

Original Research Article

Relationship between serum zinc levels and the burden of treatment in children with pneumonia

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ABSTRACT

Background: Pneumonia is a common childhood disease often requiring hospitalization, with the potential for rapid progression and complications, particularly in children under five years old. Zinc plays a crucial role in various organ systems, especially the respiratory system. However, data on zinc levels and pneumonia in Vietnamese children remain limited. This study aimed to investigate the relationship between serum zinc levels and the treatment burden in children with pneumonia.

Methods: A prospective observational study was conducted involving 200 children aged 2 to 59 months who were diagnosed with pneumonia and hospitalized at Can Tho Children's Hospital, Vietnam. Serum zinc levels were measured, and treatment characteristics were monitored, including the need for respiratory support, antibiotic escalation, and treatment duration. Data were analyzed using descriptive statistics, independent t-tests, simple linear regression and multivariable linear regression to determine associations between serum zinc levels and treatment outcomes.

Results: Children who were not exclusively breastfed for the first six months had significantly lower serum zinc levels compared to those who were exclusively breastfed ($p < 0.001$). Lower serum zinc levels were significantly associated with the need for respiratory support ($p = 0.001$), antibiotic escalation ($p = 0.002$), prolonged antibiotic use ($p = 0.01$), and longer treatment duration ($p = 0.011$). Multivariate linear regression revealed that each unit decrease in serum zinc levels increased treatment duration by 0.218 days ($p = 0.015$).

Conclusion: Low serum zinc levels are associated with increased treatment burden in children under five years old with pneumonia.

Keywords: Children, Zinc, Pneumonia, Treatment

INTRODUCTION

Pneumonia, defined as inflammation of the lung parenchyma, is the leading cause of death and causes nearly one-third of all deaths from infection globally among children younger than five years.¹ It is estimated that about 2,000 children die every day from complications of pneumonia.² Therefore, pneumonia remains a disease burden in children. Zinc, an essential trace element, plays a multitude of vital roles in various organ systems, with its most significant impact seen in the immune and

respiratory systems.³ Zinc deficiency can impact the number and function of B and T lymphocytes, macrophages, and natural killer cells.⁴ However, zinc's role in regulating the immune system is crucial, as it protects children from respiratory tract infections by controlling the inflammatory response through immunoregulators.⁵ Furthermore, zinc's antioxidant and cytoprotective properties act as a shield against toxins and inflammatory mediators that harm the respiratory epithelium.^{3,5} Even mild to moderate low zinc levels can impair the immune system, highlighting the importance

of zinc in immune regulation.⁴ A systematic review published in the Cochrane Library suggested that zinc supplementation in children under five helps reduce pneumonia incidence and prevalence.⁶ Previous studies have demonstrated that low serum zinc levels are associated with pneumonia severity.⁷⁻⁹ Our study aimed to investigate the relationship between low zinc levels and the burden of pneumonia treatment, thereby providing a basis for whether clinical trials using zinc as an adjunct to standard treatment should be conducted.

METHODS

This prospective observational study included children aged 2 to 59 months diagnosed with pneumonia and hospitalized at Can Tho Children's Hospital in Vietnam between December 2022 and January 2024. The study enrolled patients continuously until a sufficient sample size was reached. In this study, in order to obtain a reliable estimate of serum zinc levels in children with pneumonia, we calculated the necessary sample size using a 95% confidence levels and a standard deviation of 3.33 $\mu\text{mol/l}$ from previous study.⁹ With a margin of error of 0.5 $\mu\text{mol/l}$, the calculated sample size required was at least 170 children. We factored in a 20% allowance for potential non-responses or dropouts, leading to a final sample size of 200 children.

Inclusion criteria

Children were eligible for inclusion in the study if they met all the criteria. Diagnosis of pneumonia according to the criteria for children under five years old by pediatricians. Availability of serum zinc concentration measurement.^{10,11}

Exclusion criteria

To avoid confounding factors, the study excluded children who had previously taken zinc supplements within three months before admission, those with a history of chronic illnesses (liver or kidney disease), those with a history of congenital anomalies, or those with conditions that might affect zinc metabolism.

Data collection

A standardized assessment was conducted for each child, including general characteristics (sex, age, living place, guardian's education, immunization status, exclusive breastfeeding for the first 6 months) and serum zinc levels measurement (venous blood samples were collected from each child. Serum zinc levels were measured using a colourimetric assay on an AU480 Chemistry Analyzer (Beckman Coulter, Inc, CA)) were collected at the admission. Then, the treatment process and results (respiratory support, antibiotic combination at admission, antibiotic escalation, time of antibiotic use, and duration of treatment) were evaluated when the

children were discharged from hospital and at the end of outpatient treatment (if any).

Exclusive breastfeeding in the first 6 months was defined as feeding the infant only breast milk, without any additional food or drink, except for vitamins or minerals prescribed by physicians.¹² Immunization status was categorized as vaccinated or partially vaccinated. Children were considered (a) vaccinated if they had received all vaccinations according to the National expanded program on immunization schedule for their age, or (b) partially vaccinated if they had not received any vaccines or had received some but not all vaccines according to the National Expanded Program on Immunization Schedule.¹³ Antibiotic escalation refers to intensifying antimicrobial therapy in response to clinical deterioration or lack of improvement in a patient's condition. This can involve initiating new antibiotics, adding additional antibiotics, or switching to antibiotics with a broader spectrum of activity.¹⁴ Duration of treatment is calculated as the total number of inpatient treatment days plus any outpatient treatment days after discharge.

This study was conducted under the ethical standards of the Helsinki Declaration. The Can Tho University of Medicine and Pharmacy's Ethics Committee in Biological Research granted the study ethical approval (No. 177/PCT-HĐĐĐ). We received informed consent from the parents/guardians of every child participating in the study before their involvement. They were informed that their child's medical care would not be impacted if they decided to remove their child from the study at any point.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 26.0 (IBM Corp, Armonk, NY). Descriptive statistics were used to summarize the study population's characteristics. The results of the analytical statistics were presented in tables. The independent t-test was used to compare continuously distributed variables that were normally distributed. A statistically significant result was defined as a p value less than 0.05. To assess the association between treatment duration and serum zinc levels, we included a multivariate linear regression model to control for potential factors, including age group, sex, vaccination status, antibiotic combination at admission, and exclusive breastfeeding in the first 6 months. The multiple linear regression model was evaluated to ensure its assumptions were met. (a) Linearity was assessed through residual plots, which showed no discernible patterns, indicating a linear relationship between predictors and the dependent variable. (b) The Durbin-Watson test confirmed errors' independence, revealing no significant autocorrelation with a value of 1.5-2.5. (c) Homoscedasticity was checked by plotting residuals against fitted values. (d) Lastly, the normality of residuals was verified with a Q-Q plot demonstrating that residuals

were approximately normally distributed. These diagnostic checks validate the appropriateness of the multiple linear regression model for our data p values are used for the hypothesis test, and the t-test is used to find how each estimated coefficient significantly differs from zero.

Statistical analysis

Statistical significance was set at $p < 0.05$. R-squared is the numerical value for a fraction of the variation in the dependent variable that the independent variables can explain.

RESULTS

This study included 200 children, ages 2 to 59 months, who were admitted to Can Tho Children's Hospital for pneumonia during the study period. There was little difference in zinc levels according to gender or area of residence. Children under one year old, those who were partially vaccinated or those whose guardians had less education did not exclusively significantly exhibit lower serum zinc levels. Notably, 143 out of 200, or 71.5% of the children, did not breastfeed for the first six months, and their serum zinc concentrations were significantly lower than those of their exclusively breastfeeding peers ($p < 0.001$). More information was displayed in Table 1.

Table 1: Baseline characteristics and zinc levels of the study subjects.

Characteristics	n ^a	Serum zinc levels, Mean±SD (μmol/l)	t value	P value
Sex				
Male	127	9.25±3.41	0.114	0.909
Female	73	9.19±3.82		
Age group (months)				
2<12 months	56	8.89±3.31	-0.828	0.409
12-59 months	144	9.36±3.64		
Place of residence				
Urban	88	9.25±3.41	-0.056	0.956
Rural	112	9.22±3.68		
Guardian's education				
Secondary or below	86	8.80±3.15	-1.505	0.134
High school or above	114	9.56±3.81		
Immunization status				
Partially vaccinated	53	8.60±3.09	-1.520	0.130
Vaccinated	147	9.46±3.68		
Exclusive breastfeeding in the first 6 months				
Yes	57	11.0±4.15	4.090	<0.001*
No	143	8.53±3.02		

*P value<0.05 was considered significant, ^an: number of patients.

Table 2: Treatment features and zinc levels of children with pneumonia.

Characteristics	n ^a	Serum zinc levels, Mean±SD (μmol/l)	t value	P value
Respiratory support				
Yes	38	7.94±2.04	-3.558	0.001*
No	162	9.53±3.76		
Antibiotic combination at the admission				
Yes	30	8.52±3.36	-1.180	0.24
No	170	9.36±3.58		
Antibiotic escalation				
Yes	74	8.34±2.51	-3.093	0.002*
No	126	9.76±3.96		
Time of antibiotic use (in days)				
≤ 7	86	9.99±3.69	2.657	0.009*
> 7	114	8.66±3.35		
Duration of treatment (in days)				
≤ 7	75	10.09±3.86	2.582	0.011*
> 7	125	8.72±3.26		

*P value<0.05 was considered significant, ^an: number of patients.

Table 3: Multiple linear regression model for factors correlated with the duration of treatment.

Variables	Regression coefficient (B)	95% CI of regression coefficient	Standardized coefficient	t value	P value
Constant	14.815	10.353, 19.278	-	7.503	<0.001
Serum zinc levels (µmol/l)	-0.218	-0.394, -0.042	-0.174	-2.447	0.015*
Sex (Female)	-0.793	-2.028, 0.441	-0.086	-1.267	0.207
Age group (12-59 months)	1.088	-0.267, 2.443	-0.110	1.58	0.115
Immunization status (vaccinated)	-1.908	-3.309, -0.507	-0.189	-2.687	0.008*
Exclusive breastfeeding in the first 6 months	-1.311	-2.714, 0.92	-0.133	-1.843	0.067
Antibiotic combination at the admission	-1.015	-2.688, 0.657	-0.081	-1.197	0.233

R-square=0.131, adjust R-square=0.104, 95% CI:95% confidence interval, *P value<0,05 was considered significant.

Treatment characteristics are presented in Table 2, children requiring interventions such as respiratory support, antibiotic escalation, antibiotic treatment duration exceeding 7 days, or total hospital stay exceeding 7 days exhibited significantly lower mean serum zinc concentrations compared to those who did not require these interventions ($p<0.05$). Figure 1 shows a significant negative correlation between serum zinc levels and treatment duration for children with pneumonia ($r=-0.24$, $p<0.001$). As serum zinc levels increase, the number of treatment days decreases. The regression line ($Y=-0.296 \times X + 12.24$) indicates that each unit increase in zinc reduces treatment duration by 0.296 days. This relationship explains 5.3% of the variance in treatment days ($R^2=0.053$).

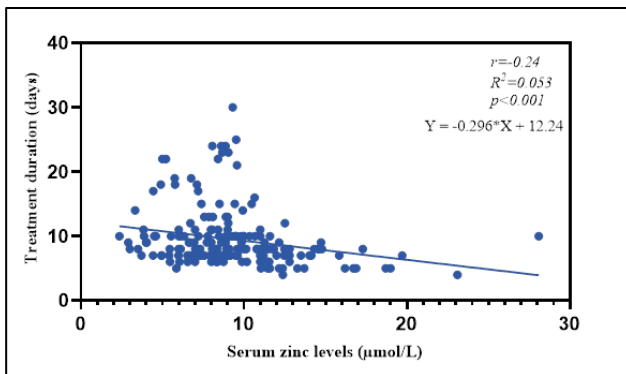


Figure 1: Simple linear regression showed the correlation between serum zinc levels and treatment duration.

The multiple linear regression analysis presented in Table 3 examines the factors associated with the number of treatment days in children with pneumonia. The regression model includes serum zinc levels, sex, age group, vaccination status, exclusive breastfeeding for the first six months, and antibiotic combination at admission. A key finding is the significant negative correlation between serum zinc levels and the number of treatment days ($B=-0.218$, $p=0.015$), indicating that lower zinc

levels are associated with longer treatment days. Specifically, for each unit of decreased serum zinc concentration, the number of treatment days increases by 0.218 days, holding other variables constant. The model explains 13.1% of the variance in treatment days (R -square=0.131), with an adjusted R -square of 0.104, suggesting that while serum zinc is a significant factor.

DISCUSSION

The results of our study show that there are no significant differences in serum zinc levels based on sex, age group, place of residence, immunization status or guardian's education. These findings align with other studies. For example, Rajasekaran J et al reported no significant differences in zinc levels between males and females (9.24 ± 4.25 vs 9.22 ± 4.69 µmol/l, $p=0.987$) or across age groups ($p=0.946$).¹⁵ Likewise, Hussain AM et al also discovered no statistically significant differences in zinc levels based on age, sex, immunization status.¹⁶ Marcos JM et al. showed results similar to ours, there were no discernible difference in zinc status between children living in rural and urban areas or between children whose parents had secondary school education or less versus higher education.¹⁷

We observed significantly higher serum zinc levels in children who were exclusively breastfed for the first 6 months compared to those who were not (11.0 ± 4.15 versus 8.53 ± 3.02 µmol/l, $p<0.001$). This finding is consistent with studies by Hussain AM et al and Hamed AMM et al, who also reported significantly lower serum zinc levels in children who were not exclusively breastfed ($p<0.05$).^{9,16} Additionally, Kumar N, et al. concluded that exclusive breastfeeding is a protective factor against zinc deficiency.¹⁸ The stable zinc content in breast milk, along with its higher bioavailability during the first 6 months, and the enhanced immune function associated with breastfeeding, effectively protect against infections and reduce the risk of zinc loss due to diarrhea.¹⁹ Therefore, promoting exclusive breastfeeding for the first 6 months of life is an essential strategy for preventing zinc deficiency in children.

Children who were required respiratory support exhibited significantly lower mean serum zinc levels compared to those who were not (7.94 ± 2.04 vs 9.53 ± 3.76 , $p < 0.001$). This observation aligns with Saleh NY et al, who also reported significantly lower serum zinc levels in children requiring respiratory support ($p < 0.001$).⁸ Furthermore, Assar EH et al demonstrated a stepwise decrease in serum zinc levels with increasing levels of respiratory support from room air to invasive mechanical ventilation ($p < 0.001$).⁷ Regarding antibiotic escalation during treatment, children who were required antibiotic escalation showed significantly lower serum zinc levels compared to those who were not (8.34 ± 2.51 vs 9.76 ± 3.96 , $p = 0.002$). This suggests that low zinc status may influence the response to antibiotic therapy. Zinc deficiency is known to impair both humoral and cellular immune responses, potentially leading to a more severe disease course and making infection control more challenging.^{4,20} Consequently, the initial treatment may be insufficient to fight the infection in children with low serum zinc levels, necessitating antibiotic escalation. Additionally, low serum zinc levels can exacerbate respiratory distress in children with pneumonia, further worsening the disease progression and prompting clinicians to change antibiotics. Brooks et al, in a double-blind, randomized controlled trial of 270 children, found that 20 mg/day elemental zinc supplementation reduced the need for multiple antibiotics to treat pneumonia.²¹

Children who needed antibiotic treatment for more than 7 days had lower serum zinc concentrations compared to those who completed the standard pneumonia treatment within 7 days (8.66 ± 3.35 vs 9.99 ± 3.69 , $p = 0.01$). This suggests that low serum zinc levels may be associated with a reduced response to antibiotic therapy. As previously mentioned, zinc deficiency can impair the immune system, potentially leading to a more severe disease course and requiring prolonged antibiotic use. Moreover, lower serum zinc levels may be associated with increased disease severity or progression.^{7-9,18} The above reasons may lead to the need to change antibiotic therapy during treatment, thus extending the duration of antibiotic use. Additionally, children with low serum zinc levels often have weaker immune systems, making it more difficult to control the causative bacteria with antibiotics, which may hinder de-escalation of antibiotic therapy (switching from broad-spectrum to narrow-spectrum antibiotics or from intravenous to oral administration). These findings suggest that improving serum zinc levels could potentially alleviate the burden of antibiotic treatment.

We observed that children with shorter treatment durations (≤ 7 days) had significantly higher serum zinc concentrations compared to those with prolonged treatment (> 7 days). Simple linear regression analysis between treatment duration and serum zinc concentration revealed a negative correlation ($r = -0.24$, $p < 0.001$), although zinc levels could only explain 5.3% of the variation in treatment duration. After adjusting for

potential confounders in a multivariate linear regression model, we confirmed a significant inverse relationship between treatment duration and serum zinc levels (with each 1 $\mu\text{mol/l}$ decrease in zinc concentration, treatment duration increased by 0.218 days $p = 0.015$). This model explained 13.1% of the variation in treatment duration. Similarly, Khera D et al in a prospective interventional study of 465 children, found that zinc-deficient children with lower respiratory tract infections had significantly longer illness durations compared to those without zinc deficiency ($p < 0.001$).²² Assar EH et al also reported that lower serum zinc concentrations were correlated with longer hospital stays ($r = -0.2$, $p = 0.029$).⁷ Additionally, Saleh NY et al found a negative correlation between PICU length of stay and serum zinc levels ($r = -0.383$, $p = 0.002$).⁸ This suggests that low zinc levels may significantly impact the recovery process in children with pneumonia. Zinc is important for maintaining immune function, regulating excessive airway inflammation improving mucus clearance and preserving respiratory muscle function.^{23,24} Children with low serum zinc levels may experience a more severe disease course and require more intensive interventions, leading to prolonged treatment durations.^{4,5} There are some limitations in our study. Firstly, serum zinc levels were measured only at the time of hospital admission, and variations in zinc levels during the treatment period were not accounted for, which could provide a more comprehensive understanding of the relationship between zinc status and treatment burden. Secondly, the sample was drawn from a single hospital in Vietnam, which may limit the generalizability of the findings to other populations or regions with different healthcare practices and nutritional statuses. Besides, despite controlling for several potential confounders, other unmeasured factors may influence the outcomes. Future studies with larger, more diverse populations are needed to confirm these findings and explore the mechanisms underlying the relationship between zinc and pneumonia treatment burden.

CONCLUSION

Low serum zinc levels are associated with the need for respiratory support, antibiotic escalation, and prolonged antibiotic use in children with pneumonia. There is a negative correlation between serum zinc levels and treatment duration in children with pneumonia. These findings indicated an association between low serum zinc levels and increased treatment burden in children under 5 years old with pneumonia, suggesting that adding zinc supplementation to the standard treatment for pneumonia could be beneficial, especially in severe cases, and could potentially reduce the overall treatment burden. Further research is necessary to assess the effectiveness of zinc supplementation in treating pneumonia in children.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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