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Article

Impact of zinc supplementation on cellular and molecular biomechanical alterations and critical outcomes in pediatric patients with sepsis: A randomized controlled trial

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Abstract: Background: Sepsis remains a significant contributor to illness and death in children. Studies suggests that potential benefits of zinc supplementation in patients with sepsis, such as reduced inflammation and mortality rates. Zinc is involved in maintaining the structural integrity and function of cell membranes, which is essential for proper cell signaling and biomechanical responses. It can also influence the activity of key enzymes and proteins that regulate intracellular and extracellular forces, thereby affecting cell adhesion, migration, and overall tissue mechanics. Therefore, this study aimed to evaluate the occurrence of Acute Respiratory Distress Syndrome (ARDS), Septic Shock, Acute Kidney Injury (AKI), and Mortality in Pediatric Sepsis receiving Zinc supplementation, with a focus on the underlying cellular and molecular biomechanical mechanisms. **Methods:** This study was a Randomized Control Trial (RCT) conducted using a parallel-group, double-blind design and prospective cohort approach. Participants were selected through consecutive sampling and then randomized into two groups: one receiving standard therapy plus zinc supplementation and the other receiving standard therapy plus a placebo. **Results:** Among pediatric patients with sepsis, the incidence of septic shock was significantly lower in the group receiving standard therapy with zinc supplementation (34.4%) compared to the placebo group (65.6%) (p = 0.00, OR 2.29, 95% CI: 1.28–4.11). The incidence of ARDS was 66.7% in the placebo group, versus 33.3% in the zinc group (p = 0.00, OR 0.37, 95% CI: 0.22–0.64). For acute kidney injury (AKI), 65.7% occurred in the placebo group compared to 34.3% in the zinc group (p = 0.04, OR 2.09, 95% CI: 0.99–4.40). Mortality in the placebo group was 64.3%, while in the zinc group it was 35.7% (p = 0.01, OR 0.48, 95% CI: 0.26–0.88). **Conclusion:** Zinc supplementation significantly reduces the incidence of acute respiratory distress syndrome, acute kidney injury, septic shock, and mortality in pediatric patients with sepsis. These outcomes may be attributed to zinc's role in modulating cellular signaling pathways, enhancing cellular integrity under stress, and improving the biomechanical properties of cell membranes, thereby promoting better physiological responses in the context of sepsis.

Keywords: zinc supplementation; ARDS; AKI; shock; sepsis; biomechanical responses; children

1. Background

Sepsis remains a significant contributor to illness and death in children admitted to both general inpatient wards and Pediatric Intensive Care Units (PICUs)1. A study conducted at Cipto Mangunkusumo Hospital (RSCM) in Jakarta from 2009 to 2010 found that 19.3% of pediatric patients in the PICU had sepsis, with a high mortality

rate of 54.6% [1]. More recent global data from 2017 estimated around 20.3 million sepsis cases in children under 5 years and 4.9 million cases in children aged 5–19 [2]. Epidemiological studies in the United States found the occurrence of sepsis in children reached 8% in the PICU [3]. The pathogenesis of sepsis involves a dysregulated immune response, leading to endothelial dysfunction and potential organ failure [4]. This dysregulation is characterized by an overwhelming inflammatory response that can result in widespread tissue damage and the failure of multiple organ systems. The immune system, in its attempt to combat infection, releases a cascade of inflammatory mediators. While this response is essential for fighting off pathogens, its excessive nature can lead to detrimental effects, including the breakdown of the endothelial barrier, increased vascular permeability, and ultimately, shock. Zinc, an essential trace element, plays a critical role in immune function. It is involved in various cellular processes, including the regulation of immune cell development and function, antioxidant defense, and the modulation of inflammatory responses. Zinc deficiency is prevalent among Indonesian children, with reported rates between 17% and 38.8% [5]. This deficiency can impair immune function, making children more susceptible to infections and exacerbating the severity of conditions like sepsis. The link between zinc status and immune response is particularly relevant in the context of sepsis, as adequate zinc levels may enhance the body's ability to respond to infections effectively.

Studies suggests that potential benefits of zinc supplementation in patients with sepsis, such as reduced inflammation and mortality rates. Zinc has been shown to have anti-inflammatory properties, which could mitigate the excessive inflammatory response seen in sepsis. Furthermore, zinc supplementation may improve the overall immune response, potentially leading to better outcomes in septic patients. However, in Indonesia—particularly in Eastern regions like Makassar, its effects have not yet been explored. This gap in research is critical, as understanding the role of zinc in managing pediatric sepsis could have significant implications for treatment protocols in resource-limited settings. Therefore, this study aimed to evaluate the potential benefits of zinc supplementation on critical outcomes in pediatric sepsis, specifically its impact on Acute Respiratory Distress Syndrome (ARDS), septic shock, Acute Kidney Injury (AKI), and mortality rates. By investigating these outcomes, the study sought to determine if zinc could serve as an effective adjunct therapy in managing pediatric sepsis in the PICU setting. In the context of pediatric sepsis, ARDS is a severe complication characterized by acute lung injury and respiratory failure. Children with sepsis are at an increased risk for developing ARDS due to the inflammatory mediators released during the septic process, which can lead to increased permeability of the alveolar-capillary membrane. This condition complicates the management of sepsis and is associated with higher mortality rates. Understanding whether zinc supplementation can reduce the incidence or severity of ARDS in septic children could provide a valuable therapeutic strategy.

Similarly, septic shock represents a critical state of sepsis where there is profound circulatory, cellular, and metabolic abnormalities. The management of septic shock often requires aggressive fluid resuscitation and vasopressor support; however, these interventions may not always be sufficient. Investigating the role of zinc in this context could reveal whether it helps stabilize hemodynamics and improve outcomes for

children experiencing septic shock. Acute Kidney Injury (AKI) is another serious complication associated with sepsis, characterized by a rapid decline in kidney function. The inflammatory response in sepsis can lead to renal hypoperfusion and direct tubular injury, resulting in AKI. The potential protective effects of zinc on renal function during sepsis warrant exploration, as zinc may play a role in reducing oxidative stress and inflammation in renal tissues. Moreover, mortality rates in pediatric sepsis remain alarmingly high, underscoring the urgent need for effective therapeutic interventions. If zinc supplementation demonstrates a significant reduction in mortality rates among septic children, it could represent a simple and cost-effective adjunct therapy that could be easily implemented in clinical practice, especially in resource-limited settings.

In conclusion, the investigation into the effects of zinc supplementation in pediatric sepsis is timely and essential. By focusing on critical outcomes such as ARDS, septic shock, AKI, and mortality rates, this study aims to fill a significant gap in the existing literature and provide evidence-based recommendations for clinical practice. As sepsis continues to pose a serious threat to pediatric populations, exploring novel therapeutic strategies like zinc supplementation could lead to improved management and outcomes for affected children. This research not only has the potential to enhance our understanding of sepsis pathophysiology but also to contribute to the development of effective treatment protocols that could save lives in the PICU setting.

2. Methods

2.1. Study design and data collection

This Randomized Controlled Trial (RCT), designed as a parallel group study with a double-blind approach and a prospective cohort design, was conducted in the inpatient ward and PICU of Dr. Wahidin Sudirohusodo Hospital from January 2023 to July 2024, following the ethical approval obtained from the Ethics Commission for Biomedical Research on humans at the Faculty of Medicine, Hasanuddin University, and research permission was granted by the Director of Wahidin Sudirohusodo Hospital in Makassar.

Inclusion criteria comprised patients with sepsis aged 1 month to 18 years who underwent laboratory tests and consented to participate, while patients with a history of zinc allergy or diarrhea were excluded. The sample size is calculated using the following formula: $n = \sigma^2 (Z1 - \alpha_2 + Z1 - \beta)^2/(\mu_0 - \mu_a)^2$, resulting in minimum sample size in each group was 70. During the study, a total of 280 pediatric patients with sepsis met the inclusion criteria and were subsequently randomized using a table of random sampling numbers into two groups: the first group, consisting of 140 patients, received standard therapy plus zinc supplementation, while the second group, also comprising 140 patients, received standard therapy plus a placebo (**Figure 1**).

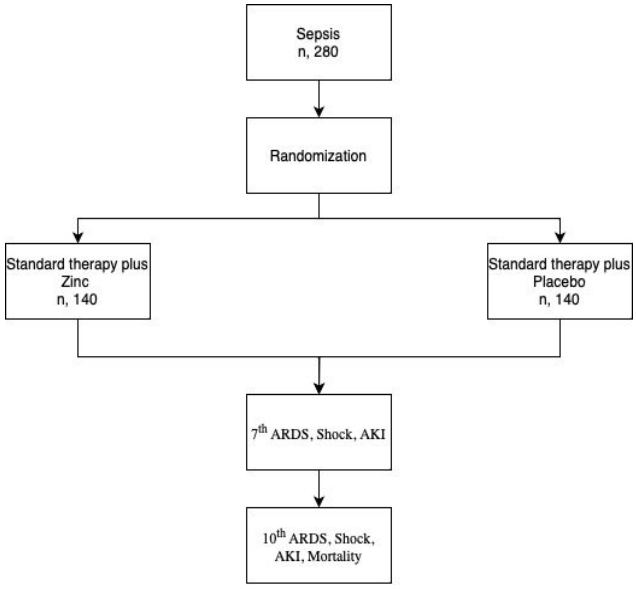

Figure 1. Research flow chart.

The study utilized consecutive sampling followed by randomization (using a table of random sampling numbers) to assign participants into two groups: one group received standard therapy along with zinc supplementation, while the other group received standard therapy in combination with a placebo. Zinc supplementation and placebo were administered orally for 10 days, with dosages of 10 mg per day for patients under 6 months of age and 20 mg per day for those over 6 months.

Follow-up assessments for ARDS, septic shock, and AKI were conducted on day 7, with further evaluations of ARDS, septic shock, AKI, and mortality on day 10. The provision, storage, and administration of zinc and placebo supplementation were managed by the hospital pharmacy team. Zinc supplementation was found to have no side effects during the study.

2.2. Operational definition

The standard therapy for sepsis adheres to the 2019 guidelines of the American Academy of Pediatrics, with necessary adaptations to accommodate specific conditions in Indonesia as outlined by the Ministry of Health. ARDS was diagnosed based on the Pediatric Acute Lung Injury Consensus Conference (PALICC) criteria. For noninvasive mechanical ventilation, ARDS is defined by an Oxygen Index (OI) (PaO2/FiO2 ratio) ≤ 300 or a Saturation Index (OSI) (SpO2/FiO2 ratio) ≤ 264. In cases requiring invasive mechanical ventilation, the severity of ARDS is categorized as follows: mild (OI between 4 and 8, or OSI between 5 and 7.5), moderate (OI between 8 and 16, or OSI between 7.5 and 12.3), and severe (OI > 16 or OSI > 12.3) [6].

AKI was diagnosed according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Stage 1 is defined as a serum creatinine level 1.5 to 1.9 times the baseline value, an increase of more than 0.3 mg/dL, or a urine output of less than 0.5 mL/kgBW/h for 6 to 12 h. Stage 2 is characterized by serum creatinine levels of 2.0 to 2.9 times the baseline or a urine output of less than 0.5 mL/kg/h for more than 12 h. Stage 3 occurs when serum creatinine is 3.0 times the baseline, serum creatinine exceeds 4.0 mg/dL, renal replacement therapy is initiated, or in patients under 18 years

old, the Glomerular Filtration Rate (GFR) decreases to less than 35 mL/min per 1.73 m^2, urine output is less than 0.3 mL/kg/h for more than 24 h, or there is anuria for 12 h [7].

Sepsis shock is a condition of persistent severe sepsis with organ dysfunction, hypotension (systolic blood pressure < 90 mmHg), and lactate levels > 5 mmol. Mortality is defined as the occurrence of patient death during their care in the PICU or hospital.

3. Data analysis

Data analysis using the SPSS version 21 for Windows computer program. Univariate analysis for description of data characteristics in the form of frequency, mean, standard deviation, median and range. The Kolmogorov-Smirnov test is used to determine whether the data distribution is normal or not. Unpaired (Independent) t test to compare two unpaired numerical variables, data are normally distributed and have the same variance. Mann-whitney U test is used to compare two unpaired numerical variables, the data that is not normally distributed and has different variances. *Chi-Square* Test to compare 2 unpaired categorical variables. The results of the hypothesis testing are not significant if the *P* value > 0.05 and significant if $p \leq 0.05$.

4. Results

The baseline characteristics of patients with sepsis prior to intervention were meticulously examined to ensure a comprehensive understanding of the population under study. Key factors such as gender, age, nutritional status, mean arterial pressure, lactate levels, mechanical ventilation status, leukocyte counts, platelet counts, and the presence of underlying diseases, particularly pneumonia, were compared between the two groups: those receiving standard therapy plus zinc supplementation and those receiving standard therapy plus placebo. This comparative analysis aimed to establish that both groups were similar in their initial health profiles, which is crucial for the validity of the study's outcomes. The results indicated that there were no significant differences between the groups across these baseline characteristics, with p-values exceeding 0.05. This lack of significant variation suggests that the observed effects of zinc supplementation on sepsis outcomes can be attributed to the intervention itself rather than pre-existing disparities between the groups. Such rigorous evaluation of baseline characteristics strengthens the reliability of the study's conclusions regarding the efficacy of zinc in the management of pediatric sepsis. (**Table 1**).

Table 1. Characteristics of patients before zinc supplementation.

Variables	**Standard Therapy plus Zinc *n* = 140**	**Standard Therapy plus Placebo *n* = 140**	***P* value**
Sex, *n* (%)			
Male	76 (55.9)	60 (44.1)	
Female	64 (44.4)	80 (55.6)	0.056*
Age, years, mean (SD)	6.7 (3.7)	5.5 (3.9)	0.171**

Table 1. (*Continued*).

Variables	Standard Therapy plus Zinc *n* = 140	Standard Therapy plus Placebo *n* = 140	*P* value
Nutritional Status, *n* (%)			
Normal	68 (53.1)	60 (46.9)	0.337*
Malnutrition	72 (47.4)	80 (52.6)	
GCS, mean (SD)	13.6 (1.2)	13.9 (1.1)	0.167**
Mean Arterial Pressure, n (%)			
Normal	140 (100)	140 (100)	-
Abnormal	-	-	
Lactate Level, mean (SD)	6.3 (0.9)	6.2 (0.6)	0.603**
PELOD-2 Score, mean (SD)	11.3 (0.4)	11.2 (0.4)	0.576**
Mechanical Ventilator, *n* (%)			
Yes	40 (45.5)	48 (54.5)	
No	100 (52.1)	92 (47.9)	0.303*
Leukocyte Level, *n* (%)			
Normal	12 (54.54)	10 (45.46)	
Not normal	128 (49.62)	130 (50.38)	0.092*
Platelet Level, *n* (%)			
Normal	132 (51.6)	124 (48.4)	
Abnormal	8 (33.3)	16 (66.7)	0.088*
Pnemonia, *n*(%)			
Yes	79 (51.29)	5 (48.71)	
No	61 (48.42)	65 (51.58)	0.241*

*p chi square, **unpaired T test, SD: standard deviation, PELOD: Pediatric Logistic Organ Dysfunction.

During the study, follow-up assessments were conducted, and on the 7th day of the supplementation, the occurrences of ARDS, AKI, and septic shock were evaluated. The results indicated that the incidence of ARDS in the standard therapy plus zinc group was 45.7%, which was lower than the 54.3% in the standard therapy plus placebo group, although this difference was not statistically significant ($p = 0.15$). For AKI, the zinc group had an incidence of 44%, compared to 66% in the placebo group, which was also not significant ($p = 0.13$). However, the incidence of septic shock was higher in the placebo group at 65.6%, compared to 34.4% in the zinc group, showing a significant difference ($p = 0.00$) with an odds ratio of 2.29 (95% CI 1.28–4.11) (**Table 2**).

Table 2. ARDS, AKI, and septic shock in patients with sepsis on 7th day of zinc supplementation.

Zinc Supplementation Day 7				
Variables	**Standard Therapy plus Zinc *n* = 140**	**Standard Therapy plus Placebo *n* = 140**	***P* value**	**OR (95% CI)**
ARDS, *n* (%)				
Yes	64 (45.7)	76 (54.3)	0.15	0.70 (0.44–1.13)
No	76 (54.3)	64 (45.7)		
AKI, *n* (%)				
Yes	44 (44)	56 (56)	0.13	0.68 (0.42–1.12)
No	96 (53.3)	84 (46.7)		

Table 2. (*Continued*).

Zinc Supplementation Day 7				
Variables	**Standard Therapy plus Zinc *n* = 140**	**Standard Therapy plus Placebo *n* = 140**	***P* value**	**OR (95% CI)**
Shock, *n* (%)				
Yes	22 (34.4)	42 (65.6)	0.00	2.29 (1.28–4.11)
No	119 (54.6)	98 (45.4)		

*Chi-square test, ARDS: acute respiratory distress syndrome, AKI acute kidney injury, OR odds ratio, CI: confidence interval.

On the 10th day of the intervention, assessments of ARDS, AKI, septic shock, and mortality were conducted. The results showed that the incidence of ARDS was significantly lower in the standard therapy plus zinc group at 33.3% compared to 66.7% in the standard therapy plus placebo group, with a *p*-value of 0.00 and an OR of 0.37 (95% CI: 0.22–0.64). Similarly, AKI was observed in 34.3% of the zinc group, compared to 65.7% in the placebo group, yielding a *p*-value of 0.04 and an OR of 2.09 (95% CI: 0.99–4.40). For septic shock, the incidence in the zinc group was 44%, while it was 56% in the placebo group; however, this difference was not statistically significant ($p = 0.34$, OR 1.34; 95% CI: 0.72–2.48). Lastly, mortality in the standard therapy plus zinc group was 35.7%, significantly lower than the 64.3% observed in the placebo group, with a *p*-value of 0.01 and an OR of 0.48 (95% CI: 0.26–0.88) (**Table 3**).

Table 3. ARDS, AKI, septic shock, and mortality in patients with sepsis on 10th day of zinc supplementation.

Zinc Supplementation Day 10				
Variable	**Standard Therapy plus Zinc *n* = 140**	**Standard Therapy plus Placebo *n* = 140**	***P* value**	**OR (95% CI)**
ARDS, *n* (%)				
Yes	28 (33.3)	56 (66.7)	0.00	0.37
No	112 (57.1)	84 (42.9)		(0.22–0.64)
AKI, *n* (%)				
Yes	12 (34.3)	23 (65.7)	0.04	2.09* (0.99–4.40)
No	128 (52.2)	117 (47.8)		
Shock, *n* (%)				
Yes	22 (44.0)	28 (56.0)	0.34	1.34 (0.72–2.48)
No	118 (51.3)	112 (48.7)		
Mortality, *n* (%)				
Survive	120 (53.6)	104 (46.4)	0.01	0.48
Died	20 (35.7)	36 (64.3)		(0.26–0.88)

*Chi-square test, ARDS acute respiratory distress syndrome, AKI acute kidney injury, OR odds ratio, CI confidence interval.

This research found a decrease in the incidence of Acute Respiratory Distress Syndrome (ARDS) and Acute Kidney Injury (AKI) among patients with sepsis who received standard therapy plus zinc between day 7 and day 10. However, the incidence of septic shock remained unchanged from day 7 to day 10 (**Figure 2**).

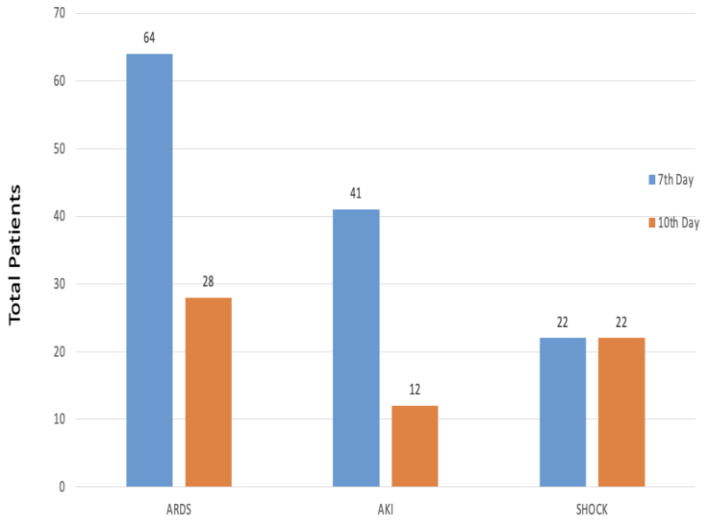

Figure 2. ARDS, AKI and Shock on sepsis group of standard therapy plus zinc supplementation.

5. Discussion

The findings of this study illustrate the potential advantages of zinc supplementation in pediatric patients with sepsis. Sepsis, a life-threatening condition caused by the body's response to infection, is particularly dangerous for children. It can lead to multiple organ failure and death if not managed promptly and effectively. The role of nutrition, especially micronutrients like zinc, has garnered increasing attention in the management of sepsis. Specifically, the reduced occurrence of shock, ARDS, AKI, and mortality in the zinc-supplemented group relative to the placebo group indicates a protective role of zinc against these severe sepsis sequelae. These findings suggest that zinc may play a crucial role in supporting the immune system and maintaining overall health during critical illness. Notably, septic shock was occurred more frequently in patients with sepsis receiving standard therapy with placebo than in those receiving standard therapy with zinc, indicating that patients with sepsis without zinc supplementation have a 2.29 times higher risk of experiencing shock. This statistic is significant because it highlights the importance of addressing zinc deficiency in pediatric patients who are already vulnerable due to their medical condition. The increased risk of shock among those not receiving zinc suggests that supplementation could be a simple yet effective intervention to improve outcomes in this population.

Supporting this observation, a 2011 study by Besecker et al. [8] on children aged 1 to 6 years found a correlation between zinc deficiency and diminished systolic arterial blood pressure, as well as reduced activity of serum angiotensin-converting enzyme and carbonic anhydrase. This relationship between zinc levels and cardiovascular measures corroborates our findings and underscores the potential significance of zinc in maintaining hemodynamic stability during sepsis. Maintaining stable blood pressure is critical in sepsis management, as fluctuations can lead to further complications and worsen patient outcomes.

The observation of reduced occurrences of ARDS and AKI in patients receiving zinc supplementation is particularly significant. This finding align with the previous studies which indicated elevated incidences of AKI, septic shock, organ failure, and mortality in pediatric patients with sepsis-associated ARDS relative to those with non-sepsis ARDS [9–11]. The preventive effect of zinc against ARDS may be attributed to its function in regulating the inflammatory response and augmenting antioxidant capability. Previous preclinical research has demonstrated that zinc-dependent matrix metalloproteinases (MMPs) are integral to the pathophysiology of lung conditions, such as pneumonia. Additionally, zinc supplementation has been shown to reduce levels of inflammatory cytokines, including Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), and IL-1β. This reduction in inflammatory markers may help decrease the incidence of ventilator-associated pneumonia while also improving immune function in patients with sepsis, highlighting the multifaceted benefits of zinc supplementation in this context [12].

The observed reduction in the mortality rate among our zinc-supplemented cohort is particularly encouraging and aligns with findings from earlier research. A meta-analysis conducted by Tang et al. [13] in 2017 demonstrated that zinc supplementation significantly decreased mortality rates in individuals with sepsis. In a similar vein, Newton et al.'s 2016 study reported significantly lower mortality rates and improved mental development quotients among infants who received zinc supplementation during sepsis treatment [14]. This highlights not only the immediate benefits of zinc in reducing mortality but also its potential long-term benefits for cognitive development in children recovering from severe illness.

Nonetheless, it is crucial to acknowledge that not all studies have shown consistent benefits of zinc supplementation in sepsis. For instance, Haque et al.'s [6] 206 study revealed no significant differences in hospital stay duration or fatality rates between neonates receiving zinc supplements and those who did not. These conflicting results underscore the necessity for additional study to refine zinc supplementation techniques in the treatment of sepsis. It is essential to understand that while zinc shows promise, the variability in study outcomes may be attributed to differences in study design, patient populations, and zinc supplementation protocols.

Zinc supplementation will also increase glutathione levels in various tissues, leading to increased antioxidant capacity [15-16]. Glutathione is a critical antioxidant that protects cells from oxidative stress, which can be particularly harmful in conditions like sepsis. Zinc deficiency has been associated with reduced DNA integrity, elevated oxidative stress, and impaired DNA repair capacity [17]. This is particularly concerning as oxidative stress can exacerbate the inflammatory response, leading to further tissue damage and organ dysfunction. Zinc deficiency results in lower oxygen uptake, less carbon dioxide removal and decreased skeletal muscle work capacity and muscle fatigue [18]. These physiological changes can contribute to the overall deterioration of a patient's condition during sepsis, emphasizing the importance of adequate zinc levels [19].

Our data indicate that zinc supplementation may serve as a beneficial complement to conventional sepsis treatment in pediatric patients. The noted decreases in shock, ARDS, AKI, and death rates suggest that zinc supplementation may confer a comprehensive protective impact against the severe consequences of sepsis. The

ideal dosage and duration of zinc supplementation in pediatric patients with sepsis have yet to be established. Determining these parameters is crucial for optimizing treatment protocols and ensuring the safety and efficacy of zinc supplementation in clinical practice.

A limitation of our study is the absence of zinc level assessments before and following supplementation. This information would have offered significant insights into the baseline zinc status of our research sample and the efficacy of our supplementation protocol in attaining appropriate zinc levels. Subsequent research should include zinc level assessments to enhance comprehension of the correlation between blood zinc concentrations and clinical outcomes in pediatric sepsis. In addition to addressing zinc levels, it is essential to explore the mechanisms through which zinc exerts its protective effects. Understanding these pathways could lead to more targeted interventions and help identify which patient populations are most likely to benefit from zinc supplementation. For example, further investigation into the role of zinc in modulating immune responses and reducing inflammation could provide insights into its therapeutic potential in other critical illnesses beyond sepsis. Moreover, future studies should consider the timing of zinc supplementation in relation to the onset of sepsis. Early intervention may be key to maximizing the benefits of zinc, as the body's response to infection can rapidly escalate. Investigating the optimal timing for supplementation could help establish guidelines for clinicians managing pediatric patients with sepsis.

It is also worth exploring the potential interactions between zinc and other nutrients in the context of sepsis. For instance, the combined effects of zinc with other micronutrients, such as vitamin C or selenium, may enhance overall immune function and improve patient outcomes. Nutritional interventions that incorporate multiple micronutrients could provide a more comprehensive approach to managing sepsis. The potential for zinc supplementation to improve clinical outcomes in pediatric sepsis patients opens up exciting avenues for further research. As our understanding of the role of micronutrients in critical illness evolves, it is likely that zinc will become an integral part of nutritional strategies in the management of sepsis. By prioritizing research in this area, we can work towards developing evidence-based guidelines that optimize the use of zinc and other nutrients in clinical practice.

In conclusion, the findings of this study highlight the promising role of zinc supplementation in pediatric patients with sepsis. The evidence suggesting reduced occurrences of shock, ARDS, AKI, and mortality in those receiving zinc is compelling. While challenges remain in standardizing treatment protocols and understanding individual patient needs, the potential benefits of zinc supplementation warrant further investigation. By continuing to explore the relationship between zinc and sepsis outcomes, we can enhance our approaches to treating this complex and life-threatening condition, ultimately improving the health and well-being of vulnerable pediatric patients.

6. Conclusion

In conclusion, our results confirm the prospective therapeutic advantage of zinc supplementation in pediatric patients with sepsis. The noted decreases in shock,

ARDS, AKI, and mortality rates indicate that zinc may significantly influence the inflammatory response and safeguard against organ failure in sepsis. Further study is necessary to refine zinc supplementation procedures and to clarify the specific mechanisms via which zinc has protective effects in sepsis. Extensive multicenter randomized controlled studies with standardized zinc supplementation regimens and thorough outcome assessments are necessary to validate these findings and include zinc supplementation as a standard element of pediatric sepsis therapy.The findings of this study indicate the potential advantages of zinc supplementation in pediatric patients with sepsis. The reduced occurrence of shock, ARDS, AKI, and mortality in the zinc-supplemented group relative to the placebo group indicatesÏ a protective effect of zinc against these severe sepsis sequelae.

Author contributions: Conceptualization, IJG; methodology, IJG; software, IJG and AJO; validation, NMP, AL, SBS and SR; formal analysis, IJG; investigation, AJO; resources, IJG; data curation, AJO; writing—original draft preparation, IJG; writing—review and editing, IJG; visualization, IJG; supervision, NMP, AL, SBS, and SR; project administration, IJG; funding acquisition, IJG. All authors have read and agreed to the published version of the manuscript.

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Ethical approval: Ethical approval has been obtained from the Ethics Commission for Biomedical Research on humans at the Faculty of Medicine, Hasanuddin University with approval number UH23120898 dated 3 January 2024, and research permission was granted by the Director of Wahidin Sudirohusodo Hospital in Makassar.

Conflict of interest: The authors declare no conflict of interest.

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