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The Relationship of Serum Zinc Level in Patients with Pneumonia and Its Effect on Their Outcome

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ABSTRACT

Background: Pneumonia remains the leading infectious cause of death among children worldwide. Zinc plays a crucial role by activating numerous enzymes participating in various metabolic and immune functions.

Objective: To evaluate serum zinc levels in children hospitalized with pneumonia and to investigate the relationship between zinc concentrations, the severity of pneumonia, and patient outcomes.

Patients and Methods: The study involved 120 children diagnosed with pneumonia, categorized into two groups based on their need for Pediatric Intensive Care Unit (PICU) admission: Group I: 45 children who required PICU admission, while Group II: 75 children who did not. Comprehensive medical histories, thorough clinical examinations, laboratory tests, radiological evaluations, and serum zinc measurements were conducted for all participants

Results: Children admitted to the PICU had significantly lower serum zinc levels (62.8±26.7 μg/dL) compared to those not admitted (93.4±30.2 μg/dL), p<0.001. Severe pneumonia, increased oxygen support, and mortality were associated with lower serum zinc levels. Serum zinc levels positively correlated with weight, height, BMI, hemoglobin, and blood pH, and negatively correlated with blood CO_2, C-reactive protein, and hospital stay duration. At a cutoff of <67.1 μg/dL, serum zinc was able to predict severe cases of pneumonia in children, with sensitivity of 83.1% and specificity of 74.3%. At a cutoff of <47 μg/dL, serum zinc was able to predict mortality in children with pneumonia, with 80.8% sensitivity and 73.2% specificity.

Conclusion: A deficiency in zinc was linked to more severe cases of pneumonia, increased necessity for mechanical ventilation, higher mortality rates, and prolonged hospital stays.

Keywords: Zinc; Children; Pneumonia; PICU.

INTRODUCTION

Pneumonia remains the leading infectious cause of pediatric mortality globally, accounting for 14% of all deaths among children under five years old. In 2019, pneumonia claimed the lives of 740,180 children worldwide. This disease poses a significant public health challenge, impeding healthy childhood development and imposing a substantial economic burden on patients, families, and society, exceeding that of other common pediatric illnesses [1].

Zinc is an essential micronutrient, second only to iron in abundance in the human body, and is a component of over 70 enzymes. It plays a crucial role in the function of biomembranes and protects against oxidative damage by competing with redox metals for binding sites. Zinc exhibits both acute and chronic antioxidant properties [2].

Research has shown that the prevalence of zinc deficiency among apparently healthy children and adolescents ranges from 44% to 72% [3]. Zinc is a trace element that activates multiple enzymes involved in various metabolic and immune responses. It possesses direct antiviral properties and influences the immune-mediated production of interferon. Additionally, zinc prevents pathogens from entering cells and inhibits their intracellular multiplication. Zinc deficiency impairs the body's ability to respond to infections and negatively affects both cell-mediated and humoral immune responses [4].

Zinc is integral to numerous immune system functions, including phagocytosis, maintenance of gastrointestinal and respiratory tract linings, and the development and function of T and B cells. Zinc deficiency is proposed to exacerbate inflammatory pathology in the respiratory tract, leading to increased cellular damage [5].

In developing countries, zinc deficiency is linked to up to 4.4% of infection-related deaths. Zinc also inhibits the recruitment of white blood cells and the release of cytokines from these cells, with its effectiveness purportedly increasing with the severity of pneumonia [6].

This study aimed to assess the serum zinc levels in children admitted with pneumonia and to explore the relationship between zinc levels, the severity of pneumonia, and the impact on patient outcomes.

PATIENTS AND METHODS

This comparative cross-sectional study was conducted on children diagnosed with pneumonia, admitted to Benha Fever Hospital and Benha University Hospital from June 2023 to December 2023. The study included 120 children who met the World Health Organization (WHO) clinical and radiological criteria for pneumonia [7]. Exclusion criteria were children on

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zinc supplementation, those with aspiration or chemical pneumonia, severe acute malnutrition, and other coexisting illnesses.

The participants were divided into two groups based on the need for inpatient admission or PICU admission according to WHO pneumonia guidelines [7].

Group I: This group consisted of 45 children (23 males and 22 females) admitted to the PICU, with a mean age of 2.8 ± 1.6 years. Group II: This group included 75 children (41 males and 34 females) who were not admitted to the PICU, with a mean age of 2.3 ± 1.9 years.

All included patients underwent a comprehensive history taking, complete clinical examination, laboratory investigations, chest X-ray, and CT chest if necessary. A single serum zinc measurement was performed for all patients within 24 hours of admission, in the morning, while they were non-fasting.

Ethical considerations

The study was done after being accepted by the Research Ethics Committee, Benha University. All patients' parents provided written informed consents prior to the enrolment of their children. The consent form explicitly outlined their agreement that their children would participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The data were reviewed, coded, and analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp. Released 2017. Armonk, NY, USA). Quantitative data were presented as mean, standard deviation (± SD), and range. Student's T-test assessed differences between two group means, while ANOVA compared means among more than two groups. Categorical data were presented as frequency and percentage and Chi-square test examined the relationships between them. Correlation analysis evaluated the strength and direction of associations between quantitative variables. The ROC curve analyzed the sensitivity and specificity of diagnostic measures, with the optimal cutoff point maximizing the AUC value. P value < 0.05 was considered significant.

RESULTS

This study included 120 children with pneumonia, patients were divided according to need of PICU admission into two groups: Group 1: included 45 children who were admitted to PICU, Group 2: included 75 children who weren't admitted to PICU. There was no statistical difference between the studied groups as regards to sex, age, history of NICU or PICU admission **(Table 1)**.

Table 1: Sociodemographic data of the studied groups

		Group 1		Group 2		Test	P value
		N=45	%	N=75	%		
Sex	**Male**	23	51.1%	41	54.7%	X^2=0.14	0.71
	Female	22	48.9%	34	45.3%		
Age (years)	**Mean ±SD**	2.8 ±1.6		2.3 ±1.9		t=1.1	0.29
	Range	2 months-10 years		3 months-10 years			
History of NICU admission	**No**	26	57.8%	46	61.3%	X^2=0.15	0.70
	Yes	19	42.2%	29	38.7%		
History of previous PICU admission	**No**	43	95.6%	71	94.7%	X^2=0.05	0.83
	Yes	2	4.4%	4	5.3%		

X^2: Chi-Square test, t: Student t-test, SD: Standard Deviation, NICU: Neonatal Intensive Care Unit, PICU: Pediatric Intensive Care Unit.

Children admitted to PICU had statistically lower level of serum zinc (62.8±26.7 μg/dL) compared to children who weren't admitted to PICU (93.4±30.2 μg/dL), p< 0.001 **(Figure 1)**.

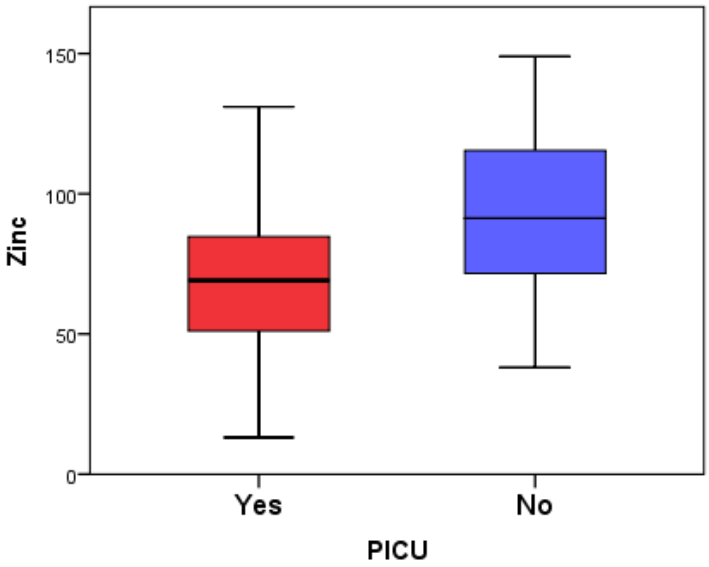

Figure 1: Level of serum zinc in the studied groups.

Children with severe pneumonia and children with higher need of oxygen support and died children had statistically lower levels of zinc level. **Table 2**

Table 2: Level of serum zinc according to disease severity and outcome

		Zinc (µg/dL)		Test	P value
		Mean ±SD	Range		
Severity	**Mild**	99.00±29.92	47.2-149	F=12.1	<0.001*
	Moderate	85.26±30.33	17.8-146.1		
	Severe	64.45±24.09	13.1-107.2		
Oxygen support	**No**	103.36±29.31	51.1-149	F=8.9	<0.001*
	Nasal O_2	86.38±29.38	17.8-146.1		
	CPAP	69.66±26.44	17.8-107.2		
	MV	49.52±22.52	13.1-77.5		
Death	**No**	86.25±30.09	13.1-149	t=3.6	<0.001*
	Yes	41.48±24.07	13.1-77.5		

t: Student t-test, F: F value of one-way ANOVA, *: significant, CPAP: Continuous Positive Airway Pressure, MV: Mechanical Ventilation.

Level of serum zinc had a significant positive correlation with (weight, height, BMI, hemoglobin and blood pH) and a significant negative correlation with (blood CO_2 and C-reactive protein and duration of hospital stay). While there was no significant correlation between serum zinc and (age, WBC, platelets, RBS, serum level of ALT, AST, urea, creatinine, sodium, potassium, calcium). **Table 3**

Table 3: Correlation between level of zinc and other clinical data

	Zinc (µg/dL)	
	r	P value
Age	-0.013	0.885
Weight	0.341	<0.001*
Height	0.322	<0.001*
BMI	0.237	0.009*
Hemoglobin	0.296	0.031*
WBC	-0.171	0.150
Platelets	0.114	0.217
C-reactive protein	-0.336	<0.001*
RBS	0.098	0.289
ALT	0.021	0.824
AST	0.037	0.685
Urea	-0.070	0.448
Creatinine	0.028	0.758
Sodium	-0.035	0.706
Potassium	0.074	0.425
Calcium	-0.102	0.267
pH	0.218	0.048*
CO_2	-0.295	<0.001*
HCO_3	-0.156	0.088
Duration of hospital stay	-0.199	0.029*

r: Correlation coefficient, *: significant, BMI: Body Mass Index, WBC: White Blood Cells, RBS: Random Blood Sugar, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, CO_2: Carbon Dioxide, HCO_3: Bicarbonate.

ROC analysis was done to assess the performance of serum zinc to predict need of PICU admission in children with pneumonia; AUC was 0.809 (CI: 0.690-0.881), p<0.001. At a cutoff point ≤ 74 µg/dL, the sensitivity was 86.8 % and specificity was 75.2% **(Figure 2)**.

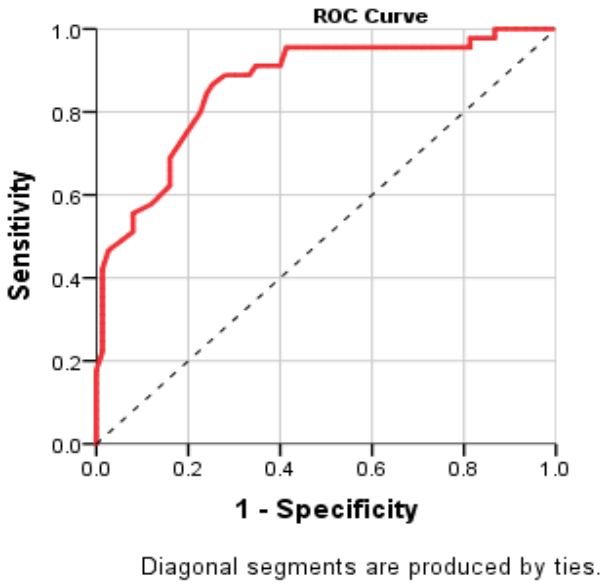

Figure 2: ROC curve of performance of zinc to predict need of PICU admission in children with pneumonia

ROC analysis was done to assess the performance of serum zinc to predict severe cases in children with pneumonia; AUC was 0.859 (CI: 0.646-0.932), p<0.001. At a cutoff point ≤ 67.1 µg/dL, the sensitivity was 83.1 % and specificity was 74.3% **(Figure 3)**.

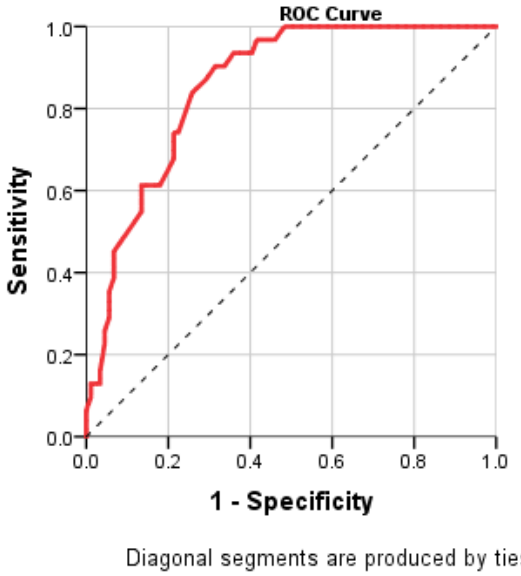

Figure 3: ROC curve of performance of zinc to predict severe cases in children with pneumonia

ROC analysis was done to assess the performance of zinc to predict mortality in children with pneumonia; AUC was 0.809 (CI: 0.690-0.881), p<0.001. At a cutoff point ≤ 68 µg/dL, the sensitivity was 80.8 % and specificity was 73.2% **(Figure 1)**.

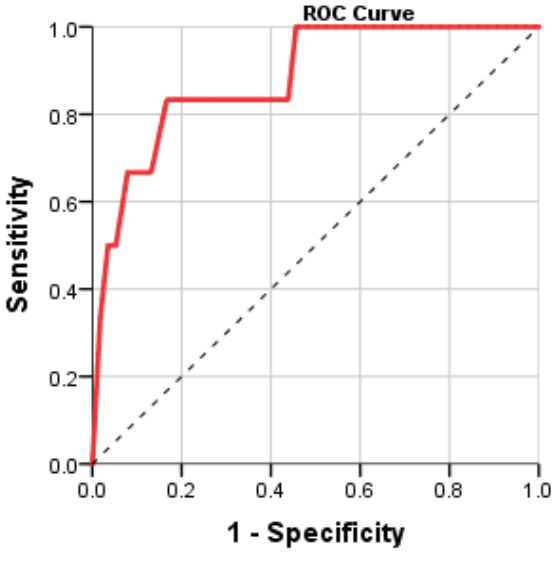

Figure 4: ROC curve of performance of serum zinc to predict mortality in children with pneumonia.

DISCUSSION

Children admitted to PICU had statistically lower level of serum zinc (62.8±26.7 µg/dL) compared to children who weren't admitted to PICU (93.4±30.2 µg/dL).

Our findings align with those of **Saleh and Abo El Fotoh** [8], who identified a statistically significant difference in mean total serum zinc levels at admission between Group 1 (PICU admission, 50.7 ± 27.4 μg/dL) and Group 2 (ward admission, 81.0 ± 14.4 μg/dL), with P < 0.001. Similarly, **Alsharkawy and Rezk** [9] noted significantly lower zinc levels in the patient group compared to the control group, suggesting a link between low serum zinc levels and community-acquired pneumonia.

Yuan *et al.* [10] found that 76% of critically ill infants with community-acquired pneumonia had reduced peripheral blood zinc levels. **Barnett *et al.*** [11] observed that zinc supplementation positively influenced the clinical course and incidence of pneumonia. This reduction in serum zinc concentrations during acute infections and inflammation is likely due to the redistribution of zinc from plasma to the liver, driven by cytokines released during the acute phase response, which activate hepatic metallothionein (MT) synthesis, a metal-binding protein that modifies hepatic zinc uptake [12].

In the current study, children with severe pneumonia and children with higher need of oxygen support and children who died had statistically lower levels of zinc level.

Similarly, **Ahmed** [12] discovered an inverse relationship between serum zinc levels and the necessity for respiratory support. He also found that patients who died had lower plasma zinc levels compared to those who recovered and were discharged. Our findings are consistent with those of **Saleh and Abo El Fotoh** [8], who reported higher zinc levels associated with lower grades of respiratory distress. The mortality rate was 26.67%, with significantly higher mean serum zinc levels in patients who were discharged compared to those who died, linking serum zinc levels to patient outcomes. This is supported by **Gonçalves *et al.*** [13], who observed low serum zinc levels in critically ill patients with severe ARDS due to SARS-CoV-2. **Jothimani *et al.*** [14] also noted that COVID-19 patients with zinc deficiency experienced more complications and longer hospital stays. However, contrary to our results, **Linko *et al.*** [15] found that zinc levels did not predict 30-day mortality in critically ill adults with ARDS.

Zinc is thought to be an essential element for epithelial cell integrity, reducing lower respiratory tract inflammation and improving respiration [12].

In the present study, zinc levels showed a significant positive correlation with weight, height, BMI, hemoglobin, and pH, and a significant negative correlation with CO_2, C-reactive protein, and duration of hospital stay. However, there was no significant correlation between zinc levels and age, WBC, platelets, RBS, ALT, AST, urea, creatinine, sodium, potassium, or calcium.

Our findings are consistent with those of **Saleh and Abo El Fotoh** [8], who observed a significant positive correlation between serum zinc levels and patients' mean weight and height, while noting a significant negative correlation between serum zinc levels and the duration of PICU stay (r = −0.383, P = 0.002). Similarly, **Goyena *et al.*** [16] found that zinc deficiency was significantly more prevalent among underweight (21.0%) and stunted children (24.5%) compared to those with normal nutritional status. Additionally, a study on preschool children aged 2–3 years in Laguna, Philippines, reported a negative association between zinc status and stunting, indicating that zinc deficiency was less common among children with normal height for their age [17]. This correlation is attributed to zinc's crucial role in protein synthesis, cellular differentiation, and growth, including DNA replication, particularly in young children. These results support experimental human intervention trials showing that zinc deficiency limits growth [16].

Our findings are consistent with those of **Cole *et al.*** [18], who identified a significant relationship between serum zinc concentrations and hemoglobin levels (r = 0.26, P < 0.001). Anemia has been proposed as an indicator of zinc deficiency because iron and zinc share similar food sources and distribution in the diet, both having low bioavailability in cereals due to phytates, and because of zinc's role in erythropoiesis [19].

Similarly, previous studies [12,20] have also reported a significant negative correlation between zinc levels and CRP, supporting the notion that serum zinc concentrations decrease during acute infections and inflammation [21].

In the current study, ROC analysis was done to assess the performance of zinc to predict need of PICU admission in children with pneumonia; AUC was 0.809 (CI: 0.690-0.881), p<0.001. At a cutoff point ≤ 74 μg/dL, the sensitivity was 86.8 % and specificity was 75.2 %. ROC analysis was done to assess the performance of zinc to predict severe cases in children with pneumonia; AUC was 0.859 (CI: 0.646-0.932), p<0.001. At a cutoff point ≤ 67.1 μg/dL, the sensitivity was 83.1 % and specificity was 74.3 %. ROC analysis was done to assess the performance of zinc to predict mortality in children with pneumonia; AUC was 0.809 (CI: 0.690-0.881), p<0.001. At a cutoff point ≤ 68 μg/dL, the sensitivity was 80.8 % and specificity was 73.2 %.

In the same way, **Ahmed** [12], observed that the sensitivity and specificity of using the serum zinc of 70.6 μg/dL as a cutoff value to predict susceptibility to sepsis were 90.2% and 59.2%, This was in line with the study by **Adnan *et al.***, [22], which yielded a cutoff of 75 μg/dL of serum zinc level correlated with the prognosis of early-onset neonatal sepsis. A high zinc serum was associated with a better prognosis.

A major limitation of our study was the inability to determine if decreased serum zinc concentrations were due to pre-existing nutritional deficiency, metabolic changes from critical illness and infection, or both. This highlights the need for a reliable biomarker to assess zinc status in vulnerable populations, especially children in developing countries. Additionally, further research is needed to understand whether zinc redistribution is a beneficial compensatory mechanism or an indicator of declining function and worse outcomes.

CONCLUSIONS

Our results showed a correlation between serum zinc and pneumonia severity. Low zinc level was associated with severe pneumonia, need of MV, death and higher duration of hospital stay.

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