Original Article

Vitamin D status in adult critically ill patients in Eastern India: An observational retrospective study

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ABSTRACT

Background: The prevalence of vitamin D deficiency in critically ill patients has been reported to be as high as 80%. There is insufficient data regarding the relationship between 25-hydroxyvitamin D [25(OH) D] levels and outcomes in medical intensive care unit (MICU). The goal of this study was to evaluate the prevalence of 25(OH) D deficiency in MICU and its relationship with outcomes. **Subjects and Methods:** This was a retrospective study in a MICU of a teaching medical college hospital of Eastern India. All patients admitted to MICU, who had levels of 25(OH) D available, were included in the study. The discriminative powers of admission and lowest 25(OH) D values regarding day-30 mortality were evaluated by producing receiver operating curves (ROC). Binary end points were analyzed by means of a Fisher's exact test. Continuous variables were compared by using unpaired t-tests, Welch's tests, or Wilcoxon ranksum tests. All odds ratios and their corresponding 95% confidence intervals were calculated according to the profile-likelihood method. The time from inclusion to death in the two groups was compared with the use of the log-rank test, and the results are presented as Kaplan–Meier curves. Hazard ratios for death from hypo 25(OH) D were calculated by logistic regression model. All *P* values were 2-tailed and $P < 0.05$ was considered statistically significant. **Results:** Of the 300 patients admitted during the study period, 25(OH) D levels were available in 152 patients (50.6%). Of these 152 patients, 15 patients (9.8%) had 25(OH) D insufficiency (20-29.9 ng/dL), 79 (51.9%) had 25(OH) D deficiency (0-19.9 ng/dL), and the levels were normal (>30 ng/dl) in 58 (38.2%) patients. Most of the patients with deficient 25(OH) D levels were females ($P < 0.05$). Higher mortality ($P = 0.01$), increased length of MICU stay, and prolonged ventilation were observed in patients with 25(OH) D deficiency. **Conclusions:** Patients with 25(OH) D deficiency in MICU have increased hospital mortality, longer mechanical ventilation, and longer MICU stay.

KEY WORDS: Critical illness, intensive care, mortality, vitamin D

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INTRODUCTION

Vitamin D plays a vital role in maintaining adequate serum calcium and phosphate levels for bone mineralization and optimal cardiac and skeletal muscle function.[1] Recent studies, however, have indicated a much broader role to vitamin D than simply the regulation of calcium metabolism alone. Vitamin D likely confers physiologically relevant pleiotropic functions that include cardioprotective and immunomodulatory effects as well as enhances antimicrobial function.[2] Vitamin D deficiency is a frequent disorder; about 50% of the elderly in North America and 65% of the elderly in the rest of the world are not getting enough vitamin D.[3]

Vitamin D deficiency has been associated with excess mortality in general population,[3] it has anti-inflammatory and anti-proliferative properties[4] and its deficiency could lead to increased risk of cardiovascular disease and cancer.[2,5] The prevalence of 25-hydroxyvitamin D [25(OH) D] deficiency in critically ill patients ranges from 17 to 79%[6-9] but more recent studies suggest that the prevalence of 25(OH) D deficiency in critically ill patients may be as high as 100%, which might impact clinical outcomes in this specific population.[10] There is a paucity of data regarding the general prevalence of vitamin D deficiency and its association with any adverse outcomes. The present study aimed to evaluate the prevalence of 25(OH) D deficiency in the medical intensive care unit (MICU) of a teaching medical college hospital in Eastern India, and its association with hospital mortality. Secondary outcomes

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included duration of mechanical ventilation, need for renal replacement therapy, and length of MICU stay.

SUBJECTS AND METHODS

This was a retrospective study of all patients admitted to the adult MICU between March 2013 and August 2013 in a teaching medical college of Eastern Orissa, India located at latitude 20° 14′ 0″ North and longitude 85° 50′ 0″ East. All patients admitted to MICU, who had levels of 25(OH) D available, were included in the study. 25(OH) D assay was done by quantitative enzyme-linked immunosorbent assay (ELISA). 25(OH) D deficiency was defined as 25(OH) D level of <19.9 ng/dl. Baseline demographics (age, gender, and race), and history of chronic kidney disease (CKD) were collected. Clinical and laboratory variables obtained during the first 24 hours of hospital admission apart from routine investigations included serum levels of total calcium, phosphate, creatinine, glucose, albumin, and 25(OH) D. Various parameters that were specially recorded included mean arterial pressure, presence of acute renal failure (ARF), need for renal replacement therapy, need for mechanical ventilation and its duration, duration of ICU and hospital stay (days), other variables useful to calculate Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) scores.[11] Length of stay in MICU was defined as the time from MICU admission to the time of transfer out of MICU.

The medical ethics committee approved this study.

The discriminative powers of admission and lowest 25(OH) D values regarding day-30 mortality were evaluated by producing receiver operating curves (ROC). Binary end points were analyzed using Fisher's exact test. Continuous variables were compared using unpaired t-tests, Welch's tests, or Wilcoxon ranksum tests, as appropriate. All odds ratios and their corresponding 95% confidence intervals were calculated according to the profile-likelihood method. The time from inclusion to death in the two groups was compared by using the log-rank test, and the results were presented as Kaplan–Meier curves. Hazard ratios for death from vitamin D deficiency were calculated by logistic regression model. All *P* values were 2-tailed, and $P < 0.05$ were considered statistically significant.

RESULTS

Of the 300 patients admitted during the study period, 25(OH) D levels were available in 152 patients (50.67%). Fifteen patients had 25(OH) D insufficiency (20-29.9 ng/dL), 79 (51.9%) had 25(OH) D deficiency (0-19.9 ng/dl) whereas the levels were normal (>30ng/dl) in 58 (38.2%) patients. Baseline characteristics of study patients are given in Table 1. 25(OH) D deficiency was significantly more frequent among the females ($P < 0.05$). Outcomes and adverse events are given in Table 2. Hospital mortality was higher in patients with 25(OH) D deficiency and insufficiency ($P = 0.01$), odds ratio 0.39, 95% confidence interval 0.94-0.67 [Table 2 and Figure 1]. MICU patients with 25(OH) D deficiency and insufficiency had prolonged mechanical ventilation [Table 2 and Figure 2; $P < 0.05$) including a prolonged length of MICU stay [Table 2, $P = 0.01$]. There was no statistically significant difference in the need for renal replacement therapy in the three groups ($P > 0.05$).

DISCUSSION

Our results demonstrate that 51.9% patients admitted to our MICU have 25(OH) D deficiency. The prevalence is similar to other large studies reporting prevalence of 17-79%.[6-9] More recently, Sauneuf *et al*., (2013) reported a high prevalence of 80-100% of vitamin D deficiency in critically ill patients.[10] Our hospital caters to the lower middle class and below poverty line (BPL) population, who are dark-skinned although living in lower latitudes. As studied by Antony and Laxmaiah,[12] the average consumption of foods such as milk and milk products was significantly lower ($P < 0.01$) in BPL population. This group of patients coming from BPL population has less healthcare coverage and poor nutritional standards,

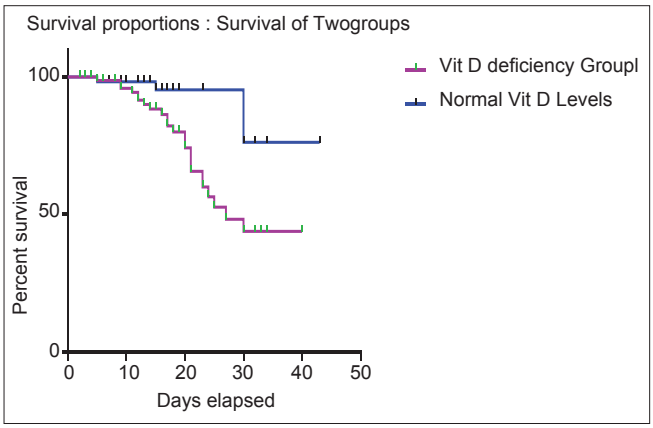

Figure 1: 30 days mortality in the two groups

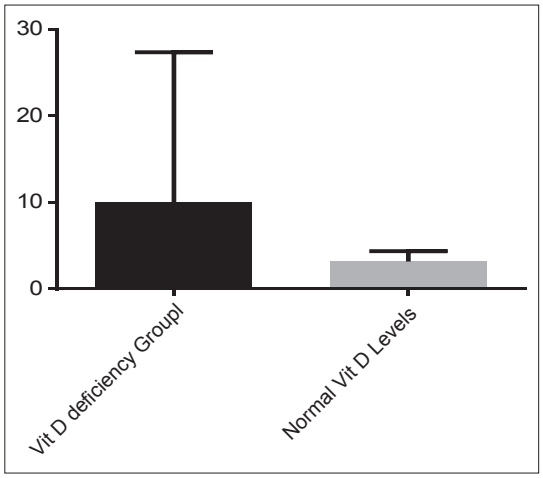

Figure 2: Ventilator days in the two groups

Table 1: Base line characteristics of study patients

Variable	25(OH) D deficiency group (0-19.9 ng/dL)	25(OH) D insufficiency group (20-29.9 ng/dL)	Normal 25(OH) D group (>30 ng/dl)	*P* value
Age-year	60.4±17.2	60.1±16	59.9±17.1	
Female sex-no./total no. (%)	55/79 (69.6)	9/15 (60)	19/58 (32.7)	*P*=0.01
Weight-kg	63.91±15.1	62.5±12.5	65.21±14.7	
Body-mass index†	27.9±7.7	27±7.0	28.0±7.2	
Interval from ICU admission to 25(OH) D estimation-hour	3.4±1.4	3.4±1.4	3.4±1.3	
Reason for ICU admission-no./total no. (%)				
Operative	27/79 (34.1)	6/15 (40)	19/58 (32.7)	
Non-operative	52/79 (65.8)	9/15 (60)	39/58 (67.2)	
Location before ICU admission-no./total no. (%)				
Emergency department	19/79 (24)	4/15 (26.7)	14/58 (24.1)	
Hospital floor (or ward)				
Without previous ICU admission	62/79 (78)	11/15 (73.4)	49/58 (84)	
With previous ICU admission	17/79 (22)	4/15 (26.7)	9/58 (16)	
Another ICU	8/79 (10.1)	2/15 (13.4)	7/58 (12.0)	
Another hospital	30/79 (37)	5/15 (33.4)	17/58 (29.31)	
Operating room				
After emergency surgery	4/79 (5)	1/15 (6.7)	3/58 (5.17)	
After elective surgery	15/79 (18.9)	14/15 (93.3)	10/58 (17.2)	
APACHE II score	27±8.98	26±5.78	26±7.68 (*P*=0.23) Wilcoxon test	
25(OH) D levels-ng/dL (mean±SD)	6.93±2.3	20±1.2	46±5.15 (*P*<0.01) Wilcoxon test	
Renal				
Dysfunction (SOFA score, 1-2)	27/79 (35)	4/15 (26.7)	18/58 (31.6)	
Failure (SOFA score, 3-4)	38/79 (19)	3/15 (20)	5/58 (8.8)	
Renal replacement therapy-no./total no. (%)	15/79 (19)	3/15 (20)	11/58 (18.9)	
Mechanical ventilation-no./total no. (%)	37/79 (47)	7/15 (46.6)	27/58 (46.5)	
Subgroup classification-no./total no. (%)				
Severe sepsis at admission	46/79 (58)	8/15 (53.4)	32/58 (55.17)	0.13
Trauma	21/79 (26.5)	4/15 (26.7)	14/58 (24.13)	0.05
APACHE II score≥25	59/79 (74.6)	11/15 (73.4)	43/58 (74.13)	0.52
Surgery				
After emergency surgery	4/79 (5)	1/15 (6.7)	3/58 (5.17)	>0.05
After elective surgery	15/79 (18.9)	3/15 (20)	10/58 (17.2)	0.12

SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II, †: The body mass index is the weight in kilograms divided by the square of height in meters

Table 2: Outcomes and adverse events*

Outcome measure	25 (OH) D deficiency group (0 to 19.9 ng/dL)	Normal 25 (OH) D group (> 30ng/dl)	Insufficient Group	Odds ratio or Absolute difference (95% CI)‡	Statistical test	*P* value
Death-no. of patients/total no. (%); all cause 30-day	23/79 (29)	3/58 (5.1)	2/15 (13.3)	0.39 (0.94 to 0.67)	Logistic regression	0.01
Days in ICU-median (IQR)	18 (16 to 34)	9 (12 to 16)	13 (12 to 18)	n/a	Log-rank test	0.01
Days in hospital-median (IQR)	23 (15 to 23.5)	21 (14 to 23)	22 (13 to 23)	n/a	Log-rank test	0.15
Mechanical ventilation-no. of patients/total no. (%)	37/79 (47)	27/58 (46.8)	7/15 (46.6)	0.99 (0.62 to1.58)	Pearson's test	0.98
Days of mechanical ventilation	10.04+1.97	3.15+0.15	9.05+0.75	n/a	Wilcoxon rank-sum test	0.003
Renal-replacement therapy-no. of patients/total no. (%)	24/79 (30.4)	10/58 (17.2)	3/15 (20)	0.53 (0.62 to1.87)	Pearson's test	0.53
Days of renal-replacement therapy	1.7+2.3	1.5+2.1	1.6+1.9	n/a	Wilcoxon rank-sum test	0.54

*Plus-minus values are means+SD. CPR denotes cardiopulmonary resuscitation, ICU: Intensive care unit, IQR: Interquartile range, n/a: Not available, †Absolute differences (percentage points) are given for median days in the ICU or hospital, and mean+SD days of mechanical ventilation or renal-replacement therapy; for all other measures, odds ratios are given, ‡Organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score of 3 or 4 for any individual organ system

all of which lead to an increased incidence of critical illness and a higher risk for hypovitaminosis. Ritu *et al*., (2014) found a prevalence of vitamin D deficiency of 70-100% in the general population of the Indian subcontinent,[13] and dark skin with its high melanin content is associated with vitamin D deficiency, as reported by Clemens.[14]

In our study, hospital mortality was higher in patients with 25(OH) D deficiency and insufficiency ($P = 0.01$). Our finding is consistent with that of the studies of vitamin D deficiency in critical illness as reported by Venkatram[6] and Lee *et al*.[15] Recently, Amrein *et al*., (2014) also found excess adjusted mortality in patients with 25(OH) D deficiency and insufficiency in critical illness.[16] The cause of this increased mortality in the critically ill with 25(OH)

D deficiency might be due to changes in glucose, ionized calcium, and parathormone metabolism as well as immunological and endothelial dysfunction arising out of 25(OH) D deficiency.[17-20]

In uniformity with the results of McKinney *et al*., (2011), we also found that 25(OH) D deficiency was associated with an increased length of stay among patients admitted to MICU.[8] Ventilator days in MICU were more in patients with 25(OH) D deficiency and insufficiency in our study. Vitamin D plays a vital role to maintain adequate skeletal muscle function.[1] Similar to our study, Kathryn West *et al*., (2013) reported that 25(OH) D deficient patients spend more time on the mechanical ventilators.[21] Vitamin D deficiency has been shown to increase exacerbations in chronic obstructive lung disease (COPD), increase hospitalization rates in children with asthma, and increase the risk of development of upper respiratory tract infections.[21] Some of these factors could be the cause of worsened lung mechanics in 25(OH) D deficiency group, leading to longer mechanical ventilation.

In our study, most of the patients with deficient 25(OH) D levels were females ($P < 0.05$). Most published data shows a higher prevalence of vitamin D deficiency in women and the elderly.[22] Risk factors for low vitamin D levels include older age, living in northern latitudes, sun avoidance, dark skin pigmentation, obesity, low dietary intake of vitamin D, and various medical conditions, especially malabsorption syndromes. These factors are especially important for older patients and the community of Indian females to whom our MICU caters. Most of our patients are dark skinned, elderly, and observe a veil.

Low 25(OH) D levels in patients admitted to ICUs can be mutifactorial. In addition to the well-known etiologies, factors such as drug interactions, altered gastrointestinal function in the critically ill, and the effect of volume resuscitation should also be taken into consideration.[23]

Our study is limited due to several factors. This study was conducted in a single MICU and the results cannot be generalized to other ICU units. We did not evaluate the association of low 25(OH) D levels with inflammatory markers neither did we attempt to see the effect of 25(OH) D replacement on mortality. Also, further studies are needed to know whether 25(OH) D deficiency is really the cause or merely another marker for the severity of illness.

CONCLUSIONS

In conclusion, our study shows a clear association between 25(OH) D deficiency and increased hospital mortality, longer mechanical ventilation, and longer MICU stay in critically ill patients. There are many research implications of the present study. As 25(OH) D is quite inexpensive, it calls for a large-scale multicentric prospective study where the effects of 25(OH) D replacement on mortality can be studied as well as the role of inflammatory markers in 25(OH) D deficiency can be evaluated. Also, further studies are needed to know whether 25(OH) D deficiency is really the cause or merely another marker for severity of illness.

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