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"Evaluation of Vitamin D Status in Children Admitted to Pediatric Intensive Care Unit "

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ABSTRACT:

Background: Vitamin D has the capability to regulate both the adaptive and innate immune systems, which contributes to its immunological and anti-inflammatory properties further more there is an evidence of significant declines in circulating 25(OH)D concentrations in critical illness. **Aim:** Our study aimed to evaluate vitamin D status in ill children admitted to pediatric intensive care unit. **Patients & methods:** This case-control research was performed on 30 children with critical illness admitted to the ICU of Pediatrics of El-Salam Port-Said General Hospital in addition to 30 healthy children as a control group and serum25(OH)D level was measured in both groups by VIDAS 25 OH Vitamin D TOTAL assay kits . **Results:** statistically significant lesser serum 25(OH)D level was noted in the patient group in relative to control one (p=.007). The vitamin D shortage status is statistically significantly greater in patients group in comparison to control group (p=.014). Vitamin D deficiency (<20 ng/ml) is statistically significantly greater in patients group in comparison to the control group (p=.0004). Vitamin D sufficiency (≥ 30 ng/ml) is statistically significantly lesser in patients group in comparison to control group (p=.0450). No statistically significant variance was noted in diagnosis amongst the three vitamin D status categories in the patients' group (p=0.278)
Conclusion: There is a significant prevalence of Vitamin D deficiency among children admitted to PICU in our study sample. The serum 25(OH)D level in PICU admitted kids was considerably lower compared to the control group.
Keywords: Serum 25(OH)D level; Vitamin D deficiency; Solid Phase Receptacle (SPR).

Introduction:

Vitamin D has the capability to regulate both the adaptive and innate immune systems, which contributes to its immunological and anti-inflammatory properties[1]. The active form of vitamin D, 1,25(OH)2D3, is essential for immune system modulation. By strengthening the innate immune system and preventing adaptive immunological responses, it demonstrates immunomodulatory effects. T helper (Th-2) lymphocytes produce more interleukin (IL-4), regulatory T lymphocytes (T-reg) are also upregulated in this process[2]. Notably, the vitamin D receptor is expressed by a variety of immune cells, involving dendritic cells (DC),macrophages, T and B lymphocytes and many of them have the ability to generate calcitriol through an independent regulatory route. Pro inflammatory substances including bacterial lipopolysaccharide and tumor necrosis factor-alpha (TNF-α) can affect this production. T helper (Th) cells can be stimulated to differentiate into Th0 cells by macrophage-derived cytokines. Afterwards, Th0 cells convert into Th1 or Th2 cells with the help of specific co stimulatory cytokines generated by antigen-presenting cells (APCs) such as DC and macrophages.The immune responses that are mediated by cells and antibodies are subsequently controlledby these differentiated cells[3] so it is essential for us to possess sufficient levels of vitamin D in order to preserve healthy bones & improve the body's response to infections.

Severe vitamin D deficiency, characterized by 25(OH)D levels falling beneath thirty nmol/L (or 12 ng/ml), is prevalent at a rate of 5.9 % in the US [4], 7.4% in Canada [5]and thirteen percent in Europe [6]. Approximately one billion individuals around the world are affected by VDD, which is a worldwide public health concern. Additionally, fifty percent ofthe population is affected by vitamin D insufficiency. There is a high prevalenceof vitamin D deficiency (VDD) across Europe and the Middle East, which is indicated by a blood 25 hydroxy vitamin D level that is below 20 ng per millilitre otherwise 50 nmol per Litre. The prevalence of this condition is less than twenty percent in Northern Europe, ranging from thirty percent tosixty percent in Western, Southern, and Eastern Europe, and reaching as high aseighty percent in nations located in the Middle East[7].

In addition, the occurrence of levels of 25(OH)D below fifty nmol/L (or 20 ng/ml) is estimated to be twenty-four percent in the US, thirty-seven percent in Canada, & forty pecent in Europe, according to the estimates[8].As to the standards of the United States Endocrine Society, a deficiency of vitamin D is identified by serum 25(OH)D levels below twenty ng/mL (50 nmol/L), whereas inadequacy of vitamin D is defined as serum 25(OH)D values between 21-29 ng/mL (52.5-72.5 nmol/L). In the case of subjects exhibiting serum 25(OH)D levels ranging from twenty to twenty one ng/mL, it is customary to interpret values under 20.5 ng/mL as 20 ng/mL and consequently, as vitamin D shortage. Conversely, values exceeding 20.5 ng/mL are interpreted as 21 ng/mL & are regarded as vitamin D not adequate [9].

Twenty nanograms per milliliter of 25(OH)D had a high sensitivity for predicting mortality risk, &enhancing the amount of vitamin D in the body had the opposite effect, reducing the sensitivity. A level of serum vitamin D of twenty ng per milliliter has a specificity of 62.1%, which means that it can accurately predict a greater death rate [10-12].
Our study aimed for estimation occurrence of vitamin D shortage in critically ill children compared to healthy compatible children group.

Patients & methods

This case-control research was performed on 30 children with critical illness requiring admission to the Intensive Care Unit of Pediatric of El-Salam Port-Said General Hospital,in addition to 30 healthy children as the control group.

Patients group

Inclusion Criteria: Children with illnesses requiring PICU stay for more than forty-eight hrs, those with ages from 2 months to 14 years old and both males and females.

Exclusion Criteria: Children admitted for monitoring after surgical operations. Patients who had chronic diseases (endocrinal diseases, renal disease, chest diseases, cardiovascular diseases, DM). Patients who

have been treated with vitamin D therapy during the past half twelve months. Parents otherwise surrogates provide written informed consent.

Control group

They were healthy volunteers matching the age group and gender.

Inclusion criteria of the control group: Those with ages from two months to 14 years old,both males and females and an informed consent was acquired from caregivers of participating kids.

Exclusion criteria of the control group: childern who had chronic diseases (endocrinal diseases, renal disease, chest diseases, Cardiovascular diseases, DM) and individuals who got vitamin D therapy throughout the last six months.

Methods

All the studied patients were subjected to: History: (personal history, present, past and nutritional history: details of the child's vitamin D intake, including vitamin D, formulas containing it, or any other vitamin D supplements), detailed physical examination and

Laboratory investigation: Samples of vitamin D were collected as early as possible upon PICU admission before the patient received treatment or parenteral nutrition.

Each sample of two ml venous blood was collected by standard technique in a plain tube and then centrifuged to obtain 100 µL serum for assay of serum 25(OH)D via VIDAS 25 OH Vitamin D TOTAL assay kit which is based on an enzyme immunoassay competition method with a final fluorescent detection (ELFA) by VIDAS instrument where wholly the assay steps are done automatically by the instrument and completed through approximately forty minutes.

. Shortage in vitamin D is indicated by serum 25(OH)D level beneath twenty ng/ml, inadequacy by 21-29 ng/ml, & sufficiency by 30-100 ng/ml [(12)].

All our individuals were followed up for detection outcomes (discharge, death and complications).

Statistical methodology:

The data were gathered & inputted into the computer utilizing the SPSS software, namely version 25, for the purpose of conducting statistical analysis. The data were inputted as either numerical or categorical, depending on their nature. The data were characterized utilizing the minimum, maximum, mean, standard deviation, & median. The tests employed included Mann-Whitney U test, frequency,percentage analysis and Kruskal-Wallis test. A significance threshold of 95 percent was used, and an alpha level of 5 percent was selected. The statistical significance was assessed using a p-value below 0.05.

Results

No statistically significant variance was noted amongst control and patient groups concerning age, sex, weight, weight Z Score, height, height Z score, BMI & BMI Z score respectively (p=.175), (p=.796), (p=.157), (p=.195), (p=.529), (p=.055), (p=.056) and (p=.318) **Table (1)**.

In the patients group (n=30), the serum 25(OH)D ranged from 8.10 to 45.00 ng/ml, with a median of 18.10 ng/ml, a 95% of CI of the median of 15.50-24.00 ng/ml, and 25^{th} Percentile –75^{th} Percentile of 15.40-26.00 ng/ml.

In control group (n=30), serum 25(OH)D ranged from 7.26 to 50.23 ng/ml, with a median of 25.33 ng/ml, a 95% of CI of the median of 21.87-34.58 ng/ml, and 25^{th} Percentile –75^{th} Percentile of 21.42-38.02 ng/ml. Was noted a statistically significant lower serum 25(OH)D level in patient group in comparison to control one (p=.007) **Table (2)**.

Vitamin D shortage status is statistically significantly greater in patients group in comparison to control group (p=.014). In the vitamin D shortage status (<20 ng/ml) (n=25), 18/25 (72.00%) were of patients group while 7/25 (28.00%) were of control group. The vitamin D deficiency (below 20 ng/ml) is statistically significantly greater in patients group relative to control group (p=.0004). In vitamin D inadequacy status (21-29 ng/ml) (n=18), 7/18 (38.89%) were of the patients group while 11/18 (61.11%) were of the control one. The vitamin D insufficiency (21-29 ng/ml) has no statistically significant variance amongst patient group in comparison to control group (p=.2597). The vitamin D sufficiency (≥ 30 ng/ml) (n=17), 5/17 (29.41%) were of the patients group while 12/17 (70.59%) were of control one. The vitamin D sufficiency (equal and more than 30 ng/ml) is statistically significantly lesser in patients group when compared to control group (p=.0450) **Table (3)**.

In the patients group (n=30), 2/30 (6.67%) were on mechanical ventilation, 2/30 (6.67%) had pleural effusion, 2/30 (6.67%) unfortunately died and 2/30 (6.67%) had vasopressor **Table (4)**.

No statistically significant difference was noted amongst the three vitamin D status categories (deficiency, insufficiency & sufficiency) in the patients' group regarding age (p=.469), sex (p=.587), weight (p=.643), weight Z Score (p=.660), height (p=.640), height Z score (p=.219), BMI (kg/m^2) (p=.483) and BMI Z score (p=.731) **Table (5)**.

There was no statistically significant variance in diagnosis amongst the three vitamin D status categories in patients' group (p=0.278) **Table (6)**.

Table 1: Basic characteristics of the two studied groups.

Basic characteristics	Group		Test of significance p value
	Patients (n=30)	Control (n=30)	
Age (years) - Min – Max - Mean±SD. - Median	 1.00-4.25 1.85±0.84 1.63	 0.42-5.00 2.43±1.41 2.25	$Z_{(MW)}$=1.356 p=.175 NS
Male - n - % within Group Female - n - % within Group	 15 50.00% 15 50.00%	 14 46.67% 16 53.33%	$\chi^2_{(df=1)}$=0.067 p=.796 NS
Weight (kg) - Min – Max - Mean±SD. - Median	 8.50-23.50 12.33±3.81 11.00	 7.50-23.50 13.29±3.63 12.95	$Z_{(MW)}$=1.416 p=.157 NS
Weight Z score - Min – Max - Mean±SD. - Median	 -1.38 -1.64 0.20±0.90 0.30	 -0.25-3.00 0.585±0.66 0.46	$Z_{(MW)}$=1.295 p=.195 NS
Length or Height (m) - Min – Max - Mean±SD. - Median	 0.70 - 1.17 0.88±0.15 0.83	 0.68-1.17 0.90±0.13 0.88	$Z_{(MW)}$=0.629 p=.529 NS
Length Z score - Min – Max - Mean±SD. - Median	 –2.70 – 3.40 –0.09±1.57 0.0	 –1.55 – 3.60 0.70±1.26 0.57	$Z_{(MW)}$=1.923 p=.055 NS
BMI (kg/m^2) - Min – Max - Mean±SD. - Median	 12.55-21.34 17.06±2.01 17.188	 13.72-17.63 16.20±1.15 16.38	$Z_{(MW)}$=1.915 p=.056 NS
BMI Z score - Min – Max - Mean±SD. - Median	 –2.75 – 1.85 0.04±1.16 0.02	 –1.75 – 0.60 –0.26±0.69 –0.15	$Z_{(MW)}$=.998 p=.318 NS

n: Number of patients Min-Max: Minimum – Maximum
SEM: Standard error of the mean CI: Confidence interval
□^{2}= Pearson Chi-Square df=degree of freedom
NS: Statistically not significant (p≥ .05)

Table 2: Serum 25(OH)D (ng/ml) in two studied groups.

Serum 25(OH)D (ng/ml)	Group	
	Patients (n=30)	Control (n=30)
- Min – Max - Mean±SD. - Median	8.10-45.00 20.85±9.87 18.10	7.26-50.23 28.66±11.94 25.33
Test of significance p value	$Z_{(MW)}$=2.691 p=.007*	

Table 3: Vitamin D status in two studied groups.

Vitamin D status	Group		Test of significance p value
	Patients (n=30)	Control (n=30)	
Deficiency (<20 ng/ml) (n=25) (41.67%) - n - % within Group	 18 60.00%	 7 23.33%	 χ^2=8.294 p=.00040*
Insufficiency (21-29 ng/ml) (n=18) (30.00%) - n - % within Group	 7 23.33%	 11 36.67%	 χ^2=1.270 p=.2597 NS
Sufficiency (≥30 ng/ml (n=17) (28.33%) - n - % within Group	 5 16.67%	 12 40.00%	χ^2=4.020 p=.0450*
Test of significance p value	$\chi^2_{(MC)(df=2)}$=8.611 p=.014 NS		

df=degree of freedom

Table 4: Course of disease in the Patient group.

	Patient (n=30)	
	n	%
- Mechanical ventilation	2	6.67%
- Pleural effusion	2	6.67%
- Death	2	6.67%
- Vasopressor use	2	6.67%

Table 5: Basic characteristics of patient group by Vitamin D status.

	Vitamin D status			Test of significance p-value
	Deficiency (<20 ng/ml) (n=18)	Insufficiency (21-29 ng/ml) (n=7)	Sufficiency (≥ 30 ng/ml) (n=5)	
Age (years) - Min – Max - Mean±SD. - Median	 1.00-4.00 1.90±0.79 1.71	 1.00-3.00 1.58±0.72 1.42	 1.33-4.25 2.07±1.23 1.67	$H_{(df=2)}$=1.513 p=.469 NS
Sex Male n (%) Female n (%)	 10 (55.56%) 8 (44.44%)	 2 (28.57%) 5 (71.43%)	 3 (60.00%) 2 (40.00%)	$\chi^2_{(df=2)}$=1.708 p=.587 NS
Weight (kg) - Min – Max - Mean±SD. - Median	 7.50-16.50 11.15±2.21 11.00	 8.50-12.50 10.29±1.55 9.50	 9.00-15.00 11.20±2.28 11.00	$H_{(df=2)}$=0.882 p=.643 NS
Weight Z score - Min – Max - Mean±SD. - Median	 -3.15 - 1.40 -0.69±1.19 -0.950	 -1.20 - 0.50 -0.481±0.730 -0.90	 -1.10 - 0.300 -0.42±0.65 -0.50	$H_{(df=2)}$=0.830 p=.660 NS
Length or Height (m) - Min – Max - Mean±SD. - Median	 0.70-1.05 0.80±0.08 0.79	 0.70-0.90 0.780±0.08 0.76	 0.74-1.00 0.83±0.10 0.80	$H_{(df=2)}$=0.890 p=.640 NS
Length Z score - Min – Max - Mean±SD. - Median	 -2.70 - 1.67 -1.52±1.10 -1.635	 -2.70 - -0.10 -1.403±0.904 -1.20	 -1.60 - 0.30 -0.89±0.72 -0.97	$H_{(df=2)}$=3.040 p=.219 NS
BMI (kg/m^2) - Min – Max - Mean±SD. - Median	 13.58-21.34 17.36±1.98 17.27	 12.55-19.04 16.91±2.29 17.35	 13.84-18.55 16.20±1.84 16.44	$H_{(df=2)}$=1.455 p=.483 NS
BMI Z score - Min – Max - Mean±SD. - Median	 -1.75- 0.40 -0.32±0.78 -0.13	 -2.45- 1.45 -0.07±0.95 0.16	 -1.67- 1.15 -0.26±0.84 -0.13	$H_{(df=2)}$=.628 p=.731 NS

H=Kruskal-Wallis H

Table 6: Diagnosis of patients by Vitamin D status.

	Vitamin D status			Test of significance p-value
	Deficiency (<20 ng/ml) (n=18)	Insufficiency (21-29 ng/ml) (n=7)	Sufficiency (≥ 30 ng/ml) (n=5)	
- Pneumonia + Septic Shock	1 (5.56%)	0 (0.00%)	0 (0.00%)	$\chi^2_{(MC)(df=10)}=12.091$ p=0.278 NS
- Myocarditis and Heart Failure	1 (5.56%)	0 (0.00%)	0 (0.00%)	
- Pneumonia	14 (77.78%)	4 (57.14%)	3 (60.00%)	
- Convulsions	1 (5.56%)	0 (0.00%)	0 (0.00%)	
- Bronchopneumona	1 (5.56%)	2 (28.57%)	0 (0.00%)	
- Status epilepticus	0 (0.00%)	1 (14.29%)	2 (40.00%)	

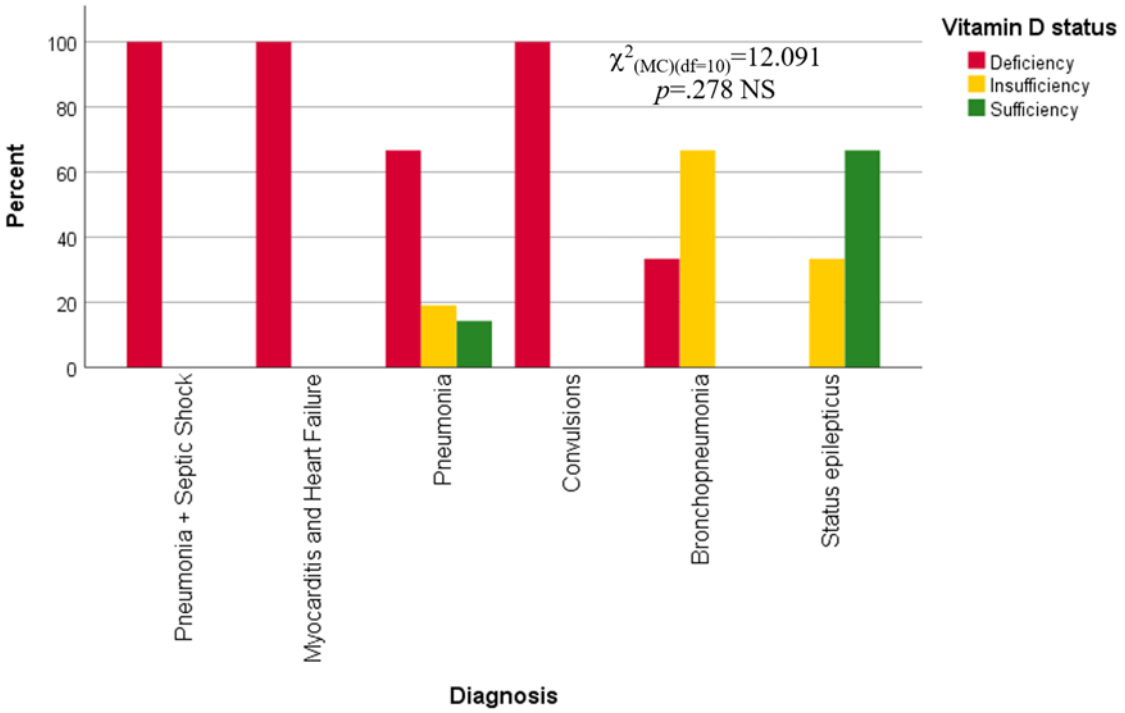

Figure 1: Cluster bar chart of diagnosis among the three Vitamin D status categories in the patients' collection.

Discussion

An expanding body of evidence supports the notion that vitamin D shortage is linked to unfavorable consequences, including extended hospitalization, increased infection rate and increased mortality. Infectious causes and sepsis accounted for the greatest proportion of mortality in PICUs. Lack in vitamin D has also been related to severe sepsis, mortality linked to sepsis and overall increase in death rates in adult ICU and pediatric ICU [11, 12].

Regarding demographic data, the current study showed no statistically significant variance amongst critically ill children and control groups as regard gender, age, weight, weight Z-score, height, height Z-score, BMI & BMI Z-score($p>0.05$).

In concordance with the current research **Ahmed et al,** found no statistically significant variance amongst critically ill children and control group as regard age, sex, weight and BMI ($p>0.05$) [13].

Concerning diagnosis of patients, our study showed that the most common diagnosis was pneumonia among 21/30 (70.00%) followed by Status epilepticus 3/30 (10%) and bronchopneumonia 3/30 (10%) ·According to **Badawi et al,** between critically ill children, respiratory illnesses were the most common diagnosis in forty-five percent of cases (43 percent for pneumonia and two percent for status asthmaticus). Neurological illnesses were present in 22.7 percent of cases (coma in 15.9 percent, Guillain–Barré syndrome in 4.5 percent and status epilepticus in 2.3 percent), heart failure in 10.5 percent of cases, diabetic ketoacidosis in 6.8 % of cases, elective postoperative disorder in 4.5 % of cases, acute hemolytic crises in 3.4 % of cases, inborn errors of metabolism in 2.2 percent of cases, hepatic encephalopathy in 2.2 % of patients, septic shock in 1.1 percent of cases, aplastic crisis in 1.1 % of patients and diabetic ketoacidosis in 6.8 % of patients [14].

Based on 25(OH)D levels in the groups studied, our results indicate that the patient group had considerably lesser serum 25(OH)D level when compared to the control group (20.85±9.87 ng/ml versus 28.66±11.94 ng/ml, correspondingly; $p=.007$), a statistically significant variance was seen amongst the two groups.

This finding was in line with **McNally et al and Madden et al** who shown that among pediatrics with critical disease the levels of 25(OH)D was significantly impaired in contrast to control group [15, 11].

Regarding the status of vitamin D, our research revealed that the prevalenceof vitamin D deficiency (under twenty ng/ml) was higher in the patient group compared to the control group, which was statistically significant (sixty percent vs. 23.33% respectively $p=.0004$). Similarly, the prevalence of vitamin D sufficiency ($\geq$ thirty ng/ml) was statistically significantly lower in the patient group compared to the control group (16.67% vs. 40% respectively $p=0.0450$). Furthermore, the prevalence of vitamin D inadequacy (between 21 & 29 ng/ml) was higher in the control group compared to the patients' one, but the variance was not statistically significant (36.67% vs. 23.33% respectively $p=.2597$).

Madden et al ,showed that a significant occurrence of vitamin D deficiency is noted in children who are critically sick, and this deficiency is correlated with the severity of critical disease [11].

We also found that occurrence of vitamin D shortage between critically ill kids was sixty percent in addition **Halwany et al,** shown that low levels of vitamin D found in the majority of severely unwell kids, specifically, 37.3 percent of instances were found to be lacking in vitamin D, 38.2 percent of individuals were found to be insufficient in vitamin D and just 24.5 percent of instances were found to be sufficient in vitamin D [16].

According to the association between basic characteristics of the patient group and vitamin d status, our results showed that no statistically significant association was found among Vitamin D status and age, sex, weight, height and BMI in the patients' group.

In concordance with our research **Aşılıoğlu et al,** found no statistically significant relationship amongst Vitamin D level & sex or BMI [17].

As well, **García-Soler et al,**found no statistically significant relationship amongst Vitamin D level & age, sex or BMI [18].

Our results showed no statistically significant difference regarding vitamin D status among different types of illnesses requiring admission to PICU,(p = 0.278 respectively).Similarly, **Deka et al,**revealed that the cause for admission had no relationship with Vitamin D status [19].

Conclusion

The current study showed that there was high occurrence of vitamin D deficiency in critically ill children in our research population. Serum 25(OH)D level was significantly decreased in critically ill children in comparison with control group.

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