The Open Biomarkers Journal
DOI: 10.2174/0118753183474457260721071706, 2026, 16, e18753183474457
ISSN: 1875-3183
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RESEARCH ARTICLE **OPEN ACCESS**

Zinc and IL-6: Biomarkers of Neonatal Sepsis Risk and Immune Response in Newborns

Niarsari Anugrahing Putri[1,*], Adelia Anggraini Utama[1], Iskandar[2], Pudji Andayani[1], Alfi Yasmina[1], Selli Muljanto[1], Edi Hartoyo[1], Ari Yunanto[1], Eko Suhartono[3] and Julia Kasab[1]

[1]*Department of Child Health, Faculty of Medicine and Health Science, Universitas Lambung Mangkurat, Banjarmasin, Indonesia*
[2]*Department of Public Health, Undergraduate Program, Faculty of Medicine and Health Science, Universitas Lambung Mangkurat, Banjarbaru, Indonesia*
[3]*Department of Public Health, Master's Program, Faculty of Medicine and Health Science, Universitas Lambung Mangkurat, Banjarbaru, Indonesia*

Abstract:

Introduction: Neonatal sepsis is one of the major causes of morbidity and mortality in newborns, particularly in developing countries. Zinc levels are involved in the outcome of sepsis, as they influence the function of the immune system and cytokine activity such as Interleukin-6 (IL-6). Data regarding the association between zinc and neonatal sepsis remain limited.

Methods: This observational, analytical, cross-sectional study investigated the correlation between zinc and IL-6 in neonates with neonatal sepsis. Participants were divided into a control group and a sepsis-risk group. Serum samples were analyzed for zinc by titration and for IL-6 by enzyme immunoassay.

Results: A total of 69 neonates were recruited and were divided into a control group of 34 neonates and a group at risk of sepsis of 35 neonates. Zinc levels in the sepsis-risk group were significantly lower than in the control group (57.34 ± 8.89 µg/dL vs. 80.47 ± 13.80 µg/dL, p<0.001). There was no significant difference in IL-6 levels between the two groups. A significant negative correlation was observed between serum zinc levels and the risk of sepsis (correlation coefficient = -0.548, $P < 0.05$).

Discussion: This study demonstrates that lower serum zinc levels are associated with a higher prevalence of sepsis risk in neonates, suggesting that susceptibility to sepsis in the early neonatal period may be associated with zinc status. The absence of a significant difference in IL-6 levels between groups may have been influenced by the timing of sample collection, as subjects were identified based on sepsis risk factors rather than confirmed infection.

Conclusion: Neonates at risk for sepsis had lower serum levels of zinc but not the level of IL-6 when compared with healthy neonates. These study findings support a relationship between the neonate's zinc status and its early immune status. Further research is required to establish its effectiveness in a clinical setting.

Keywords: Neonatal Sepsis, Zinc, Interleukin-6, Inflammation, Immune response, Biomarker, Cytokines.

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*Address correspondence to this author at the Department of Child Health, Faculty of Medicine and Health Science, Universitas Lambung Mangkurat, Banjarmasin, Indonesia; E-mail: niarsariap@ulm.ac.id

Cite as: Putri N, Utama A, , Andayani P, Yasmina A, Muljanto S, Hartoyo E, Yunanto A, Suhartono E, Kasab J. Zinc and IL-6: Biomarkers of Neonatal Sepsis Risk and Immune Response in Newborns. Open Biomark J, 2026; 16: e18753183474457. http://dx.doi.org/10.2174/0118753183474457260721071706

Received: February 27, 2026
Revised: June 06, 2026
Accepted: June 15, 2026
Published: July 23, 2026

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1. INTRODUCTION

Neonatal sepsis remains a serious health issue, causing morbidity and mortality, particularly in developing countries. The global trend shows a gradual reduction over the past three decades, but the situation remains serious in Africa and Southeast Asia [1]. Data from an observational study in Indonesia show incidence rates ranging from 9 to 30% with a mortality rate of 12 to 50% [2]. According to our regional hospital, Ulin Hospital, 123 cases of neonatal sepsis were recorded in 2013 [3].

Neonatal sepsis is the third most important cause of neonatal death worldwide [4]. The mortality caused by neonatal sepsis in 2019 has been estimated to be 226,520 deaths with an Age-Standardized Death Rate (ASDR) of 2.5 per 100,000 population [5]. Neonatal mortality is an indicator of population growth and public health conditions. Reducing neonatal mortality has been set as one of the targets of Sustainable Development Goals (SDGs) with a target of 12/1,000 live births by 2030 [6].

There are many micronutrient deficiencies, including iron, copper, vitamin A, zinc, and other minerals may increase susceptibility to sepsis [7]. Previous research has shown that zinc levels are associated with the prognosis of neonatal sepsis; lower zinc levels are associated with poor clinical outcomes. [8]. Zinc is an essential micronutrient with a key role in numerous body functions, including the immune system [9]. Zinc plays important anti-inflammatory and immunomodulatory roles in the body, largely by inhibiting the Nuclear Factor Kappa B (NF-κB) signaling pathway. This pathway regulates key cellular processes, including apoptosis, cell proliferation, and immune function. Moreover, zinc can suppress interleukin-6 (IL-6) mediated activation of signal transducer and activator of transcription 3 (STAT3) and contribute to immune homeostasis [10]. Zinc deficiency can impair thymic function and T cell maturation by reducing thymulin and antiapoptotic protein (B-cell lymphoma 2 (BCL-2) and B-cell lymphoma X (BCL-X)) activity and increasing apoptosis in developing T cells [11]. This cytokine imbalance suppresses T-helper 1 (Th1) responses (IL-2, Interferon Gamma (IFN-γ)) while retaining T-helper 2 (Th2) cytokines, IL-4, IL-6, and IL-10, which may reduce the neonate's capacity to mount an effective immune response [12, 13].

Pleiotropic cytokines such as IL-6 play an important role in the acute phase response, inflammation, and immune cell differentiation [14]. In response to infection, IL-6 is produced by a variety of maternal and fetal tissues including mononuclear cells, trophoblasts, and fetal membranes [15]. This cytokine has been identified in several studies as a sensitive and specific early indicator of neonatal sepsis, often elevated before C-Reactive Protein (CRP) levels [16, 17]. Furthermore, IL-6 regulates systemic zinc levels by enhancing hepatocyte Zrt- and Irt-like Protein 14 (ZIP14) expression, thereby reducing serum zinc levels during inflammation [14, 18]. This adaptive response limits the availability of zinc to pathogens, thereby limiting zinc availability to pathogens during infection. In neonates with immature immune systems, long-lasting elevations in IL-6 intensify systemic inflammation and tissue injury, and may even cause organ dysfunction [19, 20]. Several studies have shown a relationship between elevated IL-6 levels and disease severity and mortality risk in neonatal sepsis and Systemic Inflammatory Response Syndrome (SIRS) [21, 22].

Despite growing global evidence, no study has evaluated the comparative zinc and IL-6 levels in healthy and sepsis-risk neonates in Banjarmasin. Investigating the relationship between these markers in the early phase of infection may provide insights into potential preventive or diagnostic strategies. Therefore, this study aims to compare serum zinc and IL-6 levels in neonates at risk for sepsis and healthy controls, and to assess the correlation between zinc and IL-6 levels in the sepsis-risk group.

2. METHODS

2.1. Research Design

This was an observational analytic cross-sectional study conducted among 69 neonates born between October 2020 and July 2021 at Ulin General Hospital, Banjarmasin, South Kalimantan, Indonesia. Inclusion criteria were live-born neonates within the study period. Exclusion criteria were neonates with a birth weight of less than 2000 grams, a gestational age of less than 32 weeks, major congenital anomalies, or incomplete clinical or laboratory data. Neonates were divided into two groups: a control group (n = 34) and a sepsis-risk group (n = 35). The control group consisted of neonates without clinical or maternal risk factors for sepsis, including absence of prolonged rupture of membranes, maternal fever, chorioamnionitis, or prematurity. These neonates had normal birth weight (>2000 g), gestational age ≥32 weeks, and no congenital anomalies. The sepsis-risk group consisted of neonates identified to have risk factors for sepsis based on the American College of Obstetricians and Gynecologists (ACOG) guidelines, particularly Premature Rupture of Membranes (PROM) for more than 18 hours [23]. The study was conducted prospectively, with blood samples obtained from the umbilical cord immediately after birth.

Sample size determination was conducted using the standard formula for cross-sectional studies: $n = Z^2 \times p \times (1 - p) / d^2$, where $Z = 1.96$ (for $\alpha = 0.05$), $p = 0.08$ (estimated proportion of neonatal sepsis), and $d = 0.10$ (absolute precision). This yielded a minimum of 28 neonates per group. To minimize bias, this study performs total-population sampling method. The final number of participants is 69 subjects.

This study received approval from the Research Ethics Committee of Ulin General Hospital, Banjarmasin, South Kalimantan, Indonesia, with approval number No. 553/UN8.1.17.2/PPDS.IKA/2021. Written informed consent was obtained from the parents or guardians of every study subject. All study procedures were performed in accordance with the principles of the Declaration of Helsinki.

2.2. Serum Zinc Level Analysis

Serum zinc concentration was measured by complexometric titration using Ethylenediaminetetraacetic Acid (EDTA). Because serum zinc is highly susceptible to pre-analytical contamination and hemolysis, only non-hemolyzed serum samples were included, and trace-element clean tubes, glassware, and reagents were used throughout the procedure. Analytical-grade reagents were obtained from Merck® (Darmstadt, Germany) [24, 25].

An aliquot of 1 mL serum was diluted with distilled water to a final volume of 250 mL. Subsequently, 25 mL of the diluted solution was transferred into an Erlenmeyer flask and mixed with 15 mL distilled water, 10 mL ammonia buffer solution (pH 10), and 3 drops of Eriochrome Black T (EBT) indicator. The mixture was titrated with standardized 0.01 M EDTA solution until the endpoint color changed from wine red to blue. Zinc concentration was calculated from the volume of EDTA consumed using the equation: Zn (mg/L) = V_EDTA × M_EDTA × 65.38, where V_EDTA is the volume of EDTA used (L), M_EDTA is the molarity of EDTA (mol/L), and 65.38 is the atomic weight of zinc. Calibration was performed using zinc sulfate standards in the range of 0.1–1.0 mg/L. The use of ammonia buffer at pH 10, EDTA as the chelating titrant, and EBT as the indicator is in line with the standard complexometric titration principle for zinc determination [24, 25].

2.3. IL-6 Analysis by Enzyme-linked Immunosorbent Assay (Elisa)

Serum IL-6 levels were measured using a commercially available Human Interleukin-6 Platinum ELISA Kit (Cat. No. E4063Hu, Bioassay Technology Laboratory, China) according to the manufacturer's instructions. The assay had a detection range of 2–600 pg/mL with a sensitivity of 0.96 pg/mL. 50 µL standard solution was added to the standard wells. For sample analysis, 40 µL serum sample and 10 µL anti-IL-6 antibody were added into each sample well, followed by 50 µL streptavidin-HRP reagent in both standard and sample wells. The plate was mixed thoroughly, sealed, and incubated for 60 minutes at 37°C. The wells were washed five times using wash buffer after incubation. Each well was soaked with approximately 0.35 mL wash buffer for 30 seconds to 1 minute during each washing cycle. Subsequently, 50 µL substrate solution A and 50 µL substrate solution B were added to each well and incubated for 10 minutes at 37°C in the dark. The reaction was terminated by adding 50 µL stop solution, resulting in a color change from blue to yellow. Absorbance was measured at 450 nm using an ELISA microplate reader within 10 minutes after adding the stop solution.

2.4. Data Analysis

The study results included subject characteristics and serum levels of zinc and IL-6 in both groups. Subject characteristics were presented in tabular form with the number of subjects in both groups, gender, birth weight, gestational age, mode of delivery, major and minor sepsis risk factors, and maternal variables (age, parity, and education level). Data on sex and mode of delivery were analyzed using Chi-square tests. Birth weight and gestational age were analyzed using unpaired t-tests at the 95% confidence level ($p < 0.05$). Data on risk factor distribution were analyzed descriptively. The Mann–Whitney U test was used to compare zinc and IL-6 levels between groups. The Spearman correlation test was performed to examine the relationship between zinc and IL-6 levels within the sepsis-risk group. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). A *p*-value of <0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

This study investigated the roles of zinc and IL-6 in neonatal sepsis by analyzing differences and relationships in their levels between neonates at risk of sepsis and healthy controls. The sample included neonates at risk for sepsis and healthy neonates admitted between October 2020 and July 2021, consisting of 34 subjects of healthy neonates as controls and 35 subjects who were at risk of sepsis. The characteristics of the subjects from the two groups are presented in Table 1.

Table 1. Baseline characteristics of healthy neonates and neonates at risk of sepsis.

Characteristics	Control (n = 34)	Risk of Sepsis (n = 35)	*p*-value
Total	34	35	
Gender, n (%)			0.187
Male	23 (67)	19 (54)	
Female	11 (33)	16 (46)	
Birth weight (grams), mean ± SD	2857 ± 496	2618 ± 635	0.005*
Gestational age (weeks), mean ± SD	37.7 ± 1.4	36.9 ± 2.6	0.053
Birth delivery, n (%)			
Pervaginal	20 (59)	23 (65)	0.128
SC	14 (41)	12 (35)	
Major risk factors, n (%)			
PROM >18 h		1 (3)	
PROM >24 h		34 (97)	
Maternal Characteristics			
Age			
Low Risk	28 (82)	24 (68)	0.336
High Risk	6 (18)	11 (32)	
Parity			
Primigravida	16 (47)	19 (54)	0.464
Multigravida	18 (53)	16 (46)	
Education Level			
Low Education Level	20 (58)	22 (63)	1
High Education Level	14 (42)	13 (37)	

Note: * Statistically Significant ($p < 0.05$).

Over a 9-month period, 69 neonates were enrolled: 34 healthy (control group) and 35 at risk of sepsis (sepsis-risk group). In both groups, most subjects were male. The mean birth weight in the control group was 2857 ± 496 g,

whereas the sepsis-risk group had a mean of 2618 ± 635 g, indicating a slightly lower birth weight in the sepsis-risk group. Gestational age showed a small difference, with a mean of 37.7 ± 1.4 weeks in the control group and 36.9 ± 2.6 weeks in the sepsis-risk group. In this study, the majority of neonates in both the healthy and sepsis-risk groups were male. These findings align with those of Romli *et al*. (2021) [26], who reported that more than 59.7% of sepsis cases were male [26]. The higher proportion of males may be associated with X-chromosome factors that influence immunoglobulin synthesis and immune function. However, the association between gender and neonatal sepsis was not found consistently in other studies. A significant difference in birth weight was found between the groups (p-value < 0.05), with neonates in the healthy group having higher birth weights than those at risk of sepsis. This supports prior systematic reviews suggesting that low birth weight (< 2500 grams) increases sepsis risk by 1.42 times compared to higher birth weights, likely due to immature immune systems in low-birth-weight, often preterm, infants [27]. In addition to being a known risk factor for sepsis, low birth weight may also be associated with lower zinc status. In this study, neonates in the sepsis-risk group not only had significantly lower birth weights but also lower serum zinc levels. Although this study did not conduct multivariate analysis, the coexistence of these two factors suggests an interrelated mechanism. Zinc deficiency during pregnancy has been linked to intrauterine growth restriction in prior research. A systematic review and meta-analysis study found a significant difference in zinc levels between Small-for-Gestational-Age (SGA) and appropriate-for-gestational-age infants. Maternal blood zinc and birth weight showed a significant correlation (r = 0.09, 95% CI: 0.04-0.15) [28]. Conversely, low-birth-weight neonates may also have reduced zinc stores at birth. Further studies are needed to determine whether zinc deficiency independently increases sepsis risk or is mediated by birth weight and gestational maturity.

Vaginal delivery was the predominant method of birth for both groups (59% in the control group and 65% in the sepsis-risk group). A notable difference in PROM prevalence was observed: 97% of the sepsis-risk group experienced PROM for 24 hours or more, whereas none in the control group did. Other major risk factors were not observed in the control group but were identified in a small proportion (3%) of neonates in the sepsis-risk group. The mode of delivery was not significantly different between the two groups (*i.e.*, the most common mode of delivery was still vaginal). This finding differs from the report by Utomo at Dr. Soetomo Hospital, which showed that cesarean delivery was associated with a 1.89-fold higher risk of neonatal sepsis compared with vaginal delivery. Cesarean section, particularly when preceded by prolonged rupture of membranes, may increase the risk of infection due to greater exposure to pathogenic organisms. Nevertheless, elective cesarean delivery under controlled conditions has been suggested to lower the risk of neonatal sepsis in certain situations [29].

Maternal characteristics further distinguished the groups. While low-risk maternal age was more common in both groups, the sepsis-risk group had a higher proportion of high-risk maternal ages (32% vs. 18% in the control group). Primigravida status was more frequent among mothers in the sepsis-risk group (54%) than in the control group (47%). Additionally, mothers of neonates in the sepsis-risk group were more likely to have a low educational background (63%) and a higher likelihood of unemployment (60%) than those in the control group. Previous studies have identified several maternal factors, including maternal age, parity, route of delivery, PROM, prematurity, birth weight, neonatal gender, and age, associated with neonatal sepsis risk. Primigravida mothers had 4.8 times higher odds of neonatal sepsis compared with multigravida mothers; this may be explained by labor complications in first-time mothers such as prolonged labor [30, 31].

The study measured serum zinc and IL-6 levels in both groups (Fig. **1**). The control group had a mean serum zinc level of 80.47 ± 13.80 µg/dL, whereas the sepsis-risk group showed significantly lower zinc levels with a mean of 57.34 ± 8.89 µg/dL. In contrast, IL-6 levels showed only a slight difference between groups, with mean values of 347.6 ± 327 pg/mL in the control group and 332.4 ± 249 pg/mL in the sepsis-risk group. This aligns with Adnan *et al*. (2020) [8], who found that low zinc levels increase sepsis risk by 16.8 times [8]. Huang *et al*. (2025) [32] similarly reported lower zinc levels in children with sepsis [32]. Zinc plays an important role in immunity, supporting the function of leukocytes and lymphocytes and helping regulate inflammatory responses. Deficient zinc homeostasis has been associated with inflammation and infections such as immunodeficiency syndromes, measles, malaria, and tuberculosis [33, 34].

Data normality for zinc and IL-6 levels was assessed using the Kolmogorov-Smirnov test, which indicated non-normal distributions (P < 0.05) for both variables. Subsequent analysis using the Mann-Whitney test revealed a statistically significant difference in serum zinc levels between the control and sepsis-risk groups (P <0.001, P < 0.05), while IL-6 levels did not differ significantly (P = 0.980, P > 0.05) (Table **2**).

Table 2. Comparison of zinc and IL-6 levels and correlation analysis.

Statistical Analysis	Mann-Whitney	Spearman Correlation	
	p-value	*p*-value	Correlation Coefficient
Zinc	< 0.001	< 0.001	- 0.548
IL-6	0.980	0.792	- 0.032

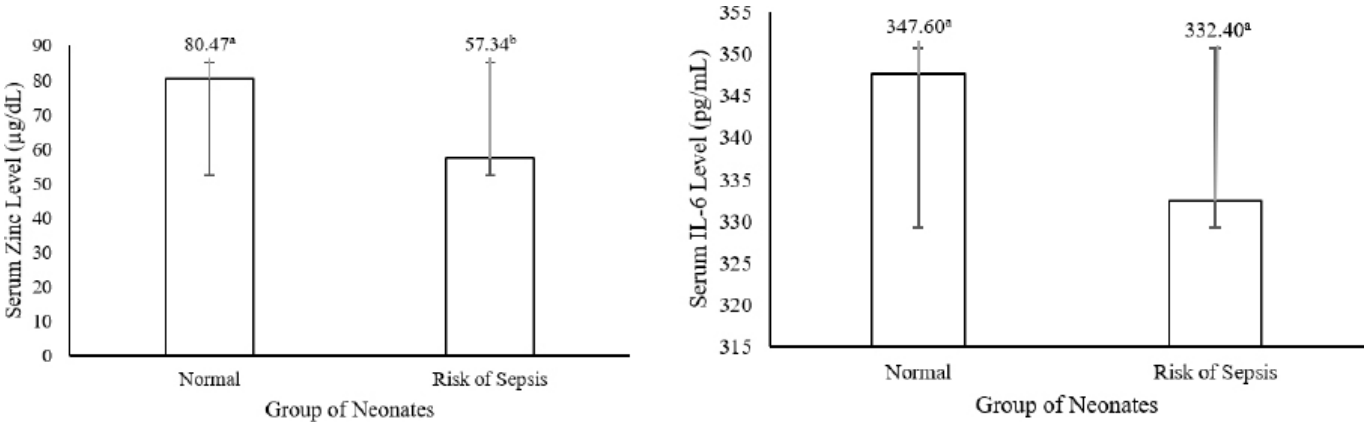

Fig. (1). Comparison of serum zinc and IL-6 levels in normal and at-risk-of-sepsis neonates. Data presented as mean ± SD. Different lowercase letter $p < 0.001$ for zinc levels between groups. Different lowercase letters indicate statistically significant differences between normal and at-risk-of-sepsis neonates ($p < 0.05$).

Spearman correlation analysis was conducted to assess the association between zinc and IL-6 levels and the risk of sepsis. A significant negative correlation was found between serum zinc levels and sepsis risk (correlation coefficient -0.548, $P < 0.05$), suggesting that lower zinc levels are associated with increased sepsis risk. However, IL-6 levels did not show a significant correlation with sepsis risk (correlation coefficient -0.032, $P > 0.05$). No significant difference in IL-6 levels was found between the sepsis-risk and healthy groups. This may be due to the inclusion of neonates at risk but not yet showing signs of sepsis, as IL-6 is a marker for early-stage infection and has a short half-life, peaking around 6 hours after bacteremia onset [35, 36]. Zinc deficiency was significantly associated with increased sepsis risk. Although this study indicates a significant negative correlation between serum zinc and IL-6 levels, IL-6 levels did not differ significantly between groups. These findings suggest that zinc may potentially not only be a risk factor but also a biomarker of neonatal sepsis. Future studies following infants over time are needed to confirm its role as an early predictive biomarker, especially when combined with inflammatory cytokines such as IL-6.

4. LIMITATIONS OF THE STUDY

This study has several limitations. First, the sample size was relatively limited and came from a single center, so generalizing the results to the general population requires caution. Second, IL-6 measurements were performed at a single sampling point, so the dynamics of changes in levels from baseline to follow-up could not be evaluated. Third, maternal infection variables were not fully assessed and may influence neonatal inflammatory markers. Furthermore, this study did not conduct a multivariate analysis to account for potential confounding factors. Therefore, additional research, conducted with a prospective, longitudinal design and a larger sample size, should be conducted to reinforce these results.

CONCLUSION

In conclusion, the average zinc levels in neonates at risk of sepsis and in healthy neonates were 57.34 ± 8.89 µg/dL and 80.47 ± 13.80 µg/dL, respectively, with a significant difference between the two groups, while IL-6 levels (332.4 ± 249 pg/mL vs. 347.6 ± 327 pg/mL) showed no significant difference. Further research with larger sample sizes and controlled variables, as well as studies on maternal zinc levels and supplementation, is recommended to better understand the role of zinc in neonatal sepsis.

AUTHORS' CONTRIBUTIONS

The authors contributed to the manuscript as follows: P.A., N.A.P., and A.Y.: Conceived and designed the study; J.K., N.A.P., and A.A.U.: Collected the data; E.S. and I.: Performed the laboratory analyses and conducted the statistical analysis and interpretation of the results; N. A. P. and A.A.U.: Prepared the initial draft of the manuscript; E.H., S.M., P.A., and A.Y.: Critically revised the manuscript. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

ACOG	=	American College of Obstetricians and Gynecologists
AUC	=	Area Under the Curve
BCL-X	=	B-cell lymphoma X (BCL-X)
BCL-2	=	B-cell lymphoma 2 (BCL-2)
CRP	=	C-Reactive Protein
EDTA	=	Ethylenediaminetetraacetic Acid
ELISA	=	Enzyme-Linked Immunosorbent Assay
IFN-γ	=	Interferon Gamma
IL-2	=	Interleukin-2
IL-4	=	Interleukin-4

IL-6	=	Interleukin-6
IL-10	=	Interleukin-10
NADPH	=	Nicotinamide Adenine Dinucleotide Phosphate
NF-κB	=	Nuclear Factor Kappa B
PROM	=	Premature Rupture of Membranes
SD	=	Standard Deviation
SDGs	=	Sustainable Development Goals
SGA	=	Small for Gestational Age
STAT3	=	Signal Transducer and Activator of Transcription 3
Th1	=	T-helper 1
Th2	=	T-helper 2
TMB	=	3,3',5,5'-Tetramethylbenzidine
ZIP14	=	Zrt- and Irt-like Protein 14
Zn	=	Zinc

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study received approval from the Research Ethics Committee of Ulin General Hospital, Banjarmasin, South Kalimantan, Indonesia, with approval number No. 553/UN8.1.17.2/PPDS.IKA/2021.

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

STANDARDS OF REPORTING

STROBE guidelines were followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This study was supported by the Research and Community Service Unit (LPPM) Universitas Lambung Mangkurat (ULM) through the PDWM Program 2024 (grant number 804/UN8.2/PP/2024).

REFERENCES

[1] Mu C, Liu F, Tian T, *et al*. Analysis of the global burden and key risk factors of neonatal sepsis and other neonatal infections in 204 countries and territories, 1990–2021. Front Med 2025; 12: 1536948. http://dx.doi.org/10.3389/fmed.2025.1536948 PMID: 40255586

[2] Putri ND, Dickson BFR, Adrizain R, *et al*. Epidemiology of sepsis in hospitalised neonates in Indonesia: High burden of multidrug-resistant infections reveals poor coverage provided by recommended antibiotic regimens. BMJ Glob Health 2025; 10(4): e016272. http://dx.doi.org/10.1136/bmjgh-2024-016272 PMID: 40204461

[3] Dini FN, Andayani P, Rosida L. The relationship between gestation period and the incidence of neonatorum sepsis at Ulin Regional Hospital, Banjarmasin, June 2014-June 2015. Berk Kedokt 2016; 12(2): 175. http://dx.doi.org/10.20527/jbk.v12i2.1865

[4] Qin C, Gao X, Yin L, *et al*. Global, regional and national disease burden of neonatal disorders from 2000 to 2021 and the comparison before and during COVID-19: A systematic analysis. BMC Public Health 2025; 25(1): 3790. http://dx.doi.org/10.1186/s12889-025-25043-7 PMID: 41194094

[5] Li J, Shen L, Qian K. Global, regional, and national incidence and mortality of neonatal sepsis and other neonatal infections, 1990–2019. Front Public Health 2023; 11: 1139832. http://dx.doi.org/10.3389/fpubh.2023.1139832 PMID: 36998277

[6] Sharrow D, Hug L, You D, *et al*. Global, regional, and national trends in under-5 mortality between 1990 and 2019 with scenario-based projections until 2030: A systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. Lancet Glob Health 2022; 10(2): e195-206. http://dx.doi.org/10.1016/S2214-109X(21)00515-5 PMID: 35063111

[7] Wei Z, Liu Y, Mei X, Zhong J, Huang F. Circulating micronutrient levels and their association with sepsis susceptibility and severity: A Mendelian randomization study. Front Genet 2024; 15: 1353118. http://dx.doi.org/10.3389/fgene.2024.1353118 PMID: 38435062

[8] Adnan C, Artana IWD, Suarta K, Sidiartha IGL, Gustawan IW, Yantie NPVK. Serum zinc level and prognosis of neonatal sepsis. Paediatr Indones 2020; 60(2): 37-42. http://dx.doi.org/10.14238/pi60.2.2020.37-42

[9] Maywald M, Rink L. Zinc in human health and infectious diseases. Biomolecules 2022; 12(12): 1748. http://dx.doi.org/10.3390/biom12121748 PMID: 36551176

[10] Gammoh N, Rink L. Zinc in infection and inflammation. Nutrients 2017; 9(6): 624. http://dx.doi.org/10.3390/nu9060624 PMID: 28629136

[11] Hojyo S, Fukada T. Roles of zinc signaling in the immune system. J Immunol Res 2016; 2016: 1-21. http://dx.doi.org/10.1155/2016/6762343 PMID: 27872866

[12] Maywald M, Wessels I, Rink L. Zinc signals and immunity. Int J Mol Sci 2017; 18(10): 2222. http://dx.doi.org/10.3390/ijms18102222 PMID: 29064429

[13] Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. J Infect Dis 2000; 182(s1): S62-8. http://dx.doi.org/10.1086/315916 PMID: 10944485

[14] Aliyu M, Zohora FT, Anka AU, *et al*. Interleukin-6 cytokine: An overview of the immune regulation, immune dysregulation, and therapeutic approach. Int Immunopharmacol 2022; 111: 109130. http://dx.doi.org/10.1016/j.intimp.2022.109130 PMID: 35969896

[15] Reis Machado J, Soave DF, da Silva MV, *et al*. Neonatal sepsis and inflammatory mediators. Mediators Inflamm 2014; 2014: 1-10. http://dx.doi.org/10.1155/2014/269681 PMID: 25614712

[16] Stanley AC, Lacy P. Pathways for cytokine secretion. Physiology 2010; 25(4): 218-29. http://dx.doi.org/10.1152/physiol.00017.2010 PMID: 20699468

[17] Uciechowski P, Dempke WCM. Interleukin-6: A masterplayer in the cytokine network. Oncology 2020; 98(3): 131-7.

http://dx.doi.org/10.1159/000505099 PMID: 31958792

[18] Alansari AN, Zaazouee MS, Elshanbary AA, Mani S, Messaoud M. Diagnostic accuracy of interleukin-6 (IL-6) as a significant biomarker in late-onset neonatal sepsis: An updated systematic review and meta-analysis. Eur J Pediatr 2025; 184(9): 587. http://dx.doi.org/10.1007/s00431-025-06409-w PMID: 40892314

[19] Tian F, Li H, Wang L, *et al*. The diagnostic value of serum C-reactive protein, procalcitonin, interleukin-6 and lactate dehydrogenase in patients with severe acute pancreatitis. Clin Chim Acta 2020; 510: 665-70. http://dx.doi.org/10.1016/j.cca.2020.08.029 PMID: 32828732

[20] Qiu X, Zhang L, Tong Y, Qu Y, Wang H, Mu D. Interleukin-6 for early diagnosis of neonatal sepsis with premature rupture of the membranes. Medicine 2018; 97(47): e13146. http://dx.doi.org/10.1097/MD.0000000000013146 PMID: 30461611

[21] Smok B, Domagalski K, Pawłowska M. Diagnostic and prognostic value of IL-6 and sTREM-1 in SIRS and sepsis in children. Mediators Inflamm 2020; 2020: 1-8. http://dx.doi.org/10.1155/2020/8201585 PMID: 32655314

[22] Eichberger J, Resch B. Reliability of Interleukin-6 alone and in combination for diagnosis of early onset neonatal sepsis: Systematic review. Front Pediatr 2022; 10: 840778. http://dx.doi.org/10.3389/fped.2022.840778 PMID: 35402358

[23] the American College of Obstetricians and Gynecologists'. ACOG Practice Bulletin No. 188: Prelabor Rupture of Membranes. Obstet Gynecol 2018; 131(1): e1-e14. http://dx.doi.org/10.1097/AOG.0000000000002455 PMID: 29266075

[24] Killilea DW, Rohner F, Ghosh S, *et al*. Identification of a hemolysis threshold that increases plasma and serum zinc concentration. J Nutr 2017; 147(6): 1218-25. http://dx.doi.org/10.3945/jn.116.247171 PMID: 28490675

[25] de Benoist B, Darnton-Hill I, Davidsson L, Fontaine O, Hotz C. Conclusions of the joint WHO/UNICEF/IAEA/IZiNCG interagency meeting on zinc status indicators. Food Nutr Bull 2007; 28(3_suppl3): S480-4. http://dx.doi.org/10.1177/15648265070283S306 PMID: 17988008

[26] Romli MI, Yuniati T, Hilmanto D. Presepsin level as risk factor for mortality in premature infants with neonatal sepsis. Paediatr Indones 2021; 61(3): 165-70. http://dx.doi.org/10.14238/pi61.3.2021.165-70

[27] Murthy S, Godinho MA, Guddattu V, Lewis LES, Nair NS. Risk factors of neonatal sepsis in India: A systematic review and meta-analysis. PLoS One 2019; 14(4): e0215683. http://dx.doi.org/10.1371/journal.pone.0215683 PMID: 31022223

[28] Shah D, Sachdev HPS. Zinc deficiency in pregnancy and fetal outcome. Nutr Rev 2006; 64(1): 15-30. http://dx.doi.org/10.1111/j.1753-4887.2006.tb00169.x PMID: 16491666

[29] Utomo MT, Sumitro KR, Etika R, Widodo ADW. Current-proven neonatal sepsis in Indonesian tertiary neonatal intensive care unit: A hematological and microbiological profile. Iran J Microbiol 2021; 13(3): 266-73. http://dx.doi.org/10.18502/ijm.v13i3.6386 PMID: 34540164

[30] Gebremedhin D, Berhe H, Gebrekirstos K. Risk factors for neonatal sepsis in public hospitals of Mekelle City, North Ethiopia, 2015: Unmatched case control study. PLoS One 2016; 11(5): e0154798. http://dx.doi.org/10.1371/journal.pone.0154798 PMID: 27163290

[31] Kayange N, Kamugisha E, Mwizamholya DL, Jeremiah S, Mshana SE. Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza- Tanzania. BMC Pediatr 2010; 10(1): 39. http://dx.doi.org/10.1186/1471-2431-10-39 PMID: 20525358

[32] Huang L, Tian X, Cheng M, Li D. Serum zinc dynamics as a diagnostic and immunomodulatory biomarker in neonatal sepsis. Sci Rep 2025; 15(1): 41920. http://dx.doi.org/10.1038/s41598-025-25828-1 PMID: 41290778

[33] Shankar AH, Prasad AS. Zinc and immune function: The biological basis of altered resistance to infection. Am J Clin Nutr 1998; 68(2): 447S-63S. http://dx.doi.org/10.1093/ajcn/68.2.447S PMID: 9701160

[34] Fraker PJ, King LE, Laakko T, Vollmer TL. The dynamic link between the integrity of the immune system and zinc status. J Nutr 2000; 130(5): 1399S-406S. http://dx.doi.org/10.1093/jn/130.5.1399S PMID: 10801951

[35] Ng PC, Li K, Wong RPO, *et al*. Proinflammatory and anti-inflammatory cytokine responses in preterm infants with systemic infections. Arch Dis Child Fetal Neonatal Ed 2003; 88(3): F209-13. http://dx.doi.org/10.1136/fn.88.3.F209 PMID: 12719394

[36] Morad EA, Rabie RA, Almalky MA, Gebriel MG. Evaluation of procalcitonin, C-reactive protein, and interleukin-6 as early markers for diagnosis of neonatal sepsis. Int J Microbiol 2020; 2020: 1-9. http://dx.doi.org/10.1155/2020/8889086 PMID: 33061986

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