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The Role of Biomarkers and Correlated Conditions in the Diagnosis of Neonatal Sepsis

Nicoleta Lungu [1], Aniko Maria Manea [1,*], Daniela-Eugenia Popescu [1], Kristian Miok [2], Florina Marinela Doandeș [1], Oana Cristina Costescu [1], Mihaela Zaharie [1], Daniela Maria Pop [3], Ana Maria Cristina Jura [1] and Mărioara Boia [1]

1. Department of Obstetrics-Gynecology and Neonatology, "Victor Babes" University of Medicine and Pharmacy, 300041 Timișoara, Romania;
2. Advanced Environmental Research Institute, West University of Timisoara, Vasile Pârvan 4 Bd. 300223 Timișoara, Romania
3. Department of Prostheses and Dental Materials, Faculty of Dental Medicine "Victor Babes" University of Medicine and Pharmacy Timisoara, 9 Revolution 1989Ave. 300070, Timisoara, Romania
* Correspondence: manea.aniko@umft.ro

Abstract: Background: Neonatal sepsis associated with severe morbidity and mortality defines the systemic condition arising from the bacterial, viral, fungal origin associated with hemodynamic and clinical alterations. Symptomatology can be different, from subclinical to severe, focal or systemic disease. The causal agent comes from maternal flora or can be of community/hospital origin. Material and method: Our retrospective study evaluated 121 newborns (both preterm and term), divided into three groups: early onset sepsis (35), late onset sepsis (39), and control group (47), from 0 to 28 days old. Blood samples and cultures were collected at admission, after 24 hours, and 72 hours. Results: The two-sample Wilcoxon signed rank test revealed a statistically significant difference between the initial and final measures of lactate dehydrogenase (LDH) and ferritin within the early onset sepsis (EOS) and late onset sepsis (LOS) groups. No significant differences were observed for those two variables within the control group. There were significant differences for first and last measurements of C-Reactive Protein (CRP) ($p = 0.029$), leukocyte count ($p = 0.002$), and platelets (TR) ($p = 0.00001$). Conclusions: Ferritin is a potential biomarker that can be associated with systemic response and sepsis in both cases of early and late onset sepsis.

Keywords: newborn; sepsis; biomarkers; early onset sepsis; late onset sepsis; ferritin; lactate dehydrogenase

1. Introduction

Neonatal sepsis is frequently associated with bacterial bloodstream infection and can lead to severe clinical manifestations and death, as well as irreversible long-term deficits [1, 2]. Neonatal sepsis diagnosis, in particular early onset sepsis is extremely difficult because of his clinical findings [3]. Because of nonspecific clinical signs early-onset sepsis (EOS) the frequently used biomarkers, such as procalcitonin, full blood count and C-Reactive Protein (CRP), have low specificity, sensitivity and positive predictive value [3]. The organ dysfunction and degree of severity are established using validated scoring systems that identify and quantify abnormalities according to laboratory data, clinical findings, or therapeutic measures [4]. The number of neonatal intensive care units and higher survival rates for preterm and low birth-weight newborns [5] have revealed an increased risk of adverse neonatal outcomes, respiratory distress [6] and infection. Studies have reported sepsis rates are inversely proportional to gestational age, with 33% of infants born less than 28 weeks acquiring sepsis compared to 60% of infants born less than 25 weeks [7, 8]. Medical evolution has made it possible for extremely premature infants with low birth weights to survive [9, 10]. Depending on the time of onset, EOS represents an infection that presents within the first 3 days of life (<72 hours) but some researchers extend this limit up to the first week of life [11–15]. LOS is described as an infection occurring after the fourth or seventh day of life within the neonatal period [3,5,16,17]. The diagnosis and treatment of sepsis can be challenging for developing countries because newborns present no

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specific symptoms and signs for sepsis [18]. Efficient and early treatment is crucial for the outcome and prognosis in neonatal sepsis, these cases requiring frequent administration of empirically broad-spectrum antibiotics [19]. Positive cultures (blood, urine, cerebrospinal fluid) are time-consuming with a low sensitivity method, but still remain the gold standard for diagnosis [20,21]. A higher perspective was given in the field by the use of biomarkers. An ideal biomarker should have a high degree of accuracy in recognizing the presence or absence of neonatal sepsis, on time [22]. Delaying treatment in a potentially infected child, is inacceptable given the rapid disease course and high fatality associated with neonatal sepsis [4].

2. Materials and Methods

2.1. Study Design and Ethics

This is a retrospective study followed by the evaluation of newborns with sepsis or suspected sepsis admitted to the Neonatal and Preterm Department of the "Louis Țurcanu" Children's Emergency Clinical Hospital Timișoara over 2 years. "Louis Țurcanu" Children's Emergency Hospital is associated with "Victor Babeș" University of Medicine and Pharmacy Timișoara (UMFT). The study was conducted with the approval of the Research Ethics Committee of the University of Medicine and Pharmacy "Victor Babeș" of Timișoara, CECS Opinion no. 57/2018 and the approval of the Ethics Committee for Scientific Research of the "Louis Țurcanu" Children's Emergency Clinical Hospital Timișoara no.12/24.03.2022. Additionally, written informed consent for the conduct of the study was obtained from the parents of the children included in the study.

2.2. Inclusion Criteria and Study Variables

The study included 121 newborns classified in three distinct populations by the onset of sepsis: Early Onset Sepsis (EOS), Late-Onset Sepsis (LOS), and a Control group. Participants of all groups, in componence both premature and term newborns, were recruited from the Department of Neonatology of "Louis Țurcanu" Emergency Hospital for Children between the first of January 2022 and 31stof December 2023 meeting predefined criteria for inclusion and exclusion. All participants of this study were born in other hospitals with inferior ranges of classification of hospitals in Romania and were transferred to our Clinic during the first hours of life.

The inclusion criteria were represented by premature newborns with gestational age between 24 and 37 weeks and term newborns but with less than 28 days of life. The exclusion criteria were congenital heart disease, neurological and renal malformations.

2.3. Demographic and exploratory data

Data were extracted from the clinical records of the studied neonates within the neonatal units. Social demographic information on newborns, along with clinical data were assessed: age in days on admission, date of birth, gender, type of delivery, gestational age, weight, Apgar score at 1 and 5 minutes, gestation and perinatal history, onset of neonatal sepsis, risk factors for sepsis, date of admission, history of prolonged rupture of membranes, including the presence of antenatal risk factors for gastrointestinal malformation and congenital anomalies of any kind.

2.4. Study Population and Period

In this study, all neonates with a diagnosis of clinically suspected neonatal sepsis and who were admitted during the period of January 2022 to December 2023 were included in the study. For neonates with several episodes of sepsis during prolonged hospital stays, only the first episode of sepsis was included in the study.

2.5. Laboratory Procedures

For each group blood samples were collected at admission, and 24 and 72 hours after onset, respectively. All blood cultures were collected from a peripheral vein with proper aseptic

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precautions. Hemoculture sample of blood must be 1 ml for preterms under 1 kilogram and 1-2 ml of blood for newborn that weigh 1.1-4 kilograms, according to protocols. The blood sample was inseminated in BacTALERT PF blood culture flask and set on BacTALERT system in less than 2 hours from blood collection. The sample was taken before antibiotherapy was initiated.

2.6. Statistical Analysis

An exploratory analysis was conducted to comprehend the distribution and characteristics of the variables of interest within each population group. Descriptive statistics (frequency distribution for categorical variables; mean and standard deviation for continuous variables) were employed to summarize the data.

As the numerical variables considered in our study were found not to be normally distributed, differences between the initial and final measures within each group (EOS, LOS, Control), were tested using the Wilcoxon rank sum test. This statistical test evaluated the significance of differences between the first and last measurements, gestation and perinatal history, and was further reviewed, including the presence of antenatal risk factors for gastrointestinal malformation and congenital anomalies of any kind providing insights into temporal changes within these populations. Additionally, pairwise comparisons were conducted using the same test between the second measurements of numerical variables across EOS, LOS, and Control groups. These comparisons aimed to discern specific differences between these populations at a particular time point.

The association between categorical variables was investigated using the chi-square test. This test evaluated the presence of statistically significant relationships or dependencies among categorical variables within and between the EOS, LOS, and Control groups. The results were interpreted to understand the potential correlations or associations between these variables.

All statistical analyses were performed using ***R-4.3.2*** with a significance level set at $\alpha = 0.05$.

3. Results

In this section, we will present the data patterns and results of the applied statistical models.

The demographic data, including delivery mode, sex, gestational age, and birth weight, collected from the patient's medical records for retrospective and prospective studies, are shown in Table 1**.**

The sample sizes differed across the three groups: Early Onset Sepsis (EOS) had 35 participants, Late-Onset Sepsis (LOS) had 39 participants and the Control group had 47 participants.

The distribution across delivery modes showed higher cesarean deliveries within the LOS group (49% of all cesarean deliveries) compared to the EOS group (33.3%). Analyzing estimated gestational age (EGA), LOS group had a higher percentage of newborns after 38 weeks of gestation (41.7%) compared to the EOS group (8.3%).

As expected, the onset of sepsis varied significantly between the EOS and LOS groups having means of 18.3 hours (~0.75 days) and 13 days, respectively.

Table 1. Descriptive Statistics.

Variables	EOS	LOS	Control	Overall
Sample Size	35 (28.92%)	39 (32.23%)	47 (38.84%)	121
Delivery Mode				
Vaginal	17 (24.6%)	13 (18.8%)	39 (56.5%)	69
Cesarian section	18 (35.3%)	25 (49.0%)	8 (15.7%)	51
GA				
24-28 weeks	4 (44.4%)	4 (44.4%)	1 (11.1%)	9
29-32 weeks	8 (30.7%)	6 (23.1%)	12 (46.2%)	26

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33-37 weeks	21 (33.8%)	19 (30.7%)	22 (35.5%)	62
>38 weeks	2 (8.3%)	10 (41.7%)	12 (50.0%)	24
Onset of Sepsis[1]	18.3(14.0) hours	13.0(7.1) days		

[1] For this variable we calculated the mean (with standard deviation). Notes: GA-gestational age.

As depicted in Table 2, the two-sample Wilcoxon signed rank test revealed a statistically significant difference between the initial (at admission) and final measures (at 72 hours after onset) of lactate dehydrogenase (LDH) and ferritin within the EOS and LOS groups. However, no significant differences were observed for those two variables within the Control group. Within the Control group, significant differences were noted between the first and last measurements for C-Reactive Protein (CRP) ($p = 0.029$), leukocyte count ($p = 0.002$), and platelets (TR) ($p = 0.00001$).

Table 2. Comparing the first and last measured values for continuous variables using the two-sample Wilcoxon signed rank test. Presented are the p-values.

Variables	EOS	LOS	Control
CRP	0.787	0.798	**0.029**
Procalcitonin	0.081	0.934	0.739
Leukocyte	0.740	0.214	**0.002**
Neutrophils	0.245	0.942	0.144
Platelets	0.342	0.364	**0.00001**
LDH	**0.006**	**0.00001**	0.061
Ferritin	**0.0002**	**0.0038**	0.529

In bold are statistically significant differences. Notes: CRP-C reactive protein, LDH-Lactate dehydrogenase.

Pairwise comparisons proved that from most of the variables, there is a significant difference between the Control and the two sepsis groups. However, it was discovered that leukocyte levels did not show statistical differences when comparing EOS vs Control, LOS vs Control, and EOS vs LOS groups. On the other hand, a statistically significant difference was observed in CRP levels when comparing EOS and LOS groups ($p = 0.00001$).

Table 3. Comparing the second values using the two-sample Wilcoxon signed rank test. Presented are the p-values.

Variable	EOS vs Control	LOS vs Control	EOS vs LOS
CRP	**0.0015**	**0.000005**	**0.00001**
Procalcitonin	**0.00005**	**0.00001**	0.741
Leukocyte	0.4655	0.254	0.926
Neutrophils	**0.00001**	**0.000001**	0.668
Platelets	**0.0076**	**0.0008**	0.956

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LDH	**0.0009**	**0.0006**	0.130
FERRITIN	**0.00001**	**0.000001**	0.063

In bold are statistically significant differences.

Notes: CRP-C reactive protein, LDH-lactate dehydrogenases

In Table 4 we present the results of studying the relationship between the Surgical Intervention and variables related to mechanical ventilation: oxygen therapy, high flow nasal canula, nasal CPAP (nCPAP), nasal IPPV (nIPPV and invasive mechanical ventilation (SIMV). The chi-square test was utilized to statistically test the relation between those categorical variables. Statistically significant associations were found between Surgical Intervention and SIMV variables (p= 0.0344).

Table 4. Relationship among the categorical variables.

Variable		Surgical Intervention		p-value
		No	Yes	
Oxygen therapy	No	6	2	1
	Yes	22	9	
High flow nasal canula	No	21	10	0.397
	Yes	7	1	
nCPAP	No	27	9	0.189
	Yes	1	2	
nIPPV/nCPAP	No	27	11	1
	Yes	1	0	
Number of days of ventilation	No	27	11	1
	Yes	1	0	
SIMV	No	19	3	**0.0344**
	Yes	9	8	

In bold are statistically significant differences.

Notes: n CPAP-nasal continuous positive airways pressure, n IPPV- Noninvasive positive pressure ventilation

SIMV-Synchronized intermittent Mandatory Ventilation

4. Discussion

To our knowledge, this is the first study in Timișoara to investigate the frequency of neonatal bacterial sepsis, associated risk factors, degree of antibiotic resistance, time of onset, association of mechanical ventilation or use of oxygen supplementation and clinical outcomes among infants admitted to a neonatal intensive care unit (NICU).

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The proportion of neonatal EOS versus LOS was nearly equal between the two (35 and 39, respectively), although previous hospital data showed the prevalence of late-onset sepsis was predominant. There may be a disproportionate amount of EOS cases reported because neonates who presented an episode of early-onset sepsis and then later developed findings consistent with LOS during a prolonged hospital stay, were only counted as EOS.

The diagnosis of neonatal sepsis remains a significant challenge in clinical practice due to the non-specific nature of its early clinical manifestations. Our retrospective study focused on evaluating biomarkers and their relevance in diagnosing neonatal sepsis within distinct onset groups: early-onset sepsis (EOS), late-onset sepsis (LOS), and a control group.

Preterms often come from pregnancies with increased risk of maternal-fetal infection, these newborns have low immunity and antibiotic therapy is necessary, but it should not be given in excess. Both the number of antibiotics administered and the duration of treatment should be reduced [23]. Preterm and low birth weight (LBW) neonates are more susceptible to infections due to their less mature immune system and the deficit of protective maternal IgG antibodies that cross the placenta of term neonates [24,25]. In our study, LOS was more common than EOS (the median onset time was 13 days). Infants at the NICU are highly susceptible to LOS [24]. A multicenter survey by Stoll et al. [26] suggested that 21% of VLBW infants had at least one episode of sepsis.

Biomarkers' Utility and Limitations. We investigated established biomarkers like C-reactive protein (CRP), procalcitonin (PCT), leukocyte count, neutrophil count, lactate dehydrogenase (LDH), and ferritin (FERRITIN) in aiding the diagnosis of neonatal sepsis. Our findings align with existing challenges in relying solely on traditional biomarkers for accurate diagnosis. While CRP and PCT showed significant differences between sepsis and control groups, their sensitivity, specificity, and positive predictive values were inconsistent across EOS and LOS groups. Interestingly, leukocyte levels didn't exhibit significant differences when comparing EOS vs Control, LOS vs Control, and EOS vs LOS groups. However, considering their role in innate immunity, their static levels might indicate their limited utility as standalone biomarkers for neonatal sepsis diagnosis. Some studies evaluate the CRP value, along with total number of white blood cells, which has been for years the most used biomarker to identify neonates with sepsis and remains the most used tests in this regard [1]. CRP production is stimulated by proinflammatory cytokines like interleukin (IL)-6, IL-1, and tumor necrosis factor α (TNFα) [26].

Biomarker Dynamics and Clinical Correlation. The temporal dynamics of LDH and ferritin levels demonstrated significant alterations within the EOS and LOS groups, indicating their potential as biomarkers on reflecting disease progression. The distinct patterns observed in biomarkers' changes between sepsis and control groups substantiate the utility of these markers in disease monitoring and prognosis determination. Ferritin and CRP levels can be used together to distinguish groups of neonates with sepsis who have different mortality risks and systemic inflammation responses [27]. Ferritin is a key molecule that serves to limit pro-oxidant stress that typifies inflammatory conditions [28]. Ferritin can also be a member of the protein family that conducts the cellular defense against stress and inflammation, not only as an iron regulatory protein [29].

Comparative Analysis of Biomarkers. Comparisons across EOS, LOS, and Control groups highlighted CRP's significant variation between EOS and LOS, emphasizing its potential as a discriminating factor between the onset types. However, the lack of significant differences in other biomarkers across these groups indicates the need for a more nuanced understanding of biomarker behavior in different sepsis subtypes.

Clinical Correlates and Interventions. Furthermore, we identified statistically significant associations between specific clinical interventions, such as surgical interventions, and mechanical ventilation-related variables, highlighting potential clinical indicators that could guide treatment strategies in neonatal sepsis cases. Intubation for long periods of time and mechanical ventilation is a common occurrence in newborns. Ventilation-associated pneumonia is usually considered a nosocomial infection [22,30,31] and the criteria for diagnosis include: temperature instability, changes in blood gases; tachypnea, need of increased ventilation parameters, and more than 48 hours of mechanical ventilation [32]. The incidence of late onset sepsis ranges from 0.6% to 14% of all neonates

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admitted to the hospital according to the literature [28]. Risk factors for LOS include prematurity, a prolonged exposure to invasive procedures, delayed enteral feeding, the need for surgical intervention and underlying respiratory and cardiac disease [33].

Study Limitations and Future Directions. Our study had certain limitations, including a retrospective design and a relatively small sample size. Future investigations with larger cohorts and a prospective design could enhance the robustness of our findings. Additionally, exploring novel biomarkers such as presepsin or endocan or combining multiple biomarkers' panels could enhance diagnostic accuracy and aid in better delineating sepsis subtypes.

Endothelial cell-specific molecule-1 named Endocan – is a circulating 50-kDa dermatan sulphate proteoglycan expressed by endothelial cells [31]. Serum concentration of endocan is elevated in patients with sepsis and its level is correlated with disease severity [22,34].

Clinical Implications. Despite our limitations, the study provides insights into the complexities of diagnosing neonatal sepsis and the challenges associated with relying solely on conventional biomarkers. The varying performance of different biomarkers across different onset groups emphasizes the need for a multifaceted approach to diagnosis, incorporating clinical assessments, imaging studies, and evolving biomarker panels to improve diagnostic precision and inform targeted therapeutic interventions.

5. Conclusions

In conclusion, while biomarkers offer valuable insights, their utility in diagnosing neonatal sepsis requires a cautious interpretation. Integrating multiple facets of clinical data alongside biomarker assessments could pave the way for more accurate and timely diagnosis, ultimately improving outcomes for neonates at risk of sepsis.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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