ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2019; 5(2): 46-50
www.allresearchjournal.com
Received: 18-12-2018
Accepted: 21-01-2019

Zubair A Bhat
Department of Pediatrics and Neonatology, Sher-I-Kashmir Institute of Medical Sciences Hospital, Srinagar, Jammu & Kashmir, India

Sheeraz A Dar
Department of Pediatrics and Neonatology, Sher-I-Kashmir Institute of Medical Sciences Hospital, Srinagar, Jammu & Kashmir, India

Duri S Yetoo
Department of Obstetrics and Gynecology, Sher-i- Kashmir institute of medical sciences, Medical college hospital Bemina Srinagar, India

Qazi I Ahmad
Department of Pediatrics and Neonatology, Sher-I-Kashmir Institute of Medical Sciences Hospital, Srinagar, Jammu & Kashmir, India

Bashir A Charoo
Department of Pediatrics and Neonatology, Sher-I-Kashmir Institute of Medical Sciences Hospital, Srinagar, Jammu & Kashmir, India

Correspondence
Zubair A Bhat
MD, Department of Pediatrics and Neonatology, Sher-I-Kashmir Institute of Medical Sciences Hospital, Srinagar, Jammu & Kashmir, India

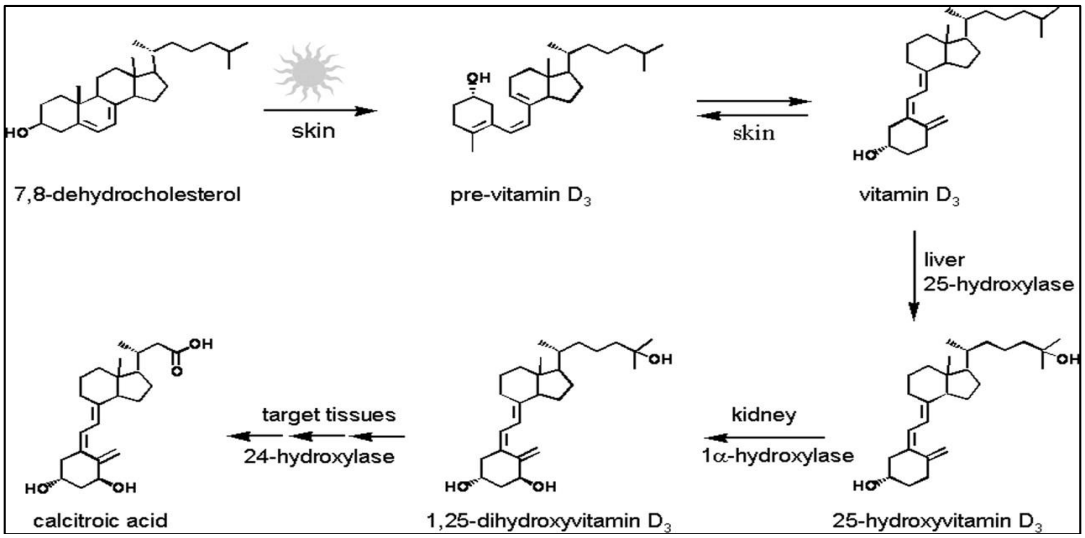
A prospective study for vitamin D levels and its impact on prognosis of pediatric septic shock

Zubair A Bhat, Sheeraz A Dar, Duri S Yetoo, Qazi I Ahmad and Bashir A Charoo

Abstract
Background: Vitamin D enhances the anti-microbial response of monocytes, suggesting a protective role of vitamin D in infection.
Objectives: The main objective of this study is to look for prognostic importance of vitamin D levels in pediatric septic shock.
Method: All pediatric patients with septic shock were included in study except patients in neonatal age group (>1 month), patients with underlying co morbidities, patients who die within 2 days of onset of septic shock, patients with birth weight of <2.5 kgs and patients who took vitamin D supplements in last 15 days.
Results: Among the 50 septic shock patients 24 were having deficient vitamin D levels, 12 were having insufficient and 14 were having sufficient levels. Among the deficient group 13 patient died while remaining 11 were discharged from PICU, among insufficient group 9 died while 3 were discharged from PICU, and among sufficient group 8 died and 6 were discharged from PICU, giving the P-Value of 0.469.
Conclusions: Our study shows that there is very high prevalence of Vitamin D deficiency in pediatric septic shock patients, however outcome in terms of mortality is not related to vitamin D deficiency.

Keywords: Vitamin D deficiency, PICU, PRISM III score, septic shock

Introduction
Vitamin D is a group of fat-soluble prohormones which were identified after the discovery of the anti-rachitic effect of cod liver oil in the early part of the 20th century. [1] The two major biologically inert precursors of vitamin D are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) [2] Vitamin D3 is formed when 7-dehydrocholesterol in the skin is exposed to solar ultraviolet B (UVB, 290-320 nm), and is then converted to pre-vitamin D3 in a heat-dependent process, pre-vitamin D3 is immediately converted to vitamin D3. Excess UVB rays transform pre-vitamin D3 into biologically inactive metabolites, tachysterol and lumisterol. Vitamin D2 is plant derived, produced exogenously by irradiation of ergosterol, and enters the circulation through diet. Both vitamin D precursors resulting from exposure to the sunshine and the diet are converted to 25-hydroxyvitamin D [25(OH)D] (calcidiol) when they enter the liver. [3] 25(OH) D is the major circulating form of vitamin D and is used to determine vitamin D status. In order to be biologically active, additional hydroxylation in the kidneys is needed to form active 1, 25-dihydroxyvitamin D [1, 25(OH) 2 D] (calcitriol). Humans obtain vitamin D through dietary intake and exposure to sunlight. Very few foods naturally contain vitamin D. Oily fish such as salmon, mackerel, and sardines are rich in vitamin D3 [5]. Egg yolks are reported to contain vitamin D though the amounts are highly variable [5]. An overview of vitamin D synthesis [6]



Vitamin D plays an important role in maintaining an adequate level of serum calcium and phosphorus [7]. Without vitamin D, only 10 to 15% of dietary calcium and about60% of phosphorus is absorbed [8]. The most important function of vitamin D is to maintain normal calcium homeostasis. Vitamin D increases the total intestinal absorption of calcium and phosphorus from 10-20% and 60% to 30-40% and 80%, respectively. In the setting of hypovitaminosis D, serum level of calcium is first to fall, but phosphorus level is maintained within the normal range. This hypocalcaemia then leads to secondary hyperparathyroidism, resulting in an increased serum level of 1, 25 dihydroxycholecalciferol, normalization of serum calcium and a fall in plasma phosphorus level. This homeostasis is achieved by PTH-induced bone re-sorption, which also increases the serum level of alkaline phosphatase. This condition, if left untreated, eventually leads to exhaustion of bone stores and recurrence of hypocalcaemia.[9] Therefore vitamin D has a great effect in forming and maintaining strong bones. Studies have shown correlations between low vitamin D levels and certain cancers, immune system dysfunction, diabetes, cardiovascular disease, hypertension and metabolic syndrome [10]. Thus, investigators in several fields, including critical care medicine, have turned their attention to the nonskeletal effects of vitamin D. Vitamin D plays an important role, not only for bone health, but also in the immune system [11] Both in vitro and clinical studies have demonstrated that vitamin D is important for the innate and adaptive immune response. In adults, vitamin D insufficiency is common in patients who are hospitalized or have a severe infectious process and is associated with increased mortality. Vitamin D enhances the anti-microbial response of monocytes of adults suggesting a protective role of vitamin D in infection. Particularly, anti-microbial peptides such as human cathelicidin antimicrobial peptide (hCAP18) and b-defensin are up-regulated in response to vitamin D therapy [12]. In adult patients with sepsis, plasma LL-37, the active cathelicidin protein cleaved from hCAP18, is positively correlated to vitamin D status [13, 14]
The evidence of Vitamin D status in critically ill children is lacking from developing countries, like India. To make conclusive statement regarding the association of Vitamin D deficiency with the outcome in pediatric septic shock, we conducted a prospective study in the Department of Pediatrics and Neonatology SKIMS Srinagar.

Materials and Methods

Study Design

We performed a prospective observational study in the department of pediatrics Sher-I-Kashmir Institute of Medical Sciences, Srinagar. This is an urban academic medical center in Srinagar, over a period of 3 years from May 1, 2016, through April 31, 2018. This study was approved by the institutional ethical committee. Informed written consent from parents of the infants was obtained.

Participants, Case definitions: All pediatric patients with septic shock were included in study except patients in neonatal age group (>1 month), patients with underlying co morbidities, patients who die within 2 days of onset of septic shock, patients with birth weight of <2.5 kgs and patients who took vitamin D supplements in last 15 days.

Defining septic shock: Sepsis was defined as SIRS associated with infection. The presence of at least two of four criteria: temperature, leukocyte, tachypnea and tachycardia. One of which must be abnormal temperature or leukocyte count. Core temperature of >38.5 °C or <36 °C. Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period, or for children <1-year- old. Bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period. Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia. Leukocyte count elevated or depressed for age (not secondary to chemotherapy- induced leukopenia) or >10% immature neutrophils [15] Infection defined as suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (white blood cells in a normally sterile body fluid, perforated viscus, chest radio- graph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans). Sepsis defined as SIRS in the presence of or as a

result of suspected or proven infection. Severe sepsis defined as sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions. Septic shock is sepsis induced low blood pressure that cannot be maintained with fluid resuscitation or use of vasopressors in any dose [15]

Determination of severity of illness: Severity of illness was determined by Pediatric Risk of Mortality score III (PRISMIII).

Defining vitamin D deficiency: Vitamin D status was assessed by measurement of plasma 25-Hydroxy vitamin D (25 (OH) D. Vitamin D status was defined as vitamin D sufficient (25(OH) D >20 ng/mL), vitamin D insufficient (25(OH)D 10-20 ng/mL), and vitamin D deficient (25(OH)D <10 ng/mL). These categories are consistent with definitions used to define vitamin D status reporting vitamin D status in children participating in the National Health and Nutrition Examination Survey (NHANES).
Blood was drawn for Vitamin D levels from septic shock patients on the first day of diagnosis. Progression of shock severity was assessed by periodic clinical and laboratory assessment on first day of enrollment and third day. Final outcome was defined at the time of discharge from PICU in terms of Passive shock or death.

Determination of vitamin D levels: The serum 25(OH) D level was measured using an chemiluminescence enzyme immunoassay method in the department of Immunology and Molecular Medicine SKIMS Soura Srinagar.

Statistical methods: The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were summarized as Mean±SD and categorical variables were expressed as frequencies and percentages. Graphically the data was presented by bar diagrams, pie diagrams and scatter plots. Chi-square test was employed to determine the association of vitamin D Levels with outcome in study patients. Karl Pearson's coefficient of correlation was employed to determine the correlation between vitamin D Levels and PRISM score. A P-value of less than 0.05 was considered statistically significant. All P-values were two tailed.

Results

A total of 50 patients fulfilling the inclusion criteria were included in the study. Among the total 50 studied patients, 16(32%) were of infantile age, 14(28%) were aged 1 to 5 years, 7(14%) were 5 to 10 years and 13(26%) were ≥ 10 years of age with the Mean ± SD of 5.1±5.21 respectively. Of these 50 studied patients, 30 (60%) were males and 20 (40%) were females. fig 1.

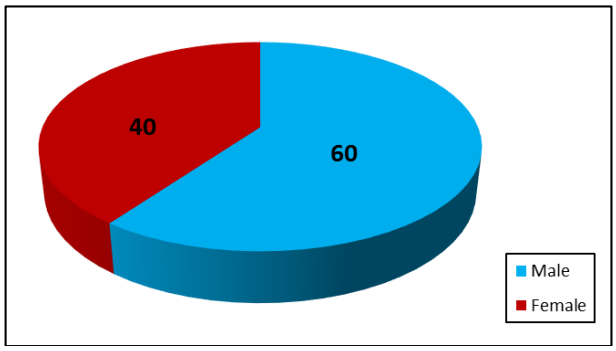


Fig 1: Gender distribution of study patients

Among these 50 septic shock patients 24 were having deficient vitamin D levels, 12 were having insufficient and 14 were having sufficient levels. Among the deficient group 13 patient died while remaining 11 were discharged from PICU, among insufficient group 9 died while 3 were discharged from PICU, and among sufficient group 8 died and 6 were discharged from PICU, giving the P-Value of 0.469 on student t- test. Table 1 and fig. 2

Table 1: Showing correlation of vitamin D Levels with outcome in study patients

Vitamin D Levels	Dead		Discharge from PICU		P-value
	No.	%age	No.	%age	
Deficient	13	43.3	11	55	0.469
Insufficient	9	30.0	3	15	
Sufficient	8	26.7	6	30	
Total	30	100	20	100	

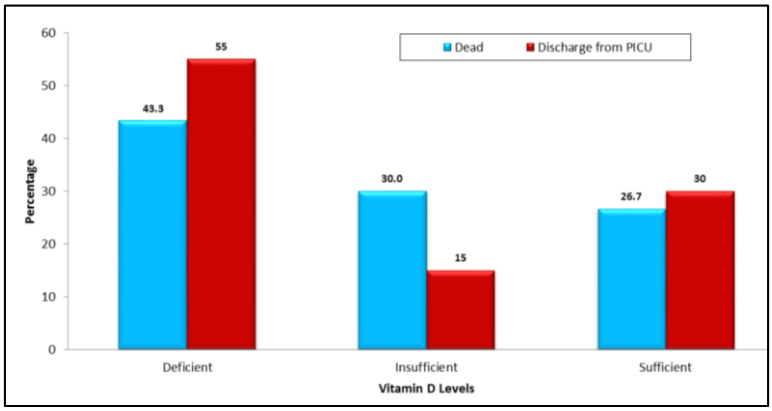


Fig 2: Showing correlation of vitamin D Levels with outcome in study patients

To asses severity of septic shock PRISM III score was calculated from all patients and to find its correlation with patients serum vitamin D levels Scatter Plot was drawn with PRISM III score on y-axis and serum vitamin D levels on x-axis. Fig 3

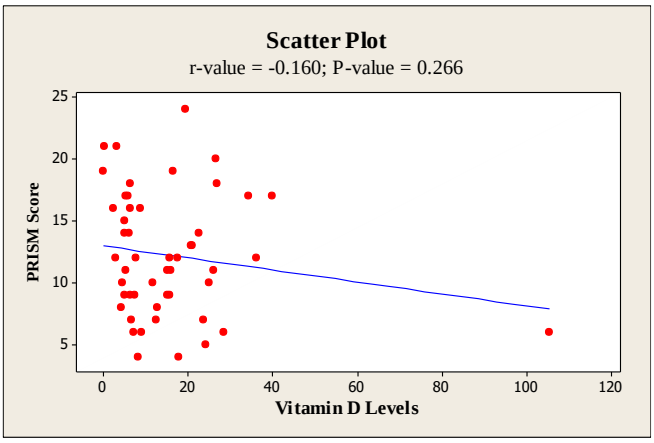


Fig 3: Scatter Plot

Discussion

The association of Vitamin D deficiency (VDD) in critically ill adults has been well studied, with a recent Meta‑analysis demonstrating a significant increase in infection rate, sepsis, and mortality in deficient patients [21-24] Recent research of critically ill children has demonstrated that VDD is common and a few studies have also identified that VDD is associated with more severe illness and a longer stay in the pediatric intensive care unit (PICU) [25-30]. No consensus has as yet been reached regarding the optimal definition of VDD, nor the threshold levels to define health benefits. Due to the lack of interventional studies to show that administration of Vitamin D improves clinical outcomes, opinion is still divided as to whether it is association or causality. The evidence of Vitamin D status in critically ill children is lacking from developing countries, like India. To make conclusive statement regarding the association of Vitamin D deficiency with the outcome in pediatric septic shock, we conducted a prospective study in the Department of Pediatrics and Neonatology SKIMS Srinagar.

The study demonstrated that in a sample of critically ill children with septic shock admitted to PICU, the prevalence of hypovitaminosis D was high. This result supports recent investigation showing that hypovitaminosis D is common in critically ill children [31, 32] It was observed that 72% of the study patients had 25(OH)D<20 ng/mL, higher to the rate of 29.5% from the study by Rey *et al.* in north of Spain [33], the rate of 34.5% from Rippel *et al.* in a cohort of critically ill Australian children [34], and also higher than the 40.1% and 69% reported by McNally *et al.* from North American and Canadian children [35]. Our prevalence of vitamin D deficiency in critically ill PICU patients is in full agreement with study conducted by Azam *et al.* in Indian children (80.4% Vs 72). The probable reason for high prevalence of deficiency in our population is that the quality of daily dietary intake in children in our setting. Beside dietary cause of Vitamin D deficiency, other potential causes may include poor nutritional status of mothers and improper weaning, less time spent in outdoor sunshine, religious covering of body as well as low socioeconomic situation.

In our study the correlation between outcome (in terms of death or discharge from PICU) and Vitamin D levels revealed no significant difference among vitamin D sufficient (>20ng/ml) and deficient patients (<20ng/ml). Out of total 36 deficient patients, 22 patients died (61%), whereas among 14 vitamin D sufficient patients 8 patients died (57%). The difference was statistically insignificant with p value of 0.469. Our results in terms of correlation between mortality and vitamin D levels are in full agreement with Adams *et al.* who in 2012 concluded no significant difference in 28 days mortality between Vitamin D sufficient and deficient patients, p value of 0.645 [17]. Franz Ratzinger *et al.* in 2017 also concluded that Vitamin D deficiency fails to predict mortality risk in SIRS cohort with p value of 0.198 [18] Nazik *et al.* also found no association between Vitamin D deficiency and other illness severity factors including mortality [19] Nurnaningsih *et al.* in 2018 found in Forty-two patients of diagnosis of sepsis, severe sepsis or septic shock on PICU admission, mortality was higher in patients with 25(OH)D deficiency patients, but it did not show any statistical significance compared to the group of patients with 25(OH)D insufficiency or normal level of 25(OH)D group of patients (p=0.78) [20].

In addition present study demonstrated negative correlation between severity of septic shock as assessed by PRISM III score and serum vitamin D levels. Correlation coefficient R value of -0.16 and p value of 0.266 was obtained indicating an insignificant weak negative correlation. Similar results by Kate Madden *et al.* in 2012 were obtained, they identified a relationship between illness severity, as defined by PRISM-III score on admission, and 25(OH) D level but were not sure about the effect of multiple fluid boluses on vitamin levels and that their results were not statistically significant [16] In contrast Missy Sturges & John cannel in 2017 found that severely vitamin D deficient children required more fluid boluses within first 6 hrs. (p=0.02) and it was associated with catecholamine refractory shock; treatment resistant form of septic shock. (p=.04)

In conclusion, our study shows that there is very high prevalence of Vitamin D deficiency in pediatric septic shock patients, however outcome in terms of mortality is not related to vitamin D deficiency and there exist an insignificant weak negative correlation between severity of septic shock and serum vitamin D levels.

Reference

1. Wolpowitz D, Gilchrest BA. The vitamin D questions: how much do you need and how should you get it? J Am Acad Dermatol. 2006; 54:301-317.
2. Holick MF, The use and interpretation of assays for vitamin D and its metabolites. J Nutr. 1990; 120:1464-1469.
3. Holick MF. The role of vitamin D for bone health and fracture prevention. Curr Osteoporos Rep. 2006; 4:96-102.
4. Malone RW, Kessenich C. Vitamin D deficiency: implication across the lifespan, the journal for nurse practitioners. J Nurse Practitioners. 2008; 6:448-454.
5. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr. 2004; 79:362-371.
6. Adriana S Dusso, Alex J Brown. Eduardo Slatopolsky American Journal of Physiology - Renal Physiology Published. 2005; 289(1):F8-F28.

DOI: 10.1152/ajprenal.00336.2004
7. Tangpricha V, Koutkia P, Rieke SM, Chen TC, Perez AA, Holick MF. Fortification of orange juice with vitamin D: a novel approach to enhance vitamin D nutritional health. Am J Clin Nutr. 2003; 77:1478-1483.
8. Holick MF, Garabedian M. Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In Primer on the metabolic bone diseases and disorders of mineral metabolism. 6 edition. Edited by: Favus MJ. Washington, DC: American Society for Bone and Mineral Research, 2006, 129-137.
9. Ben-Mekhbi H. Rickets and vitamin D deficiency. In: Holick MF, editor. Vitamin D physiology, molecular biology, and clinical application. Totowa (NJ): Humana Press. 1999, 273-86.
10. Jeng L, Yamshchikov AV, Judd SE, Blumberg HM, Martin GS, Ziegler TR *et al.* Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. J Transl Med. 2009; 7:28,
11. Kamen DL, Tangpricha V, Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. J Mol Med (Berl). 2010; 88(5):441e50.
12. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J *et al.* Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol. 2004; 173(5):2909e12.
13. Jeng L, Yamshchikov AV, Judd SE, Blumberg HM, Martin GS, Ziegler TR *et al.* Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. J Transl Med. 2009; 7:28
14. Simpson JL, Brooks C. Innate immunity in asthma. Paediatr Respir Rev. 2008; 9(4):263e70.
15. Nelson CD, Reinhardt TA, Beitz DC *et al. In vivo* activation of the intracrine vitamin D pathway in innate immune cells and mammary tissue during a bacterial infection. PloS One. 2010; 5:e15469
16. Kate Madden, Henry A Feldman, Ellen M Smith, Catherine M Gordon, Shannon M Keisling, Ryan M Sullivan *et al.* Vitamin D Deficiency in Critically Ill Children: Pediatrics. 2012; 130(3)
17. Adams, Jacob, Foster, Charles, Friedman, Keller. Vitamin D levels on ICU admission, sepsis severity, and Hospital outcomes ; Critical Care medicine, 2012
18. Franz Ratsinger, Helmuth, Haslacher, Markus Stadlberger, Ralf L, Markus Thomas *et al.* 25(OH)D and 1,25 OHD fails to predict sepsis mortality in prospective cohort study; Scienctic reports7:40646/DOI:10.1038/srep40646
19. Nazik Aşılıoğlu, Halit Çiğdem, Muhammed Sükrü Paks. Serum Vitamin D Status and Outcome in Critically Ill ChildrenIndian Journal of Critical Care Medicine 2017; 21(10):662
20. Nurnaningsih, Desy Rusmawatiningtyas. Vitamin D deficiency and outcome of patients with sepsis in pediatric intensive care unit: a prospective observational study: Crit Care Shock. 2018; 21:70-77
21. de Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: Systematic review and meta-analysis. Crit Care. 2014; 18:660.
22. Arnsom Y, Gringauz I, Itzhaky D, Amital H. vitamin D deficiency associated with poor outcome and increased mortality in severely ill patients. QJM. 2012; 105:633-9
23. Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y, Giovannucci E *et al.* Association of low serum 25OH D levels and mortality in critically ill. Crit care Med. 2011; 39:671-7
24. Braun A, Gibbons FK, Litonjuaa AA, Giovannucci E, Christopher KB. Low serum 25 OH D at critical care initiation is associated with increased mortality. Crit care med. 2012; 40:63-72
25. Madden K, Feldman HA, Smith EM, Gordon CM, Keisling SM, Sullivan RM *et al.* Vitamin D deficiency in critically ill children. Pediatrics. 2012; 130:421-8.
26. McNally JD, Menon K, Chakraborty P, Fisher L, Williams KA, Al-Dirbashi OY *et al.* The association of Vitamin D status with pediatric critical illness. Pediatrics. 2012; 130:429-36.
27. Rippel C, South M, Butt WW, Shekerdemian LS. Vitamin D status in critically ill children. Intensive Care Med. 2012; 38:2055-62.
28. Rey C, Sánchez-Arango D, López-Herce J, Martínez-Camblor P, García-Hernández I, Prieto B *et al.* Vitamin D deficiency at pediatric intensive care admission. J Pediatr (Rio J). 2014; 90:135-42.
29. Prasad S, Raj D, Warsi S, Chowdhary S. Vitamin D deficiency and critical illness. Indian J Pediatr. 2015; 82:991-5.
30. Sankar J, Lotha W, Ismail J, Anubhuti C, Meena RS, Sankar MJ *et al.* Vitamin D deficiency and length of pediatric Intensive Care Unit stay: A prospective observational study. Ann Intensive Care. 2016; 6:3.
31. Rippel C, South M, Butt WW, Shekerdemian LS. Vitamin D status in critically ill children. Intensive Care Med. 2012; 38:2055-62.
32. Moraes RB, Friedman G, Wawrzeniak IC, Marques LS, Nagel FM, Lisboa TC *et al.* Vitamin D deficiency is independently associated with mortality among critically ill patients. Clinics (Sao Paulo). 2015; 70:326-32.
33. Corsino Rey, David Sanchez-Arango, Jesus Lopez-Herce *et al.* Vitamin d deficeicy at pediatric intensive care admission; Jornal de Pediatria 2013, 134-42
34. Rippel C, South M, Butt WW, Shekerdemian LS. Vitamin D status in critically ill children. Intensive Care Med. 2012; 38:2055-2062.
35. McNally JD, Menon K, Chakraborty P, Fisher L, Williams KA, Al-Dirbashi OY *et al.* The association of vitamin D status with pediatric critical illness. Pediatrics. 2012; 130:429-36.