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Research Article

Assessing Vitamin A Status in Septic Critically Ill Children

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Abstract

Background: Sepsis is a life-threatening condition characterized by a dysregulated systemic inflammatory response to infection. Vitamin A is an essential micronutrient that plays an important immunomodulatory role. Emerging evidences suggests that vitamin A deficiency (VAD) may had a significant potential for the development and progression of sepsis. **Aim:** to assess VAD prevalence in septic critically ill paediatric patients, and its effect on their clinical outcomes. **Patients and methods:** This is a cross-sectional study that included two groups; a group of 37 critically ill children with sepsis, and control group of 37 non critically ill children attending to the outpatient clinics. Full history and clinical examination were done to the patients, in addition patients of both groups were screened for serum vitamin A levels. **Results:** We found that VAD was significantly higher in critically ill children with sepsis (n = 10) compared to the controls group (n=0, $p < 0.001$). Also, most of vitamin A deficient patients had increased pediatric risk of mortality (PRISM) III scores at time of the paediatric intensive care unit (PICU) admission ($P < 0.001$), and all of them died in the follow-up compared to patients with normal vitamin A levels. **Conclusion:** Vitamin A deficiency was linked to sepsis severity and higher PRISM III score at PICU admission for critically ill paediatric patients. In addition, serum vitamin A level may be used as a marker for predicting mortality in those septic critically ill paediatric patients.

Keywords: Vitamin A, Sepsis, Septic shock, Children

Abbreviations

ARDA: Acute respiratory distress syndrome
CBC: Complete blood count
CRP: C-reactive protein
ELISA: Enzyme linked immunosorbent assay
MODS: Multiple organ dysfunction syndrome
MRSA: Methicillin- resistant Staphylococcus aureus
PICU: Pediatric intensive care unit
PRISM III: Pediatric Risk of Mortality III
SIRS: Systemic inflammatory response syndrome
TLC: Total leucocytic count
VAD: Vitamin A deficiency

Introduction

Vitamin A is an essential micronutrient that plays a vital role in various physiological processes, including vision, immune function, and cellular differentiation[1].

Vitamin A deficiency (VAD) is a significant public health worldwide, particularly in the developing countries. It is estimated that globally, around 250 million preschool-age children are affected by VAD. Insufficient

intake of foods rich in vitamin A, such as fruits, vegetables, and animal products, is the primary cause of deficiency. Inadequate absorption and impaired metabolism of vitamin A due to certain medical conditions can also contribute to deficiency[2]. The consequences of VAD can be severe and wide-ranging. In children, it can lead to vision impairment and blindness. It also increases the susceptibility to infections, particularly respiratory and gastrointestinal infections[3].

Sepsis is a life-threatening condition caused by a dysregulated immune response to an infection. It is characterized by systemic inflammation, organ dysfunction, and can progress to septic shock, leading to high mortality rates[4] .

In 2020, there were about 49 million cases of sepsis globally, leading to 11 million sepsis-related deaths. This accounted for over 20% of all deaths worldwide, with nearly half of these deaths occurring in children under 5 years old[5].
As Vitamin A plays a crucial role in modulating immune responses and maintaining the integrity of epithelial barriers, both of which are important in the pathogenesis of sepsis, VAD may impair immune function, leading to an increased risk of infection and a dysregulated inflammatory response[6] .
Vitamin A is essential for immune response and maintaining epithelial barriers, which are crucial in sepsis. In critically ill sepsis patients, VAD can worsen the condition, leading to multiple organ dysfunction syndrome (MODS) and higher mortality rates. Vitamin A supplementation in these patients has shown benefits, such as reducing mechanical ventilation duration, improving clinical outcomes, and lowering mortality rates[7].

The aim of the present study is to to assess VAD prevalence in septic critically ill paediatric patients, and its effect on their clinical outcomes.

Methodology

Study design

This is a prospective study done from January 2023 to June 2023 enrolling 37 critically ill children with sepsis who were admitted to pediatric intensive care units (PICUs) of our University children's hospital and 37 non-critically ill children attending to the outpatient clinics as control group.

The study protocol was approved by the ethical committee of the Faculty of Medicine, Cairo University, with an approval number MS-576-2021. Written informed consent was taken from the care givers of the children.

Patients

- Eligible participants were children aged 1 month to 12 years, of both genders of critically ill children with sepsis diagnosed according to Surviving Sepsis Campaign International Guidelines. Sepsis was defined as a suspected or confirmed infection, along with at least two criteria for systemic inflammatory response syndrome (SIRS), with at least one abnormal temperature or leukocyte count. Specific criteria included a core temperature exceeding 38.5°C or dropping below 36°C, tachycardia with a mean heart rate above 2 standard deviations for age (or bradycardia below the 10th percentile for children under one year), respiratory rate more than 2 standard deviations above normal, or mechanical ventilation requirement. An abnormal leukocyte count or over 10% immature neutrophils was also a criterion. Severe sepsis was defined as having at least two SIRS criteria and signs of suspected or proven invasive infection, cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or dysfunction in two or more non-cardiovascular organ systems[8].
- The control group enrolled 37 non-critically ill children attending the outpatient clinics of our hospital.
- Exclusion criteria included premature and low birth weight infants, and patients with primary or acquired immunodeficiency.

Sample size:
As evident from previous studies, and by encountering Vitamin A deficiency in critically ill children with sepsis as a primary outcome, the Epi-calc was used to calculate the sample size for this cross-sectional analytical study. Assuming 80% power, 0.05 level of significance, 43% null hypothesis value and estimated proportion of 58.8%, Sample size will be = 67 participants. Considering drop-outs rate

of 10%, therefore the final sample size will be 74 participants. Ratio between control group to cases will be 1:1.

Therefore, the study included 74 patients divided into two groups, whereas the first group enrolled critically ill children with sepsis admitted at the pediatric intensive care units and the control group included 37 non-critically ill children at the outpatient clinics.

Assessments and data collection

The data were collected by reviewing critically ill pediatric patients with sepsis in the first 24 hours of PICU admission, including personal history, cause of PICU admission, history of recurrent infections, recurrent hospital admissions, and duration of illness. Symptoms of vitamin A deficiency was asked for including: skin lesions, vision affection or night blindness. Full physical examination assessing each patient to examine for the presence of sepsis criteria according to its definition. The patients' weight, vital signs (adjusted for age), were recorded in the first 24 hours of PICU admission. The Pediatric Risk of Mortality III (PRISM III) score ranging from 0-74, assessing 17 physiological variables in the first 12 hours from PICU admission was calculated, were higher PRISM III score predicts higher risk of mortality. Laboratory investigations were retrieved from patients' medical records including investigations to prove sepsis, Complete blood count (CBC), C- Reactive protein (CRP), blood, urine and/or other body fluid cultures.

Interventions

Serum samples were collected from all participating patients through the first 24h of admission, and before any enteral and/or parenteral nutrition. Since vitamin A is light-sensitive, venous blood sample tubes withdrawn were immediately -after collection- wrapped into aluminum foil. Then, the samples were centrifuged at 2000-3000 RPM for 20 minutes to separate the serum. The serum was collected in Eppendorf test tubes and frozen at−80°C until measuring vitamin A concentrations of the serum samples by Enzyme linked immunosorbent assay (ELISA) technique. Serum vitamin A was then determined using Human vitamin A ELISA kits, NO., 201-12-1549, manufactured by SunRed Biotechnology company (Shanghai, China) (June 2022- June 2023).

Statistical analysis

The Statistical analysis was performed using the Statistical package of social sciences (SPSS) version 26 (Chicago, USA). Mean and standard deviation were used to express continuous normally distributed data, while, Kolmogorov Smirnov test was used to examine the quantitative data for its normality. For continuous not normally distributed data, Kruscal Wallis test was used. Categorical data were expressed as numbers and percentages, and were the Chi square test was used for analysis. Statistical significance was considered when probability (P) value is less than or equal to 0.05. Mann Whitney U-test was used to compare Medians of both groups. Fisher's exact test was used to compare the frequency between groups.

Results

Our study included 37 critically ill children with sepsis, with median (IQR) age of 0.833 (2.99-3.8) years, 62.16% were males, and the median (IQR) weight was 9 (12-7.29) Kg. In contrast to the control group (n=37), the median (IQR) of age was 8 (7.62-3.35) years, with the same male: female ratio (Table 1). This difference was adjusted later with the multivariable logistic regression models.

Critically ill children with sepsis were significantly higher than controls regarding the heart rate, respiratory rate and temperature values (P< 0.001), with mean (SD) PRISM III score at PICU admission of 12.2±4.5. Also, critically ill children with sepsis had significantly higher CRP, and TLC levels than controls (Table 1).

The most common presentations of the septic enrolled patients were fever 59.5% (n=22), respiratory distress 40.5% (n=15) and irritability in 29.72% (n=11). Most of our patients had pneumonia 45.9% (n=17), heart failure secondary to congenital heart diseases 13.75% (n=5), and hepatic failure in 8.1% (n=3); Also, we had 4 other enrolled septic patients, a chronic kidney disease patient with central line related infection, a post burn septic patient, a patient with intracranial hemorrhage, and a septic patient on top of Steven Johnson syndrome. Sixteen patients (43.24%) had

positive culture findings, of which blood stream infections were in 68.75% (n=14), with Klebsiella pneumonia was the most common finding in 37.5% (n=6), followed by Methicillin- resistant Staphylococcus aureus (MRSA) in 25% (n=4) (Table 2).

Critically ill children with sepsis showed significantly ($p = 0.048$) lower median (IQR) vitamin A levels (62 (0.1 - 265) mcg/dl) compared to control group (69 (9.5 - 482) mcg/dl). Likewise, vitamin A deficiency was significantly observed higher in critically ill children with sepsis (n = 10, (27%)) compared to the controls (0%) ($p < 0.001$) (Table 3).

In consistence with standard conservative care for septic critically ill patients in the PICU with intravenous fluid balance management, antimicrobials, monitoring and managing their vital signs, 23 (62.16%) patients needed supplementary 2 liters nasal oxygen, 10 patients (27%) needed mechanical ventilation, and 14 patients (37.8%) needed inotropic support to maintain their hemodynamic stability. Most of our patients 62.16% (n=23) were discharged, with mean hospital stay of 4.59 (± 1.96) weeks, while 37.8% (n=14) died from sepsis and/ or its complications (Table 2).

The multivariable logistic regression models of the independent association between vitamin A deficiency and critically ill children with sepsis showed that, with 1year increase in the patient's age there was 29% (OR = 0.712, 95% CI; 0.611 – 0.826) reduction in the chance of getting critically ill after sepsis ($p < 0.001$); In contrast, with 1mg/dl increase in the CRP level there was 7.3 times (OR = 7.278, 95% CI; 1.762 – 12.8 24) increase in the risk of getting critically ill after sepsis ($p = 0.048$). And, after adjusting for all factors, with 1mcg/dl increase in the vitamin-A level there was 0.7% (OR = 0.993, 95% CI; 0.984 – 0.999, $p = 0.047$) reduction in the possibility of getting critically ill after sepsis (Table 4).

Addressing the subgroup analysis of critically ill patients with sepsis, we found that vitamin A was deficient in only ten patients, and it is statistically significant with age, outcome and PRISM III score of patients at PICU admission. Vitamin A levels were inversely associated with higher PRISM III scores in septic children with VAD, with median PRISM III score of 18.5 in VAD, versus 9 in non- vit A deficient ones ($P < 0.001$). Unfortunately, all of the 10 VAD patients, with cut-off level of 0.7 µ/L (or 20 mcg/dl), died in the follow-up, compared to patients with no vitamin A deficiency ($P < 0.001$) (Table 5, Figure 1,2).

Table (1): Demographic characteristics, initial vitals and laboratory findings of both groups.

Variables	PICU cases (n = 37)	Control (n = 37)	P value
Age (years) Median (IQR)	0.833 (2.99-3.8)	8 (7.62-3.35)	**<0.001**
Sex Male (%) Female (%)	23 (62.16%) 14 (37.83%)	23 (62.16%) 14 (37.83%)	1
Weight (Kg) Median (IQR)	9 (12-7.29)	30 (30.4-7.3)	**<0.001**
Heart rate (bpm) Normal for age (%) Tachycardia (%)	7 (19%) 30 (81%)	37 (100%) 0 (0%)	**<0.001**
Blood pressure (mmHg) Normal for age (%) Hypotension (%)	30 (81%) 7 (19%)	37 (100%) 0 (0%)	**<0.001**
Respiratory rate (/min) Normal for age (%) Tachypnea (%)	16 (43.25%) 21 (56.75%)	37 (100%) 0 (0%)	**<0.001**
Temperature (C) Mean (SD)	37.8 (0.997)	36.6 (0.5)	**<0.001**
CRP (mg/L) Median (IQR)	100 (116- 85)	3 (3.35- 1.36)	**<0.001**
TLC (/mm^3) Median (IQR)	13 (15.5- 9.63)	7.56 (7.6- 2)	**<0.001**
Platelet (/mm^3) Median (IQR)	308 (298- 233)	307 (303- 70.8)	0.658
PRISM III score Median (IQR)	12 (12.2-4.48)		

SD: standard deviation; IQR: interquartile range; CRP: c-reactive protein; TLC: total leucocytic count.

Table (2): Clinical presentation, diagnosis, culture results, the need for vasopressors , oxygen supplementation needed and outcome of critically ill septic enrolled patients.

Variables	Critically ill children with sepsis (n = 37)	Percentage
Clinical presentation		
Irritability	11	29.72%
Disturbed consciousness	6	16.21%
Fever	22	59.5%
Convulsions	7	19%
Respiratory distress	15	40.5%
Vomiting	9	32.43%
Jaundice	3	8.25%
Anuria	1	2.75%
Diagnosis		
Pneumonia	17	45.9%
Heart failure	5	13.75%
Liver cell failure	3	8.1%
Nephrotic syndrome	3	8.1%
Post operative surgical	6	16.21%
Others	4	10.81%
Culture results (n=16)		
Source Blood	14	68.75%
Sputum	2	12.5%
Organism		
Klebsiella	6	37.5%
Pseudomonas	2	12.5%
E-coli	1	6.25%
MRSA	4	25%
Gram negative bacilli	2	12.5%
Candida	1	6.25%
Management		
Nasal oxygen supplementation	23	62.16%
Mechanical ventilation	10	27.02%
Inotropic support	14	37.83%
Outcome		
Mortality	14	37.83%
PICU length of stay (days)	4.59*	(4.59±1.96) *

* Mean (standard deviation); MRSA: Methicillin- resistant Staphylococcus aureus; PICU: pediatric intensive care unit.

Table (3): Vitamin A levels and its interpretation of both groups.

Variables	Critically ill children with sepsis (n = 37)	Control (n = 37)	P value
Vitamin A Level (mcg/dl) Median (IQR)	62 (0.1 - 265)	69 (9.5 - 482)	**0.048**
Vitamin A level interpretation			
Deficient (%)	10 (27%)	0 (0%)	**<0.001**
Not deficient (%)	27 (73%)	37 (100%)	

SD: Standard deviation; IQR: Interquartile range.

Table (4): Independent predictors of critically ill children with sepsis: Logistic Regression analysis

Variable	Multivariable	
	OR (95% CI)	**P-value**
• **Age/years**	0.712 (0.611 – 0.826)	**< 0.001**
• **Sex (Male)**	0.842 (0.280 – 2.536)	= 0.761
• **Weight/kg**	0.729 (0.626 – 2.848)	= 0.441
• **HR (beat/min.)**	5.624 (0.924 – 16.854)	= 0.624
• **RR (Cycle/min.)**	3.524 (0.816 – 9.654)	= 0.425
• **Temperature**	1.752 (0.544 – 5.902)	= 0.610
• **CRP**	7.278 (1.762 – 12.824)	**= 0.048**
• **Vit-A Level (mcg/dl)**	0.993 (0.984 – 0.999)	**= 0.047**

OR: Odds Ratio; CI: Confidence Interval; HR: heart rate; RR: respiratory rate; CRP: C-reactive protein.

Table (5): Subgroup analysis of critically ill patients according to vitamin A deficiency.

Vitamin A deficiency	Deficient (n =10)	Not deficient (n=27)	P value
Age (Years)			
Median (IQR)	4.5 (1.31-8.75)	0.75 (0.25- 2.5)	**0.033**
Sex			
Male	5 (50%)	18 (66.67%)	0.353
Female	5 (50%)	9 (33.33%)	
Weight (Kg)			
Median (IQR)	18.5 (8.75- 20.8)	9 (4.5-15)	0.057
Herat rate			
Median (IQR)	155 (135- 160)	155 (138- 166)	0.823
Respiratory rate			
Median (IQR)	39 (35- 48.5)	45 (40- 49)	0.258
CRP			
Median (IQR)	88.5 (49-154)	100 (53- 150)	0.745
TLC			
Median (IQR)	8.35 (6.12- 21.3)	13.9 (9- 21.4)	0.356
Culture			
Positive	3 (30%)	13 (48.14%)	
Negative	7 (70%)	14 (51.85%)	0.461
O2 Support			
No need	1 (10%)	3 (11.11%)	
Nasal oxygen	6 (60%)	17 (62.96%)	1
Mechanical ventilation	3 (30%)	7 (25.92%)	
Inotropic Support			
No need	4 (40%)	19 (70.37%)	0.132
On inotropic	6 (60%)	8 (29.62%)	
Length of stay (week)			
Median (IQR)	5 (3.25- 6.75)	4 (3- 6)	0.446
Outcome			
Discharge	0 (0%)	23 (85.18%)	**<0.001**
Death	10 (10%)	4 (14.81%)	
PRISM III			
Median (IQR)	18.5 (17.3-19.8)	9 (8-12)	**<0.001**

SD: Standard deviation; IQR: Interquartile range; TLC: total leucocytic count ; CRP: C-reactive protein.

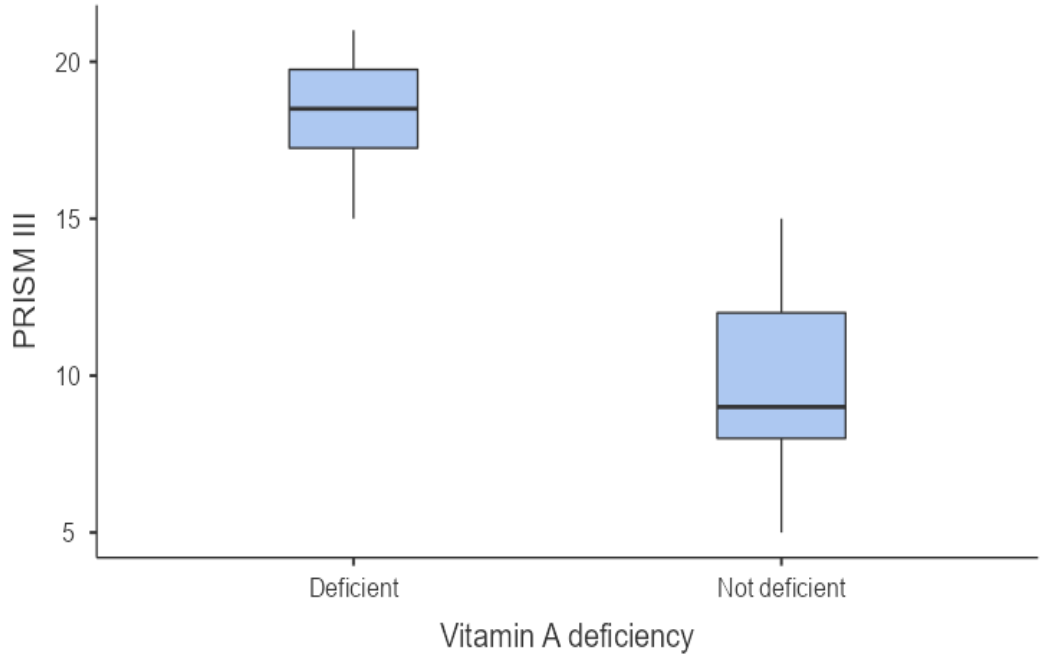

Figure (1): A box plot of PRISM III in patients with and without vitamin A deficiency(p <0.001).

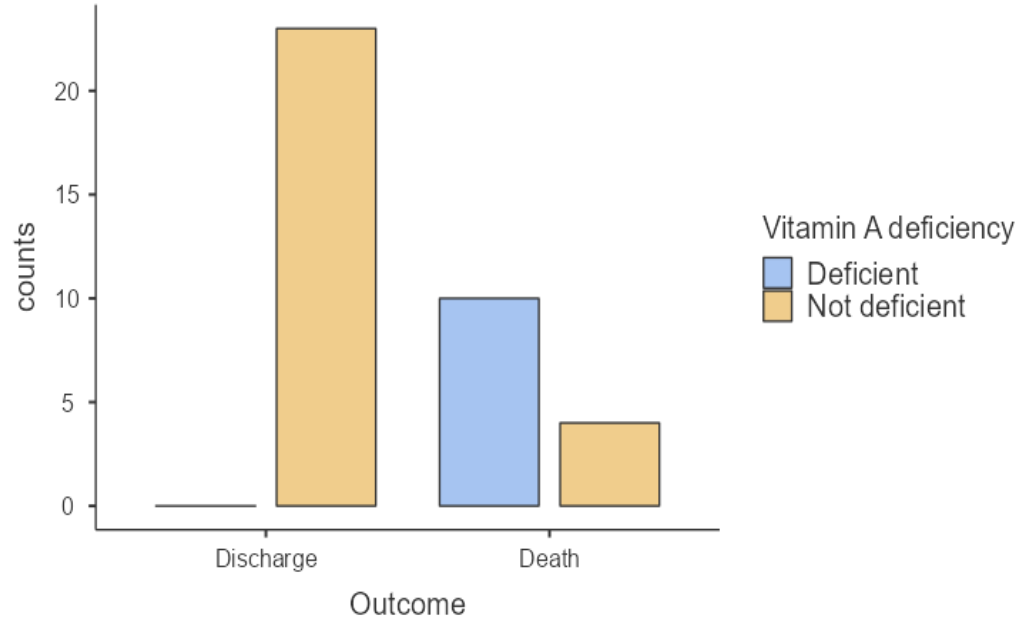

Figure (2): A bar chart of the outcome in patients with and without vitamin A deficiency (p <0.001).

Discussion

Vitamin A has an essential role in the immune system functions and integrity, and its deficiency may lead to great imbalance between pro- and anti-inflammatory mediators, impairing the immune function, precipitating to sepsis severity, and its deficiency may be a contributing factor for unfavorable clinical outcomes especially in septic patients [9].

A recent study found that 76.1% of Egyptian children had inadequate vitamin A intake, with urban areas of Lower Egypt, Upper Egypt, and frontier regions reporting insufficient levels at 9.4%, 10.8%, and 13.0%, respectively.

Additionally, Abd El-Shaheed et al., (2018) reported that 56.6% of healthy participants had

VAD. The WHO global database indicates that VAD prevalence among preschool children in the Middle East ranges from 1.0% to 12%.[10-12].

As we hypothesize that lower vitamin A serum levels may play an important role in the pathogenesis and severity of pediatric sepsis, the aim of our study was to to assess VAD prevalence in septic critically ill paediatric patients, and its effect on their clinical outcomes.

The age of our patients was significantly lower compared to the control group ($P < 0.001$), this wasn't an attributed confounder, as later we found that VAD in our critically ill patients was significantly correlated with older patients, and although, the controls were older, no VAD was encountered in them.

In concordance with Zhang et al., (2019), and Ibrahim et al., (2024) results, we observed that our critically ill children with sepsis had significantly lower levels of serum vitamin A compared with controls, likewise, vitamin A deficiency was significantly higher in critically ill children with sepsis[6,13].

Additionally, Choobdar et al., (2023), found that the mean vitamin A level was significantly lower in septic than non-septic group of patients with 13.5 ± 3.3 µg/dl versus 24.7 ± 10.2 (11.6 – 54.9) µg/dl; also, VAD patients were significantly more in the septic group than the non-septic group with 95% versus 25%[14].

Our study showed that all of our patients with VAD had higher PRISM III scores ($P < 0.001$), and all of them died in the follow-up compared to patients with no vitamin A deficiency ($P < 0.001$), illustrating that VAD may be had a role in sepsis related morbidity and mortality.

In consistence to this finding, recently, several literatures have found evidence of association between VAD and mortality in children. A large study conducted in Indonesia found that those children not receiving Vit A capsules in their last 6 months were more susceptible to infections. Not only that, but also, in a large prospective study on VAD children, it was observed that the risk for enteric infections was almost 2 folds higher and the risk for respiratory infections was 2.3 folds higher than in children having adequate Vit A levels [15,16].

Finally, we found that VAD with vitamin A values lower than 0.70 micromoles/L (or 20 micrograms [mcg]/dL) is more associated with severe sepsis, higher PRISM III score at PICU admission, and had a bad prognostic value. Furthermore, future large-scale researches are needed to validate and address the effect of vitamin A routine supplementation to those critically ill septic pediatric patients and its effect on their outcome, morbidity and mortality.

Conclusion

Vitamin A deficiency is a major health hazard that positively correlates with sepsis, sepsis severity, and mortality of pediatric critically ill septic patients in PICU. Future researches should address the effect of vitamin A supplementation in management of critically ill pediatric patients with sepsis on their outcome.

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