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Serum vitamin D level was not associated with severity of ventilator associated pneumonia

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Background and Objective. Vitamin D deficiency is considered one of the most common nutritional deficiencies associated with weakened immune system and increased likelihood of sepsis. The current study was conducted to investigate the association between serum vitamin D level and the severity and prognosis of ventilator associated pneumonia (VAP) in inpatients in intensive care unit (ICU).

Methods. Eighty-four consecutive patients with VAP were enrolled in this observational, prospective study conducted in the ICU of Besat Hospital, Hamadan. The patients were examined for serum 25-hydroxyvitamin D (vitD3) level and VAP severity and prognosis. Clinical pulmonary infection score was used for the diagnosis, and Sequential Organ Failure Assessment (SOFA) Score was used to determine the severity of VAP.

Results. Low level serum vitD3 (under 30 ng/mL) was found in 66 (78.6%) patients. In this series of VAP patients, there were no significant differences in blood culture results, 14 and 28-day sepsis-associated mortality, mechanical ventilation duration, or SOFA Score on days 3, 7, and 14 between the low level and normal level vitD3 patients ($p > 0.05$).

Conclusion. Serum vitD3 level was not associated with mortality from VAP or complications due to sepsis in the inpatients in the ICU.

Keywords: Vitamin D, Pneumonia, Ventilator-Associated.

INTRODUCTION

Vitamin D deficiency is considered nowadays one of the most important nutritional deficiencies, associated with several complications [1]. Vitamin D plays an important role in the immune system's and skeletal system's health as well as in regulating the intrinsic and acquired immune system [2], such that its deficiency leads to autoimmune diseases and weakened immune system [3]. Vitamin D plays a part in local immune responses to pathogens and the inflammatory pathways of systemic infections, and its deficiency is associated with acquisition of sepsis and other clinical infections; however, the causal relationship and its clinical effect have not yet been clearly explained, and the mechanism of mortality from vitamin D deficiency should be further studied [4, 5].

As underlying factors, seasonal variations [4] and length of hospitalization [6] can affect vitamin D levels in patients. In this regard, a study demonstrated that approximately 93.5% of inpatients in intensive care units (ICUs) suffered from vitamin D deficiency and insufficiency [7].

Ventilator-associated pneumonia (VAP) is one of the causes of death among critically ill patients in clinical settings [8, 9]. VAP occurs mainly due to hospital equipment including endotracheal tube, and defects in the immune system and pulmonary cleanup function [10, 11]. The pathogenic agents of VAP are Acinetobacter, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, Proteus species, Enterobacter species, and *Serratia marcescens* [12]. The presence of antibiotic-resistant pathogens in the ICUs and hospital settings has intensified this problem [11]. Besides that, due to lack of definite and standard criteria, VAP is still considered to be clinical syndrome without a specific test for diagnosis, which may challenge the diagnosis and treatment of this disease [11].

It seems therefore necessary to seek out therapeutic and supportive approaches to address and reduce mortality due to VAP. This study was conducted to investigate association of serum vitamin D (25-hydroxyvitamin D, vitD3) level with microbial blood culture, 28-day mortality, mechanical ventilation duration, and the organ failure in sepsis in patients with VAP.

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MATERIALS AND METHODS

The observational, prospective study was conducted in the ICU of Besat Hospital, Hamadan from June 2015 until December 2015. All consecutive patients with VAP occurring were enrolled (84 patients). The sample size was determined according to the information from a pilot study of 10 samples. An odds ratio (OR) equal to 0.70 for occurring VAP had been found. By considering this value of OR; with a proportion of occurring VAP 0.50, 95% confidence level, and power of 90%, sample size was calculated at 70 patients. Considering a dropout rate of 10%, the final sample size was determined to be 77 patients, but the useful samples were 84. The study protocol was approved by the Ethics Committee of the Hamadan University of Medical Sciences (approval code: IR.UMSHA.REC.1394.277). The inclusion criteria were being over 18 years old and under mechanical ventilation for over 48 hours and suffering from VAP according to the Clinical Pulmonary Infection Score (CPIS). The exclusion criteria were non-VAP-associated mortality and Acute Physiology and Chronic Health Evaluation (APACHE II) score over 25. APACHE II is a checklist serving as a severity-of-disease classification system in the ICU that was used control for certain confounders such as the severity of disease or to match the participants [13]. The measurement of serum vitamin D level was conducted by measuring blood 25-hydroxyvitamin D levels of patients with VAP [4], and then, those with < 30 ng/mL serum 25-hydroxyvitamin (VitD3) level were assigned to one group and those with serum vitD3 level ≥ 30 ng/mL to another group. We draw blood for the measurement of vitamin D after diagnosis of VAP. Afterwards, the patients were examined based on serum VitD3 level and VAP severity. To diagnose VAP, the CPIS was used [14]. The CPIS integrates a combination of clinical, radiologic, physiological, and microbiological criteria into a numerical value that represents VAP if it is over 6. To determine VAP severity, different parameters such as duration of mechanical ventilation, positive culture results, 14 and 28-day sepsis-associated mortality, and the Sequential Organ Failure Assessment (SOFA) Score were assessed on days 3, 7, and 14. SOFA checklist is used to determine certain degrees of organ failure in sepsis and the failure of six organs according to objective and tangible criteria [15]. Dysfunction of each organ is classified according to a scoring system according to which score 0 represents normal function and score 4 does organ failure. Final score is determined by the sum of the scores for the organs function such as respiratory system, cardiovascular system, liver system, coagulation system, neurologic system, and renal systems. Mortality in 14 days and mortality in 28 days were measured since admission in ICU but SOFA scores were measured 3,7 and 14 days after diagnosis of VAP. Length of ICU stay was measured since admission in ICU.

Data analysis was conducted by descriptive statistics, *t*-test, chi-square test, and non-adjusted and adjusted ANOVA in SPSS version18.

RESULTS

A total of 84 patients were investigated in this study. The mean age of the patients was 51.91 (18.90) (range: 18-82) years, 72.6% (n: 61) of the patients were male. Fifty-four (64.3%) patients were hospitalized for trauma and the rest for non-traumatic events. Serum vitD3 level was under 30 ng/dL in 66 (78.6%) patients and over 30 ng/dL (normal serum vitD3 level) in the remaining (n: 18) patients (Table 1). In patients with vitD3 deficiency, eight (12.1%) patients had positive blood culture test, and none of those without vitD3 deficiency had positive blood culture test ($p = 0.192$).

Table 2 showed that the results of comparing the basic of CPIS and the duration of mechanical ventilation in two groups low (< 30) and high (> 30) VIT D3. The independent sample t-test did not show any statistical differences (P = 0.490 and P = 0.878, respectively); moreover, the independent sample t-test did not explain statistical differences between having mortality in 14 and 28 days (P = 0.956 and P = 0.937, respectively). Blood culture from positive or negative perspective had not statistical significance (P = 0.255).

Table 3 showed that the Kendall's tau correlation coefficient did not show a statistical relationship between SOFA scores with VIT D3 levels (P-value 0.381, 0.175, and 0.370, respectively); the relationship between the SOFA scores with VIT D3 was a non-significant and negative one.

Table 4 showed non-adjusted and adjusted analyses of low and high VITD3 groups with SOFA scores. Non adjusted and adjusted one-way analysis of variance did not show statistical analysis between different SOFA 3 (P = 0.762 *vs*. P = 0.610), SOFA 7 (P = 0.676 *vs*. P = 0.068), and SOFA 14 (P =

0.650 *vs*. P = 0.147) scores in two groups high and low VITD3, respectively. It is while that adjusted comparison of SOFA score 7 between two groups had near difference to statistical significance (P = 0.068). The adjusted variables were sex, age, basic SOFA and CPIS scores (Table 4).

Table 1
Demographic characteristics of the study

Variable		No.	%
Gender	Female	23	27.4
	Male	61	72.6
Reason for hospitalization	Trauma	54	64.3
	Non trauma	30	35.7
Serum vitamin D3 level	Under 30 ng/dL	66	78.6
	Over 30 ng/dL	18	21.4
Tracheal primary culture result	*Staphylococcus aureus*	11	13.1
	Escherichia coli	26	31
	Acieneto	13	15.5
	Pseudomonas	7	8.3
	Klebsiella	19	22.6
	Proteus	8	9.5

Table 2
Comparing the basic CPIS, duration of mechanical ventilation, mortality in 14 and 28 days, and blood culture in two groups VIT D < 30 and > 30 and overall VIT D3

Variable	Group	Mean ± Standard Deviation	P-Value
CPIS	VIT D<30	6.95 ± 0.64	0.490
	VIT D>30	6.8 ± 0.71	
Duration of mechanical ventilation	VIT D<30	13.38 ± 6.12	0.878
	VIT D>30	13.67 ± 9.76	
Mortality in 14 days	Yes	24.87 ± 10.36	0.956
	No	24.70 ± 8.56	
Mortality in 28 days	Yes	24.61 ± 9.49	0.937
	No	24.77 ± 8.33	
Blood culture	Positive	21.37 ± 4.90	0.255
	Negative	25.07 ± 8.93	

Table 3
Correlation between SOFA scores with VIT D3 levels

Variable	SOFA 3	SOFA 7	SOFA 14
VIT D3 levels	r = -0.070 P-Value = 0.381	r = -0.107 P-Value = 0.175	r = -0.070 P-Value = 0.370

Table 4
Adjusted and non-adjusted analyses of low and high VITD3 groups with SOFA scores

Variables	≤30 ng (n = 66) Mean ± SD	>30 ng (n = 18) Mean ± SD	Unadjusted between group Comparisons	Adjusted between group Comparisons
SOFA 3	8.62 ± 2.61	8.83 ± 2.68	0.762	0.610
SOFA 7	8.97 ± 2.77	8.67 ± 2.50	0.676	0.068
SOFA14	9.41 ± 3.48	9.00 ± 2.93	0.650	0.147

* Unadjusted and adjusted of analysis of covariance (adjusting factors sex, age, baseline SOFA and CIPS scores).

DISCUSSION

The present study was conducted to investigate association between serum vitamin D (25OH vit D) level and VAP-associated mortality in inpatients in the ICU of Besat Hospital, Hamadan. In this study, serum vitD3 level was under 30 ng/dL in 66 (78.6%) patients. Consistently, a study in Iran demonstrated that over 93.5% of the inpatients in the ICUs had vitamin D deficiency [7].

In our study, no significant difference was noted in the blood culture results between the VAP patients with vit D3 deficiency and those with normal serum vit D3 levels. Amrein *et al*. who studied to investigate the association between vitamin D level and sepsis-associated mortality, reported consistent

findings with the current study. They demonstrated that 25(OH) vit D level was not significantly associated with positive blood culture [16], which is in agreement with Moraes *et al*. study [17]; however, a study on association between serum 25-hydroxyvitamin D level and mortality among critically ill patients determined that vitamin D deficiency was associated with positive blood culture results in these patients [18].

Our results demonstrated that blood culture, 14day mortality, 28day mortality, MV duration and baseline CPIS were not significantly different between two groups whose vitamin D level is under 30 ng/mL and above 30 ng/mL. According to the study of Murat Haliloglu *et al*., they reported that the clinical scores (SOFA, CPIS, and CEPPIS) and biomarkers (NT-proBNP, PCT) were negatively correlated with 25(OH)D levels in all study groups. Unlike our study their results declared the 28-day mortality in patients with 25(OH)D levels ≤ 10 ng/mL was significantly higher than in patients with 25(OH)D > 10ng/mL, that may be related to their cut-off point (10ng/mL) [19]. Amrein *et al*. demonstrated that critically ill patients with low PTH or serum calcium levels, as well as low 25(OH)D levels (cut-off 12 ng/mL) were all at significantly greater risk for all-cause mortality [20]. Weenink *et al*. measured that 25-hydroxyvitamin D (25-OH-D) on admission and after 48 hours in all consecutive patients admitted to 20-bed general ICU and compared observed and predicted mortality (APACHE IV) their results showed that observed mortality was significantly lower than predicted in all patients and in patients with 25-OH-D > 25 nmol/L, but not in those < 25 nmol/L [21].

A study found that intake of lower-than-normal levels of vitamin D was associated with lower acute respiratory infections in children, and the intake of the sufficient amounts of this vitamin can contribute to decreasing this complication [22]. De Haan *et al*. study indicated that the low level of vitamin D was associated with acquisition of infection and sepsis [1]. Although the number of deaths on days 14 and 28 of follow-up was higher in patients with lower serum 25(OH) D level, this association was not statistically significant. In contrast a study demonstrated that 28-day mortality was higher in patients with serum 25(OH) D levels ≤ 10 than in those with normal serum vitamin D level [23]. De Haan *et al*. study also reported that the low vitamin D level was significantly associated with 30-day mortality [1]. A number of studies on critically ill inpatients in the ICUs have reported consistent findings including Amrein and colleagues who reported that low 25(OH) D status is significantly associated with mortality in the critically ill [24]; Braun and colleagues reported deficiency of 25-hydroxyvitamin D at the time of critical care initiation is a significant predictor of all-cause patient mortality in a critically ill patient population [25]; Zhao and colleagues reported concentrations of 25(OH)D were inversely associated with all-cause and cardiovascular diseases mortality among adults with hypertension in the US. Enhancing vitamin D intake may contribute to a lower risk for premature death; and finally Braun and colleagues [26] reported association of low serum 25-hydroxy-vitamin D levels and acute kidney injury in the critically ill patients [27].

In the present study, no significant association was observed between length of mechanical ventilation and normal vit D3 levels in the VAP patients with vit D3 deficiency. Inconsistent with our study, a study in India reported that 25 (OH) D deficiencies led to lengthened mechanical ventilation in critically ill inpatients. In this regard, the sample size is important the current data did not show significant analysis but the Padhi and colleagues reported a significant association. In that study, from 300 admitted patients, 152 patients (50.6%) 25(OH) D levels were available and from 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 [28].

In the current study, mean SOFA Score on day 14 was higher in the group with mean vitD3 level under 30 ng/dL than in the group with normal serum vitD3 level yet without a statistically significant difference. A study to investigate the association of baseline and synthetic vitamin D level, with mortality in critically ill inpatients in ICU, demonstrated that it was the same in patients with 25(OH) D deficiency and in those without such deficiency [17]. However, a study reported that SOFA Score on days 4 and 7 was higher in the group with serum 25(OH) D levels ≤ 10 than in another group [19]. As an index of predicting mortality of critically ill patients [26], SOFA Score can be influenced by several environmental and physiological factors, which may confound the findings of the current study.

Our results demonstrated that a statistically insignificant correlation was found between SOFA 3, SOFA 7 and SOFA 14 with vitamin D3 levels. Leo Jeng *et al*. demonstrated that critically ill subjects had significantly lower plasma 25(OH)D concentrations compared to healthy controls and these subjects with sepsis exhibited higher severity of illness scores (APACHEII and SOFA) than critically ill subjects without sepsis [29]. Also Priya Nair *et al*.

declared that there was no relationship between admission levels of calcium, PTH or 1,25-(OH)2-D and SAPS-II or APACHE- II scores; however, there was a significant correlation between admission calcium levels and SOFA [30]. Gulbin Aygencel *et al*. demonstrated that risk assessment scores including APACHE II and SOFA scores in critically ill patients were higher in the vitamin D insufficient group [31].

The inconsistency in the current results with other studies can be explained in several reasons including the current study was the first one in Iranian population, the sample size was partially lower than in other similar studies, and finally we studied the serum 25(OH) D levels on the patients with VAP diagnosis but others on the sepsis.

CONCLUSION

A large number of inpatients in the ICUs suffer from vitamin D deficiency. Although the rates of 28-day mortality and organ failure were higher in patients with vitamin D deficiency, no association was found between 25OH vit D and 28-day mortality, microbial blood culture, the length of mechanical ventilation, and organs failure in sepsis in VAP inpatients in the ICU in the current study. It is recommended to control for more confounding factors, including SOFA Score at admission, in additional studies.

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Conflict of Interest. All authors approve that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Hamadan University of Medical Sciences) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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Introducere. *Deficitul vitaminei D este foarte frecvent şi asociază slăbirea sistemului imunitar cu creşterea riscului pentru dezvoltarea sepsisului. Studiul şi-a propus să investigheze relaţia dintre nivelurile vitaminei D şi severitatea şi prognosticul pneumoniei de ventilaţie (VAP) la pacienţii internaţi în secţiile de terapie intensivă (ICU).*

Materiale şi metode. *În acest studiu observaţional şi prospectiv au fost recrutaţi 84 de pacienţi consecutivi cu VAP din secţia de terapie intensivă a spitalului Besat din Hamadan. Pacienţilor le-au fost dozate niveluirile serice ale vitaminei D şi au fost evaluate severitatea şi prognosticul VAP. Au fost folosite scoruri pentru a evalua severitatea şi prognosticul VAP.*

Rezultate. *Niveluri scăzute ale vitaminei D3 serice (sub 30 ng/mL) au fost detectate la 66 de pacienţi (78.6%). Între pacienţii cu niveluri scăzute ale vitaminei D3 şi cei cu niveluri normale ale vitaminei D3 nu au fost observate diferenţe semnificative din punctul de vedere al rezultatului la hemocultură, mortalitatea la 14 şi 28 zile post sepsis, durata ventilaţiei mecanice, scorul SOFA.*

Concluzii. *Nivelurile serice ale vitaminei D3 nu s-au asociat cu mortalitatea prin VAP şi nici cu complicaţii datorate sepsisului la pacienţii internaţi în secţiile de terapie intensivă.*

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REFERENCES

1. DE HAAN K, GROENEVELD AJ, DE GEUS HR, EGAL M, STRUIJS A. *Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis*. Critical care. 2014;**18**(6):660.

2. KENNEL KA, DRAKE MT, HURLEY DL, EDITORS. *Vitamin D deficiency in adults: when to test and how to treat*. Mayo Clinic Proceedings; 2010: Elsevier.
3. ARANOW C. *Vitamin D and the immune system*. Journal of investigative medicine. 2011;**59**(6):881-6.
4. KEMPKER JA, HAN JE, TANGPRICHA V, ZIEGLER TR, MARTIN GS. *Vitamin D and sepsis: an emerging relationship*. Dermato-endocrinology. 2012;**4**(2):101-8.
5. UPALA S, SANGUANKEO A, PERMPALUNG N. *Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis*. BMC anesthesiology. 2015;**15**(1):84.
6. DAYAL D, KUMAR S, SACHDEVA N, KUMAR R, SINGH M, SINGHI S. *Fall in vitamin D levels during hospitalization in children*. International journal of pediatrics. 2014; http://dx.doi.org/10.1155/2014/291856.
7. VOSOUGHI N, KASHEFI P, ABBASI B, FEIZI A, ASKARI G, AZADBAKHT L. *The relationship between Vitamin D, clinical outcomes and mortality rate in ICU patients: A prospective observational study*. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2016;**21**(3):84-90.
8. RAMÍREZ-ESTRADA S, LAGUNES L, PEÑA-LÓPEZ Y, VAHEDIAN-AZIMI A, NSEIR S, ARVANITI K, *et al*. *Assessing predictive accuracy for outcomes of ventilator-associated events in an international cohort: the EUVAE study*. Intensive care medicine. 2018;**44**(8):1212-20.
9. VAHEDIAN-AZIMI A, EBADI A, SAADAT S, AHMADI F. *Intelligence care: a nursing care strategy in respiratory intensive care unit.* Iranian Red Crescent Medical Journal. 2015;**17**(11).
10. ZOLFAGHARI PS, WYNCOLL DL. *The tracheal tube: gateway to ventilator-associated pneumonia*. Critical Care. 2011;**15**(5):310.
11. KALANURIA AA, ZAI W, MIRSKI M. *Ventilator-associated pneumonia in the ICU*. Critical care. 2014;**18**(2):208.
12. HUNTER JD. *Ventilator associated pneumonia*. BMJ. 2012;**344**(e3325):e3225.
13. PARAJULI BD, SHRESTHA GS, PRADHAN B, AMATYA R. *Comparison of acute physiology and chronic health evaluation II and acute physiology and chronic health evaluation IV to predict intensive care unit mortality*. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2015;**19**(2):87.
14. CELIK O, KOLTKA N, DEVRIM S, SEN B, CELIK MG. *Clinical pulmonary infection score calculator in the early diagnosis and treatment of ventilator-associated pneumonia in the ICU*. Critical Care. 2014;**18**(1):P304.
15. JENTZER JC, BENNETT C, WILEY BM, MURPHREE DH, KEEGAN MT, GAJIC O, *et al*. *Predictive Value of the Sequential Organ Failure Assessment Score for Mortality in a Contemporary Cardiac Intensive Care Unit Population*. Journal of the American Heart Association. 2018 Mar 10;**7**(6). PubMed PMID: 29525785. Pubmed Central PMCID: PMC5907568. Epub 2018/03/12. eng.
16. AMREIN K, ZAJIC P, SCHNEDL C, WALTENSDORFER A, FRUHWALD S, HOLL A, *et al*. *Vitamin D status and its association with season, hospital and sepsis mortality in critical illness*. Critical care. 2014;**18**(2):R47.
17. MORAES RB, FRIEDMAN G, WAWRZENIAK IC, MARQUES LS, NAGEL FM, LISBOA TC, *et al*. *Vitamin D deficiency is independently associated with mortality among critically ill patients*. Clinics. 2015;**70**(5):326-32.
18. BRAUN A, CHANG D, MAHADEVAPPA K, GIBBONS FK, LIU Y, GIOVANNUCCI E, *et al*. *Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill*. Critical care medicine. 2011;**39**(4):671.
19. HALILOGLU M, BILGILI B, HALILOGLU O, YAVUZ DG, CINEL I. *Vitamin D level is associated with mortality predictors in ventilator-associated pneumonia caused by Acinetobacter baumannii*. The Journal of Infection in Developing Countries. 2016;**10**(06):567-74.
20. AMREIN K, AMREIN S, HOLL A, WALTENSDORFER A, PIEBER T, DOBNIG H. *Vitamin D, parathyroid hormone and serum calcium levels and their association with hospital mortality in critically ill patients*. Critical Care. 2010;**14**(1):P589.
21. WEENINK J, OUDEMANS-VAN STRAATEN H, YAP H, SLAATS E, VAN DER VOORT P. *High prevalence of severe vitamin D deficiency in intensive care patients*. Critical Care. 2010;**14**(1):P588.
22. LEIS KS, MCNALLY JD, MONTGOMERY MR, SANKARAN K, KARUNANAYAKE C, ROSENBERG AM. *Vitamin D intake in young children with acute lower respiratory infection*. Translational pediatrics. 2012;**1**(1):6.
23. AMREIN K, ZAJIC P, SCHNEDL C, WALTENSDORFER A, FRUHWALD S, HOLL A, *et al*. *Vitamin D status and its association with season, hospital and sepsis mortality in critical illness*. Critical care (London, England). 2014:24;**18**(2):R47.
24. BRAUN AB, GIBBONS FK, LITONJUA AA, GIOVANNUCCI E, CHRISTOPHER KB. *Low serum 25-hydroxyvitamin D at critical care initiation is associated with increased mortality*. Critical care medicine. 2012;**40**(1):63-72.
25. ZHAO G, FORD ES, LI C, CROFT JB. *Serum 25-hydroxyvitamin D levels and all-cause and cardiovascular disease mortality among US adults with hypertension: the NHANES linked mortality study*. Journal of hypertension. 2012;**30**(2):284-9.
26. BRAUN AB, LITONJUA AA, MOROMIZATO T, GIBBONS FK, GIOVANNUCCI E, CHRISTOPHER KB. *Association of low serum 25-hydroxyvitamin D levels and acute kidney injury in the critically ill*. Critical care medicine. 2012;**40**(12):3170-9.
27. PADHI R, PANDA B, JAGATI S, PATRA SC. *Vitamin D status in adult critically ill patients in Eastern India: An observational retrospective study*. Lung India : official organ of Indian Chest Society. 2014;**31**(3):212-6.
28. JAIN A, PALTA S, SAROA R, PALTA A, SAMA S, GOMBAR S. *Sequential organ failure assessment scoring and prediction of patient's outcome in Intensive Care Unit of a tertiary care hospital*. Journal of anaesthesiology, clinical pharmacology. 2016;**32**(3):364.
29. JENG L, YAMSHCHIKOV AV, JUDD SE, BLUMBERG HM, MARTIN GS, ZIEGLER TR, *et al*. *Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis*. Journal of translational Medicine. 2009;**7**(1):28.
30. NAIR P, LEE P, REYNOLDS C, NGUYEN ND, MYBURGH J, EISMAN JA, *et al*. *Significant perturbation of vitamin D–parathyroid–calcium axis and adverse clinical outcomes in critically ill patients*. Intensive care medicine. 2013;**39**(2):267-74.
31. AYGENCEL G, TURKOGLU M, TUNCEL AF, CANDIR BA, BILDACI YD, PASAOGLU H. *Is vitamin D insufficiency associated with mortality of critically ill patients? Critical care research and practice*. 2013; http://dx.doi.org/10.1155/2013/856747.

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