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Case Study

Procalcitonin and Interleukin-18 in Umbilical Cord Blood as Early Diagnostic Biomarkers for Early-Onset Neonatal Sepsis: A Case-Control Study

^{1,2}Devi Gusmaiyo, ³Efrida Efrida, ⁴Hardisman Hardisman and ⁵Mayetti Mayetti

¹Doctoral Program of Biomedical Science, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

²Department of Pediatrics, Faculty of Medicine, Universitas Abdurrahman, Pekanbaru, Indonesia

³Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Universitas Andalas/M. Djamil General Hospital, Padang, Indonesia

⁴Department of Public Health and Community Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

⁵Department of Pediatrics, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

Abstract

Background and Objective: Early-onset neonatal sepsis (EONS) is a major cause of neonatal morbidity and mortality globally, yet its early diagnosis remains challenging due to the limited availability of rapid, reliable biomarkers at the time of birth. This study aimed to analyze procalcitonin (PCT) and Interleukin-18 (IL-18) levels measured from umbilical cord blood as early diagnostic biomarkers for EONS. **Materials and Methods:** An observational case-control study was conducted on 66 neonates born with at least one EONS risk factor at four hospitals in Riau Province, Indonesia. Subjects were classified into an EONS group (n = 33) and a non-EONS group (n = 33). Umbilical cord blood PCT and IL-18 were measured using an enzyme-linked immunosorbent assay. Normality was assessed using the Shapiro-Wilk test. Between-group differences were analyzed using the Mann-Whitney U test ($\alpha = 0.05$). **Results:** The PCT levels in umbilical cord blood were significantly higher in the EONS group compared to the non-EONS group [median 322.77 (range: 66.70-2599.57) pg/mL vs. 45.9 (4.90-321.97) pg/mL; $p < 0.001$]. The IL-18 levels were similarly elevated [median 564.00 (216.40-1979.00) pg/mL vs. 107.60 (-19.60-773.38) pg/mL; $p < 0.001$]. Maternal fever history was significantly more frequent in the EONS group (36.4% vs. 6.1%; $p = 0.005$), as was colored amniotic fluid (93.9% vs. 45.5%; $p < 0.001$). **Conclusion:** Umbilical cord blood PCT and IL-18 levels are significantly elevated in neonates with EONS and may serve as early diagnostic biomarkers for EONS when measured at the time of birth. Their combined use may improve early risk stratification and clinical decision-making in at-risk neonates.

Key words: Procalcitonin, interleukin-18, early-onset neonatal sepsis, umbilical cord blood, biomarker, early diagnosis

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Corresponding Author: Efrida Efrida, Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Universitas Andalas/M. Djamil General Hospital, Padang, Indonesia

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Early-onset neonatal sepsis (EONS), defined as sepsis occurring within the first 72 hrs of life is one of the most critical contributors to neonatal morbidity and mortality worldwide. The World Health Organization estimates that approximately 2.9 mL neonatal deaths occur annually due to sepsis, representing up to 25% of all neonatal mortality^{1,2}. In developing countries, neonatal sepsis accounts for roughly 15% of neonatal deaths, underscoring the urgent global need for improved early detection strategies².

The current gold standard for diagnosing neonatal sepsis is blood culture; however, this method requires 48-72 hrs for results, has variable sensitivity (38-73%) and may yield false-negative results in antibiotic-exposed neonates³. This diagnostic delay often leads to either empirical over-treatment with broad-spectrum antibiotics or missed early intervention, both carrying significant clinical consequences. Consequently, there is an unmet need for rapid, reliable biomarkers obtainable at the time of birth.

Procalcitonin (PCT), the 116-amino acid precursor of calcitonin, is well established as a sepsis biomarker in neonatal medicine. The PCT rises sharply in response to bacterial endotoxin stimulation and is typically measured from venous or arterial neonatal blood after clinical symptom onset^{4,5}. Importantly, PCT levels in umbilical cord blood collected immediately after delivery offer a unique diagnostic window, enabling biomarker assessment prior to symptom manifestation. Frerot *et al.*⁶ demonstrated that cord blood PCT concentrations exceeding 500 pg/mL (0.5 µg/L) were independently associated with higher EONS risk in extremely preterm infants (OR 2.18; 95% CI 1.58-3.02; $p < 0.0001$). Recent prospective studies have further confirmed PCT as a high-accuracy early sepsis marker⁷.

Interleukin-18 (IL-18), a pro-inflammatory cytokine of the IL-1 superfamily, plays a central role in the innate immune response by inducing IFN-γ production, activating Th1 pathways and amplifying systemic inflammatory cascades⁸. Li *et al.*⁹ first demonstrated that serum IL-18 levels were significantly elevated in neonates with sepsis and correlated positively with disease severity. Wynn *et al.*¹⁰ further elucidated the mechanistic role of IL-18 in neonatal sepsis. Despite this compelling evidence, the diagnostic utility of IL-18 measured specifically from umbilical cord blood for EONS prediction has not been investigated.

No prior study has simultaneously evaluated PCT and IL-18 from umbilical cord blood in the context of EONS diagnosis. This study aimed to analyze umbilical cord blood PCT and IL-18 levels in neonates with and without EONS and evaluate their potential as early diagnostic biomarkers.

MATERIALS AND METHODS

Study design: This was an observational case-control study.

Study setting and population: The study was conducted from October 2023 to November 2025 in the perinatology units of four referral hospitals in Riau Province, Indonesia: RSUD T. Rafian, RSUD Selasih, RS Amelia Medika and RS Annisa. The study population comprised all neonates born at these facilities with at least one EONS risk factor as defined by the Indonesian Pediatric Society (IDAI) Clinical Practice Guidelines on Neonatology.

Sample selection: Subjects were selected by consecutive non-probability sampling.

The minimum sample size was estimated for comparison between two independent groups using:

$$n_1 = n_2 = \frac{2(Z_{\alpha} + Z_{\beta})^2 s^2}{(x_1 - x_2)^2}$$

with $\alpha = 0.05$, $Z_{\alpha} = 1.96$, power = 80%, $Z_{\beta} = 0.842$, pooled standard deviation = 0.0419 and expected difference = 0.053¹¹.

The calculation yielded a minimum of 10 subjects per group. To ensure adequate statistical analysis, the target was increased to 30 subjects per group and corrected for an anticipated 10% dropout rate using $n' = n/(1-f)$, resulting in 33 subjects per group and 66 subjects in total. Neonates with at least one risk factor of EONS were enrolled and classified into two groups: The EONS group (culture-proven or clinically diagnosed EONS, $n = 33$) and the non-EONS control group (blood culture-negative, $n = 33$). Inclusion criteria were: Neonatal gestational age ≥ 28 weeks, presence of ≥ 1 EONS risk factor and availability of an umbilical cord blood specimen. Exclusion criteria included: Major congenital anomalies, chromosomal abnormalities and maternal autoimmune disorders. EONS was defined based on the combination of clinical signs, laboratory results and blood culture findings according to established diagnostic criteria¹².

Biomarker measurement: Umbilical cord blood samples were collected immediately after delivery. The PCT and IL-18 concentrations were measured using commercially validated enzyme-linked immunosorbent assay ELISA kits (Elabscience, China). The PCT concentrations were determined using the Human PCT ELISA Kit, catalog number E-EL-H1492, with sensitivity 18.75 pg/mL and assay range 31.25-2000 pg/mL. IL-18 concentrations were determined using the Human IL-18

ELISA Kit, catalog number E-EL-H0253, with sensitivity 9.38 pg/mL and assay range 15.63-1000 pg/mL. Both assays were performed according to the manufacturer's instructions¹³⁻¹⁵. All analyses were performed at the Clinical Pathology and Laboratory Medicine Laboratory, Universitas Andalas. Results are expressed in picograms per milliliter (pg/mL).

Statistical analysis: Data normality was assessed using the Shapiro-Wilk test (appropriate for $n < 50$). Because both PCT and IL-18 data were not normally distributed, between-group differences were analyzed using the Mann-Whitney U test. Categorical variables were compared using the Chi-squared test or Fisher's exact test (when expected cell counts were < 5). Results are presented as median (minimum-maximum) and mean $\pm$ SD. A p-value of < 0.05 was considered statistically significant¹⁶. Statistical analyses were performed using SPSS version 25.

Ethics: This study received ethical approval from the Ethics Committee of the Faculty of Medicine, Universitas Andalas, Padang, with registration number 622/UN.16.2/KEP-FK/2023. Written informed consent was obtained from the parents or guardians of all study participants.

RESULTS

Baseline characteristics and EONS risk factors: A total of 66 neonates were enrolled: 33 in the EONS group and 33 in the non-EONS control group. Table 1 presents the baseline demographic and clinical characteristics, as well as the distribution of EONS risk factors between the two groups. The median gestational age was similar between groups ($p = 0.138$), although prematurity (< 37 weeks) was significantly more frequent in the non-EONS group (27.3% vs. 6.1%; $p = 0.044$). Median birth weight was significantly higher in the EONS group (3310 g vs. 2940 g; $p = 0.002$) and low birth weight was more prevalent among non-EONS subjects (33.3% vs. 9.1%; $p = 0.033$). Among maternal risk factors, history of maternal fever was significantly more frequent in the EONS group (36.4% vs. 6.1%; $p = 0.005$), as was the presence of colored amniotic fluid (93.9% vs. 45.5%; $p < 0.001$). PROM prevalence, intrapartum antibiotic use, maternal leukocytosis, sex and mode of delivery did not differ significantly between groups.

Procalcitonin levels in umbilical cord blood: Umbilical cord blood PCT levels were significantly higher in the EONS group compared to the non-EONS group (Table 2). The median PCT concentration in the EONS group was 322.77 pg/mL

(range: 66.70-2599.57 pg/mL), compared to 45.9 pg/mL (range: 4.90-321.97 pg/mL) in the non-EONS group. The Mann-Whitney U test revealed a highly significant between-group difference ($p < 0.001$), indicating that PCT was substantially elevated in neonates with proven EONS at the time of birth.

Interleukin-18 levels in umbilical cord blood: IL-18 levels in umbilical cord blood were also significantly elevated in the EONS group (Table 3). The median IL-18 concentration in the EONS group was 564.00 pg/mL (range: 216.40-1979.00 pg/mL), compared to 107.60 pg/mL (range: -19.60-773.38 pg/mL) in the non-EONS group ($n = 33$). The Mann-Whitney U test confirmed a highly significant difference between the groups ($p < 0.001$).

DISCUSSION

This study found a highly significant elevation of PCT in umbilical cord blood among EONS neonates compared to non-EONS controls (median 322.77 vs. 45.9 pg/mL; $p < 0.001$). This finding is consistent with Frerot *et al.*⁶, who reported that cord blood PCT above 500 pg/mL (0.5 μ g/L) was independently associated with a significantly higher EONS risk in extremely preterm infants (OR 2.18; 95% CI 1.58-3.02). The median PCT value in our EONS group (322.77 pg/mL) falls below the 500 pg/mL threshold, which may reflect differences in gestational age distribution or the mixed-term and preterm composition of our cohort. Despite this, the approximately 6-fold higher median PCT in the EONS group is clinically meaningful.

These findings are further supported by Hincu *et al.*⁷, who prospectively evaluated PCT and presepsin at early neonatal timepoints and demonstrated that PCT exhibited high diagnostic accuracy with favorable sensitivity-specificity balance for predicting EONS. In contrast to prior studies, which measured PCT from venous or arterial neonatal blood after birth, the current study uniquely quantified PCT from umbilical cord blood at the moment of delivery, allowing zero-time biomarker assessment before clinical signs emerge. Hue-Bigé *et al.*¹⁷ demonstrated that early PCT-guided algorithms significantly reduced unnecessary antibiotic exposure in premature neonates without increasing mortality, highlighting the clinical utility of PCT-based decision support at birth.

The IL-18 levels in umbilical cord blood were substantially elevated in EONS neonates compared to controls (median 564.00 vs. 107.60 pg/mL; $p < 0.001$), with a nearly 4.5-fold increase in median IL-18 in the EONS group. This finding aligns

Table 1: Baseline characteristics and EONS risk factors of study subjects

Characteristic	EONS group (n = 33)	Non-EONS group (n = 33)	p-value
Gestational age (weeks), median (range)	39.5 (36-42)	38.5 (32-42)	0.138
Preterm (<37 weeks), n (%)	2 (6.1%)	9 (27.3%)	0.044*
Birth weight (g), median (range)	3310 (2425-4800)	2940 (1240-4000)	0.002*
LBW (<2500 g), n (%)	3 (9.1%)	11 (33.3%)	0.033*
Male sex, n (%)	16 (48.5%)	16 (48.5%)	1.000
Caesarean delivery, n (%)	25 (75.8%)	29 (87.9%)	0.339
Maternal risk factors			
Maternal fever (by history), n (%)	12 (36.4%)	2 (6.1%)	0.005*
PROM (any duration), n (%)	21 (63.6%)	19 (57.6%)	0.801
Colored amniotic fluid †, n (%)	31 (93.9%)	15 (45.5%)	<0.001*
Maternal leukocytosis ($\geq 15,000/\mu\text{L}$), n (%)	15 (45.5%)	12 (36.4%)	0.617
Intrapartum antibiotics, n (%)	23 (69.7%)	29 (87.9%)	0.116

EONS: Early-onset neonatal sepsis, PROM: Premature rupture of membranes, LBW: Low birth weight. Values represent median (range) or n (%). p-values derived from Mann-Whitney U test (continuous variables) or chi-squared/Fisher's exact test (categorical variables). *Statistically significant ($p < 0.05$). † Colored amniotic fluid includes meconium-stained, turbid, or foul-smelling fluid; data extracted from amniotic fluid characteristic records

Table 2: Comparison of umbilical cord blood procalcitonin (PCT) levels between groups

Variable	Non-EONS group (n = 33)	EONS group (n = 33)	p-value*
PCT in cord blood (pg/mL)			
Median (Min-Max)	45.9 (4.90-321.97)	322.77 (66.70-2599.57)	<0.001
Mean $\pm$ SD	63.63 $\pm$ 64.59	666.72 $\pm$ 839.70	

EONS: Early-onset neonatal sepsis, SD: Standard deviation, PCT: Procalcitonin. *Mann-Whitney U test. Primary statistic is median (min-max) and mean $\pm$ SD provided for reference

Table 3: Comparison of umbilical cord blood interleukin-18 (IL-18) levels between groups

Variable	Non-EONS group (n = 33)	EONS group (n = 33)	p-value*
IL-18 in cord blood (pg/mL)			
Median (Min-Max)	107.60 (-19.60-773.38)	564.00 (216.40-1979)	<0.001
Mean $\pm$ SD	136.91 $\pm$ 178.50	667.66 $\pm$ 349.98	

EONS: Early-onset neonatal sepsis, SD: Standard deviation, IL-18: Interleukin-18. *Mann-Whitney U test. Primary statistic is median (min-max) and mean $\pm$ SD provided for reference

with Li *et al.*⁹, who reported significantly elevated serum IL-18 in neonates with sepsis and demonstrated a positive correlation between IL-18 concentration and clinical disease severity. The concordance between our cord blood measurements and their serum-based findings suggests that the systemic IL-18 inflammatory response is already detectable and markedly elevated at the time of birth in EONS neonates.

Ahmed *et al.*¹⁸ evaluated serum IL-18 and IL-22 as diagnostic and prognostic biomarkers for neonatal sepsis in a case-control study and concluded that both interleukins are promising candidates for sepsis identification and mortality prediction. Our findings corroborate this conclusion, extending the evidence to umbilical cord blood specimens in a specifically EONS-defined population. Wynn *et al.*¹⁰ provided a mechanistic framework: IL-18 drives a neonatal-specific inflammatory amplification loop via IL-18-IL-1-IL-17A signaling that promotes severe tissue injury. The significantly elevated cord blood IL-18 in our EONS group is consistent with early activation of this destructive cascade at the peripartum period. A network meta-analysis by Xing *et al.*¹⁹ found that IL-8 was the most accurate interleukin for EONS detection; IL-18 may complement existing panels given its distinct pro-inflammatory pathway activation.

A noteworthy finding in the present study was that maternal fever history was significantly more frequent in the EONS group (36.4% vs. 6.1%; $p = 0.005$), as was colored/meconium-stained amniotic fluid (93.9% vs. 45.5%; $p < 0.001$). These findings align with established EONS risk factors, as maternal intrapartum fever and meconium-stained amniotic fluid are both recognized indicators of intra-amniotic infection and fetal inflammatory response^{20,21}. Interestingly, prematurity and low birth weight were paradoxically more prevalent in the non-EONS group, possibly reflecting selection bias related to gestational age-dependent immune competence or antibiotic prophylaxis patterns in premature neonates at these centers.

The simultaneous elevation of both PCT and IL-18 in cord blood reflects two distinct but interconnected arms of the neonatal innate immune response to systemic infection. The PCT rises acutely in response to bacterial endotoxins via non-thyroidal calcitonin gene expression⁵, while IL-18 orchestrates downstream pro-inflammatory cascades including IFN- γ , IL-17A and CXCL8 expression^{8,22}. By capturing both the initial bacteriological signal (PCT) and the downstream inflammatory amplification (IL-18), combined measurement of these two biomarkers in umbilical cord blood

may provide superior diagnostic sensitivity compared to either marker alone^{23,24}. Formal diagnostic accuracy analyses incorporating receiver operating characteristic (ROC) curves and combined biomarker panels are needed to establish evidence-based cut-off values for clinical implementation.

This study has several limitations. First, the modest sample size (n = 66) limits statistical power for subgroup analyses. Second, blood culture used as the reference standard may have limited sensitivity in antibiotic-exposed neonates, potentially introducing group misclassification. Third, the absence of ROC analysis and diagnostic cut-off values precludes direct clinical implementation of reported biomarker thresholds. Fourth, longitudinal biomarker trajectories were not assessed. Finally, the "colored amniotic fluid" variable was derived from amniotic fluid characteristic records rather than formal chorioamnionitis diagnosis, limiting the specificity of this risk factor classification.

CONCLUSION

This study demonstrated that umbilical cord blood PCT and IL-18 levels are significantly elevated in EONS neonates compared to non-EONS controls ($p < 0.001$ for both biomarkers). Additionally, maternal fever history and colored amniotic fluid were identified as EONS risk factors significantly associated with the EONS group. These findings support the potential utility of PCT and IL-18 measured from umbilical cord blood as early diagnostic biomarkers for EONS, enabling risk stratification before clinical symptoms emerge. Larger prospective studies incorporating ROC analysis, established cut-off values and multi-biomarker panels are recommended to advance clinical translation of these findings.

SIGNIFICANCE STATEMENT

Early infections in newborns can be life-threatening if they are not detected and treated quickly. However, reliable early tests are limited, making these infections still difficult to diagnose soon after birth. This study investigated whether two substances found in umbilical cord blood, called procalcitonin and interleukin-18, may help identify newborns at risk of early-onset neonatal sepsis. This study included 66 newborns with risk factors for infection from four hospitals in Riau Province, Indonesia. The results showed that procalcitonin and interleukin-18 levels were significantly higher in newborns with infection than in those without. These findings suggest that testing umbilical cord blood at birth may help enable

earlier recognition and treatment decisions for newborn infections. Early diagnosis would improve newborn outcomes and help reduce complications and deaths caused by severe newborn infections.

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