Blood cord's zinc serum level is associated with general health status and outcomes: A suggestion of cut-off novelty in newborns

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ABSTRACT

Purpose: This study aims to analyze the associations of zinc serum levels in the blood cord with the general health status of neonates, along with the characteristics and outcomes in Ulin General Hospital, Banjarmasin.

Design/Methodology/Approach: A cross-sectional study was conducted in October-November 2021. The subjects were divided into two groups based on the zinc serum level (≤67.5 µg/dl and >67.5 µg/dl). The cut-off was determined by the receiver operating characteristic (ROC).

Findings: There were 35 subjects in the group with zinc serum level ≤67.5 µg/dl and 34 subjects in the group with zinc serum level >67.5 µg/dl. Neonates with zinc serum level over the cut-off significantly had a higher birth weight (p=0.038), lower incidence of prematurity (p=0. 02, OR 0.21; 95%CI: (0.05-0.84)), lower incidence of anemia (p=0.001, 95%CI: 0.1(0.012-.89)), neonatal jaundice (p=0.02, OR 0.3; 95%CI: 0.1-0.85), and neonatal infections (p=0.000 OR 0.008; 95%CI: 0.001-0.067).

Conclusion: The zinc serum level of the blood cord is strongly associated with the general health status and outcomes of the newborn. It is also associated with the general health of neonates, birth weight, prematurity, the incidence of infection, jaundice, anemia of newborns, and the need for NICU during the treatment.

Limitations: A relatively short period of observation and a small number of subjects due to the limitation of resources.

Practical Implications: propose the importance of zinc intake in pregnancy as it strongly implicates the general health status and outcomes of neonates.

Contribution to Literature: This study provides a cut-off value with significant results and encourages further investigation to determine the need and effects of early zinc supplementation.

Keywords: *Blood cord zinc serum level, Cut-off zinc serum level in neonates, General health status, Maternal characteristics, Neonatal outcomes, Pregnancy nutrition.*

1. INTRODUCTION

Zinc is an essential micronutrient involved in the synthesis of ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and proteins. Also, it plays a significant role in the transcription, gene expression, cellular division, and development of cells in general (Terrin et al., 2015). Zinc adequacy is crucial for the developmental process of many fetal organ systems, including metabolic, digestive, skin-mucosal integrity, bone growth, immunity, vision, brain, and nervous system (Brion, Heyne, & Lair, 2021; Dey et al., 2010). Zinc deficiency during pregnancy is a well-known factor related to increased neonatal morbidity and mortality, such as prematurity, low weight baby, intrauterine growth restriction, and even congenital abnormalities (Dey et al., 2010; Wang et al., 2015).

Zinc has no long-term storage system in the body. Consequently, serum zinc levels of pregnant women are highly dependent on daily intake, and fetal zinc serum levels depend on the placental transfer of the mother (Liu et al., 2021). Zinc deficiency during pregnancy is prevalent due to the increase in demand for the growth of the fetus, especially in the second and third trimesters. At the same time, dietary intake is highly dependent on physical, psychological, socioeconomic, and even cultural-environmental factors. Several conditions during pregnancy can affect zinc transplacental transport, namely smoking, alcohol consumption, preeclampsia, obesity, and diabetes (Kumera et al., 2015; Liu et al., 2021).

The World Health Organization (WHO) reports that zinc deficiency is common in underdeveloped nations and that 14-68% of pregnant women globally are affected. (World Health Organization, 2021). Although some research claims that a range of zinc blood levels between 40 and 60 g/dl is considered a deficit and can appear clinically, there is currently no universally accepted definition of zinc deficiency. (King, 2011; Maxfield, Shukla, & Crane, 2021). In Indonesia, there is also no agreed reference to normal or deficient zinc serum levels, especially in newborns, but some studies put out a level >65 µg/dl as a normal level (Adnan et al., 2020; Martadiansyah, Maulina, Mirani, & Kaprianti, 2021; Rohmawati, 2021). Zinc deficiency in the early stages is difficult to assess because it has no specific symptoms, but in the chronic states, it is associated with increased incidence of severe dermatitis, metabolic impairment, stunting, congenital anomalies, and death (Dassoni et al., 2014; Maxfield et al., 2021).

Low birth weight, infections, stunting, and wasting are the most prevalent issues with regard to children's health in Indonesia because of the country's high mortality rates and failure to fulfil the Sustainable Development Goals (SDGs) objectives of 15 (newborn) and 32 (infant) per live birth. (Ministry of Health of the Republic of Indonesia, 2021). Child health status is influenced by many interrelating factors, one of them being nutrition status. Macro and micro-malnutrition deficiencies that start early (during pregnancy) are one crucial risk factor for poor child health outcomes. Zinc is a contributing factor in the growth and immune system. Hence, its deficiency is estimated to be associated with impaired growth, impaired immunity, and a higher risk of infection (Rohmawati, DewiTanjung, & Sari, 2021; Sezer et al., 2013).

Ulin General Hospital is a tertiary referral hospital in South Kalimantan, Indonesia, where the society has diverse cultures, socioeconomic, and environmental factors. The provincial government is actively pursuing various efforts to achieve a good child health status following the SDGs (South Kalimantan Provincial Health Office, 2020). The vast range of zinc blood levels that are accessible and their possible correlations with outcomes and the overall health of newborns interest authors.

2. METHOD

2.1. Study Design

This is an observational study with a cross-sectional approach. The study was conducted in October-November 2021 at a tertiary hospital (Ulin General Hospital, Banjarmasin). This study aims to analyze the association of zinc serum levels in the blood cord with the general health status of neonates, along with the characteristics and outcomes of newborns in Ulin General Hospital, Banjarmasin. The cut-off of zinc serum level in this study is determined with receiver operating characteristic (ROC). The hospital's ethics council had previously authorized this study, and the parents of each baby participant provided written permission. In this study, the maternal variables that were observed as age, parity, educational attainment, and employment position. Neonatal anthropometric chart: sex, birth weight, length, head circumference, preterm status as newborn features, a Lubchenco chart (LC), a history of asphyxia at delivery, and additional illnesses such neonatal infection, neonatal sepsis, anemia, and neonatal jaundice were gathered. The neonatal outcomes were observed in the form of the general condition of the neonates (healthy or unhealthy), length of stay, history of NICU (Neonatal Intensive Care Unit) stay, and mortality.

The following is the operational definition defined for the research variables:

- The zinc serum level was put into less than 67.5 mcg/dl and over or equal to 67.5 mcg/dl (AUC 0.79 p-value 0.05, sensitivity 80% specificity 25.6%) by receiver operating characteristic (ROC) based on the general status of the neonates.
- Healthy neonates are those that don't need any further care beyond what is required for healthy neonates.

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- Low birth weight (LBW) was defined as less than 2500 g, normal birth weight (NBW) as between 2500 and 3999 g, and excessive birth weight (EBW) as over 4000 g.
- Lubchenco's curve was used to classify anthropometric measurements based on gestational age into three categories: short for gestational age (SGA), appropriate for gestational age (AGA), and large gestational age (LGA).

2.2. Subjects

The subjects were selected using the purposive sampling method. The inclusion criteria were:

- Singleton neonates born in Ulin General Hospital.
- Mothers with no prior history of severe malnutrition or significant chronic medical conditions that interfere with zinc absorption or metabolism processes, such as celiac disease, Crohn's disease, ulcerative disease, chronic anemia, chronic kidney disease, alcoholism, and cancer.
- Neonates were not diagnosed with major congenital abnormalities.

The exclusions criteria were: mother's not willing to be included in this study and apply for discharge at their request. Twin pregnancy is estimated to have a significantly lower zinc serum level than a singleton pregnancy, hence excluded from this study due to its potential bias effect.

2.3. Materials and Procedure

The materials used in this study were: informed consent, register book, 5cc syringe, 5 ml vacutainer tube, 1 ml bullet tube, tube rack, tube label, Oregon LC-04S centrifuge, refrigerator temperature -80° Celsius, serum zinc assay kit. Three to five milliliters of newborn blood samples were taken from the blood cord using a 5 ml syringe immediately after birth. The blood was collected in a labeled red cap vacutainer tube and kept at room temperature to clot for 30–60 min. Samples were then centrifuged using Oregon Centrifuge LC-04S at 2000 rpm for 10 minutes. Blood serum will be taken using a micropipette and put in a 1 ml bullet tube and directly stored in a refrigerator at -80°C.

Examination of zinc levels was carried out collectively using the complexometric titration method. A serum sample of 100 µl was diluted with distilled water to 250 ml into a flask. Then 25 ml of liquid was taken and mixed with 15 ml of aquadest, ammonia buffer pH 10 10 ml, and 3 drops of Eriochrome Black (EB). The liquid was titrated with 0.01 ethylene diamine tetra-acetate disodium (EDTA). Zinc levels were determined by calculating Zn = molarity x titration volume x 65.38 mg/ml (molecular weight). The complexometric titration method is a standard method for routine examination of zinc level, it is usually preferred because of the convenient and inexpensive materials, as well as more accurate results. The examination was carried out at the Biochemistry Laboratory, Faculty of Medicine, Lambung Mangkurat University, Banjarbaru.

2.4. Statistical Method

The data were tabulated with the Microsoft Excel 2013 application and analyzed with the IBM SPSS version 21 application. The cut-off of zinc serum level based on the general condition of the neonates was measured using receiver operating characteristic (ROC). The cut-off is determined based on the desired values of sensitivity and specificity. Quantitative data were assessed for normality using the Saphiro-Wilk, normally distributed data were compared using the T-test, and abnormal data is used for the Mann-Whitney test. Chi-square was used to compare categorical data between control and case groups. When the table did not meet the requirements, the data was analyzed with a substitute test (Fisher's Exact test) instead. The p-value <0.05 on the test results was considered significant. Odd ratio and 95%CI (95% confidence interval) were calculated on the examination with significant results.

3. RESULTS

3.1. Zinc Serum Level and General Health Status of Newborn

The number of samples in this study were 69 newborns, later divided into two groups based on the zinc serum levels with a determined cut-off using the receiver operating characteristic (ROC) between zinc levels and the baby's general health as the status variable. The ROC evaluation results obtained Area Under Curve (AUC) 0.8; p-value 0.00; 95%CI 0.69-0.9 Figure 1. The cut-off chosen was 67.5 µg/dl (80% sensitivity and 25.6% specificity) concerning the balance of the sample between the two groups. It was found that there were 35 subjects with zinc serum levels <67.5 µg/dl, and 34 subjects with zinc serum levels ≥67.5 µg/dl.

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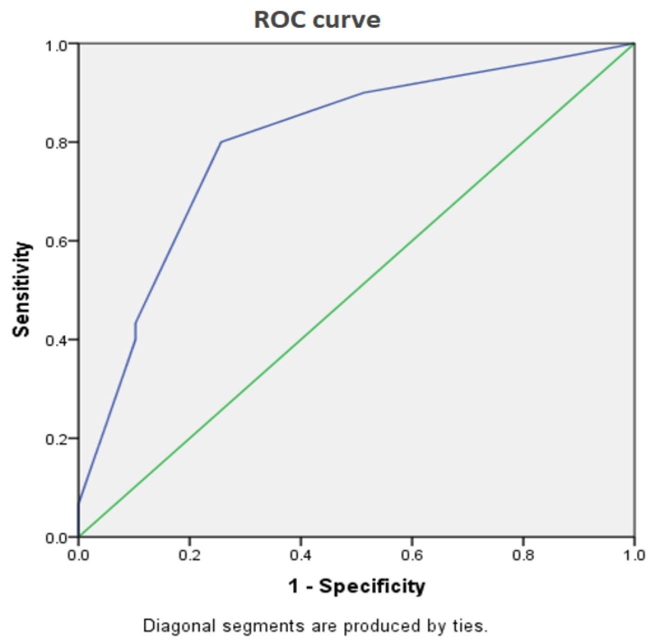

Figure 1. Receiver operating characteristic (ROC) curve.

Table 1. shows the results of the Chi-square analysis between zinc serum levels and the general health status of neonates with significant results (p-value 0.000 OR 11.6 95% CI 3.68-36.5). This study included 30 healthy and 39 unhealthy neonates. In the group of newborns with zinc levels above 67.5 mcg/dl, 24(70.5%) neonates were diagnosed as healthy, and only 10 (29.5%) required further treatment. While in the group of neonates with blood cord's zinc level <67.5 mcg/dl, 29(82.9%) were unhealthy, meaning that they required additional care beyond the standard of care for healthy neonates.

Table 1. Chi-square analysis of group serum zinc levels and general health status of neonates.

General health status	Group		P-value	OR (95%CI)
	<67.5 µg/dl	≥67.5 µg/dl		
	n (%)	n (%)		
Healthy neonates	6 (17.1)	24 (70.5)	0.000	11.6 (3.68-36.5)
Unhealthy neonates	29 (82.9)	10 (29.5)		

3.2. Maternal and neonatal characteristics

The maternal and neonatal characteristics of this study are shown in Table 2 and Table 3. The mean age of the mothers in the group of infants with zinc levels below the cut-off was 29.7 ± 6.87, while in the group of infants with zinc levels above the cut-off was 27.8 ± 6.24, the difference between both groups was not significant (p value=0.58). According to the mother's parity status, 35 of the moms were primigravida and 34 were multigravida. Neither the group of newborns with zinc levels below the cut-off nor the group of infants with zinc levels beyond the cut-off showed any appreciable variations in the study's parity status ratio.

In this study, mothers with primary to secondary education were more prevalent than mothers who were gone to college. Moreover, stay-at-home mothers were also more common than working mothers. However, the ratio did not differ significantly between the two groups as determined by zinc levels.

The distribution of the male neonates was more common in the group with serum zinc levels above the cut-off (54.8%), while female neonates were more common in the group of neonates with serum zinc levels below the cut-off (59.2%), although the difference is not statistically significant. The mean birthweight of neonates in the group with zinc levels below 67.5 g/dl was 2565.6 g, which was significantly lower than the mean birthweight of neonates in the group with zinc levels above 67.5 g/dl, which was 2862.9 g (p-value 0.038), while the mean birth length and head circumference did not differ significantly between the two groups.

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Preterm neonates are more prevalent to be found in the group with zinc levels <67.5 µg/dl (p-value 0.02 OR 0.21 95%CI 0.05-0.84). This study found that the distribution of small gestational age neonates (SGA) was also more prevalent to be found in the group of neonates with zinc 67.5 g/dl, though the difference was not significant (p-value 0.3 OR 2.13 95%CI 0.49- 9.3). This was based on the Lubchenco curve's measure of growth appropriateness.
Anemia, neonatal infection, and neonatal jaundice are the diagnoses encountered frequently in neonates with zinc levels below the cut-off of 67.5 µg/dl (p<0.005). This group also had a higher prevalence of other diseases like hypoxia and newborn sepsis, although these differences were not statistically significant.

Table 2. Maternal characteristics.

No	Maternal characteristics	Group		P-value
		<67.5 µg/dl	≥67.5 µg/dl	
		Mean±SD n (%)	Mean±SD n (%)	
1	Age	29.7±6.87	27.8±6.24	0.58
2	Parity			
	Primigravida	19 (54.2)	16 (47.05)	0.54
	Multigravida	16 (45.8)	18 (52.05)	
3	Educational background			
	Primary - middle - secondary	21 (60)	21 (61.7)	0.88
	Tertiary (College)	14 (40)	13 (39.3)	
4	Occupational background			
	Working mother	14 (40)	12 (35.3)	0.55
	Stay at home mother	21 (60)	22 (64.7)	

Table 3. Neonatal characteristics.

No	Neonatal characteristics	Group (Mean±SD or n (%))		P-value	OR (95%CI)
		<67.5 µg/dl	≥67.5 µg/dl		
1	Sex				
	Male	19 (45.2)	23 (54.8)	0.25	0.5 (0.21-1.50
	Female	16 (59.2)	11 (40.8)		
2	Anthropometry				
	Birth weight	2565.6±654.9	2862.9±500.1	0.038	
	Birth length	47 (5)	47. 25 (5.3)	0.37	
	Birth head circumference	32.5±2.7	32.5±1.6	0.82	
3	Prematurity				
	Aterm	24 (68.6)	31 (91.2)	0.02	4.74 (1.18-18.8)
	Preterm	11 (31.4)	3 (8.8)	0.02	0.21 (0.05-0.84)
4	Birth weight classification				
	Normal birth weight (NBW)	24 (68.6)	26 (76.5)	0.46	0.61 (0.2-1.95)
	Low birth weight (LBW)	11 (41.4)	8 (33.5)		
5	Growth appropriateness				
	Appropriate for gestational age (AGA)	29 (48.3)	31 (51.6)	0.3	2.13 (0.49-9.3)
	Small for gestational age (SGA)	6 (66.7)	3 (33.3)		
6	Diagnoses				
	Anemia	8 (88.9)	1 (11.1)	0.014	0.1 (0.012-.89)
	Asphyxia	11 (68.8)	5 (31.3)	0.1	0.3 (0.11-1.23)
	Neonatal infection	28 (96.6)	1 (3.4)	0	0.008 (0.001-0.067)
	Neonatal sepsis	7 (70)	3 (30)	0.18	0.37 (0.09-1.64)
	Neonatal jaundice	18 (69.2)	8 (30.8)	0.02	0.3 (0.1-0.85)

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Table 4. Neonatal outcomes.

No	Neonatal characteristics	Group Mean±SD or n (%)		P-value	OR (95%CI)
		<67.5	≥67.5		
1	Days of hospitalization	5.57±4.5	2.79±2.82	0.25	-
2	Need for NICU	12 (35.3)	4(11.4)	0.027	0.25 (0.07-0.8)

3.3. Neonatal Outcomes

The outcomes of newborns evaluated in this study were the length of stay and number of neonates requiring intensive care in the NICU (Neonatal Intensive Care Unit), while mortality could not be compared because all study subjects were discharged from the hospital in healthy or stable conditions for home care. The group of neonates with blood cord zinc serum levels below the cut-off had a longer length of stay at the hospital Table 4, but the difference with the other group was not statistically significant (p-value 0.25). The need for intensive care at NICU (Neonatal Intensive Care Unit) was significantly higher in the group with zinc levels below 67.5 µg/dl, as 35.5% of the neonates required intensive care in the NICU (Neonatal Intensive Care Unit), while in the other group, only 11.4% of neonates required NICU (p-value 0.027 OR 0.25 95%CI 0.07-0.8).

4. DISCUSSION

The general health status of neonates is influenced by the optimal growth and the development of organ systems that are primary elements for the fetus to be born into a healthy baby. Zinc is known as an essential mineral that plays a significant role in many organ systems. This study discovered strong correlations between neonatal outcomes and zinc serum levels in the blood cord, with a calculated cut-off of 67.5 µg/dl. The adequacy of zinc in infants is thought to be associated with maternal factors because zinc has no long-term storage system in the body, so the serum zinc level of the fetus depends on the transfer and compensation mechanism of the mother (Abdellatif, Elhawary, Mahmoud, Youness, & Abuelhamd, 2021; Jyotsna, Amit, & Kumar, 2015). In this study, there were no significant differences in maternal characteristics such as age, parity, education level, and occupation between the two groups. Similar findings from a large population cohort research including 3187 pregnant women in China showed that blood zinc levels were unaffected by the mother's age, monthly family income, parity, or gravidity. (Wang et al., 2015).

A Cross-sectional study in Southern Ethiopia involving 424 pregnant women that used a questionnaire to assess the level of nutritional knowledge of pregnant women showed that the zinc status of pregnant women was strongly affected by nutritional knowledge regardless of formal education status. Additionally, economic position (wealth index) and knowledge of the need for prenatal care were major influences on the research. (Agedew et al., 2022).

A study in Nigeria that assessed the relationship between zinc serum level in mothers, the baby's umbilical cord, and the birth weight of 190 subjects showed that there was no correlation between maternal serum zinc levels and umbilical cord levels or birth weight, suggesting there was a certain maternal compensatory mechanism to meet the needs of zinc in the fetus, however, the pathophysiology is not clearly explained (Ofakunrin, Collins, Diala, Afolaranmi, & Okolo, 2017).

Zinc deficiency would lead to a decline in cell proliferation and protein synthesis that leads to infant growth disorder. In this study, the birth weight of neonates in the group with the blood cord's zinc serum level above the cut-off was significantly higher than the birth weight of neonates with a zinc serum level below the cut-off. A cross-sectional study in Nigeria that involved 190 subjects assessed the relationship between zinc serum levels of the mothers and umbilical cord with the birth weight at term also showed a significant relationship between zinc levels in the baby's umbilical cord and birth weight ($p < 0.001$, $r = 0.02$, $p = 0.04$) (Ofakunrin et al., 2017).

Jyotsna et al. (2015) who conducted a prospective study of 100 subjects of mothers and newborns also showed that serum zinc levels were significantly lower in low-birth-weight neonates than in term neonates for gestational age ($p<0.05$) (Jyotsna et al., 2015). In Medan, Indonesia (Rohmawati et al., 2021). conducted a cross-sectional study assessing the relationship between maternal zinc level with newborn anthropometrics, and the results of the study showed a significant relationship between maternal zinc levels and the infant's anthropometric status (birth weight and length) (Rohmawati et al., 2021). Alongside the argument that maternal and infant zinc levels coincide, this might also complement the results of this study.

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A cross-sectional study by Abdellatif et al. (2021) that observed zinc levels with gestational age showed a significant relationship between zinc levels in infants, mothers, and infant anthropometric status within the preterm and full-term groups (Abdellatif et al., 2021). Seriana, Yusrawati, and Lubis (2015) conducted a cross-sectional study assessing zinc serum levels with anthropometric status in neonates born at term and showed a significant positive correlation between zinc serum levels with birth length and head circumference, but not with the birth weight. According to the authors, this uncommon finding was in consequence of the too-small sample size (n=38) and the other confounding factors that could not be controlled within the study (Seriana et al., 2015).

The relationship between zinc levels and prematurity has been known for a long time. Neonates born prematurely are at higher risk of developing zinc deficiency. Moreover, mothers with zinc deficiency during pregnancy are also at risk of preterm labor (Deger, Turan, & Peker, 2022). A meta-analysis evaluated the association of enteral zinc supplementation with morbidity and mortality of premature infants, the key points of the result of the study were zinc supplementation in premature infants does have benefits in terms of mortality and anthropometric outcomes but does not affect the outcomes of preterm complications such as necrotizing enterocolitis (NEC), retinopathy of preterm (ROP), and pulmonary dysplasia (Staub, Evers, & Askie, 2021; World Health Organization, 2021).

Gupta, Bansal, Gupta, and Nadda (2020) compared serum zinc levels in 100 small-gestational-age infants (SGA) and 100 appropriate-gestational-age infants (AGA) showed a significant difference in zinc serum levels in SGA (56.8±40.6 µg/dl) were significantly lower than zinc levels in infants AGA (107.4±72 µg/dl), but the symmetricity status was not significantly different (Gupta et al., 2020). The insignificant result in this study may be due to the ratio of study subjects that had more appropriate gestational age (AGA) neonates.

The group of infants with blood cord zinc serum levels below the cut-off in this study were more frequently diagnosed with neonatal infections, anemia, and neonatal jaundice. This finding is consistent with the theory that zinc has an important role in the immunity system, such as the function of T cells, B cells, phagocytosis, and the production of cytokines (Brion et al., 2021). In the hematological system, zinc is also required in the synthesis and production of red blood cells.

In this study, the duration of hospitalization for infants with blood cords' zinc serum level below the cut-off tended to be longer, although the difference was not significant. Another outcome that was assessed was the need for intensive care, in this case, the group with zinc levels below the cut-off level often required more NICU than the other groups. A similar result shown by a prospective study in Denpasar, Bali that attempted to use zinc levels as a predictor of the prognosis of infants with early onset sepsis showed that the higher the serum zinc level, the better the prognosis of infants diagnosed with early onset sepsis (Adnan et al., 2020).

The results of this study provide the basic data for the assessment of the need for intervention such as early zinc supplementation in further studies. As the results presented in this study support the theory and previous studies that zinc does have a critical role in many organ systems, and it is important to have a deficient zinc level to maximize the process of growth and development in early life. Zinc supplementation to infants is still conflicting as it shows varied results, so further investigation and research is mandatory.

5. LIMITATIONS

The number of subjects in this study was relatively small with a short study period. Some detailed and possibly influential maternal data such as monthly income, history of routine prenatal check-ups, health problems during pregnancy, nutritional status before and during pregnancy, history of taking supplements during pregnancy and mother's laboratory history were not included in this study. Future study is expected to contain a larger sample size and put attention to maternal history in more detail.

6. CONCLUSION

Blood cord's zinc serum level at determined cut-off 67.5 µg/dl is strongly associated with general health of neonates, birth weight, prematurity, the incidence of infection, jaundice, anemia of newborns, and the need for NICU during the treatment.

7. RECOMMENDATION

This study provides a cut-off value with significant results and encourages further investigation to determine the need and effects of early zinc supplementation, especially in newborns under the cut-off blood cord's zinc serum level.

FUNDING
This study received no specific financial support.

INSTITUTIONAL REVIEW BOARD STATEMENT
The Ethical Committee of the Ulin General Hospital, Banjarmasin, Indonesia has granted approval for this study on 21 October 2021 (Ref. No. 98/X-Reg Riset/RSUDU/21).

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS
The study conception and design, P.A. and J.K.; data collection, J.K., P.G.H. and E.H; analysis and Interpretation of result, P.A., A.Y. and W.M.; draft manuscript preparation, J.K. and A.B. All authors have read and agreed to the published version of the manuscript.

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