Vitamin-D Status and Clinical Outcomes in Critically Ill Children

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Abstract

Aims and background: To study if 25-hydroxy cholecalciferol levels correlate with clinical outcomes in a cohort of critically ill children requiring pediatric intensive care unit (PICU) admission.

Materials and methods: All children between the ages of 1 month and 14 years admitted to a PICU were included in this study. The vitamin-D level was measured within 24 hours of admission to the PICU for each patient. The patient's clinical details, vitamin-D levels, and biochemical parameters were collected.

Results: There were 119 critically ill children (47 females and 72 males) admitted to our PICU. A total of 56 children were in the vitamin-D-deficient group, giving a prevalence of 47.05%. Sixty-three children had either insufficient or normal levels of 25(OH)D. Mean serum 25-OH cholecalciferol was 22.82 ± 16.48 nmol/L. There were no significant differences in O2 utilization, ventilation requirement, length of PICU stay, or the frequencies of use of antibiotics and steroids between the groups. The overall mortality rate in this study was 5.8% (three children died in the deficient group as compared with four in the insufficient/normal group).

Conclusion: Even though vitamin-D deficiency was highly prevalent in the PICU, there were no statistically significant differences in O2 utilization, length of PICU stay, duration of mechanical ventilation, the use of antibiotics/steroids, and mortality outcome for both deficient and insufficient/normal groups.

Keywords: Children, Critical illnesses, Vitamin-D levels.

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Highlights

The vitamin-D deficiency (VDD) is highly prevalent in the pediatric intensive care unit. We did not find any statistically differences for O_2 utilization, duration of mechanical ventilation, the length of stay in the PICU, or the use of antibiotics/steroids and mortality outcome between the deficient and insufficient/normal groups.

Introduction

Vitamin D regulates many important physiological functions. Vitamin-D deficiency has been linked to cardiovascular disease, metabolic syndrome, cancer, and infection.[1] Vitamin-D intake is met either by food or is synthesized by our skin into 7-dehydrocholesterol under ultraviolet light (296–310 nm) to produce vitamin D3, which binds to vitamin-D-specific binding protein (VDBP). Subsequently, it is hydroxylated by the liver and kidney from 25-hydroxylase and 1-ahydroxylase into biologically active 1,25(OH)D, and then transported by VDBP to different organs through blood circulation such as the intestine, kidney, and bones. Vitamin-D receptors located in tissues and cells can express and accommodate for the active enzyme required for the hydroxylation, which generates 1,25(OH)2D3. Based on this concept, vitamin D plays a vital role in infectious diseases, autoimmune diseases, diabetes, cancer, cardiovascular diseases, etc.[2,3]

The prevalence of VDD in the general population varies from 20 to 80%.[4–6] Vitamin D plays a very critical role in both calcium homeostasis and bone metabolism, respectively.[5,6] In addition, vitamin D is also essential in controlling cell differentiation, apoptosis and growth, inflammatory, immunomodulatory, and anticoagulant effects.[3,7–11]

A 2020 study of healthy children of Bahrain showed that 93.4% of them had low vitamin-D levels (78.3% were vitamin-D deficient, 15.1% vitamin-D insufficient, and 6.6% were vitamin-D sufficient).[12] From the pediatric intensive care unit (PICU), there are no studies that report the vitamin-D status of critically ill patients from the Kingdom of Bahrain. In the United States, they reported a prevalence of VDD that ranges from 9 to 18%,[13] and these are according to the NICE pediatric guidelines 2022–2024, where VDD is defined as a vitamin-D level of less than 25 nmol/L and insufficiency as a level of less than 50 nmol/L (Table 1).[14]

Increased requirement of inotropes, the requirement and duration of mechanical ventilation, the duration of hospitalization, and mortality rate were shown to be associated with VDD in children with critical illness at hospital admission.[15–23] On the other hand, other studies did not report these correlations.[24–26] In Bahrain, there

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Table 1: Vitamin-D levels[14]

Serum 25-(OH)D		*Vitamin-D*	
nmol/L	*Micrograms/L*	*status*	*Treatment*
<25	<10	Deficient	Treatment dose of vitamin D followed by preventive dose and lifestyle advice
25–50	10–20	Insufficient	Preventive dose of vitamin D and lifestyle advice
50–75	20–30	Adequate	Lifestyle advice
>75		Optimal	None

are no studies associating VDD with clinical outcomes such as the duration of PICU stay or hospital stays, pediatric risk of mortality (PRISM score), necessary ventilation, and its duration.[24,25,27]

Therefore, we performed a prospective observational study to look at the association between VDD and the O_2 requirement, the duration of PICU stay, the duration of ventilation antibiotic usage, use of steroids, pediatric index of mortality-3 (PIM-3) score, and mortality outcomes.

Methods

This study was carried out in the PICU of King Hamad University Hospital, Bahrain from 11th April 2021 to 15th July 2022 (15 months) after hospital ethics committee approval was granted (IRB Ref# 21–419).

Aims and Objectives

- To measure the 25-hydroxy cholecalciferol levels in PICU admissions and predict the mortality and morbidity outcome in them.
- To measure the prevalence of hypovitaminosis D in children admitted to the PICU.
- To compare PIM-3 prediction scores in vitamin-D-deficient children and children with normal vitamin-D levels.
- To study the biochemical response in vitamin-D-deficient children.
- To analyze if VDD influences PICU length of stay, O2 requirements, mechanical ventilation days, and mortality outcomes.

Inclusion Criteria

All children admitted to the PICU between the ages of 1 month and 14 years whose vitamin-D levels are measured within 24 hours of admission.

Exclusion Criteria

Children with known diagnosis of parathyroid disease, rickets, renal tubular acidosis, chronic kidney disease (CKD), or a diagnosis of acute kidney injury (AKI) on admission. Any readmission was excluded, and those who passed away within 24 hours of admission.

Informed consent was sought for each child admitted to the PICU from either of the parents after explaining the study plan, including benefits and side effects. Those who refused consent were excluded from the study.

Statistical Analysis

Data analysis was done using SPSS v 25.0. Descriptive statistics were used to compute the frequencies (percentages) for categorical data and mean ± SD for continuous data. The Chi-square test was used to compare significant differences between two groups with categorical data. Nonparametric tests (Mann–Whitney *U* test) were used to compute the significant differences between continuous scores of the groups. All the statistical tests were two-tailed, and a *p*-value of < 0.05 was considered significant.

The following parameters were collected on admission to the PICU:

- Patient details, including name age, sex, date of admission, and address.
- Weight on admission and BMI.
- Reason for the PICU admission, including presenting complaints and positive history.
- Vitals and examination findings.
- Diagnosis.
- Nutritional status of the child.
- Ventilator days.
- Inotropic support days.
- ABG on admission to the PICU.
- Serum calcium.
- Serum 25-hydroxy cholecalciferol.
- Serum PO4 level.
- Alkaline phosphatase level (ALP).
- Serum Mg+ level.
- Serum PTH level.
- PICU number of days.
- Mortality rate.
- Morbidity rate.
- Complete blood count (total WBC, differential WBC, and platelet)
- Blood glucose level.
- Antibiotics usage.
- PIM3 score.

For critically ill children, the pediatric index of mortality (PIM) 3 score, having 10 simple variables was calculated with the below formula, and it provides a validated method of predicting mortality.

Results

There were 119 critically ill children (47 females and 72 males) admitted to our PICU over the period of this study. A total of 56 children were in the vitamin-D-deficient group, giving a prevalence of 47.05%. Sixty-three children had either insufficient or normal levels of 25(OH)D. Mean serum 25-OH cholecalciferol was 22.82 ± 16.48 nmol/L. The mean serum 25-OH cholecalciferol was 13.54 ± 5.39 nmol/L in the deficient group and was 40.14 ± 16.28 nmol/L in the insufficient/normal group. A greater number of children in the age group 3–14 years were vitamin-D deficient as compared with children under 3 years old ($p = 0.020$) (Table 2). Children whose nutritional status (weight for age) was less than the 2nd percentile (Fig. 1) tended to be more vitamin-D deficient; however, the *p*-value was not significant. A higher association of VDD or insufficiency was observed with the central nervous system and respiratory system diseases without statistical significance (Table 3). Gamma-glutamyl transferase was high in the deficient group; however, serum phosphate was low in the deficient group as compared with the insufficient/normal group significantly (Fig. 2). A significant rise in alkaline phosphatase (Fig. 3) and alanine transaminase levels was noted in the deficient group. Mean PIM3 scores were higher in the deficient group as compared with the insufficient/normal group (5.71 ± 16.73 vs 1.71 ± 1.80), but this

Table 2: Patient demographics

Parameter	*Deficient (n = 56)*	*Insufficient/Normal (n = 63)*	*p-value*
Gender			0.574
Female	24 (42.8%)	23 (36.5%)	
Male	32 (57.1%)	40 (63.5%)	
BMI	22.56 ± 26.03	27.49 ± 32.11	0.734
Mean age (yrs)	5.32 ± 4.41	3.04 ± 3.75	0.004*
Age			0.020*
<1 yr	11 (19.6%)	26 (41.3%)	
1–3 yrs	13 (23.2%)	18 (28.6%)	
3–8 yrs	17 (30.4%)	10 (15.9%)	
9–14 yrs	15 (26.8%)	9 (14.3%)	
Nutrition (weight for age)			
<2 centile	16 (28.6%)	9 (14.3%)	0.159
2–99 centile	32 (57.1%)	44 (69.8%)	
>99 centile	8 (14.3%)	10 (15.9%)	

*indicates statistically significant *p*-value

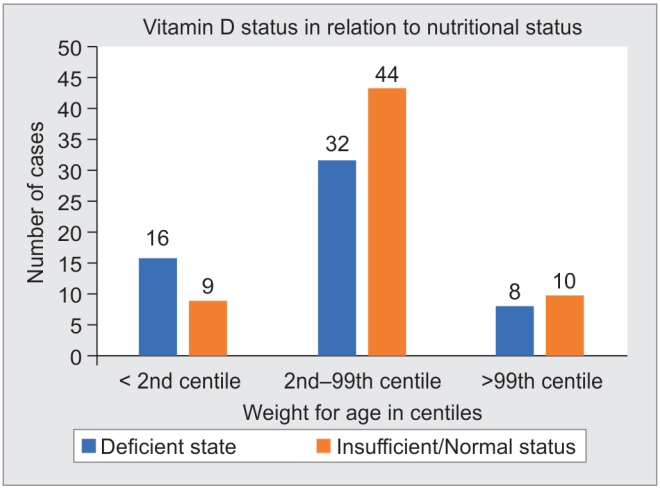

Fig. 1: Frequency distribution of vitamin-D-deficient and insufficient/normal vitamin-D level groups with nutritional status

Table 3: Vitamin-D status in relation to predominant disease system

Type	*Deficient (n = 56)*	*Insufficient/ Normal (n = 63)*	*Total*	*p-value*
CNS	16 (28.6%)	20 (31.7%)	36 (30.0%)	0.291
RS	14 (25.0%)	21 (33.3%)	35 (29.4%)	
CVS	2 (3.6%)	2 (3.2%)	4 (3.4%)	
GIT	7 (12.5%)	6 (9.5%)	13 (10.9%)	
Hematological	3 (5.4%)	7 (11.1%)	10 (8.4%)	
Renal	0 (0.0%)	1 (1.6%)	1 (0.8%)	
Others	14 (25.0%)	6 (9.5%)	20 (16.8%)	

difference did not reach statistical significance. There were no significant differences in O2 utilization, ventilation requirement, length of PICU stay, or the frequencies of use of antibiotics and steroids between the groups (Table 4). The overall mortality rate

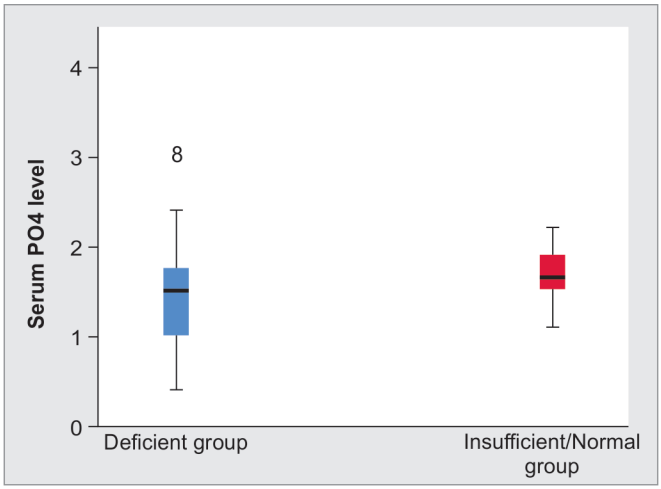

Fig. 2: Serum phosphorus levels in different groups

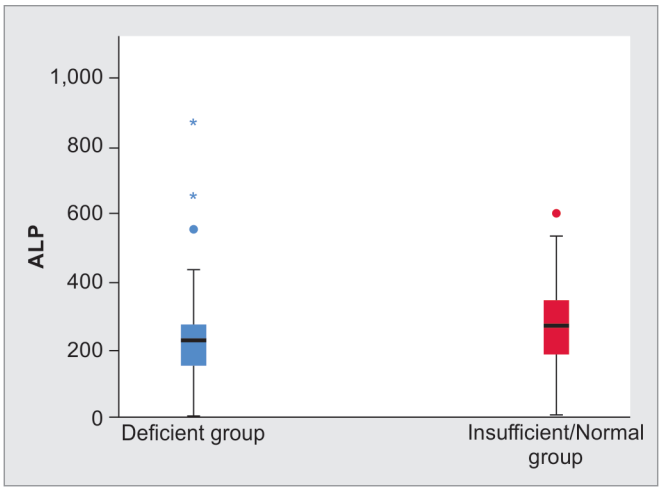

Fig. 3: Level of enzyme in relation to the vitamin-D status

in this study was 5.8% (Fig. 4). There were three children that died in the deficient group as compared with four in the insufficient/normal group.

Discussion

To our knowledge, this is the first study of vitamin-D status in critically ill children in the Kingdom of Bahrain. Fifty-six out of 119 children had VDD in this study, hence the prevalence was 47.05%, which is comparable to many studies, including two large metanalysis and systemic reviews in the frequency of 23–70%.[15–22,24,25,27] The worldwide prevalence of VDD is 54% at the time of PICU admission. The reason for higher prevalence of VDD or insufficiency in Bahrain could be because of multifactorial reasons like poor nutritional intake or lack of sun exposure, or not supplementing vitamin D routinely. A total of 63 children were classified as the non-vitamin-D-deficient group, that includes both insufficient and normal levels of 25(OH)D (sufficient vitamin-D levels).

Vitamin-D deficiency had been observed in all types of nutritional status in children but is relatively more common among children with poor nutritional status (weight for age less than 2nd percentile) (Fig. 1). Most children in the age group 3–14 years were

Table 4: Vitamin-D status in relation to clinical intervention and outcome variables

Parameters	*Deficient (n = 56)*	*Insufficient/ Normal (n = 63)*	*p-value*
Ventilation			0.171
Yes	13 (23.2%)	8 (12.7%)	
No	43 (76.7%)	55 (87.3%)	
Invasive ventilation			0.066
Yes	12 (21.4%)	8 (12.7%)	
No	41 (78.5%)	55 (87.3%)	
Invasive ventilation days (in days)	2.27 ± 8.04	2.0 ± 4.97	0.252
O_2 requirement			0.419
Yes	24 (42.9%)	21 (33.3%)	
No	32 (57.1%)	42 (66.6%)	
Antibiotics usage			0.161
Yes	40 (71.4%)	54 (85.7%)	
No	16 (28.6%)	9 (14.3%)	
Steroids usage			1.00
Yes	14 (25.0%)	16 (25.4%)	
No	42 (75.0%)	47 (74.6%)	
PIM3 score	5.71 ± 16.73	1.71 ± 1.80	0.661
PICU length of stay	11.02 ± 24.52	7.47 ± 9.23	0.761
Morbidity			0.930
Yes	10 (17.9%)	12 (19.0%)	
No	46 (82.1%)	48 (81.0%)	
Outcome			0.403
Expired	3 (5.4%)	4 (7.9%)	
Survived	53 (94.6%)	59 (92.1%)	

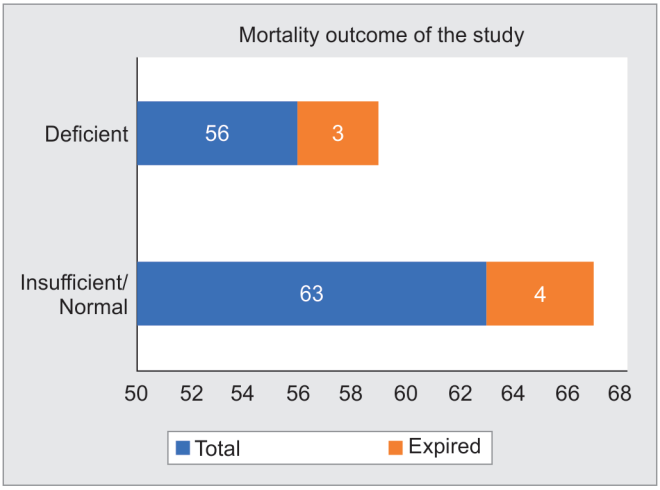

Fig. 4: Vitamin-D status and outcome

vitamin-D deficient as compared with children under the 3-years age group (p = 0.020) (Table 2). The mean age was 5.32 ± 4.41 years in the deficient group as compared with the 3.04 ± 3.75 in the insufficient/normal group with statistical significance. There is a higher tendency toward VDD as age advances (Table 2), which is

Table 5: Vitamin-D status in relation to biochemical variables

Parameter	*Deficient (n = 56)*	*Insufficient/ Normal (n = 63)*	*p-value*
Calcium	2.11 ± 0.39	2.25 ± 0.20	0.078
Serum 25-hydroxy cholecalciferol	13. 54 ± 5.39	40.14 ± 16.28	0.000*
Serum PO_4 level	1.45 ± 0.61	1.65 ± 0.28	0.034*
ALP	232.9 ± 139.49	266.8 ± 119.7	0.028*
Mg	0.79 ± 0.14	0.99 ± 1.14	0.347
PTH	62.69 ± 74.18	69.12 ± 85.98	0.377
Albumin	41.83 ± 6.50	38.41 ± 8.19	0.020*
ALT	34.11 ± 52.22	66.46 ± 184.99	0.005*
GGT	50.22 ± 164.03	47.50 ± 58.24	0.004*
AST	50.98 ± 88.14	109.20 ± 393.76	0.248
Blood glucose level	10.46 ± 10.45	6.74 ± 4.60	0.047*

*indicates statistically significant p-value. ALP, alkaline phosphatase; AST, Aspartate amino transferase, GGT, gamma glutamyl transferase

consistent with the findings of Madden et al.[15] A higher association of VDD or insufficiency was observed with CNS disease (28.6%) as well as respiratory system disease (25%) predominantly. This association did not reach statistical significance in our study, but a similar association has been noted in other studies.[15,18,28]

The mean serum 25-OH cholecalciferol among the vitamin-D-deficient group was 13.54 ± 5.39 nmol/L and 22.82 ± 16.48 nmol/L among all children (Table 5), which is comparable to the study done by Sankar et al.[29] [median serum vitamin D-level of 14.5 (IQR: 10–20)] in 25(OH)D-deficient patients and a median 25(OH)D level of 56.25 nmol/L (IQR 41–78.25). A significant difference for alkaline phosphatase and alkaline transferase elevation was observed among insufficient/normal groups as compared with the deficient group, but gamma glutamyl transferase and serum PO4 were high in the deficient group as compared with the insufficient/normal group significantly (Table 5, Figs 2 and 3). The serum calcium and PTH levels were not statistically correlated to vitamin-D status in critically ill children. The lower PO4 level among deficient groups is due to the decreased physiological function due to low vitamin-D levels (Table 5, Fig. 2).[1,2,4]

Our study has observed that there was a greater need for mechanical ventilation in the vitamin-D-deficient group as compared with the insufficient/normal group, however, it is not significant statistically (21.4% vs 12.7%, p = 0.066) (Table 5). This is consistent with other studies done such as Madden et al.,[15] McNally et al.,[16] Ponnarmeni S et al.,[24] and Das S et al.[27] Some studies like Bansal S et al.[29] and Vipul et al.[23] showed a significant association between the requirement of mechanical ventilation and VDD. The mean ventilation days in our study (Table 4, Fig. 5) in the vitamin-D-deficient group were 2.27 ± 8.04 days as compared with 2.0 ± 4.97 days in the vitamin-D insufficient/normal group with no statistical difference, and this is comparable to mean ventilation of 3 days by Das S et al.[27] and 2.98 days by Bansal S et al.[28] The O2 requirement in our study was 42.9% and 33.3%, respectively, in the vitamin-D-deficient group and vitamin-D insufficient/normal groups (Table 4). The mean PICU length of stay was higher in the vitamin-D-deficient group as compared with the insufficient/normal group (11.02 ± 24.52 vs 7.47 ± 9.23 days with p-value of 0.761)

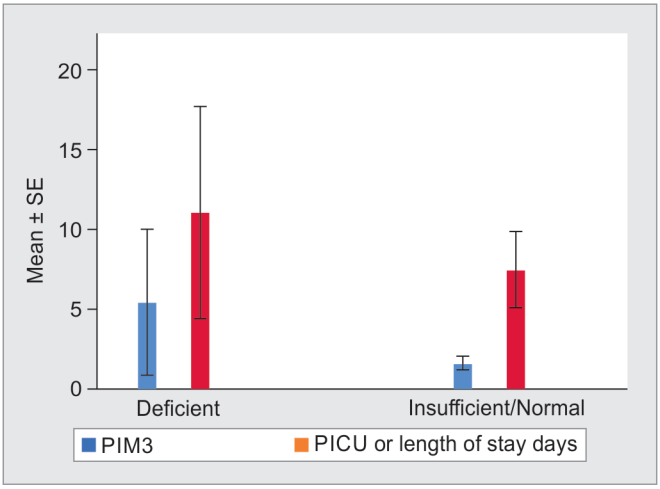

Fig. 5: PIM-3 score and PICU length of stay in relation to vitamin-D status

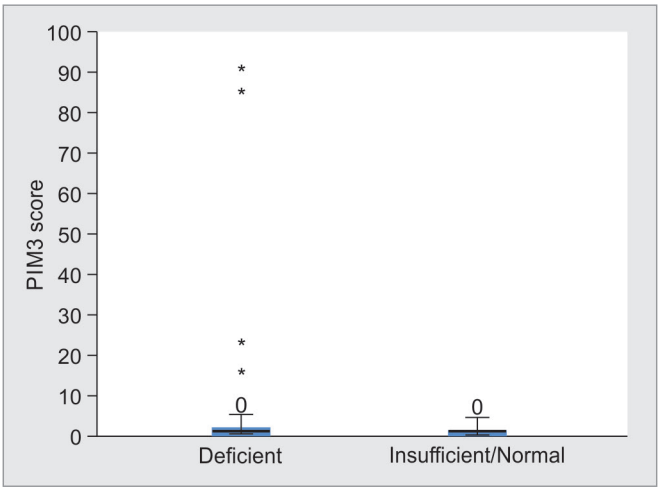

Fig. 6: PIM-3 score and vitamin-D status

without statistical significance (Table 4, Fig. 5). The median length of PICU stay was 4 days (IQR: 2–8), and the mean length of PICU stay was 9.33 ± 18.50 (Table 4), which is higher than other studies like McNally JD et al.[16] with mean PICU stay of 4 days, Rey C et al.[19] with mean PICU stay of 3 days. The same negative correlation was also observed by Ponnarmeni S et al.[24] and Bansal S et al.,[28] and the reason for higher PICU length of stay in our study is because our PICU caters to long-term patients with neurological disabilities. There were no correlations between the use of antibiotics and steroids among both groups (Table 4).

Mean PIM-3 scores (Table 4, Figs 5 and 6) were high in the vitamin-D-deficient group as compared with the insufficient/normal groups (5.71 ± 16.73 vs 1.71 ± 1.80), so there was inverse correlation between the levels of vitamin D and PIM-3 scores without a statistical difference among them, which are comparable to other studies, i.e., no such association was observed between vitamin-D status and predicted PRISM-III and PIM-2 score in the Australian,[17] Indian,[18] and South American studies.[19]

Vitamin-D deficiency was shown to be independently associated with all-cause mortality in some cohorts of severely ill adults, while other studies have not found this relationship like a recent systemic review done in adults by Kaur M et al.[26] We did not observe the association between vitamin-D status and actual or predicted (PIM-3) mortality. A total of seven children with long-term comorbidities expired (3 cases in the deficient group and 4 cases in children insufficient/normal group), hence, the overall mortality rate was 5.88% (Fig. 4). In the vitamin-D-deficient group, one child died due to severe hypocalcemic seizure, cardiac arrythmias leading to cardiac arrest with hypoxic–ischemic brain insult due to suspected familial rickets (VDDR-type genetic tests were not sent), so our study did not find the increased mortality among the vitamin-D-deficient groups as compared with the insufficient/normal group (5.3% vs 6.3%) (Fig. 4), which is comparable to the study done by Sankar J et al.[29] and Kaur M et al.[26] Vitamin-D deficiency does not cause increased mortality among the children admitted to the PICU, however, severe critical illnesses in the PICU have been associated with increased VDD. We added vitamin-D treatment doses for all the vitamin-D-deficient group children and preventive doses of vitamin-D therapy in the insufficient group orally for 8 weeks with nutritional rehabilitation program, however, health education alone was done for the normal group as per NICE pediatric guidelines 2022–2024 even though vitamin-D supplementation in critically ill adults did not improve mortality outcome.[14,26]

Limitations of the Study

The study population was small, and we have based our analysis on only two groups for statistical reasons. It is very difficult to predict the actual morbidity and mortality outcomes among the insufficient and normal groups. We took VDD as less than 25 nmol/L (<10 ng/dL), insufficient levels with vitamin-D levels between 25 and 50 nmol/L (10–20 ng/dL), and sufficient levels with vitamin-D levels >50 nmol/L as per NICE guidelines 2022–2024. However, most of the research studies, including meta-analysis on vitamin-D status in critically ill children, have taken vitamin-D level of 50 nmol/L as a cutoff for defining the deficiency status, so our study might have underestimated the VDD and overestimated the vitamin-D insufficiency status.

Conclusion

Even though VDD is highly prevalent in the PICU, there were no statistically significant differences for O_2 utilization, duration of mechanical ventilation, PICU length of stay, the use of antibiotics/steroids, and mortality outcome between the deficient and insufficient/normal groups.

What is Already Know on this Topic

The higher prevalence of VDD among critically ill children is present. There was some good evidence of VDD and poor outcomes in the critically ill adult population in the form of higher ICU stay, increased ventilatory requirements, increased mortality, and morbidity outcomes; however, there are conflicting results of clinical outcomes with VDD in critically ill children.

What this Study Adds

The higher prevalence of VDD in critically ill children is confirmed in our study. Despite this study being a prospective cohort study on vitamin-D levels and clinical outcomes in critically ill children on a smaller population, the clinical outcomes are not affected by the vitamin-D levels.

There is a need of a large prospective study involving various governments as well as private PICU centers in the Kingdom of Bahrain. The proper study on maternal health status and dietary habits of children is needed.

Clinical Significance

The vitamin-D level estimation for all the children getting admitted to the PICU is not needed, however, on a case-to-case basis, vitamin-D assays should be performed.

Study Approval

This study was approved by KHUH hospital ethical committee, Bahrain, with registration number: IRB Ref# 21-419.

Author's Contributions

RL conceptualized and designed the study, including the material preparation. Data collections were done by SZ, FAH, IA, JG, and HM, and data analysis was performed by RL. The first draft of the paper was written by RL and GF. GF, ACD, and AF reviewed and edited the paper. All authors contributed to paper revision and approved the final article for publication. RL is responsible for the overall content as the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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