

ASSOCIATION OF VITAMIN D STATUS AND WEANING FROM MECHANICAL VENTILATION IN CRITICALLY ILL PATIENTS**Rocky Das Gupta^{*1}, Manas Kanti Mazumder², Shahadat Hossain Polash³, Sheikh Ul Alam⁴, Mirza Nahiduzzaman⁵, Nafiza Afroz⁶, Mst. Nurjahan Begum⁷ and Suman Kundu⁸**¹MD (CCM), BSMMU, Dhaka, Bangladesh.²MD resident (CCM) Phase B, BSMMU, Dhaka, Bangladesh.³MD resident (CCM) Phase B, BSMMU, Dhaka, Bangladesh.⁴MD resident (CCM) Phase B, BIRDEM, Dhaka, Bangladesh.⁵MD (CCM), DMC, Dhaka, Bangladesh.⁶MD resident (CCM) Phase B, BSMMU, Dhaka, Bangladesh.⁷MD (CCM), BSMMU, Dhaka, Bangladesh.⁸MD resident (CCM) Phase B, DMC, Dhaka, Bangladesh.***Corresponding Author: Rocky Das Gupta**

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ABSTRACT

Background: Mechanical ventilation is a supportive measure for patients with respiratory failure which has several complications especially when needed for a long period of time. Vitamin D deficiency has been reported to be associated with myopathy and decreased muscle strength especially respiratory muscles in intensive care unit patients. So, it is logical to think that there might be an association of prolonged mechanical ventilation and difficulties in weaning from ventilatory support in patients with vitamin D deficiency. Due to a scarcity of related studies in Bangladesh context, this study was aimed to investigate the association between plasma vitamin D level and weaning from prolonged mechanical ventilation in critically ill ICU admitted patients. **Objective:** To evaluate the association of vitamin D status with weaning success and weaning failure patients. **Methods:** This prospective observational study was conducted at the ICU, Department of Anesthesia, Analgesia and Intensive Care medicine, BSMMU, Dhaka for a period of one year from 1st September, 2019 to 31st August, 2020. After ethical approval from Institutional Review Board (IRB), BSMMU; fifty (50) ICU patients receiving mechanical ventilation via endotracheal tube were enrolled according to inclusion and exclusion criteria. Informed written consents were taken before commencing the study. Patient demographics and clinical information were recorded in separate Case Record Form (CRF). The cumulative duration of mechanical ventilation after ICU admission was calculated and selected patients were observed for a maximum period of 28 days according to their length of mechanical ventilation and ICU stay. The patients who were successfully weaned and those who failed weaning trials or could not be weaned within 21 days of mechanical ventilation were recorded and their plasma 25-hydroxyvitamin D levels were measured. After collection of data, all data were compiled and analyzed in SPSS version 23. **Results:** Mean age of the study population was 49.44 (\pm 11.63) years with a majority in the age group 46-60 years (48%). Among the total study population 56% patients were male and 44% patients were female. Mean value of vitamin D was 17.62 \pm 7.09 ng/mL and 54% of total patients had deficient vitamin D level. Of all the fifty patients, eighteen (36%) patients were successfully weaned and thirty two (64%) patients were failed to wean within 21 days. Thirteen (72.22%) patients from weaning successful group and ten (31.25%) patients from weaning unsuccessful group had sufficient vitamin D level whereas twenty two (68.75%) patients of weaning unsuccessful group and five (27.78%) patients from weaning successful group had deficient vitamin D level. Statistical significance was found in vitamin D level between two groups ($p < 0.05$). Mean Vitamin D level was also significantly higher in patients who were successfully weaned (23.67 \pm 5.27) compared to those who failed to wean (14.22 \pm 5.57) (p value < 0.05). Multivariate logistic regression analysis to determine the independent predictors of weaning failure showed that vitamin-D deficiency (< 20 ng/mL) was the most powerful and independent predictors of weaning failure as it had highest odds ratio (OR=49.259, p value 0.005) compared age ≥ 40 years (OR=1.23, p value 0.825), male sex (OR=2.41, p value 0.355), DM (OR=3.46, p value 0.183) and HTN (OR=11.08, p value 0.042). **Conclusion:** In this study, plasma vitamin D level was found to be associated with the weaning status among critically ill patients who underwent prolonged mechanical ventilation. Patients with lower level of vitamin D tended towards weaning failure.

KEYWORDS: Vitamin D, mechanical ventilation, immunomodulation, anti-proliferation.

INTRODUCTION

Vitamin D deficiency is a common, potentially reversible contributor to morbidity and mortality among critically ill patients. The prevalence of vitamin D deficiency in intensive care unit (ICU) has ranged from 44.2 to 82.6% (Ardehali *et al.*, 2018).^[1] In mechanically ventilated patients, vitamin D is an integral part for maintaining optimal respiratory muscle function as it is essential for maintaining musculoskeletal health. However, the relationship of serum vitamin D level with critically ill ICU admitted patients who need prolong mechanical ventilation is still unclear.

Although the main known physiologic function of Vitamin D is regulation of calcium and phosphate homeostasis, vitamin D also plays a key role in various extra skeletal metabolic processes such as glucose metabolism, immunomodulation, anti-proliferation, renin-angiotensin system regulation, cell growth and apoptosis, membrane stabilization, angiogenesis etc.^[2]

Most patients receiving mechanical ventilation in intensive care units (ICUs) require short-term ventilation for less than a week. However, 4-13% of them fail weaning attempts, resulting in prolonged mechanical ventilation (PMV).^[3]

According to Powers *et al.* (2009) prolonged mechanical ventilation is associated with a 1-year mortality of around 52%. Quality of life of the survivors is also poor.^[4] There are many complications of prolonged mechanical ventilation. Among them Ventilator-Associated Pneumonia (VAP), Ventilator-associated lung injury (VALI), Muscle wasting: specifically of respiratory muscles (which starts to happen within 18 hours of mechanical ventilation), sleep disturbance, neuropsychiatric complications and increased sedation requirements are significant. Prolonged mechanical ventilation (PMV) is also associated with high health care costs, morbidity and mortality.

Vitamin D concentrations have been associated with lung development, function and other pulmonary associated measures. Its concentrations have been shown to be directly correlated with spirometry and gas exchange in patients with interstitial lung disease. Patients with COPD and mild vitamin D insufficiency have shown a

significantly lower rate of exacerbations when given supplementation (Verceles *et al.*, 2015).^[5] Quraishi *et al.* (2016) found that among the ICU patients, use of MV results in cellular changes and respiratory muscle weakness, which is aggravated by malnutrition, severe infections and electrolyte abnormalities.⁶ In vitro studies suggest that vitamin D supplementation induces rapid changes in calcium metabolism of muscle cells. When 1,25-dihydroxyvitamin D (1,25(OH)₂D) (the most biologically active vitamin D metabolite) binds the vitamin D membrane receptor (VDR), it triggers second-messenger pathways in the muscle cell, which results in enhanced calcium uptake and helps in functioning of muscle.

There have been multiple studies linking the association of vitamin D and weaning from mechanical ventilation in ICU patients. Quraishi *et al.* (2016) showed inverse relationship between vitamin D and duration of mechanical ventilation.^[6] Yousefian, Sadegi and Sakaki (2019) demonstrated vitamin D accelerates the weaning of patients from mechanical ventilation in intensive care unit.^[7]

But some studies found no significant relation between vitamin D level and weaning outcome among critically ill patients (Verceles *et al.*, 2015, Yadav *et al.*, 2018).^[5] Yadav *et al.* (2018) demonstrated optimal serum vitamin D levels might facilitate an early SBT (Spontaneous breathing trial) and shortened duration of mechanical ventilation.^[8]

OBJECTIVES

General objectives

To evaluate the association between vitamin D status and weaning from mechanical ventilation.

Specific objectives

1. To estimate vitamin D status in patients who would be successfully weaned from mechanical ventilation within 21 days.
2. To estimate vitamin D status in patients who would not be successfully weaned from mechanical ventilation within 21 days.
3. To compare vitamin D status between weaning success and weaning failure patients.

METHODOLOGY

Type of study	Prospective observational study
Place of study	Intensive Care Unit, Department of Anaesthesia, Analgesia and Intensive Care Medicine, BSMMU, Dhaka
Study period	One year from 1 st September, 2019 to 31 st August, 2020. Patients were enrolled after the date of IRB clearance.
Study population	All newly admitted ICU patients undergoing invasive mechanical ventilation
Sampling technique	Purposive

Inclusion Criteria

1. All newly admitted ICU patients undergoing invasive mechanical Ventilation.
2. More than 18 years of age.
3. Duration of mechanical ventilation >48 hrs.

4. Surviving >48 hours following discontinuation of mechanical ventilation.
5. Patients who were successfully weaned within 21 days mechanical ventilation.
6. Patients who failed weaning trials or couldn't be weaned within 21 days of mechanical ventilation.

Exclusion criteria

1. Patients who didn't require mechanical ventilation.
2. Patients who required only noninvasive ventilation.
3. Intubated patients who died within 21 days.
4. CKD/End stage renal disease and pregnant patients.
5. Recent history of vitamin D supplementation.

Study Procedure

This study was conducted at the ICU, Department of Anaesthesia, Analgesia and Intensive Care medicine, BSMMU. A total of 50 patients were selected according to the inclusion and exclusion criteria. Patient demographics (Age, Sex, Residence), co-morbidities, APACHE II score, mechanical ventilation mode, duration and length of ICU stay were recorded in a Case Record Form (CRF).

All patients receiving mechanical ventilation at the time of admission to the ICU were assessed for readiness to discontinue respiratory support and a daily protocol was applied to all patients to determine the necessity of mechanical ventilation. The cumulative duration of mechanical ventilation after ICU admission was calculated from individual medical records.

The patients who were successfully weaned before 21 days were selected. After 48hrs of successful weaning, plasma 25-hydroxyvitamin D level (25(OH)D) levels

were measured in this group. Plasma 25(OH)D levels were assessed by Chemiluminescent Microparticle Immuno Assay using Atellica, Siemens Healthineers machine in the Biochemistry Laboratory of BSMMU.

Selected patients were observed for a maximum period of 28 days according to their duration of mechanical ventilation and length of ICU stay. Day "0" (zero) of duration of mechanical ventilation was the date of start of invasive mechanical ventilation via endotracheal tube in the present or prior ICU.

Data collection technique

- A structured questionnaire and checklist.
- Informed written consent form in Bangla.
- Informed written consent form in English.

Data processing & analysis

Data were collected, compiled and tabulated according to key variables. Categorical variables were reported as count and percentage. Normally distributed continuous data were presented as mean and 95% confidence interval where non-normally distributed data were presented as median and interquartile range. To determine any association between two categorical variables Chi-square test was used. To determine if the means of two sets of data were significantly different from each other or not, Student's t-test was used. Data were analyzed by following standard bio-statistical procedure. All p values at or below 0.05 were considered as significant. The statistical analysis was performed using the Windows based statistical software package SPSS 23.0.

RESULT

Table-I: Demographic characteristics of study subjects.

Demographic variables	Weaning within 21 days		Total (n=50) N (%)	p* value
	Successful (n=18) N(%)**	Not successful (n=32) N(%)		
Age group (in years)				
18-30	3(16.6)	1(3.1)	4(8)	0.163
31-45	5(27.8)	8(25)	13(26)	
46-60	9(50)	15(46.87)	24(48)	
>60	1(5.5)	8(25)	9(18)	
Mean \pm SD	45.61 \pm 12.62	51.59 \pm 10.64	49.44 \pm 11.63	
Sex distribution				
Male	10(55.55)	18(56.25)	28(56)	0.254
Female	8(44.45)	14(43.75)	22(44)	

* p value determined by Pearson Chi-Square test

**Values are expressed in Number and Percentage of total patients

Mean age of all patients were 49.44 \pm 11.63 years (21-68 year) with majority belonged to 46-60 years of age (48%). Patients who were weaned successfully within 21 days were mostly prevalent in 46-60 years age group

(50%). Statistically there was no difference between two groups (p>0.05).

Among the successfully weaned patients, 55.55% were male and 44.45% were female whereas in the weaning

unsuccessful group, eighteen (56.25%) were male and fourteen (43.75%) were female. Statistically there was no

difference among the respondents in relation to their sex ($p>0.05$).

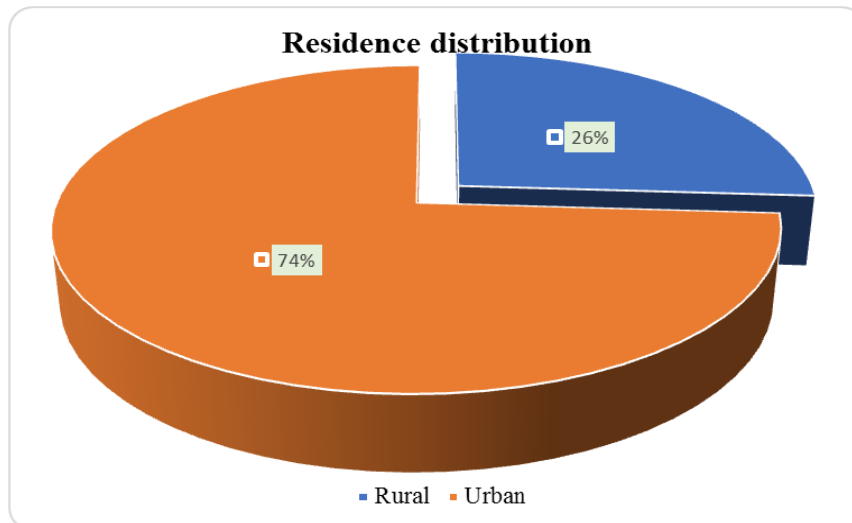


Figure 1: Pie chart showing residence distribution of study population. (n=50)

Of the fifty patients, thirty-seven (74%) were from urban residence and only thirteen (26%) patients were from rural residence.

Table-II: Comparison of vitamin D status according to residence. (n=50)

Residence	Sufficient (≥ 20 ng/mL) (n=23) N (%)**	Deficient (< 20 ng/mL) (n=27) N (%)**	p value*
Rural (n=13)	7(53.84)	6(46.16)	0.509
Urban (n=37)	16(43.24)	21(56.76)	

* p value determined by Pearson Chi-Square test

**Values are expressed in Number and Percentage of total patients

Of the rural residence group, 53.84% had sufficient vitamin D level compared to 43.24% in the urban group. 46.16% patients in rural group and 56.76% patients in

urban group had deficient vitamin D level. Statistically no difference was noted ($p>0.05$).

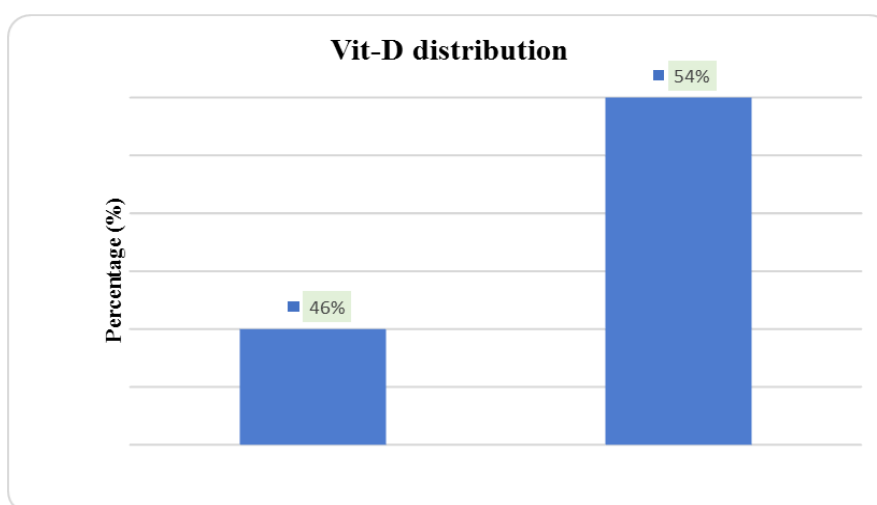


Figure 2: Bar chart showing distribution of vitamin D among study subjects. (n=50)

Mean plasma 25(OH)D of total 50 patients were 17.62 ± 7.09 ng/mL. Of the 50 patients, twenty-three (46%) patients had sufficient level of vitamin D whereas

twenty-seven (54%) patients had deficient level of vitamin D.

Table-III: Vitamin D status among study subjects according to weaning success.

Plasma 25(OH)D level	Weaning within 21 days		p* value
	Successful (n=18) N (%)**	Not successful (n=32) N (%)**	
Sufficient (≥ 20 ng/mL)	13 (72.22)	10 (31.25)	0.005*
Deficient (< 20 ng/mL)	5 (27.78)	22 (68.75)	
Mean \pm SD, ng/mL	23.67 \pm 5.27	14.22 \pm 5.57	<0.001**

Values are expressed as Mean \pm SD and within parenthesis percentage (%) over column in total.

*Pearson chi-squared Test (χ^2) was performed.

** Student t-test was performed

Thirteen (72.22%) patients from weaning successful group had sufficient level of plasma vitamin D. 68.75% patients of weaning unsuccessful group had vitamin D deficiency (p value 0.005). Mean vitamin D level was

also significantly higher in patients with successfully weaned (23.67 \pm 5.27) compared who failed to wean (14.22 \pm 5.57) (p value <0.001).

Table IV: Comparison of co-morbidities between two groups of study population. (n=50)

Co-morbidities	Weaning within 21 days		p* value
	Successful (n=18)	Not successful (n=32)	
HTN	11	25	0.198
DM	10	22	0.351
COPD	0	4	0.118
Bronchial Asthma	1	4	0.432
IHD	4	6	0.768
Hypothyroid	6	7	0.375
No co-morbidities	5	1	0.010

*p value determined by Pearson Chi-Square test.

No significant difference was found in distribution of co-morbidities between the two groups (p value > 0.05)

Table-V: Association of comorbidities with vitamin D level among study population. (n=50)

Co-morbidities	Sufficient (≥ 20 ng/mL) (n=23) N (%)	Deficient (< 20 ng/mL) (n=27) N (%)	p value*
HTN	20 (86.96)	16 (59.26)	0.03
DM	18 (78.26)	14 (51.85)	0.053
COPD	2 (8.70)	2 (7.41)	1.00
Bronchial Asthma	3 (13.04)	2 (7.41)	0.651
IHD	4 (17.39)	6 (22.22)	0.670
Hypothyroid	6 (26.09)	7 (25.93)	0.990

Values are expressed within parenthesis percentage (%) over column in total.

*Pearson chi-squared Test (χ^2) was performed.

There was significant association found in distribution of hypertension and DM with vitamin D level (p value 0.03 and 0.053 respectively) whereas no significant difference

had been found in distribution of COPD, bronchial asthma, IHD and hypothyroidism as p value >0.05.

Table-VI: Comparison of APACHE II score and Length of ICU stay according to vitamin D level.

	Sufficient (≥ 20 ng/mL) (n=23) N (%)	Deficient (< 20 ng/mL) (n=27) N (%)	p value**
APACHE II score	24.57 \pm 3.09	29.44 \pm 3.02	<0.001
Length of ICU stay, days	15.18 \pm 7.80	23.52 \pm 4.50	<0.001

Values are expressed as Mean \pm SD.

** Student t-test was performed.

Mean APACHE II score and Length of ICU stay were also significantly higher in patients with vitamin D deficiency (29.44 ± 3.02 and 23.52 ± 4.50 days respectively) compared sufficient group (24.57 ± 3.09 and 15.18 ± 7.80 days respectively) (p value < 0.001).

DISCUSSION

This prospective observational study was conducted in the Department of Anaesthesia, Analgesia & Intensive Care Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka to investigate the association between plasma 25-hydroxyvitamin D level and weaning from mechanical ventilation in critically ill ICU admitted patients. Total fifty ICU admitted, mechanically ventilated patients were included in the study. Mean age of all patients were 49.44 ± 11.63 years (21-68 year) with majority belonged to 46-60 years of age (48%). Patients who were weaned successfully within 21 days were mostly prevalent in 46-60 years age group (50%). This was lower than the findings of Quraishi et al. (2016).^[6] They investigated 94 patients for plasma 25-Hydroxyvitamin D levels at initiation of care and duration of mechanical ventilation in critically ill surgical patients from two 18-bed surgical ICUs at the Massachusetts General Hospital (MGH) in Boston, Massachusetts. Mean \pm SD age of that group of patients was 65 ± 16 years. Yadav et al. (2018) studied 40 patients to know the vitamin D status and outcome of critically ill patients on mechanical ventilation. It was a prospective observational pilot study conducted in the ICU of AIIMS (All India Institute of Medical Sciences). In that study, the mean age of the study population was 54.8 ± 17.16 years. That was also higher than the mean age of our study population. Probably this is because the life expectancy is more in those countries and people get admitted in the ICUs at much older age than us. Fifty six percent of our patients were male and forty four percent were female. In Quraishi et al. (2016) study, most of the study populations were female. It was 59% and the remaining 41% was male. In Alizadeh et al. (2015) study, 44.3% were male and 55.7% were female.^[2] But in Ardehali et al. (2017) male was 53.33% and female was 46.67% which is close to our study.^[9]

In this study, thirty-seven (74%) patients were from urban residence and thirteen (26%) patients were from rural residence. Of the rural residence group, 53.84% had sufficient vitamin D level compared to 43.24% in the urban group. 46.16% patients in rural group and 56.76% patients in urban group had deficient vitamin D level. Probably this is because people in the rural areas get more sun exposure than the people in the urban areas.

Hypertension (72%) and Diabetes mellitus (64%) were the major co-morbidities among study population. Other co-morbidities included COPD (8%), bronchial asthma (10%), ischaemic heart disease (20%), Hypothyroidism (26%). Six (12%) patients had no co-morbidities. But in Yadav et al. (2018) most frequent co morbidities were cardiac (25%) followed by metabolic (17.5%) and

neurological (15%). In Alizadeh et al. (2015) study 17.1% of patients had a history of hypertension, 8.5% suffered from ischemic heart disease, and 52.8% had gastrointestinal diseases.

In this study, significant association was found in distribution of hypertension and DM with vitamin D (p value 0.03 and 0.053 respectively) whereas no significant difference had been found in distribution of COPD, bronchial asthma, ischaemic heart disease and hypothyroidism (p value > 0.05) with vitamin D.

Mean plasma 25(OH) D of all patients were 17.62 ± 7.09 ng/mL. Of the 50 patients, twenty-three (46%) patients had sufficient level of vitamin D whereas twenty-seven (54%) patients had deficient level of vitamin D. In the weaning successful group, mean plasma 25(OH) D level was 23.67 ± 5.27 ng/ml while in the weaning unsuccessful group it was 14.22 ± 5.57 ng/ml. According to Quraishi et al. (2016) mean (SD) 25(OH) D level for the study cohort was 16 ± 7 ng/mL which was close to our study.^[6] Ardehali et al. (2017) found mean serum 25 (OH) D 21.1 ± 7.4 ng/mL in total study population and 47.7% had deficient vitamin D level.^[9] In Verceles et al. (2015) study mean serum 25 (OH) D was 18 ± 11 ng/mL with 61% deficient vitamin D level. Yadav et al. (2018) study demonstrated 65% of study Population were deficient of vitamin D.^[5]

In this study, mean APACHE II score and Length of ICU stay were also significantly higher in patients with vitamin D deficiency (29.44 ± 3.02 and 23.52 ± 4.50 days respectively) compared to sufficient group (24.57 ± 3.09 and 15.18 ± 7.80 days respectively). In Quraishi et al. (2016) study mean APACHE II score was 21 ± 10 vs. 15 ± 6 and length of ICU stay was 8(4-10) vs. 5(4-9) days between deficient and sufficient vitamin D level group respectively.^[6] Yadav et al. (2018) study demonstrated mean APACHE II score at admission was 20.2 ± 7 and ICU length of stay was 18.7 ± 8.5 vs. 23.3 ± 11.4 between low and normal level of vitamin D respectively.^[8]

However, a significant amount of literature and studies found relationships between vitamin D concentrations and lung development.^[10] Besides, some studies showed increased frequency and severity of exacerbation of both COPD (Lehouck et al., 2012) and bronchial asthma (Korn et al., 2013) are associated with lower vitamin D concentrations.^[11,12] Some studies found no significant relation between vitamin D level and weaning outcome among critically ill patients (Verceles et al., 2015, Yadav et al., 2018).^[5,8]

As a result, we infer that critically ill patients are most likely to benefit from vitamin D replacement during their ICU stay. However, this hypothesis must still be confirmed by clinical trials. Despite some limitations, to the best of our knowledge, our study is the first in Bangladesh to examine the association of vitamin D

status and weaning from prolonged mechanical ventilation.

CONCLUSIONS

In this study, plasma vitamin D level was found to be associated with weaning from mechanical ventilation in critically ill patients. Patients with lower level of vitamin D tended towards weaning failure.

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