm)</td>
<td>Diagnostic biomarker</td>
<td>[78]</td>
</tr>
<tr>
<td>CXCL8/IL8</td>
<td>Patients with sepsis</td>
<td>~306.62 pg/ml (sepsis) / -23.04 pg/ml (norm)</td>
<td>Diagnostic biomarker</td>
<td>[78]</td>
</tr>
<tr>
<td>Chemerin</td>
<td>Patients with sepsis</td>
<td>At the onset of the disease:</td>
<td>Diagnostic and prognostic biomarker: diagnostics, differential diagnostics, prognosis of the course of the disease</td>
<td>[80]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>342.3±108.1 μg/l (sepsis) / 200.8±40.1 μg/l (norm); 405.2±89.9 μg/l (septic shock) / 299.7±99.5 μg/l (sepsis); 427.2±96.7 μg/l (non-survivors) / 306.9±92.1 μg/l (survivors); a week later: 414.1±94.5 μg/l (non-survivors) / 264.2±79.9 μg/l (survivors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IncRNA UCA1</td>
<td>Patients with sepsis</td>
<td>-2.802 (sepsis) / -0.999 (norm); -4.191 (non-survivors) / -2.619 (survivors)</td>
<td>Diagnostic and prognostic biomarker</td>
<td>[83]</td>
</tr>
<tr>
<td>IncRNA CASC2</td>
<td>Patients with sepsis</td>
<td>-0.473 (sepsis) / -1.019 (norm)</td>
<td>Diagnostic biomarker</td>
<td>[84]</td>
</tr>
<tr>
<td>PSP, copeptin, apolipoprotein A5 (APOA5)</td>
<td>Children with sepsis</td>
<td>For APOA5, copeptin, and PSP, sensitivity was 96, 94, and 80%, respectively, for sepsis diagnostics; and 58, 58, and 74% for predicting mortality</td>
<td>Diagnostic and prognostic biomarkers</td>
<td>[88]</td>
</tr>
<tr>
<td>NGAL</td>
<td>Patients with sepsis</td>
<td>≥570 ng/ml (sepsis)</td>
<td>Diagnostic biomarker</td>
<td>[90]</td>
</tr>
<tr>
<td></td>
<td>Newborns with sepsis</td>
<td>&gt;475 pg/ml (sepsis); 96 h after birth:</td>
<td>Diagnostic and prognostic biomarker</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3000 pg/ml (non-survivors) / -600 pg/ml (survivors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGAL, fetuin A</td>
<td>Patients with sepsis</td>
<td>NGAL≥552 mg/l, fetuin A≥0.32 g/l (risk of 28-day mortality)</td>
<td>Prognosis of 28-day mortality</td>
<td>[92]</td>
</tr>
<tr>
<td>Factor</td>
<td>Patients</td>
<td>Threshold</td>
<td>Clinical significance</td>
<td>Reference</td>
</tr>
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<td>-----------------</td>
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</tr>
<tr>
<td>cTnT</td>
<td>Patients with sepsis</td>
<td>&gt;0.1 ng/ml (high risk of 28-day mortality)</td>
<td>Prognosis of 28-day mortality</td>
<td>[94]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased level (&gt;15 ng/l) in survivors of acute phase of disease is an independent predictor of 30-365-day mortality</td>
<td>Prognostic biomarker</td>
<td>[95]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.28±0.05 ng/ml (sepsis)/ 0.19±0.03 ng/ml (norm). At a level &gt;0.24 ng/mL, the sensitivity was 80%, specificity was 78%; when combining 3 indicators: cTnT, lactate, 5-hydroxytryptophan – sensitivity was 86%, specificity was 92.5%</td>
<td>Diagnostic and prognostic biomarker</td>
<td>[96]</td>
</tr>
<tr>
<td>Bio-ADM, penKid</td>
<td>Patients with sepsis</td>
<td>Bio-ADM: ~55 pg/ml (non-survivors) / ~44 pg/ml (survivors); penKid: ~135 pmol/l (non-survivors) / ~99 pmol/l (survivors)</td>
<td>Prognostic biomarkers</td>
<td>[2]</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>Patients with burn sepsis</td>
<td>&gt;2900 pg/ml (non-survivors)</td>
<td>Prognostic biomarker</td>
<td>[81]</td>
</tr>
<tr>
<td></td>
<td>Patients with sepsis</td>
<td>&gt;4500 pg/ml 24 h after admission and &gt;5229 pg/ml 72 h after admission (non-survivors)</td>
<td>Prognostic biomarker</td>
<td>[82]</td>
</tr>
<tr>
<td>Free T3 (FT3)</td>
<td>Children with sepsis</td>
<td>2.59±1.17 pg/ml (sepsis) 2.85±1.01 pg/ml (norm)</td>
<td>Diagnostic and prognostic biomarker</td>
<td>[104]</td>
</tr>
<tr>
<td>p-calprotec-tin</td>
<td>Patients with sepsis</td>
<td>~2.2 mg/l (infection), ~4.0 mg/l (transfer to intensive care unit)</td>
<td>Diagnostic and prognostic biomarker</td>
<td>[108]</td>
</tr>
<tr>
<td>H3K18la</td>
<td>Patients with septic shock</td>
<td>Relative density in peripheral blood mononuclear cells: 0.65 (septic shock) and 0.21 (norm); positive correlation between H3K18la level and APACHE II, SOFA parameters on the first day with the length of stay in the intensive care unit and timing of artificial ventilation</td>
<td>Diagnostic biomarker: differential diagnosis, disease severity</td>
<td>[110]</td>
</tr>
<tr>
<td>COHb</td>
<td>Late-onset sepsis in premature infants</td>
<td>~1.8% (sepsis)/~1.2% (norm); after the start of antimicrobial therapy, a decrease to ~1.45% (COHb levels were calculated as a percentage of total hemoglobin)</td>
<td>Diagnostic biomarker</td>
<td>[112]</td>
</tr>
<tr>
<td>3-phenyl lactate, N-phenylacetyl-glutamine, phenylethylamine, traumatine, xanthine, methyl Jasmonate, indole, L-tryptophan, compound 1107116</td>
<td>Patients with sepsis</td>
<td>Metabolites with levels of expression significantly different between patients with sepsis and the control group (AUC): 3-phenyllactate (0.923), N-phenylacetylglutamine (0.782), phenylethylamine (0.825), traumatine (0.941), xanthine (0.900), methyl Jasmonate (0.823), indole (0.909), L-tryptophan (0.859) compound 1107116 (0.916)</td>
<td>Diagnostic biomarkers</td>
<td>[113]</td>
</tr>
</tbody>
</table>
REFERENCES


Sepsis biomarkers


Sepsis biomarkers


