



# The Correlation between Serum Selenium Concentration and Clinical Outcomes in Critically Ill Paediatric Patients following Major Gastrointestinal Surgeries: A Cross-sectional Study

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ARTICLE INFO	ABSTRACT
<p><i>Article type:</i> Research Paper</p>	<p><b>Introduction:</b> The present study aimed to assess the possible correlation between serum selenium levels and clinical outcomes in the PICU patients undergoing major gastrointestinal surgeries.</p>
<p><i>Article History:</i> Received: 08 Jul 2023 Accepted: 17 Sep 2023 Published: 03 Apr 2024</p>	<p><b>Methods:</b> This cross-sectional study was conducted on 66 critically ill pediatric patients who were in the postoperative stage of major gastrointestinal surgeries. Serum selenium concentration was assessed using the atomic absorption method, and the clinical outcomes were collected prospectively.</p>
<p><i>Keywords:</i> Clinical outcomes Major gastrointestinal surgeries Paediatric Intensive Care Unit (PICU) Selenium</p>	<p><b>Results:</b> No significant association was denoted between serum selenium concentration and some clinical outcomes, like the duration of ventilator dependency, PICU length of stay, and PICU/28-day mortality. However, the statistical analysis of the data showed a negative but significant association between serum selenium concentration, and infection rate, and length of hospital stay (<math>P=0.01</math> and <math>P=0.04</math>, respectively).</p> <p><b>Conclusion:</b> Serum selenium concentration decreased in the post-gastrointestinal-surgery patients admitted to the PICU upon PICU admission, and the reduction was associated with prolonged hospitalization and a higher infection rate.</p>

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## Introduction

Acute stress responses following major surgeries may stimulate the immune system and increase reactive oxygen species (ROS) and inflammatory mediators, especially in the surgical site (1, 2). The pediatric patients undergoing major surgeries (e.g., gastrointestinal surgeries) may experience critical conditions, which could in turn lead to admission to the intensive care unit (ICU) (2, 3).

ROS and inflammatory cytokines are considered to be the major protective factors against acute stress in the body as they stimulate the antioxidant defense system through the

activation of the signaling pathways (2). On the other hand, the excessive production of ROS and inflammatory cytokines may lead to multiple postoperative complications in critically ill patients (2). The local and systemic inflammatory responses following surgery could induce acute damage, which is associated with hormonal and metabolic changes and may lead to immunosuppression, organ failure, cell necrosis, apoptosis, and insulin resistance (2, 3). Furthermore, these factors may affect clinical outcomes and deteriorate the patient's condition; some of these issues include the increased length of hospital stay and prolonged

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admission at the neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU) (2, 4). The balance of the anti-oxidative/anti-inflammatory defense systems is of particular importance in critically ill post-surgical children since childhood is the most significant period of growth, development, and health in life (2).

According to the literature, selenium is an essential micronutrient that plays a pivotal role in the anti-oxidative/anti-inflammatory defense systems and cellular metabolism through its presence in selenoenzymes and selenoproteins (5, 6). Selenium protects the body against lipid peroxidation and modulates the activity of B and T lymphocytes, as well as natural killer cells. Additionally, this micronutrient regulates the glycolysis pathways and subsequently affects the endogenous antioxidant defense mechanisms (5, 6).

Serum selenium level is considered to be an important determinant of clinical outcomes in critically ill adult population as increased serum selenium levels could enhance various clinical outcomes, such as the reduction of mechanical ventilation, length of ICU stay, and mortality rate (7-10). In a study performed by Broman et al., serum selenium levels were reported to be low in 90.7% of the PICU patients upon admission, and the low serum selenium concentrations were associated with the increased incidence of multiple organ failure (1). Inconsistently, children undergoing cardiac surgeries have shown increased serum selenium levels in critical conditions (11). To date, only a few studies have been focused on pediatric patients, mostly proposing inconsistent results regarding the concentration of serum selenium upon ICU admission and the association with clinical outcomes.

The present study aimed to measure serum selenium concentrations upon admission to the PICU/NICU and investigate the possible correlations with the clinical outcomes of children undergoing major gastrointestinal surgeries in the postoperative stage.

## Materials and Methods

This cross-sectional study was conducted at Akbar Children's Hospital in Mashhad, Iran on the critically ill children aged 0-10 years undergoing major gastrointestinal surgeries, including esophageal/intestinal and biliary atresia, gastric pull-up, and intestinal

obstruction. In addition, the patients with omphalocele and Hirschsprung's disease were enrolled in the study.

The exclusion criteria of the study were as follows: 1) positive history of cancer, autoimmune disorders, severe liver/kidney failure, and HIV infection; 2) severe sepsis or major bleeding upon ICU admission; 3) unwillingness of the patient's parents/legal guardians for participation and 4) preterm neonates. As this study was part of a larger project, all the participants in the main study who met the inclusion criteria were included in this study based on global sampling. Data collection was performed during 11 months (March 2019-January 2020), and the eligible critically ill patients admitted to the PICU/NICU following major gastrointestinal surgeries were enrolled in the study. The study protocol was approved by the Ethics committee of Mashhad University of Medical Sciences (ethics code: IR.MUMS.MEDICAL.REC.1397.553). Written informed consents were obtained from the parents of all patients.

## Assessments and Measurements

### Anthropometric Indices

A digital scale (Balas) with the accuracy of 10 grams was used to measure the body weight of the patients with minimum clothing. In addition, an infantometer was used for the length measurement of the children aged less than 24 months, and a stadiometer was utilized for the height measurement of the patients aged more than 24 months. Notably, an alternative predictive equation was applied for the subjects whose length/height could not be measured accurately based on the ulnar lengths.

### Laboratory Assays

The atomic absorption method was applied to measure the serum selenium concentrations (Perkins-Elmer HGA-700 Graphite Furnace, USA).

### Clinical Outcomes

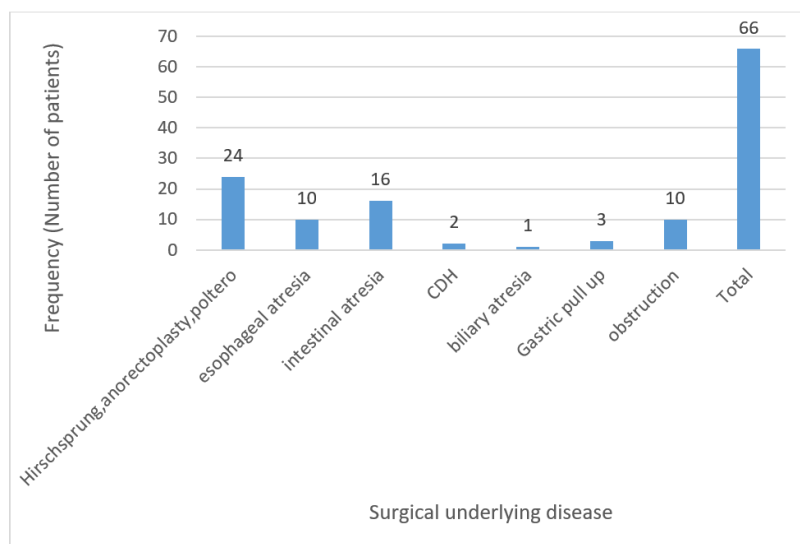
The clinical outcomes in the present study included infections, duration of ventilator dependency, length of PICU/NICU and hospital stay, and ICU/28-day mortality, which were recorded prospectively.

### Statistical Analysis

Data analysis was performed in SPSS version 20 using descriptive statistics to express the

demographic data of the subjects. The normality of data was examined using the Kolmogorov-Smirnov test. In addition, parametric quantitative data were expressed as mean and standard deviation (SD), and the data with non-normal distribution were expressed as median (interquartile range [IQR]). Pearson's/Spearman's correlation-coefficients were also applied to assess the possible

correlations between the serum selenium levels and clinical outcomes. Logistic and linear regression analyses were used to examine the possible correlations between the serum selenium levels and clinical outcomes of infection and length of hospital stay. All the statistical analyses were performed at the significance level of <0.05 and 95% confidence interval.



**Figure 1.** Frequency of Surgical Diagnosis in Children Admitted to PICU Following Gastrointestinal Surgeries  
CDH: Congenital diaphragmatic hernia

## Results

In total, 66 patients with the mean age of  $13.25 \pm 3.16$  months were enrolled in the study, including 37 males (56.1%) with the mean weight and height of  $6.13 \pm 0.55$  kilograms and  $63.7 \pm 2.4$  centimeters, respectively. Figure 1 shows the frequency of the surgical diagnosis of the subjects. Accordingly, 36.4% of the critically ill children in our study were admitted to the PICU due to Hirschsprung disease, anorectoplasty, and Poltero surgery, followed by intestinal atresia surgery (24.2%).

According to our findings, the WHO weight-for-height Z score was higher than -2 in 53 children (80.3%), indicating their normal nutritional status upon PICU admission. However, six (9.1%) and seven patients (10.6%) had moderate and severe malnutrition based on the WHO weight-for-height Z score index, respectively.

The mean postoperative selenium concentration immediately (6-12 hours) after PICU admission was  $38.99 \pm 1.23$  ng/ml in the

patients. Furthermore, the recorded clinical outcomes showed that no infection occurred in 61 patients (92.4%), while the rate of 28-day and PICU mortality was estimated at 3% ( $n=2$ ) and 4.5% ( $n=3$ ), respectively. According to the obtained results, the mean length of hospital and PICU stay was  $11.25 \pm 1.13$  and  $9.5 \pm 1.11$  days, respectively, and the mean duration of ventilation was  $2.25 \pm 0.397$  days.

Table 1 and 2 shows the correlations between the selenium concentration and clinical outcomes recorded based on spearman's test. Accordingly, significant correlations were observed between the serum selenium concentration, infection rate, and length of hospital stay in the critically ill children postoperatively ( $P=0.02$  and  $P=0.04$ , respectively). Furthermore, the results of the linear regression analysis demonstrated that per each unit of increase in the serum selenium concentration, a 0.24-day decrease occurred in the length of hospital stay ( $B=0.22$ ;  $\beta=-0.24$ ;

SE=0.11; P=0.04). Figure 2 depicts the main obtained results of the present study.

**Table 1.** Clinical Outcomes and Correlations of Postoperative Selenium Concentration

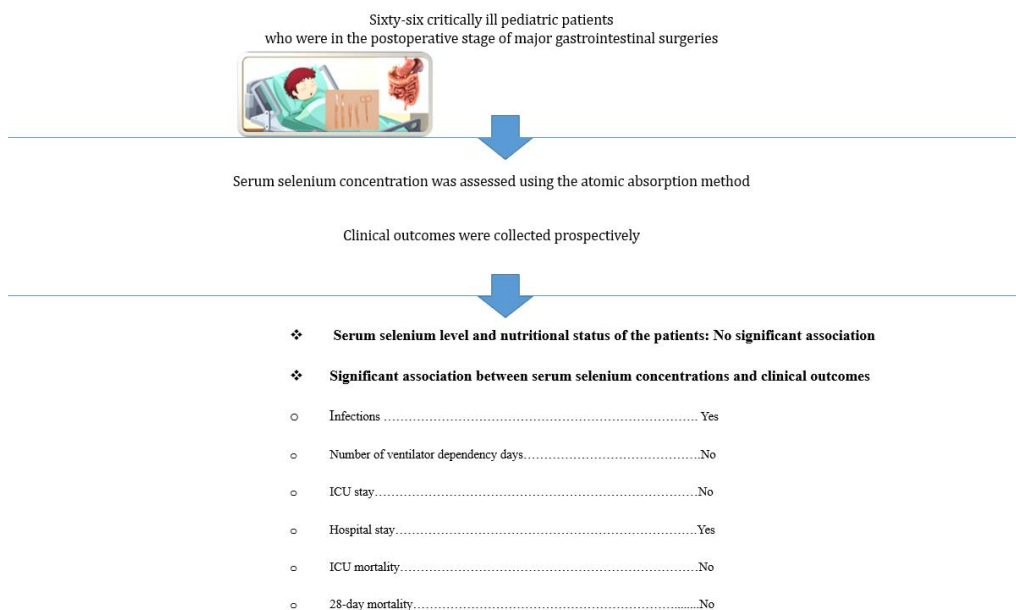
Variable	Mean ± SD	Median (IQR)	P-value*
Infection			
yes	49.32±17.47	39.0 (32.80)	0.020
no	38.42±8.64	37.0(8.75)	
ICU Mortality			
yes	50.20±21.12	50.5 (37.32)	0.507
no	38.56±8.51	37.0 (8.0)	
28-day Mortality			
yes	44.03±21.31	33.0 (9.50)	0.853
no	39.03±9.23	37.0 (8.50)	

\*spearman's test

**Table 2.** Correlations of Postoperative Selenium Concentration and Clinical Outcomes

Variable	r <sub>s</sub>	p-value
Length of Ventilator Dependency	0.090	0.475
Length of ICU Stay	-0.089	0.483
Length of Hospital Stay	-0.066	0.040

r<sub>s</sub>: Spearman correlation



**Figure 2.** The summarized main findings of the study.

### Discussion

In the present study, the serum selenium concentration of the children undergoing major gastrointestinal surgeries was measured immediately after PICU admission to investigate the possible associations between serum selenium concentrations and clinical outcomes. According to the obtained results, the serum concentration of selenium in the children after PICU admission was approximately 39 ng/ml,

which is slightly higher than the median plasma selenium concentration measured immediately after ICU admission (23.4 µg/l). our findings showed that significant correlations between clinical outcomes and postoperative serum selenium concentration, as well as a negative association with infection rate and a positive association with the length of hospital stay. According to the literature, serum selenium levels may be correlated with clinical outcomes

such as organ failure, ICU/28-day mortality, length of hospital stay, and duration of ventilator dependency in patients admitted to the ICU. However, only a few studies have been conducted in this regard, proposing conflicting results in childhood (1, 4, 11-13). In a study conducted on 99 children with acute systemic inflammation (4). This could be due to the different causes of inflammatory status and critical illness of the studied patients in the study by Leite et al., and the differences in the baseline selenium status of patients should be considered depending on the geographical region.

In the multicenter critical illness stress-induced immune suppression (CRISIS) prevention trial, the baseline serum concentration of selenium in critically ill children was measured within 72 hours of PICU admission, and the mean selenium level was reported to be 75.4 ng/ml. In the mentioned study, the selenium level was below the normal reference range in 56.1% of the children (14). Consistently, a study performed on critically ill patients admitted to the surgical ICU of Ajou University Hospital (South Korea) indicated that the serum concentration of selenium upon ICU admission was lower than the reference value in 37.8% of the patients (16).

Endothelial injury, redistribution phenomenon, hemodilution, altered metabolic pathways, and transient increased daily requirements and the subsequent insufficient intake of selenium are among the possible causes of decreased serum selenium concentrations at the acute phase of stress (8, 11, 15). However, selenium deficiency prior to acute metabolic stress (i.e., major surgery in our study) and PICU admission in the aforementioned studies should also be considered in this regard (16, 17).

Critically ill children undergoing cardiac surgeries prior to PICU admission have been reported to have increased postoperative levels of serum selenium ( $204.00 \pm 26.40$  ng/ml), which could be attributed to the different geographical regions and the subsequent fulfilled selenium storage of the patients prior to surgery (11) as the body releases the stored element into the serum to increase the selenium requirement in the acute phase of stress.

The results of the present study indicated significant correlations between clinical outcomes and postoperative serum selenium concentration, as well as a negative association with infection rate and a positive association

with the length of hospital stay. Previous studies on adult populations have also demonstrated significant correlations between serum/plasma selenium concentration (upon ICU admission) and disease severity as reduced selenium is associated with increased disease severity and mortality rate (10, 13, 18).

In a conducted study by Broman et al. on 100 critically ill children, the concentration of serum selenium was determined upon PICU admission, and the findings indicated that the low concentration of serum selenium was associated with the increased incidence of multiple organ failure and deteriorated clinical outcomes (1). Furthermore, the comparison of critically ill children with the children with organ failure and healthy subjects in Benha University Hospital (Egypt) showed that the median selenium level (within 72 hours of ICU admission) was lower in the patients with two affected organs than those with one affected organ (19). However, evidence is clearly lacking in critically ill children regarding the mentioned issue, and

Further clinical investigations are required to investigate serum selenium concentrations of the children who are candidates for major elective surgeries and monitor the trend of changes postoperatively and during PICU admission for a better understanding of possible selenium deficiency at baseline. Such studies could also contribute to reasonable and evidence-based recommendations regarding the possible beneficial effects of selenium supplementation at higher doses than the recommended dietary allowance in this patient population.

Despite the strength of the study (population-based study), one of the limitations of the current research was that serum selenium concentrations were not measured in a control group that was matched in terms of age, gender, and geographical region. In addition, we did not consider tissue biopsy due to its invasive nature to better recognize the selenium status of the participants. Moreover, more accurate results could have been yielded if we had assessed inflammatory markers and oxidant/antioxidant enzymes and analyzed their possible correlations with the selenium status. The serum selenium concentration trend was not monitored during the PICU stay of the patients, which was another limitation.

It is recommended that further investigations in this regard be conducted on larger sample sizes

in different geographical regions with varied disease severity to determine the selenium metabolism and status more accurately in critically ill pediatric patients.

## Conclusion

According to the results, the critically ill children had decreased postoperative serum selenium concentrations following major gastrointestinal surgeries, and the reduction was associated with deteriorated clinical outcomes, such as increased infection and length of hospital stay. Therefore, further multi-center studies on larger populations are required for a more reliable assessment of the selenium metabolism and status in critical illnesses and determining the possible associations with clinical outcomes in childhood.

## Declarations

### Acknowledgement

We express our appreciation to those who helped us in this study.

### Conflict of Interests

No competing of interest

### Ethical Code

The study protocol was approved by the Ethics committee of Mashhad University of Medical Sciences (ethics code: IR.MUMS.MEDICAL.REC.1397.553). Written informed consents were obtained from the parents of all patients.

### Author Contribution

FR., H R., MN, GK., GR., and HE were involved in the study design, and will contribute data collection, and data analysis. The manuscript was written by MS, FR, and ZK. All the authors read and approved the final manuscript

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