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Is There Any Relationship Between Clinical Progress and Vitamin-D Levels In Critically Ill Children?

Çocuk Yoğun Bakım Ünitesinde Yatan Kritik Hastalığı Olan Çocuklarda D Vitamini Düzeyi ile Klinik İzlem Arasında İlişki Var mı?

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ABSTRACT

AIM: Vitamin-D is a hormone that affects infections, the autoimmune system, the cardiovascular system, and the central nervous system; therefore, it is considered important for critically ill patients. This study aimed to examine the relationship between vitamin-D levels and Paediatric Risk of Mortality (PRISM) III score and mortality rates in critically ill children.

MATERIAL AND METHOD: A total of 200 patients who were admitted to Atatürk University Paediatric Intensive Care Unit between January 2016 to January 2017 were included in this study. Demographic data, PRISM III score, serum calcium, phosphorus, alkaline phosphatase, parathormone, and 25-Hydroxy-Vitamin-D [25(OH) D] levels were recorded. 25(OH)D levels were grouped as deficiency (below 12 ng/ml), insufficiency (12-20 ng/ml), sufficiency (20-100 ng/ml), and excess (above 100 ng/ml).

RESULTS: Vitamin-D levels of 23.5% of the patients were deficient, 24.5% were insufficient, and 52% were sufficient. A negative correlation was found between vitamin-D and age (r=-0.42, p<0.01). PRISM III score was found to be lower in patients with sufficient vitamin-D (p<0.01). Although the mortality rate of cases with vitamin-D deficiency was higher, it was not found to be significant. No significant relationship was found between vitamin-D level and duration of hospitalization, duration of mechanical ventilation, chronic disease status, or vasopressor need.

CONCLUSION: PRISM scoring system is a scoring system frequently used in paediatric intensive care units to predict mortality. The higher PRISM III score in patients with insufficient or deficient vitamin-D levels may suggest that vitamin-D insufficiency or deficiency is a risk factor for mortality.

Keywords: Vitamin D, mortality, pediatric intensive care, PRISM III

ÖZET:

GİRİŞ: D vitamini enfeksiyonlar, otoimmün sistem, kardiyovasküler sistem ve merkezi sinir sistemi üzerine etki gösteren bir hormondur; bu nedenle kritik hastalar için önemli olduğu düşünülmektedir. Bu çalışmada, kritik hastalığı olan çocuklardaki D vitamini düzeyi ile Pediatrik Mortalite Riski (PRISM)III skoru ve mortalite oranları arasındaki ilişkinin incelenmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Bu çalışmaya Atatürk Üniversitesi Çocuk Yoğun Bakım Ünitesine Ocak 2016 ile Ocak 2017 tarihleri arasında yatırılan toplamda 200 hasta dahil edildi. Demografik veriler, PRISM III skoru, serum kalsiyum (Ca), fosfor (P), alkalen fosfataz (ALP), parathormon (PTH) ve 25-Hidroksi-Vitamin-D [25(OH)D] seviyeleri kaydedildi. 25(OH)D seviyeleri eksiklik (12 ng/ml altı), yetersizlik (12-20 ng/ml), yeterlilik (20-100 ng/ml) ve fazlalık olarak gruplandırıldı (100 ng/ml üzeri).

BULGULAR: Hastaların %23,5'inin D vitamini düzeyi eksik, %24,5'inin yetersiz, %52'sinin yeterliydi. D vitamini ile yaş arasında negatif korelasyon saptandı (r=-0,42, p<0,010). D vitamini yeterli olan hastalarda PRISM III skoru daha düşük bulundu (p<0,010). D vitamini eksikliği olan hastaların ölüm oranı daha yüksek olmakla beraber anlamlı bulunmadı. D vitamini düzeyi ile hastanede yatış süresi, mekanik ventilatör süresi, kronik hastalık durumu ya da vazopressör ihtiyacı arasında anlamlı ilişki saptanmadı.

SONUÇ: PRISM skorlama sistemi mortaliteyi öngörme açısından çocuk yoğun bakım ünitelerinde sıklıkla kullanılan bir skorlama sistemidir. D vitamini seviyesi yetersiz veya eksik olan hastalarda PRISM III skorunun daha yüksek olması, D vitamini yetersizliği veya eksikliğinin mortalite için bir risk faktörü olduğunu düşündürebilir.

Anahtar Kelimeler: D vitamini, Mortalite, Çocuk Yoğun Bakım, PRISM III

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INTRODUCTION

Vitamin-D plays a critical role in bone metabolism, and its deficiency can result in the development of rickets[1]. Studies have demonstrated that vitamin-D has a protective effect on autoimmune diseases, inflammatory diseases, and some infectious agents through the immune system[2,3]. Although severe deficiency is now rare, the growing awareness of subclinical vitamin-D deficiency has drawn attention to its potential impact on neurological, cardiovascular, respiratory, and immune health and its possible effects on morbidity and mortality rates. Recent research suggest that vitamin-D may positively affect the course of critical illness due to its pleiotropic effects[4-6]. Low levels of vitamin-D have been reported to be associated with mechanical ventilation requirement, prolonged mechanical ventilation day, a worse Acute Physiology and Chronic Health Evaluation (APACHE) II score, length of stay, organ dysfunction, severe infections, and the mortality rate of critically ill adult and child patient[6-19]. Moreover, vitamin-D status has been reported to be associated with differential metabolic homeostasis during critical illness[7].

Although studies on the association between serum vitamin-D and morbidity/mortality in critically ill children have primarily been conducted in developed countries, limited data exist in developing countries, especially in Turkey[8]. Moreover, most studies in Turkey have focused on adults[9-11]. A recent study focused on children from the northern Anatolia region of Turkey found a high prevalence of vitamin-D deficiency in critically ill children, which was associated with higher vasopressor requirement but not mortality[8].

Because of vitamin-D levels are influenced by geographic factors, ethnic differences, and latitude, more research is needed in Turkey to explore the association between vitamin-D and mortality and morbidity in children with critical illness. Therefore, we aim to obtain the vitamin-D deficiency of children with critical illness and the association between vitamin-D deficiency and the PRISM III score, which is frequently used to predict mortality, among patients admitted to the Paediatric Intensive Care Unit (PICU).

MATERIAL AND METHOD

This retrospective study was conducted at the Paediatric Intensive Care Unit (PICU) of Atatürk University Faculty of Medicine in Erzurum, Turkey, in paediatric patients who were admitted to the intensive care unit between January 2016 and January 2017. Only the first hospitalizations of patients with a history of recurrent hospitalization within the specified period were included. Patients hospitalized for vitamin D toxicity and rickets were excluded from the study. Of the 216 cases, 14 were excluded due to recurrent hospitalizations and 2 were excluded due to vitamin-D toxicity, resulting in a total of 200 cases included in the study. This study was approved by the Ethics Committee of Atatürk University Faculty of Medicine (decision no: B.03.2.ATA.0.01.00 / 110, date: 05/05/2017).

The demographic and clinical characteristics of the patients, including their age, weight, height, body mass index (BMI), gender, hospitalization season, presence of any chronic diseases, need for mechanical ventilation, duration of mechanical ventilation day, length of PICU stay, requirement for vasopressor and/or inotropic treatment, history of vitamin-D prophylaxis (daily 400 IU vitamin-D prophylaxis given free of charge to infants under 1 year of age, conducted by the Ministry of Health) or treatment, as well as levels of calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin-D, and parathyroid hormone level were recorded. The patients were classified according to the primary reason for hospitalization, which included cardiovascular, respiratory, gastrointestinal, haematological, endocrinologic and metabolic, oncological, nephrological, neurological diseases, trauma, and poisonings.

The PRISM III score was calculated to evaluate the mortality risk of the cases. PRISM III parameters, calculated based on the worst values in the first 24 hours after the child is admitted to intensive care, consist of systolic blood pressure, body temperature, creatinine, blood urea nitrogen (BUN), Glasgow Coma Score, pupillary response, cardiac rate, leukocyte and platelet count, pH, total CO2, PaCO2, PaO2, PT/aPTT, potassium, glucose, and bicarbonate. It is a commonly used method to determine the predicted mortality risk of critically ill patients based on their clinical and laboratory findings at the time of admission to the paediatric intensive care unit[12,13].

The serum 25(OH)D level was measured using the Beckman Coulter brand UniCel DxI 800 autoanalyzer through the immunoassay method. Serum 25(OH)D levels are classified according to vitamin-D levels and are defined as deficiency (below 12 ng/ml), insufficiency (12-20 ng/ml), sufficiency (20-100 ng/ml) and excess (above 100 ng/ml).[14]. Because 400 IU vitamin-D prophylaxis is routinely recommended for infants under the age of one, a separate evaluation was conducted for this age group. Patients with 25(OH)D levels below 20 ng/ml were treated with stoss therapy[14]. Serum Ca, P, and Alkaline phosphatase (ALP) levels were analysed using spectrophotometry on a Beckman Coulter brand AU5800 autoanalyzer, while serum PTH levels were determined using chemiluminescence on a Beckman Coulter brand UniCel DxI 800 autoanalyzer. If the serum calcium level calculated according to age was below, the patient was given 1-2 ml/kg of intravenous 10% Calcium Gluconate[15].

The data was analysed using SPSS 20 package program. Categorical measurements were determined as numbers and percentages, while normally distributed data were reported as mean ± standard deviation and non-normal distribution as the median. Chi-Square test was used for categorical data, and the risk ratio was calculated for comparisons between independent groups, to compare 2 groups with numerical data that did not show normal distribution, the Mann Whitney U test was used and the Kruskal Wallis test was used when there were more than 2 groups. One-way ANOVA was used in the presence of more than 2 groups and Student-T tests were used in the presence of 2 groups in numerical analyses showing normal distribution. Correlation tests were used to determine the direction and strength of the linear relationship between vitamin-D and other variables. 5% error level was used in all statistical analysis. P value of less than 0.05 was considered to be statistically significant.

RESULTS

The mean age of the patients was 53.82±60.41 months, ranging from 1 month to 16 years. Eighty-nine (44.50%) of them were female and 111 (55.5%) were male. The most common reason for hospitalization was neurological diseases 66(33%). Of the patients, 104 (52%) had a chronic disease, with cerebral palsy being the most common (12.50%). The mean length of PICU stay was 11.72±26.34 days, 46% (n=92) 92(46%) of the patients required mechanical ventilation, while 26.50% (n=53) needed vasopressor and/or inotropic support. The mean PRISM III score was 9.64±12.51, and the mortality rate was 42(21%).

Table 1. Demographic Characteristics of the Cases

Specifications	n=200
Age (month) †	53.82 ± 60.41(1-203)
Gender*	
Girl	89(44,50)
Boy	111(55,50)
Season of the hospitalization*	
Summer	59(29,50)
Autumn	54(27)
Winter	54(27)
Spring	33(16,50)
Diagnosis*	
Neurological Diseases	66(33)
Respiratory System Diseases	41(20,50)
Cardiovascular System Diseases	25(12,50)
Trauma	22(11)
Oncological Diseases	11(5,50)
Gastrointestinal System Diseases	10(5)
Nephrological Diseases	7(3,50)
Intoxication	7(3,50)
Endocrinologic and Metabolic Diseases	6(3)
Haematological Diseases	5(2,50)
Comorbidity*	
Cerebral palsy	25(12,50)
Epilepsy	17(8,50)
Congenital Heart Disease	17(8,50)
Down Syndrome	6(3)
Chronic Lung Disease	6(3)
Lymphoma	5(2,50)
Hydrocephalus	3(1,50)
Chronic Renal Insufficiency	4(2)
Type 1 Diabetes	2(1)
Other Diseases **	19(9,50)
No Chronic Illness	96(48)
Biochemical parameters†	
25(OH)D (ng/ml)	22,82 ± 13,78 (1,5-81,6)
PTH (pg/ml)	78,31±94,93 (2,9-585,7)
Ca (mg/dl)	8,72±1,02 (4,1-11,4)
P (mg/dl)	4,58±1,64 (1,1-11,5)
ALP (U/L)	183,23±113,08 (36-647)
Mechanical Ventilatory Support*	92(48)
Duration of Hospitalization (Days)†	11.72±26.34 (1-298)
Mechanical Ventilation Day†	7,12±23,73(0-270)
Vasopressor / Inotrope Requirement*	53(26,5)0
PRISM III †	9.64±12.51(0-59)
Outcome	
Mortality*	42(21)
Transfer to Related Clinic,*	158(79)

*: n(%), †: mean±SD (Min-Max), PRISM III: The Pediatric Risk of Mortality Score **:Nephrological, Haematological, Oncological Diseases, Gastrointestinal System Diseases, Endocrine and Metabolic Diseases, BMI: Body Mass Index

A significant relationship was found between the season of hospitalization and the presence of chronic disease (p=0.042). Patients with chronic disease had a longer hospitalization stay (13.12±20.01 days) compared to those without chronic disease (10.38±31.81 days) (p=0.033).

Mean 25(OH)D, PTH, Ca, P, ALP level were 22.82±13.78 ng/ml, 78.33±94.87 pg / ml, 8.72±1.02 mg / dl, 4.59±1.61 mg / dl,183.27±113.41 U / L, respectively. The serum vitamin-D levels were insufficient or deficient in 96 (48%) of the patients. A significant relationship was observed between decreasing levels of vitamin-D and decreasing levels of calcium, as well as increasing levels of parathyroid hormone (p=0.008 and p=0.022, respectively). There was a positive correlation between vitamin-D levels and Ca (r=0.20, p=0.006), while there was a negative correlation with PTH (r=-0.19, p=0.008) and age (r=-0.42, p=0.008).

The mean age of the patients with vitamin-D deficiency, insufficiency, sufficiency was 82.01±69.84 months, 73.47±62.69 months, and 31.87±44.92 months, respectively (Table II). As the vitamin-D levels decreased, body weight and height increased significantly (p=0.002), and there was a significant relationship between vitamin-D and BMI (p=0.013). There was no significant relationship between the patients' hospitalization seasons and vitamin-D levels (p=0.581). There was no significant association between vitamin-D levels and the presence of chronic disease (p=0.062), the mechanical ventilatory support (p=0.463), length of hospital stay (p=0.512), length of mechanical ventilatory support (p=0.342), and the use of vasopressor and/or inotropic agents (p=0.981)

Table 2. Demographic Characteristics of the Cases According to Vitamin D Levels

	Vitamin D Level			
Specifications	**Deficiency**	**Insufficiency**	**Sufficiency**	**p**
Age (month) †	82,01±69.84	73,47±62,69	31,87±44,92	**0,002**
Weight (kg) †	20,91±16,62	21,41±15,72	11,52±10,71	**0,003**
Height (cm) †	105,01±34,58	106,39±33,09	79,62±27,33	**0,002**
BMI (kg/m²)*	15,69±3,79	16,12±2,59	14,70±3,08	**0,013**
Gender *				0,761
Girl	20(42,55)	24(48,98)	45(43,27)	
Boy	27(57,44)	25(51,02)	59(56,73)	
Season of the hospitalization*				0,581
Winter	15(31,91)	13(26,53)	26(25,00)	
Spring	9(19,15)	10(20,41)	14(13,46)	
Summer	9(19,15)	14(28,57)	36(34,62)	
Autumn	14(29,79)	12(24,49)	28(26,92)	
Diagnosis*				**0,003**
Neurological Diseases	5(10,64)	7(14,29)	29(27,88)	
Respiratory System Diseases	20(42,55)	14(28,57)	32(30,77)	
Cardiovascular System Diseases	9(19,15)	10(20,41)	22(21,15)	
Trauma and Intoxication	4(8,51)	8(17,02)	17(16,34)	
Other Diseases **	9(19,15)	10(20,41)	4(3,85)	
Duration of Hospitalization (Days)†	13,24±21,62	7,31±10,87	13,17±32,60	0,512
Comorbidity*	29(61,70)	19(38,78)	56(53,85)	0,062
Biochemical parameters †				
25(OH)D (ng/ml)	22,82 ± 13,78 (1,5-81,6)			**0,008**
PTH (pg/ml)	111,3±127,6	83,3±89,3	61,1±74,8	**0,022**
Ca (mg/dl)	8,7±1,0 (4,1-11,4)			
P (mg/dl)	4,6±1,6 (1,1-11,5)			
Mechanical Ventilatory Support*	25(53,19)	20(40,81)	47(45,19)	0,463
Vasopressor / Inotrope Requirement*	12(25,53)	13(26,53)	28(26,92)	0,981
Mechanical Ventilation Day†	8,61±19,92	2,82±6,29	8,33±29,71	0,342
PRISM III†	10,42±8,64	12,81±15,82	7,83±11,91	**<0,01, (r=-0,211)**
Outcome				0,243
Mortality*	12(25,53)	13(26,53)	17(16,34)	
Transfer to Related Clinic*	35(74,47)	36(73,47)	87(83,65)	
Total	47(100)	49(100)	104(100)	

*:n(%), †: mean±SD (Min-Max) **:Nephrological, Haematological, Oncological Diseases, Gastrointestinal System Diseases, Endocrine and Metabolic Diseases, BMI: Body Mass Index

The mean PRISM III score was 7.81±11.94 in cases with sufficient vitamin-D levels and 10.42±8.64 in cases with deficient vitamin-D levels, indicating a significantly higher score in patients with vitamin-D deficiency (p=0.005). Moreover, a negative correlation was found between vitamin-D levels and the PRISM III score (r=-0.21, p=0.003)

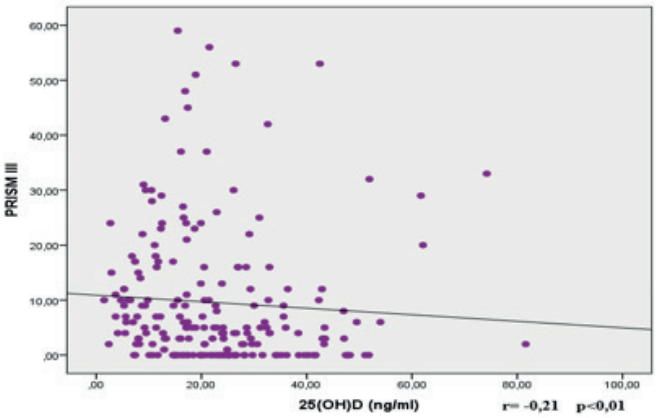

Figure 1. Vitamin D-PRISM III Correlation Graph

The rate of mortality was 17 (16.35%), 13 (26.53%), and 12 (25.53%) in children with vitamin-D sufficiency, insufficiency, and deficiency, respectively (p=0.241). The vitamin-D levels of survived patients were higher than non-survive, although this difference was not statistically significant (23.54±13.91 ng/ml vs. 20.32±13.09 ng/ml, p=0.119) (Table II).

DISCUSSION

This study showed that the PRISM III score was higher in critically ill children with vitamin-D deficiency. In the literature, no consensus has been reached regarding the association between vitamin-D deficiency and PRISM III score[8,16-19]. Although some previous studies have found no relationship between vitamin-D deficiency and PRISM III score[17-20], others reported higher PRISM III scores were associated with vitamin-D deficiency[16,21]. McNally et al. reported that every additional increase in the PRISM III score, the likelihood of vitamin-D deficiency increased by 8%[22]. Similarly, Madden et al reported that lower admission 25(OH)D level was inversely associated with PRISM III score, with a 5 ng/mL decrease in 25(OH)D levels corresponding to a 1.19-fold increase for a 1-quartile rise in PRISM III score[16]. These differences between studies may be due to sample characteristics, exposure to sunlight, geographical and ethnic features, differences in dietary or supplemental vitamin-D intake, and genotype variation in proteins involved in vitamin-D transport, functioning, and metabolism[23]. It has been shown that vitamin-D levels should be checked in patients in PICU.

Our study showed that the 48% of critically ill children have vitamin-D deficiency and insufficiency at admission to the PICU. The prevalence of vitamin-D deficiency and sufficiency was similar to that reported in a previous study from Turkey, which found that vitamin-D deficiency was observed in 58% of critically ill children[8]. Moreover, the prevalence of vitamin-D deficiency was higher in children older than one year old. Although the infants under one year of age, the frequency of vitamin-D deficiency/insufficiency was 26.9%, it is increased to 58.6% in children over one year old. Since 2005, the Ministry of Health has provided 400 IU of vitamin-D prophylaxis free of charge to infants under one year old, reducing the rate of vitamin-D deficiency in this age group[24]. These findings suggest that it is important to assess vitamin-D levels in children admitted to the PICU, especially those aged over one year, who are at a higher risk of vitamin-D deficiency or insufficiency.

Although most patients with vitamin-D deficiency (61.7%) in our study were hospitalized during the winter and autumn seasons, no correlation was found between the seasons and vitamin-D levels. A previous study in Turkey found that vitamin-D levels were significantly affected in patients admitted to the paediatric intensive care unit, especially during winter [8]. Another study of 4168 adults and children showed that vitamin-D levels were higher in spring and summer months[25]. A cohort study of critically ill adults in France found that ICU admission in spring (following winter months) was an independent predictor of severe vitamin-D deficiency (level < 30 nmol/L)[26]. Sunlight and climate conditions are known to have an impact on vitamin-D synthesis. Since there is no strong evidence on this subject in the literature, we believe that studies designed to detect the difference in seasonal variations are needed.

One of the factors that contribute to serious morbidity among critically ill paediatric patients is the presence of the chronic diseases. However, studies evaluating the vitamin-D levels of patients with chronic diseases are scarce in the literature, with most studies focusing on adult patients[27-29]. In Madden et al.'s study, 82.4% of the patients hospitalized in the PICU had an underlying chronic disease, with respiratory or neurological conditions being the most common. Patients with seizures and oncological problems had significantly higher vitamin-D levels[16]. In our study, a lower percentage of patients had an underlying chronic condition compared to Madden et al. Our percentage was similar to other studies in our country[8,30,31]. Specifically, 52% of the patients in our study had chronic diseases, with cerebral palsy being the most common diagnosis. Surprisingly, we found that chronic disease status did not significantly affect the vitamin-D levels. Although dietary and feeding problems are more common, and exposure to sunlight may also be a challenge in patients with chronic diseases, we believe that vitamin D preparations may be used more frequently in these children due to frequent hospital admissions, examinations, and blood tests [32,33]

Previous studies suggested that vitamin-D has regulatory effects on cardiac contractility and has antiatherosclerotic and renoprotective properties[34,35]. Ponnarmeni et al. (31) suggested that the vitamin-D deficiency correlated with an increased need for vasopressors. Furthermore, a meta-analysis showed that vitamin-D deficiency is associated with a 1.9 fold increase in vasopressor use [22]. However, in our study, we did not find a statistically significant relationship between vitamin-D levels and the need for vasopressors. In future research exploring the effects of vitamin-D on conditions such as hypotension and cardiac failure, it may be worthwhile to re-evaluate the use of vasopressors after controlling for 25(OH)D levels on certain days following treatment for vitamin-D deficiency.

In our study, although the vitamin-D levels of survive patients were higher than those who did non-survive, this difference was not statistically significant. One meta-analysis systematically reviewed observational cohort studies of vitamin-D deficiency in the intensive care unit, including 9.715 critically ill patients showed that vitamin-D deficiency increases the susceptibility to serious infections and mortality in critically ill patients[36]. In the other meta-analysis, reported an increase in deaths in the group with vitamin-D deficiency, but it was found to be statistically significant only in the study in Chile[37]. When developing countries were excluded from the study, the relationship with mortality was stronger and greater statistical significance was obtained (OR 2.6, p=0.003). However, since vitamin-D deficiency is seen with a rare frequency of 5% in developed countries, the sample was more limited[37]. In a meta-analysis by Su et al., it was found that the risk of mortality 1.77 times in children with vitamin-D deficiency[38]. On the other hand, there are some studies reported that vitamin-D deficiency had no effect on mortality[20,21,39,40]. These results suggest that the effect of vitamin-D on mortality is likely a result of its pleiotropic effects, leading to faster resolution of mortality and organ dysfunction, and an improvement in the quality of life.

The strength of our study is that it was a study conducted in the paediatric intensive care unit of the largest city in the region where vitamin-D deficiency is most common in our country. In addition, the exclusion of diseases that directly affect vitamin-D metabolism is another strength. The limitations of our study are that it includes 1-year data of our center and we do not have a control group. Our patient count is insufficient for such a study and power analysis could not be performed. Another limitation is that we only measured the vitamin-D levels of our patients at the time of admission.

CONCLUSIONS

Vitamin-D deficiency is a common problem in critically ill children in Turkey. In our study, although we did not find a significant relationship between vitamin-D level and mortality, we found that patients with vitamin-D deficiency had a higher PRISM III score compared to those with sufficient vitamin-D levels. Further studies are needed

to determine the relationship between vitamin-D deficiency and/or insufficiency in children hospitalized in the intensive care unit, and mortality scores and mortality.

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