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Cord Blood Levels of IL-8, MCP-1 and MIP-1α as Possible Predictors of Late Sepsis Development in Preterm Neonates

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Abstract

Background: The immature immune system of preterm neonates is a key factor in increased vulnerability to infections and sepsis. Although neonatal sepsis requires diagnostic tests, evaluating some chemokines may help predict sepsis and support early diagnosis, improving clinical outcomes.

Methods and Results: In the current study, which involved 80 participants, we analyzed the role of interleukin 8 (IL-8), monocyte chemotactic protein 1 (MCP-1), and macrophage inflammatory protein 1α (MIP-1α) in cord and venous blood plasma with C-reactive protein (CRP) and procalcitonin (PCT) for sepsis prediction and development in premature neonates. Levels of IL-8 (in cord and venous blood plasma), together with MCP-1 and MIP-1α levels in cord blood, were markedly elevated (P<0.001) in sepsis groups (early and late onset sepsis), together with venous blood PCT levels (P<0.001), compared to premature neonates without sepsis. On the other hand, CRP levels showed no significant change in the evaluated groups compared to the control group (without sepsis development).

Conclusion: These findings suggest that levels of IL-8, MCP-1, and MIP-1α in cord blood, rather than venous blood levels, together with venous blood PCT values, may have a predictive role for late sepsis development in premature neonates. Additional studies are required to evaluate the role of complex multiple mediators in predicting neonatal sepsis and to avoid unnecessary antibiotic treatment with improved clinical outcomes. (**International Journal of Biomedicine. 2026;16(3):339-345.**)

Keywords: premature neonates • late sepsis • IL-8 • MCP-1 • MIP-1α

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Introduction

Neonatal sepsis is a clinical syndrome manifested by nonspecific clinical signs and symptoms in response to pathogens[1] and still represents a major cause of morbidity and mortality in neonatal medicine.[2] This highly inflammatory disease may ultimately result in septic shock and multiple organ dysfunction as a result of enhanced activation of the inflammatory response.[3] However, the most detrimental effect is observed in preterm neonates, especially in those infants born <37 weeks of gestational age (GA).[4] Early onset sepsis (EOS) is associated with vertical acquisition of pathogens from mother to neonate and occurs in the first 72h of life, while late onset sepsis (LOS) is usually a horizontally acquired infection (hospital-acquired infection or community-acquired infection), which develops after 72h of life.[5] Even though the precise mechanisms of neonatal response to infection are not fully understood, the vulnerability of preterm neonates to infection mainly involves the status of the immune system.[6] The immune system of preterm neonates is not fully developed, including decreased numbers of certain cell frequencies and their functionality.[7] It is well known that sepsis initiation leads to an inflammatory reaction, which is useful and protective at a moderate level, but it is usually accompanied by an incompatible anti-inflammatory response.[8] Exaggerated production of pro-inflammatory mediators in sepsis may promote tissue damage and organ dysfunction,[9] suggesting that clarifying the level and type of pro-inflammatory mediators secreted during sepsis development may provide a better understanding of the immune status of preterm neonates.

Since the inflammatory process is a key step in sepsis development, many studies have evaluated inflammatory mediators that may predict or enable early sepsis diagnosis in preterm neonates. Nevertheless, it has been shown that evaluated inflammatory mediators vary among preterm neonates, and further studies are necessary to resolve their role.[10] Therefore, in the present study, we evaluated (in cord blood and venous blood plasma) the levels of some chemokines, such as interleukin-8 (IL-8), monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), and their potential predictive role in early diagnosis of sepsis in preterm neonates, along with some standard laboratory analyses.

Material and Methods

Study Population

This study was performed on newborns who were hospitalized at the Pediatric Internal Diseases Clinic, Clinical Center of Nis, Serbia. It involved a total of 101 neonates born at 36 weeks of GA. Due to maternal pregnancy-induced hypertension and premature rupture of membranes (PROMs), 21 premature neonates were excluded from the study. Furthermore, by using exclusion criteria, premature neonates with congenital malformations, laboratory-confirmed TORCH (toxoplasma, rubella virus, cytomegalovirus, herpes simplex virus-II), presence of any systemic disease, and premature neonates born to mothers with signs of infection (cervicovaginitis, chorioamnionitis, urinary tract infection, and fever during delivery) were excluded from the current study.

Sepsis Definition and Study Group Allocation

Sepsis is usually defined as a systemic inflammatory response with life-threatening organ dysfunction in the presence of suspected or proven infection, while neonatal sepsis is a clinical syndrome characterized by signs and symptoms in neonates, caused by invasion of pathogens. [11] Inclusion criteria for neonatal sepsis, in our study, were adopted according to the Criteria published by the International Pediatric Sepsis Consensus Conference.[12]

According to the infant's age, all enrolled participants in the study were classified into two groups (Group 1: <32 weeks and Group 2: 32-36 weeks of GA).[13] Also, both groups were divided into EOS (first sepsis episode occurs < 72 h of life) and LOS (first sepsis episode occurs >72 h of life), according to the time when the first sepsis episode appeared.[14]

Neonatal and Maternal Data

By using maternal and infant medical records, all neonatal and maternal data were retrospectively obtained. These data included neonatal weight and length, GA, sex, delivery mode, Apgar score at 1 minute after birth, low growth for GA, respiratory distress syndrome (RDS), pregnancy-induced hypertension, periventricular and intraventricular hemorrhage, and PROM. Low growth for GA was determined as weight and length less than the 10th percentile for GA.[15]

Blood Samples and Laboratory Data

IL-8, MCP-1, and MIP-1α were detected simultaneously in venous and cord blood samples using the ELISA technique, according to the manufacturer's instructions. To perform this analysis, we used a 96-well flat-bottom plate kit, Express Assay Format Human Cytokine Group (Bio-Rad, Hercules, USA). Following microplate reading, the results were estimated using the BioPlex 2200 system (Bio-Rad, Hercules, USA), according to the analytical methodology given by the manufacturer's instructions.

Statistical Analysis

The normality of the data was assessed by using Shapiro-Wilk and Kolmogorov-Smirnov tests. Non-normally distributed data are expressed as minimum-maximum (median), and comparisons between groups were evaluated using the Kruskal-Wallis and/or Mann-Whitney tests. Categorical variables are expressed as frequencies and compared using the chi-square test. Normally distributed data are expressed as mean ± SD and compared by using ANOVA. All statistical tests were two-sided and performed at a significance level of P=0.05. Statistical analysis was performed using SPSS Statistics in a Windows environment.

Results

Overall, 80 preterm infants were included in the study (out of 101 total preterm infants recruited), according to the inclusion criteria. Only seven infants (8.75%) were born before 32 GA, while 73 infants (91.25%) were born between 32 and 36 GA (Table 1). Other clinical and demographic features of the preterm infants and mothers enrolled in our study are shown in Table 1.

Table 1.

Clinical characteristics of the study population.

Characteristics	n (%), N=101	n (%), N=80
Prematurity-before 32 weeks of gestational age	8 (7.9%)	7 (8.75%)
Prematurity-32-36 weeks of gestational age	93 (92.1%)	73 (91.25%)
Birth by cesarean section	40 (39.6%)	28 (35%)
Low weight for gestational age	12 (11.9%)	7 (8.75%)
Low growth for gestational age	10 (9.9%)	5 (6.3)
Pregnancy-induced hypertension	14 (13.9%)	/
PROMs	9 (8.9%)	/
PDA	23 (22.8%)	22 (27.5)
RDS	32 (31.7%)	31 (38.8%)
Periventricular and intraventricular hemorrhage	8 (7.9%)	7 (8.75%)

PROMs: premature rupture of membranes; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome.

As shown in Table 2, 21 of the 80 preterm infants developed sepsis. Regarding GA, in Group 1 (infants <32 weeks of GA), 2 infants (28.6%) demonstrated EOS, 1 infant with LOS (14.3%), and 4 infants (57.2%) without septic episodes. On the other hand, in Group 2 (infants 32-36 weeks of GA), 8 infants (11%) developed EOS, 10 infants (13.7%)

developed LOS, and 55 infants (75.3%) did not develop sepsis (Table 2). There was no significant difference in sepsis incidence between the two groups (Group 1 and Group 2) and the control group (infants without sepsis development) (P>0.05). However, we should take into account that Group 1 had only 3 preterm infants who developed sepsis, and results obtained from this group should be used with caution due to the small number of participants included in this group. Moreover, clinical variables (birth weight, length, total number of leukocytes, percentage of neutrophils, lymphocytes, monocytes, sex, and Apgar score) and C-reactive protein (CRP) concentration in venous blood plasma showed no statistical significance when sepsis groups (EOS and LOS) were compared to the control group (Table 2). Nevertheless, venous blood plasma procalcitonin (PCT) concentration showed statistical significance (P<0.05) when EOS and LOS were compared, as well as when LOS and the control group were compared (P<0.001). Additionally, significantly higher (P<0.001) PCT concentrations were detected when EOS and the control group were compared (Table 2).

Table 2.

Values of some clinical and laboratory variables and their comparison among subjects by sepsis subgroups

Variable	EOS	LOS	NS	*P-value*
<32 GW	2 (28.6%)	1 (14.3%)	4 (57.2%)	0.256
32-36 GW	8 (11%)	10 (13.7%)	55 (75.3%)	
Normal growth for GA	11 (14.7%)	10 (13.3%)	54 (72%)	1
Low growth for GA	0 (0%)	0 (0%)	5 (100%)	
Female	5 (13.9%)	5 (13.9%)	26 (72.2%)	1
Male	5 (11.4%)	6 (13.6%)	33 (75%)	
Apgar score min-max (median)	4-9 (8)	8-9 (8)	4-9 (8)	0.227
Leukocytes (x10^9/L), min-max (median)	10-37.8 (17.2)	11.1-31.5 (17.97)	10.1-31.2 (19)	0.721
Neutrophils (%), min-max (median)	18-71.1 (61.45)	35.8-68.1 (58.7)	22.4-80.3 (59.7)	0.48
Monocytes (%), mean ± SD	7.49±1.4	7.47±1.44	7.72±1.69	0.846
Lymphocytes (%), mean ± SD	33.75±15.64	37.76±11.24	32.12±12.19	0.753
CRP (mg/L), min–max (median)	0-15.4 (6.42)	0.5-5.3 (2.2)	0-55.8 (1.3)	0.082
PCT (ng/mL), min–max (median)	4.85-26.59 (10.43)	3.13-16.9 (6.66)	0-4.79 (1.18)	EOS vs. LOS: <0.05 Early vs. NS: <0.001 LOS vs. NS <0.001

GW: gestational week, GA: gestational age, NS: no sepsis
CRP: C-reactive protein, PCT: procalcitonin.

To further profile potential chemokines involved in neonatal sepsis, we next measured the levels of IL-8, MCP-1, and MIP-1α in cord blood and venous blood plasma. Since there were only 3 enrolled cases in Group 1 (infants <32 weeks of GA), we focused on analyzing the named chemokines in Group 2 (infants 32-36 weeks of GA), which recruited 18 preterm infants. IL-8 concentrations in cord blood and venous blood plasma were significantly higher (P<0.001) in sepsis groups (EOS and LOS) than in the control group (Figure 1). Additionally, IL-8 concentrations in cord blood differed significantly (P=0.02) between sepsis groups (EOS and LOS), while IL-8 concentrations in venous blood plasma did not differ significantly (P=0.06) between sepsis groups (EOS and LOS). Significantly higher levels of IL-8 (P<0.001) were observed in cord blood compared to the venous blood plasma in each group of preterm infants individually (Figure 1).

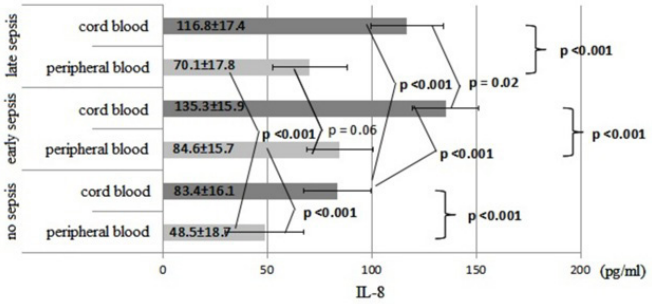

Figure 1. *Levels of IL-8 (pg/mL) in cord blood and peripheral venous blood among sepsis subgroups and the control group. IL-8 levels were evaluated as described in the Materials and Methods section. Data were presented as mean ± SD. Abbreviations: no sepsis – neonates without sepsis development; early sepsis – neonates who developed sepsis in the first 72 h of life; late sepsis – neonates who developed sepsis after 72 h of life.*

As shown in Figure 2, MCP-1 concentration in venous blood plasma did not significantly differ between sepsis groups (EON and LOS) and the control group (P>0.05). Significantly higher (P<0.001) MCP-1 values in cord blood were observed in sepsis groups (EON and LOS) compared to the control group of preterm infants. However, MCP-1 concentrations (in cord blood and venous blood plasma) did not differ significantly (P>0.05) between EON and LOS preterm infants. Significantly higher levels of MCP-1 (P<0.001) were detected in venous blood plasma than in cord blood in each group of preterm infants individually, including the LOS group (P=0.001) (Figure 2).

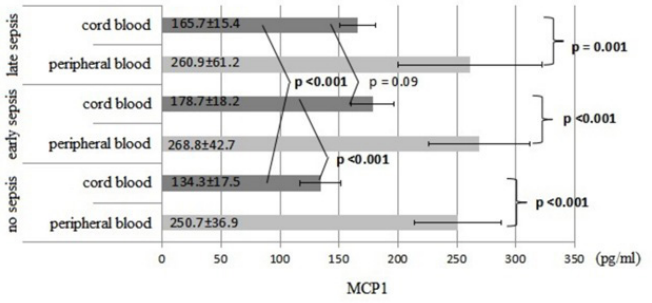

Figure 2. *Levels of MCP-1 (pg/mL) in cord blood and peripheral venous blood among sepsis subgroups and the control group. MCP-1 levels were evaluated as described in the Materials and Methods section. Data were presented as mean ± SD. Abbreviations: no sepsis – neonates without sepsis development; early sepsis – neonates who developed sepsis in the first 72 h of life; late sepsis – neonates who developed sepsis after 72 h of life.*

On the other hand, levels of MIP-1α in venous blood plasma showed no significant difference (P>0.05) between sepsis groups (EON and LOS), while MIP-1α levels in cord blood significantly differed (P=0.048) comparing EOS with the LOS group (Figure 3). Furthermore, concentrations of MIP-1α in cord blood were significantly higher (P<0.001) in sepsis groups (EOS and LOS) compared to the control group. Comparing each group individually, significantly higher values of MIP-1α (P<0.001) in cord blood than in venous blood plasma were found only in the control group of preterm infants (Figure 3).

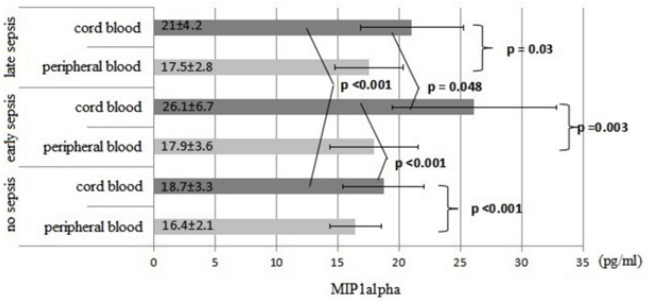

Figure 3. *Levels of MIP-1alpha (pg/mL) in cord blood and peripheral venous blood among sepsis subgroups and the control group.*
MIP-1alpha levels were evaluated as described in the Materials and Methods section. Data were presented as mean ± SD. Abbreviations: no sepsis – neonates without sepsis development; early sepsis – neonates who developed sepsis in the first 72 h of life; late sepsis – neonates who developed sepsis after 72 h of life.

Discussion

Following pathogen entry, immune cells usually produce several pro-inflammatory cytokines, chemokines, and other inflammatory mediators to eliminate the pathogen. All these released mediators induce the development of systemic inflammation in adults and infants.[16] At the same time, many studies have well documented adult sepsis,[17-19] studies involving neonatal sepsis are often limited, with conflicting results about potentially inflammatory mediators involved in sepsis prediction in premature infants.

To improve outcomes among preterm neonates with sepsis development, early detection and appropriate treatment are crucial. In the present study, we evaluated representative chemokines (IL-8, MCP-1, and MIP-1α) that may be involved in predicting sepsis development. Since there are different levels of immune system maturity in preterm neonates due to fetal development,[20] we especially focused on preterm neonates who are younger or older than 32 weeks of GA. Given that different levels of immune system maturity could result from heterogeneity in the immune response during sepsis,[21] we evaluated specific immune mediators (CRP and PCT) to improve prediction of sepsis development in preterm neonates. Current study results showed no significant differences in some clinical variables (birth weight, length, sex, and Apgar score) when comparing sepsis (EOS and LOS) and control (without sepsis development) groups. These results may indicate consistent participant enrollment and precise inclusion of preterm neonates in our study. This is in line with previous reports,[22,23] which allows more accurate estimation of predictive factors for sepsis development in preterm neonates.[24] Nevertheless, since the EOS group contains 7 participants (only 3 participants with sepsis development), results obtained from this group should be used with caution.

CRP, an acute phase protein, is the most frequently used for diagnosis of neonatal sepsis. The synthesis of this pentameric protein is stimulated mainly by IL-6 and TNF-α.[20] CRP levels obtained in our study did not differ significantly between sepsis groups (EOS and LOS) compared to the control group of premature neonates, suggesting that CRP may not be useful for early diagnosis or prediction of neonatal sepsis development. Taking into account that the half-life of CRP is 24-48 h and it needs 12 h to reach an elevated level,[25] this may partially clarify the findings in our study. Recent studies showed that CRP sensitivity for diagnosis of EOS is around 50% with high positive results.[26,27] In line with this, a previous report indicated that measuring CRP levels for LOS detection is not accurate enough for selecting neonates for further investigation or treatment.[28] A recent study[29] showed that the sensitivity of CRP to detect LOS is 62%, indicating that CRP is not a useful tool in the early diagnosis of neonatal sepsis.[21]

PCT is another acute-phase reactant protein that cannot be detected in normal human plasma. Increased levels of PCT are secreted in response to circulating bacterial toxins.[20] Our study results showed significantly increased PCT venous blood levels in the sepsis group (EOS and LOS) compared to the control group. Furthermore, markedly elevated venous blood PCT levels were detected in the EOG group compared to the LOS group, indicating that PCT plasma levels may serve as a potential biomarker for sepsis prediction. Similar observations were reported earlier, showing that increased PCT levels occur in fetal inflammatory response.[30] Since elevated PCT levels occur 2-4 h after bacterial infection and remain increased for the next 24 h,[31] it may be used as a useful biomarker for early diagnosis of neonatal sepsis, which corresponds with our study results. These findings are in line with an earlier meta-analysis which demonstrated PCT as a potential biomarker for early sepsis detection.[32] However, it should be noted that newborns, physiologically, have increased levels of PCT on the first day after birth and return to normal values 48 h after birth, indicating that levels of PCT fluctuate within three days after birth and the diagnostic value of PCT, especially for EOS detection, is still controversial.[16] The neonatal immune system is not fully developed[33] and is associated with delayed maturation of different parts of the immune system, which may lead to altered cytokine and chemokine production.[25] IL-8 is a pro-inflammatory chemokine that is produced during inflammation by immune and non-immune cells. This chemokine has a great ability to attract and stimulate neutrophils to sites of inflammation and to promote macrophage and monocyte growth and differentiation.[34] Our study results found that IL-8 concentrations in cord blood and venous blood plasma were markedly elevated in sepsis groups (EOS and LOS) compared to the control group of preterm infants, as well as in cord blood plasma in the EOS group when compared with the LOS group. Furthermore, IL-8 levels in

cord blood plasma were notably increased compared to venous blood plasma in each group of preterm infants individually. These observations may indicate that IL-8 levels in cord blood plasma, rather than in venous blood plasma, could better predict sepsis development in preterm infants. In line with our results are previous reports demonstrating that increased IL-8 production in neonates leads to enhanced activation of neutrophils and T cell activation during infection,[35] as well as a study indicating increased IL-8 levels in infants with proven LOS.[36] Similar results were confirmed in previous studies,[37, 38] while some reports documented decreased IL-8 levels in preterm neonates.[24,39] Although the reason for these conflicting results remains unclear, it is well known that some factors can modulate cytokine and chemokine production, including sepsis definition (clinical or proven), GA, or different microorganisms (which may induce various cytokine and chemokine secretion).[24] Elevated IL-8 levels were also observed in cord blood of preterm neonates, without sepsis development. Similar modified cytokine and chemokine levels were shown in other reports, but the functional significance of these findings still needs to be clarified.[40] In addition, our results showed that cord blood levels of MCP-1 and MIP-1α notably differ in sepsis groups (EOS and LOS) compared to the control group, as well as when EOS was compared with the LOS group of preterm neonates. Moreover, significantly different levels of MCP-1 and MIP-1α were observed in each group of preterm infants individually. In contrast, venous blood levels of MCP-1 and MIP-1α showed no significant difference in sepsis groups (EON and LOS) compared to the control group or in each group of preterm neonates individually. Such observations suggest that cord blood levels of MCP-1 and MIP-1α may be credible predictors for sepsis development in preterm neonates. Growing evidence indicates that levels of pro-inflammatory cytokines and chemokines increase rapidly following exposure to bacterial antigens, much earlier than elevated CRP levels.[41] Previous reports demonstrated that increased levels of neutrophil and monocyte/macrophage chemoattractants in preterm neonates could be linked with intrauterine inflammation,[42-44] which correlates with results obtained in our study. In line with previous studies, neutrophils and macrophages secrete various cytokines and chemokines to eliminate pathogens following pathogen entry, which finally may result in the development of systemic inflammation in adults and newborns.[41] Although chemokine secretion is required for host defense against bacterial infection, overproduction of these soluble inflammatory mediators has been documented to play an essential role in sepsis development,[42,43] which corresponds with our study results. Furthermore, a depleted number of monocytes in preterm neonates, with an essential role in phagocytosis and secretion of pro-inflammatory cytokines and chemokines, could have a harmful effect during infection and sepsis development[45] and needs to be considered for sepsis prediction in preterm neonates.[43]

From a clinical perspective, evaluating IL-8, MCP-1, and MIP-1α in cord blood may benefit sepsis prediction in preterm neonates, especially for late-onset sepsis, together with certain biochemical parameters. However, these observations do not exclude the role of other chemokines in sepsis development. Therefore, larger prospective studies together with multicenter studies are required to validate the clinical utility and reproducibility before any of these parameters can be routinely used into sepsis prediction algorithms.

In summary, results obtained in our study showed an evident imbalance in chemokine production, with highly elevated production of pro-inflammatory chemokines (IL-8, MCP-1, and MIP-1α), which may contribute to sepsis development in preterm neonates. We have also shown that determination of IL-8 levels (from cord blood and venous blood plasma), as well as MCP-1 and MIP-1α levels in cord blood, has predictive potential for sepsis development in preterm neonates. Assessment of PCT levels in venous blood plasma may serve as a helpful factor, together with cord blood levels of IL-8, MCP-1 and MIP-1α, for earlier detection of potential sepsis development in preterm neonates. Nevertheless, additional studies involving a larger number of cohorts and preterm neonates are required for the identification of specific markers to gain more insight into the prediction of sepsis in preterm neonates and to avoid needless antibiotic therapy and severe infectious disease.

Author Contributions

Jelena Vucic: writing – original draft, conceptualization, methodology, Supervision.
Karin Vasic: writing – review and editing, investigation, methodology, formal analysis.
Sandra Stankovic: writing – review and editing, methodology, investigation.
Voja Pavlovic: writing – review and editing, conceptualization, investigation.

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Ethical Statement

The study was approved by the Ethics Committee, Medical Faculty in Nis (35144/2017), and written informed consent was obtained from the parents for all recruited premature neonates prior to study participation.

Conflict of interest

The authors declare that they have no conflicts of interest.

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