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Inflammatory biomarkers in neonatal bacterial infections: diagnostic value of presepsin and interleukin-33

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Aim – to evaluate the diagnostic significance of the inflammatory biomarkers such as presepsin and interleukin-33 (IL-33) in preterm newborns with bacterial infections and to compare their diagnostic performance with that of traditional inflammatory markers.

Materials and methods. A prospective study was conducted involving 111 preterm newborns treated in neonatal intensive care and pathology units between 2021 and 2024. The Study group consisted of 85 preterm infants with bacterial infections (neonatal pneumonia and sepsis), while the Control group included 26 conditionally healthy newborns. All patients underwent clinical and laboratory examinations, including the assessment of hematological parameters, as well as levels of C-reactive protein, procalcitonin, lactate, presepsin, and IL-33. Presepsin and IL-33 levels were determined using the enzyme-linked immunosorbent assay (ELISA). The clinical severity was assessed using the nSOFA and NEOMOD scoring systems. Statistical analysis was performed using ROC analysis and non-parametric methods.

Results. Preterm infants with bacterial infections exhibited a pronounced systemic inflammatory response, alterations in hematological parameters, and a high incidence of multiple organ dysfunction. Compared with the Control group, presepsin levels increased 7.6-fold, whereas IL-33 levels increased more than sevenfold. ROC analysis demonstrated that presepsin had the highest diagnostic accuracy, followed by IL-33. Both biomarkers demonstrated high sensitivity (91.2%) and specificity (100%), indicating their excellent diagnostic performance in bacterial infections among preterm infants.

Conclusions. Presepsin and IL-33 demonstrated excellent diagnostic performance and represent promising complementary biomarkers for the early diagnosis of bacterial infections in preterm newborns. Their combined assessment with traditional inflammatory markers and organ dysfunction scoring systems (nSOFA and NEOMOD) may improve the accuracy of early diagnosis and risk stratification in neonatal intensive care.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent for participation was obtained from the mothers.

The authors declare no conflict of interest.

Keywords: early diagnosis, preterm infants, neonatal bacterial infection, presepsin, interleukin-33, biomarkers.

Біомаркери запалення при бактеріальних інфекціях у новонароджених: діагностична цінність пресепсину та інтерлейкіну-33

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Мета – оцінити діагностичне значення таких біомаркерів запалення, як пресепсин та інтерлейкін-33 (IL-33), у недоношених новонароджених із бактеріальними інфекціями та порівняти їхню діагностичну ефективність із традиційними маркерами запалення.

Матеріали і методи. Проведено проспективне дослідження за участю 111 недоношених новонароджених, які перебували на лікуванні у відділеннях інтенсивної терапії та патології новонароджених у період із 2021 по 2024 рік. До основної групи увійшло 85 недоношених немовлят із бактеріальними інфекціями (пневмонія та сепсис новонароджених), а до контрольної – 26 умовно здорових новонароджених. Усім пацієнтам проведено клініко-лабораторне обстеження, що охопило оцінку гематологічних показників, а також рівнів С-реактивного білка, прокальцитоніну, лактату, пресепсину та IL-33. Рівні пресепсину та IL-33 визначено методом імуноферментного аналізу (ІФА). Тяжкість клінічного стану оцінено за допомогою шкал nSOFA та NEOMOD. Статистичний аналіз здійснено з використанням ROC-аналізу та непараметричних методів.

Результати. У недоношених немовлят із бактеріальними інфекціями спостерігалися виражена системна запальна відповідь, зміни гематологічних показників і висока частота поліорганної дисфункції. Порівняно з контрольною групою рівень пресепсину зріс у 7,6 раза, а рівень IL-33 – більш ніж у сім разів. ROC-аналіз показав, що пресепсин мав найвищу діагностичну точність, за ним слідував IL-33. Обидва біомаркери продемонстрували високу чутливість (91,2%) і специфічність (100%), що свідчить про їхню відмінну діагностичну ефективність під час бактеріальних інфекцій у недоношених немовлят.

Висновки. Пресепсин та IL-33 продемонстрували відмінні діагностичні характеристики та є перспективними додатковими біомаркерами для ранньої діагностики бактеріальних інфекцій у недоношених новонароджених. Їхнє комплексне визначення разом із традиційними маркерами запалення та шкалами оцінки органної дисфункції (nSOFA і NEOMOD) може підвищити точність ранньої діагностики та стратифікації ризиків в умовах інтенсивної терапії новонароджених.

Дослідження проведено відповідно до принципів Гельсінської декларації. Отримано інформовану згоду матерів на участь у дослідженні.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: рання діагностика, недоношені немовлята, бактеріальна інфекція новонароджених, пресепсин, інтерлейкін-33, біомаркери.

Neonatal bacterial infections remain one of the leading causes of morbidity and mortality in newborns worldwide. Congenital sepsis and pneumonia are currently considered among the most relevant and debated problems in modern perinatal and neonatal medicine [5,6].

Despite achievements in neonatal intensive care, accurate and timely diagnosis of neonatal sepsis still faces significant difficulties. This is due to the non-specific clinical symptoms, the lack of a universal diagnostic standard, and the limited sensitivity of traditional methods, including blood culture. The complexity of clinical decisions is increased by the need to balance the risks of overdiagnosis and underdiagnosis. On one hand, the irrational use of antibacterial therapy contributes to the rise of antibiotic resistance; on the other hand, a delay in starting treatment can lead to rapid progression of the infection and the development of multiorgan failure [14].

Preterm newborns form a special high-risk group, accounting for a significant share of neonatal sepsis and pneumonia cases. The immaturity of innate and adaptive immunity, the insufficiency of the barrier functions of the skin and mucous membranes, as well as the need for invasive diagnostic and therapeutic interventions, contribute to the increased susceptibility of this category of patients to infections. Clinical signs of sepsis in preterm infants are often subtle and non-specific, which significantly complicates early diagnosis. Furthermore, the high rate of adverse outcomes, including the development of multiorgan failure, bronchopulmonary dysplasia, neurological disorders, and mortality, determines the need to improve methods for the early detection of the infectious process specifically in this group of newborns [4,8,15,18,19].

In this regard, the search for highly sensitive and specific biomarkers for the early diagnosis of sepsis is of particular importance [2,7,21,22]. In recent years, soluble CD14 subtype – presepsin (sCD14-ST) has been actively studied and has demonstrated high diagnostic accuracy, comparable to procalcitonin and C-reactive protein (CRP) [3,16]. Presepsin is characterized by a rapid increase in blood concentration within the first hours of the infectious process and less dependence on perinatal factors, which increases its diagnostic value [1,11].

At the same time, there is a growing interest in new immunological markers, particularly interleukin-33 (IL-33). IL-33 is a member of the IL-1 family

and acts as an alarmin released during cellular damage. It plays an important role in regulating the innate and adaptive immune response, and its elevated levels are associated with infectious and inflammatory processes in newborns [23].

Despite the accumulated data, the diagnostic and prognostic value of IL-33, as well as its comparative efficacy when combined with other biomarkers, including presepsin, remain insufficiently studied [10,20]. In this regard, a comprehensive approach using a panel of markers seems promising, as it could increase the accuracy of early diagnosis and optimize the management strategy for preterm infants with suspected sepsis.

Aim – to evaluate the diagnostic significance of the inflammatory biomarkers presepsin and interleukin-33 (IL-33) in preterm newborns with bacterial infections and to compare their diagnostic performance with traditional inflammatory markers.

Material and methods of the study

A prospective, continuous sampling study included 111 preterm newborns admitted from 2021 to May 2024 to neonatal intensive care units (NICUs) and neonatal pathology departments. The study included children born in maternity facilities across cities and regions of Azerbaijan who developed a critical condition during the neonatal period and required transfer and transportation to the intensive care unit of the Scientific Research Institute of Pediatrics. All observed preterm infants were divided into two groups: Study group and Control group. The Study group included 85 preterm newborns with a gestational age of 25–37 weeks, from 0 to 28 days old, with bacterial infections (neonatal pneumonia, sepsis). Based on the results of a comprehensive examination and considering the etiology of the disease, 35 (41.2%) of these newborns had neonatal pneumonia, and 50 (58.8%) had sepsis. The Control group consisted of 26 conditionally healthy preterm newborns without bacterial infections or congenital malformations. The newborns in the Control group were observed in the neonatal department of the Scientific Research Institute of Obstetrics and Gynecology and did not differ statistically from the Study group in terms of sex and age.

Newborns with a diagnosis of hemolytic disease of the newborn, chromosomal abnormalities, metabolic diseases, multiple congenital malformations, and TORCH infections specific to the perinatal period were excluded from the study.

The average body weight of newborns in the Study group was 2070.8 ± 70.2 g. In the Study group, there were 46 (54.1%) boys and 39 (45.9%) girls, while the Control group included 16 (61.5%) boys and 10 (38.5%) girls.

All patients underwent clinical, laboratory, and instrumental examinations, which included cardiorespiratory monitoring, temperature measurement, complete blood count and biochemical blood tests, analysis of blood gas composition and acid-base status, and evaluation of CRP, procalcitonin, presepsin, and interleukin-33 (IL-33) concentrations. Not all laboratory biomarkers were available for every enrolled infant. Therefore, the number of observations differed between parameters, and each statistical analysis was performed using all available measurements for the corresponding biomarker. Neurosonography, ultrasonography, echocardiography, and bacteriological culture of samples obtained from various sites were also performed. In addition, the severity of organ dysfunction was assessed using the nSOFA (Neonatal Sequential Organ Failure Assessment) and NEOMOD (Neonatal Multiple Organ Dysfunction) scoring systems. The nSOFA scale evaluates respiratory, cardiovascular, and hematologic disorder, whereas the NEOMOD scale is used to assess the degree of multiple organ dysfunction in neonates. Higher scores reflect more severe organ dysfunction [9,12,13].

Quantitative determination of serum presepsin and IL-33 was performed using a sandwich enzyme-linked immunosorbent assay (ELISA) with a commercial Sunred Bio (Shanghai) kit produced by Algen Diagnostik Medical LTD (Ankara, Turkey) on a BioScreen MS 500 analyzer (Stat Fax, USA).

Statistical analysis was performed using SPSS 27. Data were presented as median (Me) and quartile values (Q1; Q3), corresponding to the 25th and 75th percentiles. The significance of differences between the compared groups was assessed using the non-parametric Mann–Whitney U test. Differences were considered statistically significant at $p < 0.05$ [17].

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee. Written informed consent was obtained from the mothers of all enrolled infants.

Results of the study and discussion

The study revealed that most newborns were born to mothers with extragenital pathology (54 (63.5%)

cases), and a complicated obstetric history (99 (89.2%) cases), and a complicated gynecological history (20 (23.5%) cases). In most cases, delivery in both groups was performed by cesarean section: in 68 (80.0%) cases in the Study group and in 19 (73.1%) cases in the Control group ($p = 0.453$). Among neonates in the Study group, the 1st minute Apgar score was 5.9 ± 0.1 (1–8) points; 34 (40.0%) were born with mild asphyxia, 47 (55.3%) with moderate asphyxia, and 4 (4.7%) with severe asphyxia. The 5th-minute Apgar score was 6.9 ± 0.1 (3–9) points; 66 (77.6%) newborns were classified into the mild asphyxia group, 17 (20.0%) into the moderate asphyxia group, and 2 (2.4%) into the severe asphyxia group. Upon admission, 39 (45.9%) newborns were in severe condition, 44 (51.8%) in very severe condition, and 2 (2.4%) in a preagonal state. Resuscitation measures were performed for all newborns in the Study group. The mortality rate was 25.9% (22 patients).

Newborns in the Study group presented with respiratory failure in 70 (82.4%) cases, congenital pneumonia in 37 (43.5%), perinatal infections in 25 (29.4%), necrotizing enterocolitis in 8 (9.4%), hepatitis in 2 (2.4%), peritonitis in 1 (1.2%), cardiovascular insufficiency in 14 (16.5%), disseminated intravascular coagulation (DIC) syndrome in 9 (10.6%), pneumothorax in 3 (3.5%), neonatal coma in 3 (3.5%), intracranial hemorrhage in 8 (9.4%), neonatal seizures in 6 (7.1%), and osteomyelitis in 2 (2.4%).

Bacteriological culture was performed in 63 of the 85 neonates in the Study group. Positive culture results with microbial isolation were obtained in 54 (85.7%) neonates, while cultures from 9 (14.3%) neonates showed no growth. Gram-positive coagulase-negative staphylococci were identified most frequently, with an isolation rate of 23 (42.6%). The isolation rates for other pathogens were as follows: *Staphylococcus aureus* 10 (18.5%), *Klebsiella pneumoniae* 5 (9.3%), *Candida albicans* 3 (5.6%), *Enterobacter aerogenes* 2 (3.7%), *Pseudomonas aeruginosa* 2 (3.7%), and *Acinetobacter* 3 (5.6%). Less common pathogens included *Staphylococcus epidermidis* 1 (1.9%), *Serratia* 1 (1.9%), *Bacillus spp.* 1 (1.9%), *Sphingomonas paucimobilis* 1 (1.9%), and *Proteus* 1 (1.9%). In some cases, multiple microorganisms were isolated. In the majority of cases, the microorganisms were isolated from the blood. Thus, in most (83.1%) of the newborns upon admission to the NICU, the infectious agent was isolated from only a single site, most frequently from the blood.

Table 1

Comparison of hematological parameters between preterm infants with bacterial infections and healthy preterm controls

Parameter	Groups								PU
	Control				Study				
	M	Me	Q1	Q3	M	Me	Q1	Q3	
HGB	16.9	16.8	15.6	18.0	13.5	13.3	11.4	15.7	<0.001*
RBC	4.85	4.90	4.30	5.10	3.88	3.90	3.40	4.40	<0.001*
WBC	13.0	13.6	8.2	17.0	11.9	10.6	6.3	16.5	0.116
HCT	51.2	50.5	46.9	54.2	42.3	41.2	35.7	47.6	<0.001*
MCV	102.0	103.5	98.0	111.0	107.2	108.0	101.0	113.0	0.029*
MCH	32.2	32.0	29.0	34.0	34.4	34.7	32.9	36.3	0.001*
MCHC	33.0	32.7	31.0	34.6	32.3	32.1	31.3	33.1	0.319
RDW-SD	41.2	42.0	39.0	43.8	52.7	52.8	48.0	58.1	<0.001*
RDW-CV	17.4	17.3	15.5	18.8	16.9	16.6	15.6	17.8	0.202
PLT	277.0	290.0	218.0	320.0	231.6	208.0	132.0	302.0	0.006*
PCT	0.35	0.35	0.20	0.45	0.27	0.29	0.18	0.3	0.007*
BAS	0.85	0.80	0.70	0.90	1.26	1.16	0.80	1.7	0.001*
EOS	0.75	0.70	0.54	1.10	1.46	1.40	0.90	2.0	<0.001*
NEUT	2.12	1.90	1.20	2.73	5.96	4.89	2.79	8.5	<0.001*
MON	0.34	0.10	0.06	0.40	1.72	1.27	0.72	2.1	<0.001*
LYM	3.08	3.00	2.00	4.30	3.83	3.30	2.07	5.1	0.373

Notes: PU -statistical accuracy of the Mann–Whitney U test; * – the null hypothesis is rejected.

Blood groups O and A were the most common, each observed in 31 (36.5%) patients, whereas blood groups B and AB were identified in 18 (21.2%) and 5 (5.9%) patients, respectively presents the hematological parameters of the newborns in the Control and Study groups depending on gestational age. Newborns in the Study group showed a statistically significant decrease in hemoglobin (HGB), erythrocyte, and hematocrit (HCT) levels compared to the Control group ($p<0.001$), indicating the development of secondary anemic syndrome to the bacterial infection (Table 1).

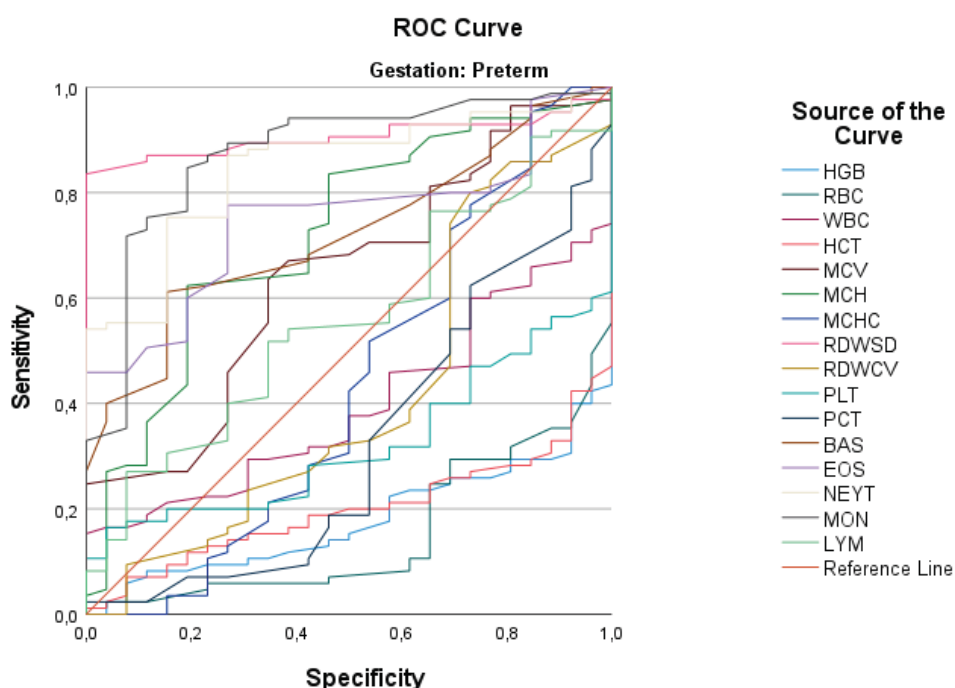
In the Study group, HGB, red blood cell (RBC) count, HCT, platelet count (PLT), and plateletcrit (PCT) were significantly lower than those in the Control group (all $p<0.05$). In contrast, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width-standard deviation (RDW-SD), basophil (BAS), eosinophil (EOS), neutrophil (NEUT), and monocyte (MON) counts were significantly higher in the Study group than in the Control group (all $p<0.05$).

No statistically significant differences were observed between the groups in white blood cell (WBC) count, mean corpuscular hemoglobin concentration (MCHC), red cell distribution width-co-

efficient of variation (RDW-CV), or lymphocyte (LYM) count (all $p>0.05$).

Thus, hematological changes in children with neonatal infections were non-specific, reflecting the activation of a systemic inflammatory process, a general response of the hematopoietic system, and, apparently, the newborn's immunity to the infectious pathogen.

ROC analysis was performed to evaluate the diagnostic performance of hematological parameters in the Study group (Fig. 1, Table 2). The highest diagnostic accuracy was demonstrated by RDW-SD (AUC=0.906, $p<0.001$), MON (AUC=0.876, $p<0.001$), and NEUT (AUC=0.846, $p<0.001$). Good diagnostic performance was also observed for EOS (AUC=0.750, $p<0.001$), BAS (AUC=0.721, $p=0.001$), and MCH (AUC=0.720, $p=0.001$), whereas MCV showed moderate diagnostic accuracy (AUC=0.642, $p=0.029$). In contrast, LYM (AUC=0.558, $p=0.373$), MCHC (AUC=0.435, $p=0.319$), RDW-CV (AUC=0.417, $p=0.202$), and WBC (AUC=0.398, $p=0.116$) did not demonstrate statistically significant discriminatory ability. AUC values <0.5 for HGB, RBC, HCT, PLT, and PCT indicate an inverse association with bacterial infection, reflecting lower values of these parameters in affected infants.



Diagonal segments are produced by ties.

Fig. 1. ROC curves of hematological parameters for the diagnosis of bacterial infection in preterm infants

The nSOFA and NEOMOD scores were calculated based on medical records after admission to the NICU within the first 72 hours after birth (the highest score recorded during this period was used). In our study, the total NEOMOD score averaged

4.8 ± 0.3 (range, 0-11), with higher values reflecting a greater severity of multiorgan failure. Respiratory dysfunction was observed in 73 (85.8%) preterm neonates: a score of 0 points in 12 (14.1%), 1 point in 24 (28.2%), and 2 points in 49 (57.6%). Cardiovas-

Table 2

Area under the Curve values for hematological parameters

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
HGB	0.180	0.039	0.000	0.104	0.255
RBC	0.154	0.038	0.000	0.079	0.230
WBC	0.398	0.054	0.116	0.292	0.504
HCT	0.200	0.041	0.000	0.121	0.279
MCV	0.642	0.060	0.029	0.525	0.759
MCH	0.720	0.057	0.001	0.608	0.832
MCHC	0.435	0.073	0.319	0.291	0.579
RDW-SD	0.906	0.029	0.000	0.850	0.962
RDW-CV	0.417	0.068	0.203	0.284	0.550
PLT	0.322	0.050	0.006	0.225	0.419
PCT	0.325	0.063	0.007	0.202	0.448
BAS	0.721	0.050	0.001	0.624	0.819
EOS	0.750	0.047	0.000	0.658	0.842
NEUT	0.846	0.039	0.000	0.771	0.922
MON	0.876	0.039	0.000	0.798	0.953
LYM	0.558	0.060	0.373	0.441	0.675

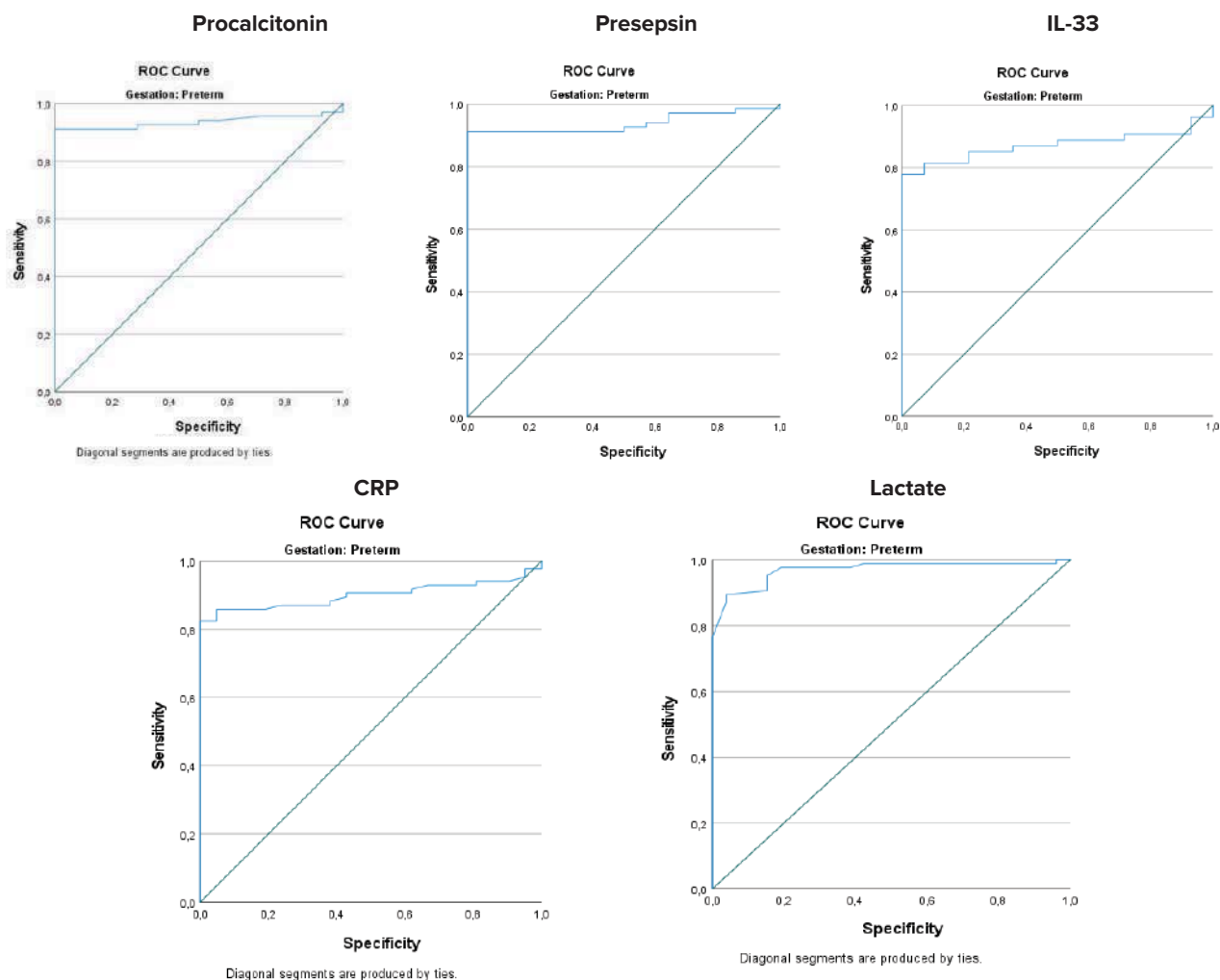


Fig. 2. ROC curves of inflammatory biomarkers for the diagnosis of bacterial infection in preterm infants

cular dysfunction was present in 39 (45.8%) patients: 0 points in 46 (54.1%), 1 point in 15 (17.6%), and 2 points in 24 (28.2%). Gastrointestinal dysfunction was noted in 83 (97.6%) newborns who were on parenteral nutrition, while the remaining 2 (2.4%) were on enteral nutrition; 75 (88.2%) scored 1 point, and 8 (9.4%) newborns scored 2 points. Renal dysfunction was observed in 36 (42.4%) cases 1 point in 23 (27.1%), 2 points in 13 (15.3%), and acid-base imbalance was recorded in 37 (43.5%) patients 1 point in 33 (38.8%), 2 points in 4 (4.7%).

Thus, according to the NEOMOD score, among preterm infants with bacterial infection, minimal organ dysfunction (0–2 points) was observed in 2 (2.4%) infants, moderate multiorgan dysfunction (3–6 points) in 46 (54.1%), and severe multiorgan failure (>6 points) in 37 (43.5%).

According to the nSOFA score, among preterm infants with bacterial infection, the mean total score

was 4.2 ± 0.4 (minimum 0, maximum 13), which was significantly higher than that in the healthy Control group ($p < 0.001$). Respiratory system dysfunction was noted in 53 cases: 18 (21.2%) scored 2 points, 27 (31.8%) scored 4 points, 6 (7.1%) scored 6 points, and 2 (2.4%) scored 8 points. Cardiovascular dysfunction was observed in 40 infants: 1 (1.2%) scored 1 point, 13 (15.3%) scored 2 points, 9 (10.6%) scored 3 points, and 17 (20.0%) scored 4 points. Hematological changes were found in 10 (11.8%) infants with a score of 1 point, 11 (12.9%) with 2 points, and 4 (4.7%) with 3 points. According to the nSOFA score, 19 (22.4%) infants had no risk of multiorgan dysfunction, 3 (3.5%) had a low risk, and 63 (74.1%) had a high risk.

In infants with a fatal outcome, the mean total scores on the NEOMOD and nSOFA scales were 4.81 and 4.2 points, respectively.

In the structure of organ dysfunction based on the NEOMOD and nSOFA scores, respiratory failure,

Table 3

Levels of inflammatory biomarkers in preterm infants in the Study and Control groups

Biomarker	Group								Pu
	Control				Study				
	M	Me	Q1	Q3	M	Me	Q1	Q3	
CRP, mg/L	2.7	2.5	2.1	3.4	38.6	23.0	9.7	55.0	<0.001*
Procalcitonin, ng/mL	0.5	0.4	0.2	0.7	11.5	4.5	1.2	10.9	0.021*
Presepsin, pg/mL	112.8	101.1	95.2	125.6	853.3	700.5	428.0	860.0	<0.001*
IL-33, pg/mL	5.1	4.7	4.4	5.6	36.6	31.4	23.7	41.9	<0.001*
Lactate, mmol/L	1.22	1.20	0.90	1.40	2.99	2.50	2.1	3.5	<0.001*

Notes: PU – statistical significance of the Mann–Whitney U test; * – the null hypothesis is rejected.

Table 4

Area under the ROC Curve (AUC) of inflammatory biomarkers in preterm infants

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Procalcitonin	0.872	0.042	0.000	0.789	0.955
Presepsin	0.938	0.026	0.000	0.886	0.990
IL33	0.936	0.028	0.000	0.882	0.990
CRP	0.900	0.030	0.000	0.842	0.959
Lactate	0.969	0.015	0.000	0.938	0.999

hemodynamic instability, and central nervous system disorders predominate in newborns with sepsis and pneumonia. Continuous standardized monitoring of the development and progression of organ dysfunction appears to be a reasonable tool for predicting mortality and morbidity in neonatal infections.

In our study, CRP values in the Study group were 14.3-fold higher than in the Control group ($p < 0.001$). Procalcitonin levels were also significantly higher in the Study group, showing a 23-fold increase compared with the Control group ($p = 0.021$). Lactate levels in the Study group exceeded those in the Control group by 2.5-fold.

Along with traditional methods for diagnosing the presence of inflammation in the newborn's body, we analyzed an early inflammatory marker – presepsin. Analysis of presepsin concentrations showed that this early inflammatory marker was significantly elevated in the Study group (Table 3). In the Study group, presepsin levels increased 7.6-fold compared with the Control group ($p = 0.001$) and averaged 853.3 ± 96.2 pg/mL (range, 88–3760 pg/mL).

In our study, the levels of the novel inflammatory biomarker IL-33 were evaluated. In Control group, the mean IL-33 concentration was 5.1 ± 0.3 pg/mL, whereas in preterm newborns Study group it increased approximately 7.2-fold to 36.6 ± 3.0 pg/mL ($p < 0.001$).

An assessment of the inflammatory markers was performed using ROC analysis. The area under the ROC curve (AUC) and the standard error were calculated, and the upper and lower bounds of the 95% confidence interval for the area, as well as the asymptotic p-values (statistical significance of the results), were determined (Fig. 2, Table 4).

The optimal cut-off values were as follows: >5.8 for CRP; >1.15 for procalcitonin; >215 for presepsin; >10.9 for IL-33; and >1.85 for lactate.

The highest sensitivity values were observed for presepsin and IL-33 (91.2% each), followed by lactate (89.4%), CRP (82.4%), and procalcitonin (77.8%).

The specificity of the studied markers was highest for CRP, procalcitonin, presepsin, and IL-33, reaching 100.0%, while for lactate, the value was slightly lower at 96.2%. The positive predictive value (PPV) was 100.0% for CRP, procalcitonin, presepsin, and IL-33, whereas for lactate it was 98.7%. The negative predictive value (NPV) varied from 53.8% for procalcitonin to 73.5% for lactate (Table 5).

The highest values for the positive likelihood ratio (LR+) were recorded for CRP, procalcitonin, presepsin, and IL-33, indicating their high diagnostic informativeness. The lowest LR- values were observed for presepsin and IL-33 ($LR- = 0.09$), demonstrating their high ability to rule out the disease given a negative test result.

Table 5

Diagnostic accuracy of biomarkers for bacterial infection in preterm infants

Parameter	CRP (n=106)	Procalcitonin (n=68)	Presepsin (n=82)	IL-33 (n=82)	Lactate (n=111)
Cut-off point	>5.8	>1.15	>215	>10.9	>1.85
Sn, %	82.4±4.1	77.8±5.7	91.2±3.4	91.2±3.4	89.4±3.3
Sp, %	100.0	100.0	100.0	100.0	96.2±3.8
GDV, %	85.8±3.4	82.4±4.6	92.7±2.9	92.7±2.9	91.0±2.7
PPV, %	100.0	100.0	100.0	100.0	98.7±1.3
NPV, %	58.3±8.2	53.8±9.8	70.0±10.2	70.0±10.2	73.5±7.6
LR+	excellent	excellent	excellent	excellent	excellent
LR-	good	moderate	excellent	excellent	good

Notes: Sn – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR- – negative likelihood ratio.

Table 6

Results of the Fisher–Snedecor analysis of biomarkers for bacterial infection in preterm infants

Indicators	Cut-off point	OR (95% Confidence Interval)	EIF (95% Confidence Interval)	p
CRP	>5.8	195.6 (11.2-3405.8)	84.3 (83.8-84.9)	<0.001
Procalcitonin	>1.15	98.6 (5.5-1772.1)	63.5 (61.4-65.7)	<0.001
Presepsin	>215	278.9 (14.9-5235.9)	147.2 (143.6-150.8)	<0.001
IL-33	>10.9	278.9 (14.9-5235.9)	147.2 (142.4-152.0)	<0.001
Lactate	>1.85	211.1 (25.4-1749.7)	161.8 (156.1-167.5)	<0.001

The highest sensitivity values were identified for presepsin and IL-33, reaching 91.2% each, followed by CRP at 82.4%, lactate at 89.4%, and procalcitonin at 77.8%. The specificity of the studied markers was highest for CRP, procalcitonin, presepsin, and IL-33, reaching 100.0%, while for lactate, the value was slightly lower at 96.2%.

Subsequently, a Fisher–Snedecor analysis of variance (ANOVA) was performed to determine the effect size of the factor for diagnostic purposes. The highest efficient influence function (EIF) was recorded for lactate (EIF=161.8), presepsin, and IL-33 (EIF=147.2), which indicates the high diagnostic significance of these parameters in neonatal sepsis and pneumonia in preterm newborns. High odds ratio (OR) values also confirm a strong association between elevated levels of the studied markers and the development of the infectious process. The highest OR values were observed for presepsin and IL-33 (OR=278.85), as well as for lactate (OR=211.11) (Table 6).

In the data analysis for preterm infants, high values of the FS-criterion were observed for lactate (EIF=161.8), presepsin (EIF=147.2), and IL-33 (EIF=147.2), indicating the high informativeness of these markers in the diagnosis of neonatal sepsis.

An analysis of the correlation relationships between proinflammatory markers in preterm newborns with bacterial infection demonstrated the presence of statistically significant positive correlations among all studied parameters ($p < 0.001$ in all cases, except for the correlation between CRP and IL-33, where $p = 0.001$). The strongest correlation was identified between the levels of presepsin and IL-33 ($\rho = 0.795$; $p < 0.001$), indicating a close relationship between these markers in the development of the inflammatory response during bacterial infection in preterm newborns. Moderate correlations were observed between: presepsin and procalcitonin ($\rho = 0.630$; $p < 0.001$); procalcitonin and lactate ($\rho = 0.614$; $p < 0.001$); CRP and procalcitonin ($\rho = 0.594$; $p < 0.001$); presepsin and lactate ($\rho = 0.533$; $p < 0.001$); and IL-33 and procalcitonin ($\rho = 0.545$; $p < 0.001$) (Table 7).

Correlation analysis revealed statistically significant positive relationships among all investigated proinflammatory markers in preterm infants with bacterial infection ($p < 0.01$) (Table 5). The strongest correlation was observed between presepsin and IL-33 levels ($\rho = 0.795$; $p < 0.001$), indicating a close association between these parameters and their potential complementary role in the development of the systemic inflammatory response.

Table 7

Correlations between proinflammatory biomarkers in preterm infants

Biomarker		CRP	Procalcitonin	Presepsin	IL-33	Lactate
CRP	ρ (Rho)	—	0.594**	0.376**	0.367**	0.564**
	p	—	0.000	0.000	0.001	0.000
	N	—	68	82	82	106
Procalcitonin	ρ (Rho)	0.594**	—	0.630**	0.545**	0.614**
	p	0.000	—	0.000	0.000	0.000
	N	68	—	59	59	68
Presepsin	ρ (Rho)	0.376**	0.630**	—	0.795**	0.533**
	p	0.000	0.000	—	0.000	0.000
	N	82	59	—	82	82
IL-33	ρ (Rho)	0.367**	0.545**	0.795**	—	0.504**
	p	0.001	0.000	0.000	—	0.000
	N	82	59	82	—	82
Lactate	ρ (Rho)	0.564**	0.614**	0.533**	0.504**	—
	p	0.000	0.000	0.000	0.000	—
	N	106	68	82	82	—

Notes: ρ (Rho) – correlation coefficient (ρ -Spearman criterion); p – statistical significance of the correlation coefficient; N – number of paired observations included in the correlation analysis. The number of observations differed because not all biomarkers were available for every enrolled infant. Correlation coefficients were calculated using all available paired measurements.

Moderate correlations were established between procalcitonin and presepsin ($\rho=0.630$; $p<0.001$), procalcitonin and lactate ($\rho=0.614$; $p<0.001$), as well as between CRP and procalcitonin ($\rho=0.594$; $p<0.001$). Lactate significantly correlated with CRP ($\rho=0.564$), presepsin ($\rho=0.533$), and IL-33 ($\rho=0.504$) ($p<0.001$ in all cases), reflecting the link between the severity of the inflammatory process, tissue hypoxia, and metabolic disturbances.

Thus, the results of the correlation analysis demonstrate a close relationship between traditional (CRP, procalcitonin) and modern biomarkers of inflammation (presepsin, IL-33), confirming their involvement in common pathophysiological mechanisms of the systemic inflammatory response during bacterial infection in preterm newborns. The strongest correlation between presepsin and IL-33 allows these parameters to be considered promising, complementary markers for the diagnosis and monitoring of the infectious-inflammatory process.

The obtained results confirm that bacterial infections in preterm newborns are accompanied by a pronounced systemic inflammatory response and a high incidence of multiple organ dysfunction. This is consistent with current concepts regarding the role of immature innate and adaptive immunity in the development and progression of neonatal sepsis [8,15].

In our study, a statistically significant increase in the levels of C-reactive protein, procalcitonin, pre-

sepsin, IL-33, and lactate was revealed in preterm newborns with sepsis and pneumonia compared to the Control group. Presepsin and IL-33 exhibited the highest diagnostic performance, with the area under the ROC curve (AUC) reaching 0.938 and 0.936, respectively. These findings agree with the results of modern studies demonstrating the high diagnostic value of presepsin in early-onset neonatal sepsis [16,22]. Presepsin levels elevate within the first hours of the infectious process and are less influenced by non-infectious factors compared to procalcitonin [3,6]. In the present study, presepsin was characterized by high sensitivity (91.2%), specificity (100%), and a high odds ratio (OR=278.85).

Of particular interest is IL-33, which is considered an alarmin involved in the activation of the innate immune response during tissue damage. In our study, the level of IL-33 was more than 7 times higher than that in the Control group, and its diagnostic performance was practically equal to that of presepsin, indicating its involvement in infectious-inflammatory processes. The identified strong positive correlation between presepsin and IL-33 ($\rho=0.795$; $p<0.001$) may reflect their participation in interconnected mechanisms of the systemic inflammatory response. Traditional markers of inflammation also demonstrated diagnostic significance; however, their performance was lower. In particular, procalcitonin parameters were inferior

to those of presepsin and IL-33, which might be attributed to the influence of non-infectious factors in the early neonatal period, including prematurity, asphyxia, and respiratory distress syndrome [5,21].

Diagnostic utility was also demonstrated by RDW-SD, alongside neutrophil and monocyte counts, reflecting the activation of innate immunity and the severity of the inflammatory reaction. However, these parameters should be considered additional markers due to their non-specific nature.

The high incidence of multiple organ dysfunction and mortality confirms the severity of the clinical course of bacterial infections in preterm newborns. The use of the nSOFA and NEOMOD scores allowed for an objective assessment of the degree of organ failure and confirmed their prognostic significance, which is consistent with the findings of current studies [6,19].

The obtained results carry important practical significance for neonatal intensive care. The high diagnostic efficacy of presepsin and IL-33, as well as the close correlation identified between them, suggest that their combined use represents a promising approach for the early diagnosis of bacterial infections in preterm newborns.

The limitations of this study include its single-center design and relatively small sample size. Nevertheless, a comprehensive assessment of traditional and novel inflammatory markers demonstrated the high diagnostic significance of presepsin and IL-33 as promising, complementary biomarkers for the early diagnosis of bacterial infections in preterm newborns. To confirm these findings, further multicenter studies with larger sample sizes and an evaluation of the prognostic significance of these markers regarding disease severity and adverse outcomes are required.

Conclusion

The study confirmed that neonatal bacterial infections are accompanied by a pronounced systemic inflammatory response, alterations in hematological parameters, and a high incidence of multiple organ dysfunction, particularly in preterm newborns. In preterm infants with sepsis and pneumonia, a statistically significant increase in presepsin and IL-33 concentrations was revealed, accompanied by the high diagnostic performance of these parameters. The presence of a strong positive correlation between them indicates their involvement in common mechanisms underlying the development of the systemic inflammatory response. The obtained results substantiate the clinical utility of utilizing presepsin and IL-33 as complementary biomarkers for early detection, severity assessment, and dynamic monitoring of bacterial infections in preterm newborns.

Changes in hematological parameters, including elevations in RDW-SD, MON, and NEUT counts, reflected the activation of the systemic inflammatory response and innate immunity. Clinical status assessment using the nSOFA and NEOMOD scores confirmed a high frequency of multiple organ failure and underscored the prognostic significance of monitoring organ dysfunction in infected preterm infants.

Thus, the findings demonstrate the severe clinical course of neonatal bacterial infections and indicate that the comprehensive use of presepsin, IL-33, traditional inflammatory markers, and organ dysfunction scoring systems enhances the accuracy of early sepsis diagnosis, facilitating the timely initiation of intensive care and the optimization of diagnostic and therapeutic strategies.

The authors declare no conflict of interest.

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