SERUM ZINC LEVEL IN CRITICALLY PEDIATRIC SEPTIC PATIENTS: A PROSPECTIVE CASE-CONTROL STUDY.

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ABSTRACT:

Background: *Zinc is a necessary trace element that is crucial for numerous vital biological processes. Children in developing countries frequently have zinc shortage; nevertheless, there is conflicting evidence regarding whether the variation in zinc metabolism is a reliable indicator of the severity of a disease when a patient is in the setting of critical illness.*

Objective: *The study aimed to estimate the serum zinc level in critically ill children and to investigate the relationship between its immunomodulatory effect and the severity of illness.*

Methods: *A prospective case-control study was conducted at a children's hospital on 100 consecutively selected critically ill patients aged 1 month-13 yrs subdivided into 50 cases(whose PRISM score>5) and 50controls (whose PRISMIII score<5).All were subjected to physical examination, nutritional assessment, laboratory investigation- complete blood count, C-reactive protein, serum albumin, serum zinc level- and outcomes.*

Results: *The study included 100 patients subdivided into 50 cases; their mean age was (37.4 ± 35.7) months, 64.0% were males, 36.0% were females, and 50 controls their mean age was (38.9 ± 49.7) months, 50.0% were males, 50% were females. The study yielded a statistically significant difference between both groups regarding albumin (P-value < 0.0001) and serum zinc level (P-value < 0.0001). In the cases group, the mean ± SD of the serum albumin was (3.0 ± 0.7) mg/dl, and the mean ±SD of the serum zinc level was (35.8 ± 25.9) (μg/dL). However, in the control group, the mean ± SD of albumin was (3.6 ± 0.6) mg/dl, and the mean ± SD of serum zinc level was (76.2 ±30.4) μg/dL. Moreover, there was a statistically significant positive correlation between the serum zinc level, the absolute lymphocytic count (r = 0.460), and the serum albumin (r = 0.445) and a statistically significant negative correlation between the serum zinc level, CRP (r = -0.378,) and PRISM III score (r = -0.496). However, no correlation was found between the zinc level and PICU stay (r = -0.246). The sensitivity and specificity of using the serum Zinc of 70.6 μg/dL as a cut-off value to predict susceptibility to sepsis were 90.2% and 59.2%, respectively.*

Conclusion *children with normal zinc levels have a decreased risk of acquiring sepsis, compared to zinc-deficient children, who were at risk of acquiring severe sepsis.*

Keywords: *Zinc; Sepsis; critically ill; PICU.*

INTRODUCTION:

Zinc is an essential trace element because small amounts of zinc are necessary for human health**[1].**

Its intake is closely related to protein intake; as a result, its deficiency is nutritionally-related morbidity worldwide. A lot of symptoms attributed to its deficiency

include growth failure, skin diseases, impaired taste and smell, primary hypogonadism, and impaired immunity and susceptibility to infection[2].

Low zinc levels were observed to be associated with lymphopenia, as true zinc deficiency has consistently been shown to result in thymic atrophy, and impaired cell and antibody-mediated immunity[3] . As a consequence, zinc deficiency has been found to be responsible for up to 4.4% of deaths attributable to infection in developing countries[4].

Critically ill children are more susceptible to severe oxidative stress, directly correlated with disease severity[5]. Zinc is the cornerstone of the antioxidant defense in acute systemic inflammatory response syndrome (SIRS)[6]. SIRS is accompanied by a redistribution of zinc to the tissues involved in protein synthesis and immune cell proliferation and this in turn leads to a decrease in its serum level[7].

Acquired critical illness stress-induced immune suppression (CRISIS) plays a crucial role in the development of nosocomial infection and sepsis. CRISIS has been shown to be associated with deficiencies in zinc, selenium, amino acids and hypoprolactinemia[8].

This study was undertaken to study the effect of critical illness on zinc levels in children regarding the outcome and PICU length of stay.

PATIENTS AND METHODS:

Study design:

A prospective case-control study was conducted at the PICU of Cairo University, Children's Hospital, Faculty of Medicine, Egypt.

Ethical approval:

The institutional review board at Cairo University approved the current study with IRB NO: MS-190-2019.

Study groups:

The study was carried out on 100 critically ill patients who were subdivided into 50 cases whose PRISM III score was>5, and 50 controls whose PRISM III score was<5 [3].

Patients' age was one month to 12 years old, and patients with gastroenteritis, known zinc-deficient children, malnourished, or on zinc supplementation were excluded.

Methodology:

Data were collected during admission to PICU. For all cases and controls: detailed medical history and demographic data were collected, including age, sex, and Pediatric Risk of Mortality III was used as a measure of disease severity, PICU length of stay, and outcome. Diagnosis on admission, need for mechanical ventilation, cause, and ventilation duration were recorded. The work-up also comprised complete blood count, C-reactive protein (CRP), serum electrolytes, and liver and kidney function tests. A single zinc measurement was performed for all patient within 24 hours of admission by withdrawing 5 ml of venous blood and determining the zinc level using a spectro-photometer RA-50 chemical analyzer and kits of spectrum 5-Bromo-PAPS.

Statistical analysis

The data were analyzed using Microsoft Excel 2016 and the Statistical Package for Social Sciences (SPSS) version 26 (IBM Corp., Armonk, N.Y., USA). The mean ± SD was used to demonstrate the continuous, normally distributed variables with a 95% confidence interval. Moreover, the median with 25% and 75% was used to represent the non-normal variables, and the frequencies and percentages were used for categorical variables. A p-value<or = 0.05 was considered statistically significant. The Student's t-test was performed to compare the means of normally distributed variables between groups, and the Mann-Whitney U

test was used for non-normal variables. The Chi-squared test or Fisher's exact test was used to determine the distribution of categorical variables between groups. The diagnostic power of Zinc was evaluated by the receiver operating characteristic (ROC) curve. A2-sided P≤0.05 considered statistically significant.

RESULTS:

100 patients were included in the study, 50 cases, and 50 controls. The descriptive statistics of the sample are displayed in Table 1. The median (IQR) for age was (18, range 3-132) months, 64.0% were males in the study group, while the median (IQR) for age was (15, range 3-156) months, and 50.0% were male in the control group. In the cases group, the median (IQR) weight was (10, range 3.5-39) kg, and the median (IQR) BMI was (17.2, range 8.9-25.5) In the control group, the median (IQR) weight was (10, range 3.6-45), and the median (IQR) BMI was (17.4, range 8.9-30.86) No significant differences were observed between both groups in terms of age, gender and baseline weight and BMI.

In the cases group, the mean TLC was 18 (±8)/mm^3, the mean ALC was 4894 (±1754)/mm^3, and the mean CRP was 118((±96) µg/mL**,** while in the controls group, the mean TLC was 12 (±4)/mm^3, mean ALC was 3549 (±2867)/mm^3, and the mean CRP was 8 (±4) µg/mL. Also, the mean albumin was 3.0 (±0.7/mg/dl) and the mean serum zinc level was 35.8 (±25.9) (µg/dL) in the case group, while the mean albumin was 3.6 (±0.6) /mg/dl and mean serum zinc level was 76.2 (±30.4) (µg/dL) in control one. There was a statistically significant difference between cases and controls as regards TLC, ALC, CRP, albumin, and zinc (p <0.0001)**.**

In cases, the mean PICU stay length was 9.2 (±6.3) days and the PRISM III score was 12 (±5.4) while in the controls, the mean PICU stay length was 3.7 (±1.9) days and the mean PRISM III score was 3.6(±0.6)**,** with statistically significant difference between both groups (p <0.001) (Table 1).

We observed a statistically significant positive correlation between zinc level and absolute lymphocytic count (r = 0.460) and albumin (r = 0.445) and, a statistically significant negative correlation between zinc level, CRP (r = -0.378,) and PRISM III (r = -0.496) as shown in (Table: 2).

The current study observed no correlation between serum zinc level and other variables such as BMI (r = 0.047), age (r =0.201), sex differences, and length of PICU stay (r = -0.246) as shown in (Table: 2).

A significant difference in zinc level was found between patients who had sepsis (mean ± SD = 39.1 ± 29.9), those who were placed on mechanical ventilation, and mortality as an outcome (P <0.0001) for each (Table:3).

By using the ROC plot, the AUC was 0.819 (95% CI:0.731-0.907; P<0.001), indicating an excellent ability of serum zinc to predict sepsis. The sensitivity and specificity of using serum zinc of 70.6 µg/dL as a cutoff to predict sepsis were 90.2% and 59.2%, respectively (Diagram).

Table 1: Clinical and laboratories characteristics of the whole studied group:

	Case (N=50)	Control (N=50)	P value
Age (months) (median (IQR)	18(3-132)	15(3-156)	0.2
Sex/male (N/%)	32(64%)	25(50%)	0.157
Female	18(36%)	25(50%)	0.157
Weight (kg) median(IQR)	10(3.5-39)	10(3.6-45)	0.926
BMI median (IQR)	17.2(8.9-25.5)	17.4(8.9-30.86)	0.910
TLC (mm^3) Mean± SD	18 ± 8	12 ± 4	<0.001
ALC (mm^3) Mean± SD	4894±1754	3549±2867	<0.001
CRP (mm^3) Mean± SD	118±96	8±4	<0.001
ALBUMIN (mg/dl) Mean± SD	3±0.7	3.6±0.6	<0.001
ZINC (µg/dL) Mean± SD	35.8±25.9	76.2±30.4	<0.001
PICU stay Mean ± SD(/days)	9.2±6.3	3.7±1.9	<0.001
PRISMIII Mean ± SD	12.0±5.4	3.6±0.6	<0.001

BMI: body mass index; TLC: total leucocytic count; ALC: absolute lymphocytic count; CRP:C-reactive protein; PICU: Pediatric intensive care; PRISM: Pediatric risk of mortality score.

Table 2: Shows significant correlations between zinc levels and other variables.

Zinc level (µg/dL)		
Variables	R	Pvalue
Absolute lymphocytic count	0.460**	<.0001
Albumin	0.445**	<.0001
PRISMIII	-0.496**	<.0001
CRP	-0.378**	<.0001
BMI	0.047	0.640
Age	0.201*	0.045
PICU stay	-0.246*	0.014

**.Correlation is significant at the 0.01 level (2-tailed).*. Correlation is significant at the 0.05 leve l(2-tailed). • BMI: body mass index; PICU: pediatric intensive care unit.

Table 4: Shows association between Zinc levels and other variables.

Serum zinc				
		Mean±SD		Pvalue
		Median	Range	
Sex	Male	51.7	±34.5	0.128
		44.0	10-143.8	
	Female	61.7	±34.4	
		59.0	11.6-155.7	
Septic	Yes	39.1	±29.9	<.0001
		32.0	10-143.8	
	No	73.7	±30.4	
		73.6	11.6-155.7	
Survival	Yes	61.9	±34.4	<.0001
		60.0	10.5-155.7	
	No	25.4	±13.4	
		19.4	10-51	
MV	Yes	32.9	±25.3	<.0001
		27.9	10-123	
	No	62.2	±34.3	
		65.0	10.5-155.7	

- MV: mechanical ventilation

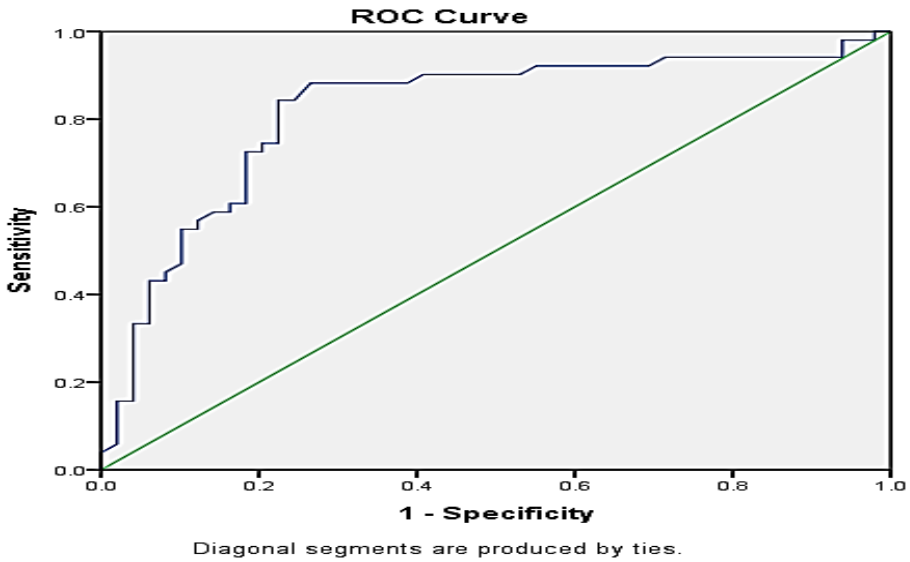

Diagram : Shows sensitivity, specificity, and Receiver operating characteristic curve for serum zinc level.

DISCUSSION:

The current study was done to explore the zinc status in critically ill children admitted to PICU. After exclusion of patients with manifestations of zinc deficiency. To prove that zinc deficiency is associated with a critical illness. Our results demonstrated low serum zinc levels among patients admitted to PICU with PRISM III score >5.

The interest in micronutrients and their impact on human health was a paradigm shift in the introduction of these elements to increase immunity in the face of oxidative stresses in the critically ill **[9&10].**

Zinc is the most abundant trace element of importance in the body, its circulating levels are less than <0.1% of the total body zinc, which is found intra cellular **[3].** Serum zinc concentrations are reduced during acute infections and inflammation, which is likely because of the redistribution of zinc from the plasma to the liver; cytokines released during the acute phase response activate hepatic metallothionein (MT) synthesis, a metal-binding protein which appears to alter the hepatic uptake of zinc**[11].** Low serum zinc levels in critically ill patients in other studies**[12&13].**

Zinc, also, has been shown to play a crucial role in the regulation of the immune response, particularly T cell-mediated function, as the immune system is particularly affected by zinc deficiency, being highly proliferating and zinc is essential for DNA synthesis**[14&15]**.

In our study we observed that low zinc levels were associated with lymphopenia, as true zinc deficiency results in thymic atrophy and impaired cell-and antibody-mediated immunity. Therefore, our study observed a significant positive correlation between zinc levels and TLC and ALC. This result was observed in other studies**[16,17&11]**.

Furthermore, we found a significant negative correlation between zinc level and CRP which is in line with Cvijanovich et al.**[3].** All are in line with that serum zinc concentrations are reduced during acute infections and inflammation**[11].**

In addition, the inverse relationship between zinc level and PRISM111 score observed in our study. This reflecting more

impaired mucosal barrier function, lower epithelial cell integrity, lower innate and acquired immunity, and disturbed oxidative stress responses were associated with lower serum zinc levels in critically ill, septic children[18]. This aligns with this Saleh and Abo El Fotoh study[19].

The acute inflammatory response results in albumin levels decline. As a consequence, its ability to bind zinc during the inflammatory process is reduced[20]. This is in line with our study that found a strong correlation between albumin levels, the primary zinc-binding protein, and blood zinc levels. Also, This agrees with several studies: Tsutsumi et al. and Ghashut et al.[21&22].

In addition, Zinc is thought to be an essential element for epithelial cell integrity, reducing lower respiratory tract inflammation and improving respiration[23]. Our study found an inverse relationship between serum zinc levels and the need for respiratory support. This finding agreed with Gonçalves et al., who found low serum zinc levels in critically ill patients with SARS-CoV-2 presented by severe ARDS[24].

Additionally, we found patients who died had a lower plasma zinc level than those who recovered and were discharged. These findings are similar to a study on a patient infected with the COVID-19 virus, which showed that patients with zinc deficiency had more complications and prolonged hospital stays[25]. However, contrary to others who found that the zinc level had no predictive value for 30-day mortality[26].

The results showed no correlation between zinc level, BMI (r = 0.047), age (r = 0.201), and PICU stay length. These results agree with Thein et al., who found no significant association between anthro-pometric indices and zinc deficiencies[27]. However, these results are inconsistent with other studies that showed a significant positive correlation between anthropometric indices and serum zinc level[19]. and another that showed a positive correlation between zinc level and PICU stay length[28].

In our study, the sensitivity and specificity of using serum zinc of 70.6 µg/dL as a cut-off to predict the severity of sepsis were 90.2 % and 59.2 %. This was in line with the study, which yielded a cut-off of 75 µg/dL of Serum zinc level correlated with the prognosis of early-onset neonatal sepsis. A high zinc serum is associated with a better prognosis[29].

The study recommends Zinc therapy administration in PICU may help to improve the prognosis and decrease the severity of sepsis. There is a need for a reliable biomarker to assess zinc metabolism in vulnerable populations, particularly children in underdeveloped countries.

Our study's major limitation is that we did not mention the diagnosis of our studied population, didn't distinguish between the decrease in serum zinc level and changes in metabolism brought on by the critical illness and/or infection. And couldn't study the effect of zinc supplementation on patient outcome.

Conclusion:

Zinc level was decreased in critically ill children, especially those with severe sepsis and who need more respiratory support. There was no correlation between the zinc level, PICU staying length, and BMI, but it strongly correlates with the PRISM 111 score, absolute lymphocytic count, CRP, and albumin.

Conflict of interest:

"No potential conflict of interest relevant to this article was reported."

Funds: the study received no funds.

The manuscript has been read and approved by all authors, that the requirement for the authorship as stated earlier in the

document have been met, and that each author believes that the manuscript represent honest work.

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مستوى الزنك فى الامراض الحرجة للأطفال : دراسه حالات وشواهد

بسنت المليجى 1, منى محى الدين 2, بدر على الشيمي 1,الشيماء صلاح احمد1

قسم الاطفال 1

2و قسم الباثولوجيا الاكلينيكيه, كليه الطب, جامعه القاهره

المقدمه : الزنك هو عنصر أساسي يلعب دورًا مهمًا في العديد من الوظائف البيولوجية .غالبًا ما يكون الأطفال من الدول الناميه يعانون من نقص فى مستوى نسبه الزنك بالدم .نظرا لاختلاف والتضارب بين الدراسات السابقه الى الان. هل الاختلاف فى نسبه الزنك ممكن ان يستخدم كمؤشر عن درجه شده المرض

الهدف من الدراسه : أجريت دراستنا الحالية للتحكم في الحالة ، وقياس مستوى الزنك بين الأطفال المصابين بأمراض خطيرة للتحقيق في دور الزنك كمحسّن مناعي مهم في الأطفال المصابين بأمراض خطيرة وللتحقيق في العلاقة بين مستوى الزنك وشدة المرض والوفيات.

طريقه البحث : أجريت الدراسة على ٥٠ طفلاً مصاباً بأمراض خطيرة خلال ٧٢ ساعة من دخول وحدة العناية المركزة و ٥٠ طفلاً من وحدة العناية المركزة كضوابط. تم جمع عينات الدم من المجموعتين لقياس مستوى الزنك.

أسفرت الدراسة عن النتائج التالية:

- بالمقارنة مع الأشخاص الخاضعين للمراقبة ، فإن الأطفال في حالات وحدة العناية المركزة لديهم تركيز زنك أقل بشكل ملحوظ.
- لاحظنا أنه في وجود التسمم بالدم ، كان هناك انخفاض أكبر في مستويات عنصر الزنك في مرضى وحدة العناية المركزة.
- كان هناك ارتباط كبير بين مستوى الألبومين ومستوى عنصرالزنك ، حيث يعتبر الألبومين البروتين الرئيسي لربط الزنك.
- لاحظنا في دراستنا أن المستويات المنخفضة من الزنك ارتبطت بنقص إفراز الغدد الليمفاوية حيث ثبت باستمرار أن نقص الزنك الحقيقي يؤدي إلى ضمور الغدة الصعترية وضعف المناعة بالخلايا والأجسام المضادة. وجود علاقة ارتباطيه معنوية ذات دلالة إحصائية بين مستوى الزنك وعدد اللمفاويات.
- في الدراسة الحالية ، هناك علاقة سلبية ذات دلالة إحصائية بين مستوى الزنك ومدة الاقامةبوحدة العناية المركزة , التسسم بالدم و درجة البريزم.

وتخلص الدراسة إلى أن مكملات الزنك مهمة للأطفال المصابين بأمراض خطيرة وقد يلعب نقصها دورًا في التسبب في التسسم بالدم الحاد.