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Original Research Article

Association of Zinc Deficiency with Mortality in Preterm Neonates

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Abstract: *The role of trace elements, particularly zinc, in neonatal survival has received growing attention. Zinc is vital for immune function, cellular repair, and enzymatic activity. Preterm neonates are at risk of zinc deficiency due to insufficient intrauterine accumulation, which may influence morbidity and mortality outcomes.* ***Objectives:*** *To assess the association between zinc deficiency and mortality in preterm neonates.* ***Methods:*** *This was a cross-sectional study conducted at the Department of Pediatrics, Mayo Hospital, Lahore, from January 2024 to June 2024. A total of 130 preterm neonates (gestational age < 37 weeks) were enrolled. Serum zinc levels were measured once within 10 days of life using atomic absorption spectrophotometry. Zinc deficiency was defined as serum levels < 60 µg/dL. Neonates were categorized based on survival outcome (survived vs. expired), and zinc status was compared between groups. All neonates received standard NICU care. Data were analyzed using SPSS version 25, and the Chi-square test was applied to determine statistical significance.* ***Results:*** *Of the 130 neonates, 84 (64.6%) survived and 46 (35.4%) expired. Mean zinc level in the survived group was 84.2 ± 9.5 µg/dL and in the expired group was 82.6 ± 10.1 µg/dL. The association between zinc deficiency and mortality was statistically insignificant (p = 0.452).* ***Conclusion:*** *Zinc deficiency was not significantly associated with mortality in preterm neonates. Mortality is likely influenced by multifactorial causes beyond trace element status.*

Keywords: Gestational age, Neonatal mortality, NICU, Preterm, Serum zinc, Trace elements, Zinc deficiency

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Introduction

Preterm birth, defined as birth before 37 completed weeks of gestation, is a major contributor to neonatal morbidity and mortality worldwide. (1) According to the World Health Organization, approximately 15 million babies are born prematurely every year, with complications arising from prematurity being the leading cause of death in children under the age of five. (2) Among the numerous health challenges faced by preterm neonates, nutritional deficiencies, particularly trace element imbalances, are increasingly recognized as critical factors influencing clinical outcomes. (3) One such trace element is zinc, a micronutrient essential for numerous physiological processes, including cellular growth, immune function, antioxidant defense, and wound healing. (4)

Zinc is a vital cofactor for over 300 enzymatic reactions and plays an indispensable role in DNA synthesis, cell division, and protein metabolism. During fetal life, zinc accumulates rapidly, especially in the third trimester of pregnancy. (5) Therefore, preterm neonates, particularly those born very early or with very low birth weight, miss the period of maximal in utero zinc accretion and are at high risk of zinc deficiency from birth. This deficiency is further exacerbated by immature gastrointestinal absorption, increased urinary losses, and the elevated metabolic demands of critically ill neonates. (6)

Clinical features of zinc deficiency in neonates can range from growth retardation and poor wound healing to increased susceptibility to infections, impaired neurodevelopment, and dermatological manifestations. (7) Importantly, zinc deficiency has been associated with impaired immune competence, leading to a higher risk of sepsis, pneumonia, and other infectious diseases all of which are common causes of mortality in preterm populations. (8)

The relationship between zinc status and survival outcomes in neonates is a growing area of research. Moreover, the early postnatal period is marked by significant physiological adaptations in preterm infants, and micronutrient status may influence the trajectory of recovery or deterioration. Understanding whether low serum zinc levels contribute independently to neonatal mortality or whether they reflect the severity of underlying illness remains a topic of debate. Identifying associations between zinc status and mortality could open avenues for early detection, targeted nutritional interventions, and improved neonatal outcomes.

Methodology

This cross-sectional study was conducted over six months from January 2024 to June 2024 in the Pediatrics Medicine department of Mayo Hospital, Lahore. The study was approved by the Institutional Review Board (IRB) of our hospital, and written informed consent was obtained from the parents or guardians of all participants. A total of 130 preterm neonates, born before 37 completed weeks of gestation, were included. The sample size of 130 was calculated using OpenEpi software, considering a 95% confidence level, 80% power, and an anticipated prevalence of zinc deficiency of 40%, with an estimated 15% difference in mortality between zinc-deficient and non-deficient groups. Neonates with major congenital malformations, chromosomal abnormalities, or those who had received zinc supplementation prior to admission were excluded. Relevant demographic and clinical data, including gestational age, birth weight, Apgar scores, and mode of delivery, were recorded. Blood samples were drawn within the first 10 days of life to assess serum zinc levels, using atomic absorption spectrophotometry. Zinc deficiency was defined as serum zinc levels below 60 µg/dL.

All neonates were managed as per unit protocol and were followed during their NICU stay to document outcomes, particularly survival or mortality. Neonates with congenital anomalies, chromosomal disorders, or those who received zinc supplementation prior to admission were excluded. All enrolled neonates received standardized neonatal care as per NICU protocol. Blood samples were obtained within 10 days of life to measure serum zinc levels using atomic absorption spectrophotometry. Zinc status was categorized based on standardized reference values for neonates; levels below 60 µg/dL were considered deficient.

The primary outcome measured was mortality during the hospital stay. Patients were grouped into "survived" and "expired" categories, and their serum zinc levels were compared. Data were entered and analyzed using SPSS version 25. Quantitative variables such as gestational age, birth weight, and zinc levels were expressed as mean ± standard deviation. Categorical variables, including gender, mode of delivery, and mortality, were presented as frequencies and percentages. Independent t-test and Chi-square test were applied where appropriate, and a p-value < 0.05 was considered statistically significant.

Results

Table 1 presents the baseline characteristics of the study population, which included 130 preterm neonates. The mean gestational age was 32.6 ± 2.3 weeks, and the average birth weight was 1608 ± 315 grams. In terms of gender distribution, 71 (54.6%) of the neonates were male, and 59 (45.4%) were female. The majority of deliveries were via cesarean section, accounting for 78 cases (60.0%), while 52 neonates (40.0%) were delivered vaginally. The mean Apgar score at five minutes was recorded as 6.8 ± 1.1, indicating a moderate neonatal condition at birth.

Table 2 shows the survival outcomes among the enrolled neonates. Out of 130 preterm neonates, 84 (64.6%) survived, whereas 46 (35.4%) expired during their hospital stay. This highlights a significant mortality burden in the studied population, justifying the evaluation of potential contributing factors like poor antenatal care, maternal nutritional status, services provided at the time of delivery, postnatal care, lack of breastfeeding, economic burden, and so on.

As shown in Table 3, the mean serum zinc levels among the survivors were 84.2 ± 9.5 µg/dL, while the mean zinc levels of the expired group were 82.6 ± 10.1 µg/dL. Both values fall within the normal reference range, and no case in either group exhibited zinc deficiency (defined as < 60 µg/dL). The difference was not statistically significant (p = 0.452) using the Chi-square test. This indicates that all neonates, regardless of outcome, had adequate zinc levels during the first 10 days of life.

Table 1: Baseline Characteristics of Study Population (N = 130)

Variable	Mean ± SD / n (%)
Gestational Age (weeks)	32.6 ± 2.3
Birth Weight (grams)	1608 ± 315
Gender	
Male	71 (54.6%)
Female	59 (45.4%)
Mode of Delivery	
Cesarean Section	78 (60.0%)
Vaginal Delivery	52 (40.0%)
Apgar Score at 5 minutes	6.8 ± 1.1

Table 2: Neonatal Outcomes Based on Survival Status

Outcome Status	Frequency (n)	Percentage (%)
Survived	84	64.6%
Expired	46	35.4%

Table 3: Serum Zinc Levels Among Survived and Expired Groups

Outcome Group	Mean Zinc Level (µg/dL) ± SD	Zinc Status*
Survived	84.2 ± 9.5	Normal
Expired	82.6 ± 10.1	Normal

***Zinc deficiency defined as < 60 µg/dL; no case in either group fell below this threshold**

Discussion

Preterm neonates are highly vulnerable to morbidity and mortality due to immature organ systems and nutritional deficiencies. Zinc is an essential trace element involved in immune function, enzymatic processes, and cellular growth. (9) Its deficiency has been linked to poor outcomes, including infections and delayed recovery in neonates. Zinc stores are primarily accumulated during the third trimester, placing preterm infants at risk of deficiency. (10) Limited data exist on the direct relationship between zinc levels and mortality in this population. This study was designed to evaluate the association between zinc deficiency and mortality in preterm neonates.

In this cohort of 130 preterm neonates, 84 (64.6%) survived and 46 (35.4%) expired; mean serum zinc levels were 84.2 ± 9.5 µg/dL in the survived group and 82.6 ± 10.1 µg/dL in the expired group, with no neonate meeting the study definition of zinc deficiency (< 60 µg/dL). A two-sample t-test comparing mean zinc concentrations between survivors and non-survivors yielded a t = 0.88 with Welch degrees of freedom ≈ 88 and p = 0.38, indicating no statistically significant difference in zinc levels between outcome groups. These findings contrast with several interventional and observational studies that reported lower mortality or case-fatality in zinc-treated or zinc-replete groups. For example, Heba et al. (2020) reported total mortality of 16/90 (17.8%) with a markedly higher mortality among controls (24.4%) compared to 11.1% in the zinc-receiving group;(11) El Frargy et al. (2017) similarly documented fewer deaths in the zinc cohort (10%) versus the non-zinc cohort (18%). (12) Mahmood et al. (2015) reported mean zinc levels of 9.71 ± 0.71 g/dL among preterm infants, suggesting that baseline zinc concentrations in some populations may be lower than in ours, potentially explaining why supplementation trials in such contexts show mortality benefit. (13) Banupriya et al. (2018) also found a significantly higher mortality in the no-zinc group (13 deaths) compared with the zinc group (5 deaths, P = 0.04). (14) These studies support a protective effect of zinc supplementation or adequate zinc status on mortality in pediatric and neonatal populations.

Conversely, several studies have reported either no significant mortality benefit or mixed results that more closely align with our observations. Newton et al. (2016) found mean post-treatment serum zinc 737.09 ± 219.97 versus 801.26 ± 405.56 (p = 0.20) and reported similar hospital stay (15 vs 15 days; p = 0.69) and non-significantly different mortality

(4.5% vs 13.6%; p = 0.27). (15) Saleem et al. (2016) observed mortalities of 19% (zinc) versus 25% (no zinc), a difference that was not presented as strongly significant;(16). Smucker et al. (2020) reported 4.5% mortality in the zinc group versus 13.6% in controls. (17) The heterogeneity in effect sizes and statistical significance across these reports—ranging from clear reductions (11, 12, 14) to non-significant trends (15,16) highlights variability by study design, population, baseline zinc status, and severity of illness. Hafeez et al. reported that in an Egyptian study of neonatal sepsis, they documented significantly lower mortality in the zinc-supplemented group (10%) compared to controls (18%). (18)

Several methodological and biological factors may explain why our study did not find an association between zinc status and mortality, whereas many supplementation trials reported benefits. First, in our population, all measured serum zinc concentrations were within normal reference ranges (means ≈ 83–84 µg/dL), so the absence of zinc deficiency limited the possibility of observing an effect driven by correcting a true deficiency. In contrast, trials that demonstrated mortality or morbidity reductions often enrolled populations with baseline zinc insufficiency or administered therapeutic zinc dosing (11, 12, 14), which could produce a measurable clinical effect. Second, the timing and frequency of zinc assessment vary across studies. We measured zinc levels once, in first ten days of life, whereas some trials assessed serial levels or provided early supplementation and monitored the response, potentially capturing dynamic changes relevant to outcomes (Newton et al. reported 10-day measures). (15) Third, outcomes such as mortality are multifactorial—severity of prematurity, birth weight, infection burden, respiratory support requirements, and other micronutrient deficiencies all contribute, so zinc status alone may be insufficient to predict mortality without accounting for these confounders. Fourth, study designs differ: randomized supplementation trials can demonstrate causality more readily than observational studies, where residual confounding may mask or mimic associations.

The study included a well-defined sample of 130 preterm neonates from a tertiary care NICU. Zinc levels were measured using standardized laboratory methods within the first 10 days of life. Both groups received uniform neonatal care, minimizing treatment bias. However, the study did not assess other micronutrients or inflammatory markers—the single-center design limits the generalizability of the findings. Additionally, zinc status was assessed only once, without serial monitoring.

Conclusion

Zinc deficiency was not significantly associated with mortality in preterm neonates. All deaths occurred despite normal or slightly increased zinc levels. Neonatal mortality appears to be multifactorial rather than solely linked to zinc status.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC--24)

Consent for publication

Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

SL (MBBS, FCPS Peads, Clinical fellow in Neonatology)
Original idea for programme of work, acquisition of ethical approval, data collection and interpretation, writing and final approval of the draft.
MHH (MBBS, FCPS, MRCP, FRCP, Master Medical Education, Professor, Chairman Pediatric Medicine)
Supervised all steps, proofreading and critical review of the article
AA (MBBS, FCPS Paeds, Woman Medical Officer)
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ST (MBBS, FCPS, Peads, Women Medical Officer)
Data collection and analysis

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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