JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Vitamin D level is associated with mortality predictors in ventilator-associated pneumonia caused by *Acinetobacter baumannii*

Murat Haliloglu[1], Beliz Bilgili[1], Ozlem Haliloglu[2], Dilek Gogas Yavuz[3], Ismail Cinel[1]

[1] *Department of Anesthesiology and Reanimation, Marmara University School of Medicine, Istanbul, Turkey*
[2] *Department of Endocrinology and Metabolism, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey*
[3] *Department of Endocrinology and Metabolism, Marmara University School of Medicine, Istanbul, Turkey*

Abstract

Introduction: Vitamin D plays a role in host defense and is known to be associated with mortality in patients in the intensive care unit (ICU). We aimed to evaluate the relationships between vitamin D levels and predictors of mortality in patients with ventilator-associated pneumonia (VAP) caused by extensively drug-resistant *Acinetobacter baumanii* (XDR *A. baumanii*).

Methodology: A retrospective single-center study was conducted in an 18-bed adult ICU of a teaching hospital, including all patients with VAP due to XDR *A. baumanii*. Levels of 25(OH)D, procalcitonin (PCT), C-reactive protein (CRP), n-terminal pro-BNP (NT-proBNP), as well as clinical scores (Sequential Organ Failure Assessment [SOFA], Acute Physiology And Chronic Health Evaluation [APACHE II], Clinical Pulmonary Infection Score [CPIS) were recorded.

Results: Forty-for patients were studied over six months. All patients had vitamin D deficiency. The 28-day mortality in patients with 25(OH)D levels ≤ 10 ng/mL was higher than in patients with 25(OH)D > 10ng/mL ($p = 0.001$). The fourth- and seventh-day SOFA scores ($p= 0.04$ and $p= 0.001$) and first- and fourth-day procalcitonin levels ($p = 0.03$ and $p = 0.004$) were higher in patients with 25(OH)D levels ≤ 10 ng/mL. The clinical scores (SOFA, CPIS, and CEPPIS) and biomarkers (NT-proBNP, PCT) were negatively correlated with 25(OH)D levels in all study groups.

Conclusions: Severe vitamin D deficiency was associated with adverse outcome in VAP due to XDR *A. baumanii*. Vitamin D levels may be a prognostic predictor of VAP. It is also important to evaluate the effect of rapid vitamin D replacement on mortality.

Key words: vitamin D deficiency; nutrition; ventilator-associated pneumonia; infection; *Acinetobacter baumanii*; mortality.

J Infect Dev Ctries 2016; 10(6):567-574. doi:10.3855/jidc.8206

(Received 03 February 2016 – Accepted 07 March 2016)

Introduction

Ventilator-associated pneumonia (VAP) is a nosocomial infection that develops 48 hours after intubation and mechanical ventilation [1]. It is a common and serious problem in the intensive care unit (ICU), with an estimated incidence of 10% to 25%, and the risk of VAP increases 1%–3% for each day of invasive mechanical ventilation [2]. VAP accounts for prolonged mechanical ventilation and length of stay, as well as poor outcomes [1]. Despite technological advances, the mortality rate for VAP ranges between 24% and 50% [1,3]. Studies aiming to find prognostic markers to quickly distinguish patients who will have unfavorable outcomes are ongoing [4,5]. Early identification of patients with poor prognosis may improve treatment strategies.

Recent studies reported that *Acinetobacter baumannii* has become an increasingly significant cause of VAP in ICUs, and the mortality rate can reach up to 84.3% [6,7]. This may be attributed to pathogens that are multidrug resistant (MDR) and extensively drug resistant (XDR) [8]. In our center, *A. baumanii* is the most common pathogen that causes VAP, and new XDR species have recently emerged. For this reason, it is crucial to investigate the prognostic factors related to VAP by XDR *A. baumanii*.

Vitamin D has well-known effects on bone metabolism as a hormone, but there are increasing data about its additional effects. One of these extra-musculoskeletal effects is on both the innate and adaptive immune systems. Vitamin D increases the production of cathelicidin and defensin and hence plays a role in the innate immune system [9]. In addition, it shows its effects on the adaptive immune system via vitamin D receptors on monocytes and T and B cells [9].

Vitamin D deficiency is very common worldwide and there are increasing data about hypovitaminosis D and increased susceptibility to infections [10-12]. Additionally, it was also documented that a relationship

between vitamin D deficiency and increased mortality in community-acquired pneumonia (CAP) and sepsis was found [13-16]. Despite the increasing number of studies about CAP, there are scarce data about VAP, and to our knowledge, there are no studies related to the effects of vitamin D on specific pathogens such as XDR *A. baumanii* in the literature.

Our single-center retrospective study was designed to investigate the relationships between vitamin D levels and mortality and known predictors of mortality in patients with VAP caused by XDR *A. baumannii*.

Methodology

Subjects and study design

This retrospective study recruited patients admitted to an 18-bed adult ICU of Marmara University Pendik Training and Research Hospital in Istanbul (41°N), from November 2014 to May 2015; a total of 50 adult patients with microbiologically-confirmed VAP caused by XDR *A. baumanii* were selected. Six patients whose 25-hydroxyvitamin D [25(OH)D] levels were not measured were excluded from the final analysis. After obtaining approval from the Marmara University Ethics Committee, the study was conducted in accordance with the Declaration of Helsinki including current revisions and Good Clinical Practice guidelines. Informed consent was not obtained from all patients due to the retrospective study design.

Data were obtained from medical charts and electronic records. For each patient, the following data were collected: age, sex, medical history, duration of mechanical ventilation, clinical scores (sequential organ failure assessment [SOFA], acute physiology and chronic health evaluation [APACHE II], clinical pulmonary infection score [CPIS]), laboratory and microbiologic data, and 28-day mortality.

The diagnosis of microbiologically confirmed VAP was made when a patient who had been intubated and mechanically ventilated for ≥ 48 hours developed a new or persistent lung infiltrate and the tracheal aspirate culture results were positive (count > 10^4 colony-forming units/mL) [17]. The day of VAP diagnosis was defined as day 1. XDR *A. baumanii* was defined as resistance to all standard antimicrobial agents except colistin or tigecycline [18]. Patients' progress was followed until the 28th day after the diagnosis of VAP, when they were categorized as survivors. Patients who died before the 28th day were non-survivors. Patients discharged from the ICU before the 28th day were also considered survivors.

Clinical scores

The APACHE scoring system appraises disease severity by quantifying 34 physiologic variables [19]. The SOFA score was designed as a tool for describing the severity of organ dysfunction, and serial assessments of the scores were associated with outcomes [20]. CPIS is a diagnostic scoring system that predicts VAP; patients were assumed to have VAP when the CPIS score was > 6 [21]. APACHE II was assessed on the first day of ICU admission and SOFA at day 1, day 4, and day 7 of diagnosis of VAP. CPIS was determined on day 1.

Biochemical parameters

Serum C-reactive protein (CRP) concentrations were measured using nephelometry (840 nm) with a BN II nephelometer (Siemens, Erlangen, Germany). Serum procalcitonin (PCT) and n-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations were measured using an electrochemiluminescence immunoassay (Roche Cobas e411; Roche Diagnostics, Indianapolis, USA). The 25(OH)D concentrations were measured using high-performance liquid chromatography (HPLC; Recipe Chemicals, Munich, Germany). Serum calcium concentrations were measured with an enzymatic colorimetric assay (Roche Diagnostics, Indianapolis, USA). Serum intact parathyroid hormone (PTH) was determined using an immunochemiluminescence assay (Modular Analytics E170; Roche Diagnostics, Mannheim, Germany).

Vitamin D deficiency was considered as 25(OH)D < 20 ng/mL, insufficiency as 25(OH)D = 20–29 ng/mL, and sufficiency as 25(OH)D ≥ 30 ng/mL in accordance with the guidelines of the Endocrine Society [22]. Additionally, 25(OH)D ≤ 10 ng/mL was defined as very severe vitamin D deficiency. Serum PCT, CRP, and NT-proBNP levels were evaluated every day in thr ICU but only day 1, day 4, and day 7 measurements were evaluated in this study. Serum 25(OH)D, calcium, and PTH values were evaluated routinely as part of the ICU care on the day the patients were admitted to the ICU.

Statistical analysis

R version 2.15.3 programme was used for statistical analysis. When evaluating study data, in addition to descriptive statistical methods (mean, median, standard deviation, Q1, Q3, frequency, ratio, minimum, maximum), student's t-test was performed to compare two groups of normally distributed variables and the Mann-Whitney U test was performed to compare two groups of non-normally distibuted variables in the evaluation of quantitative data. The Kruskal-Wallis test

was used to test the difference of non-normally distributed variables between more than two groups, with the Mann-Whitney U test as post-hoc analysis. Pearson's Chi-square test, Fisher-Freeman-Halton exact test, Fisher's exact test, Yates's continuity corrected Chi-square test, McNemar test, and sensitivity values were used to test the association between nominal variables. Wilcoxon's signed-rank test was used to assess the significance of the changes at different time points. Pearson's correlation analysis and Spearman's correlation analysis were used to evaluate the relationships of the variables. Significance level was evaluated at $p < 0.01$ and $p < 0.05$.

Results

There were 27 (61.3%) men and 17 (38.6%) women with a mean age of 54.6 ± 16.1 years. The most frequent cause of ICU admission was postoperative respiratory failure. Other causes were polytrauma, intracranial hemorrhage, and thrombotic stroke. The mean duration of mechanical ventilation before VAP onset was 14 days.

The baseline characteristics of the 44 patients and stratifications as survivors or non-survivors are given in Table 1. Patients with cardiovascular diseases ($p = 0.049$) or diabetes mellitus ($p = 0.039$) had higher 28-day mortality than did the others.

Table 1. Baseline characteristics of 44 patients who developed VAP from XDR *A. Baumanii.*

Variables	Survivors (n = 21)	Non-survivors (n = 23)	p
Age (years)*	50.57 ± 19.31	58.26 ± 20.18	0.205
Duration of MV before VAP$^{\beta}$	14 [7–17.5]	14 [8–20]	0.841
	n (%)	**n (%)**	
Sex			
Male	14 (51.9)	13 (48.1)	**0.704**
Female	7 (41.2)	10 (58.8)	
Cause of admission			
Postoperative	8 (53.3)	7 (46.7)	
Polytrauma	7 (63.6)	4 (36.4)	**0.502**
Intracranial hemorrhage	1 (20)	4 (80)	
Thrombotic stroke	2 (50)	2 (50)	
Others	3 (33.3)	6 (66.7)	
Comorbidities			
Cardiovascular disease	4 (25)	12 (75)	0.049
Chronic renal failure	3 (60)	2 (40)	0.658
Chronic lung diseases	3 (50)	3 (50)	0.999
Cerebrovascular diseases	2 (28.6)	5 (71.4)	0.416
Diabetes mellitus	3 (21.4)	11 (78.6)	0.039
Malignancy	4 (40)	6 (60)	0.416
Other	5 (71.4)	2 (28.6)	0.232

* Results are given as mean ± standard deviaton; $^{\beta}$ Results are given as median and [interquartile range]; VAP: ventilator-associated pneumonia; XDR: extensively drug-resistant; MV: mechanical ventilation.

Table 2. Evaluation of clinical scores and laboratory parameters.

		Alive (n = 21)	Exitus (n = 23)	p
SOFA*	Day 1	6.86 ± 2.73	9.09 ± 3.98	0.037
	Day 4	6.57 ± 2.52	9.74 ± 3.41	0.002
	Day 7	5.95 ± 2.73	9.20 ± 3.14	0.002
CRP$^{\beta}$	Day 1	115 [68.1–194]	116.4 [57–254]	0.925
	Day 4	110 [50.5–148.7]	143 [110–219]	0.025
	Day 7	77.9 [48.7–150]	116.7 [87.5–180]	0.105
Procalcitonin$^{\beta}$	Day 1	1.2 [0.3–4.2]	2.1 [0.5–6.3]	0.518
	Day 4	0.9 [0.2–9.6]	4.6 [1.9–15]	0.044
	Day 7	1.4 [0.3–5.1]	2.7 [0.8–5.4]	0.312
NT-ProBNP$^{\beta}$	Day 1	1,331 [403.6–6406]	5,536 [2,605–7,400]	0.072
	Day 4	1,395 [439–4560.5]	7,200 [4,100–15,250]	0.001
	Day 7	1,111 [271.8–3397.5]	8,765 [5,025–16,360]	< 0.001

* Results are given as mean ± standard deviation; $^{\beta}$ Results are given as median and [interquartile range]; SOFA: sequential organ failure assessment; CRP: C-reactive protein; NT-ProBNP: n-terminal pro-brain natriuretic peptide.

Clinical scores and laboratory parameters are shown in Table 2.

All patients involved in the study had vitamin D levels < 20 ng/mL. The median 25(OH)D levels of the survivors were significantly higher than that of the non-survivors (10 [8.2–11.9] and 3 [2-4.8], respectively; p < 0.001). The relationship between 25(OH)D levels and demographic parameters are shown in Table 3. There was no statistically significant difference between age and duration of mechanical ventilation and 25(OH)D levels. Diabetic patients had lower vitamin D levels than did non-diabetics (p = 0.001). Similarly, vitamin D levels were significantly lower in patients with cerebrovascular diseases (p = 0.035).

The correlations between 25(OH)D levels and biochemical parameters and clinical scores are presented in Table 4. There was a negative correlation found between vitamin D levels and CPIS scores (r: -0.335, p = 0.026); day 4 (r: -0.428, p = 0.006) and day 7 (r: -0.519, p = 0.001) SOFA scores; day 4 (r: -0.376,

Table 3. The relationship between 25(OH)D levels and demographic parameters.

		25(OH)D	p
Sex*	Female	5.77 ± 2.67	0.090
	Male	7.73 ± 4.80	
Admission$^{\beta}$	Postoperative	6.8 [3.9–10.9]	0.361
	Polytrauma	7.8 [3–10.7]	
	Intracranial hemorrhage	5 [3–6.8]	
	Thrombotic stroke	7.6 [5.9–8.8]	
Comorbidities$^{\beta}$	None	9.6 [5–10.7]	0.143
	Present	5.1 [3–9.2]	
Malignancy$^{\beta}$	None	6.7 [3–10]	0.945
	Present	5.1 [3.8–9.2]	
DM$^{\beta}$	None	8.2 [4.3–10.7]	0.001
	Present	3 [3–5.6]	
COPD$^{\beta}$	None	6.2 [3–10]	0.881
	Present	5.8 [3–8.5]	
Cerebrovascular disease$^{\beta}$	None	6.8 [3.8–10]	0.035
	Present	3 [3–6.8]	
Cardiovascular disease*	None	7.81 ± 4.09	0.081
	Present	5.52 ± 4.06	
Chronic renal disease$^{\beta}$	None	6.6 [3–10]	0.494
	Present	5.6 [4.9–12.9]	

*Data are expressed as mean ± standard deviation; $^{\beta}$ Data are expressed as median [interquartile range]; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease.

Table 4. The correlations between 25(OH)D levels and biochemical parameters and clinical scores.

		25(OH)D	
		r	p
APACHE II		-0.073	0.639
CPIS		-0.335	0.026
SOFA	Day 1	-0.265	0.082
	Day 4	-0.428	0.006
	Day 7	-0.519	0.001
CRP (mg/L)	Day 1	-0.082	0.595
	Day 4	-0.303	0.057
	Day 7	-0.222	0.192
Procalcitonin (ng/mL)	Day 1	-0.151	0.328
	Day 4	-0.376	0.017
	Day 7	-0.161	0.349
ProBNP (pg/mL)	Day 1	-0.301	0.047
	Day 4	-0.522	0.001
	Day 7	-0.505	0.002
Parathormone (pg/mL)		0.058	0.711
Calcium (mg/dL)		0.149	0.334

APACHE II: acute physiology and chronic health evaluation; CPIS: clinical pulmonary infection score; CRP: C-reactive protein; proBNP: pro-brain natriuretic peptide; SOFA: sequential organ failure assessment.

p= 0.017) procalcitonin levels; and day 1 (r: -0.301, p= 0.047), day 4 (r: -0.522, p = 0.001), and day 7 (r: -0.505, p = 0.002) NT-proBNP levels.

Table 5 demonstrates clinical and biochemical prognostic parameters according to stratification of vitamin D status. When patients with very severe vitamin D deficiency were compared with those with 25(OH)D > 10 ng/mL, day 4 (p = 0.04) and day 7 (p = 0.001) SOFA scores and day 1 (p = 0.036) and day 4 (p = 0.004) procalcitonin levels were significantly higher in patients with 25(OH)D ≤ 10 ng/mL. Vitamin D levels of non-survivors were significantly lower than those of survivors (p = 0.001).

Discussion

In this study, our data showed that hypovitaminosis D was very prevalent in patients with VAP caused by XDR *A. baumanii*, and very severe vitamin D deficiency was related to poor prognosis. We also demonstrated that vitamin D concentrations at admission to the ICU were an important predictor of 28-day mortality, and as such, it could function as an adjunctive parameter to clinical scores and inflammatory biomarkers.

There are very few studies in the literature about the relationship of vitamin D status with *A. baumanii* infections. Turkoglu *el al*. reviewed vitamin D deficiency and the development of *A. baumanii* infections in critically ill patients and showed that vitamin D deficiency was an independent risk factor of *A. baumanii* infections [23]. Consistent with their study, we also found that the vitamin D levels of patients in both survivors and non-survivors were within deficient status (< 20 ng/mL). Additionally, the vitamin D status of non-survivors was lower than that in the survivors. The high prevalence of vitamin D deficiency found in patients with VAP was comparable to that reported in previous studies [23-25].

It has been demonstrated that vitamin D had immunomodulatory activities [26,27]. In cases of hypovitaminosis D, these immunomodulatory effects are disruptive, and a tendency to infections occurs. One of the most frequently studied infections with respect to vitamin D deficiency is CAP. Increased mortality in CAP was found to be related to vitamin D deficiency [13,14]. There are also growing data about vitamin D status on the prediction of outcomes in CAP, sepsis, and critically ill patients [24,25,28]. Nonetheless, to our knowledge, no studies have specifically related vitamin D status to patients with VAP. In this study, we evaluated a more specific subgroup of patients with VAP who had microbiologically documented XDR *A. baumanii* infections. The reason for choosing this subgroup was that XDR *A. baumanii* was the most prevalent and mortal infectious agent in our institute. Consistent with the literature, we also found that vitamin D deficiency could be a predictor of mortality in patients with VAP caused by XDR *A. baumanii*.

The prognostic performance of PCT, CRP, SOFA, and APACHE II scores were previously evaluated, which produced variable results [5,29]. The prognostic value of serum 25(OH)D was not evaluated previously in VAP associated with XDR *A. baumannii*. The comparision of the prognostic value of 25(OH)D with the predictive ability of clinical scores and biomarkers was a novel aspect of our study. Vincent *et al*. showed that multiple organ dysfunction and high SOFA scores for any individual organ were associated with increased

Table 5. Clinical and biochemical prognostic parameters according to stratification of vitamin D status.

		25(OH)D ≤ 10 ng/mL (n = 35)	25(OH)D > 10 ng/mL (n = 8)	P
APACHE II*		18.91 ± 6.00	19.88 ± 8.48	0.708
SOFA*	Day 1	8.37 ± 3.75	6.75 ± 2.71	0.256
	Day 4	8.68 ± 3.40	6.00 ± 2.39	0.044
	Day 7	8.33 ± 2.92	4.13 ± 2.47	0.001
CRP (mg/L)β	Day 1	144 [59.1–210]	93.6 [53.5–158.5]	0.530
	Day 4	129.8 [105–185]	63.6 [31.7–154]	0.123
	Day 7	97.9 [75.6–176]	76.4 [43.9– 161.5]	0.406
Procalcitonin (ng/mL) β	Day 1	2.3 [0.5–6.3]	0.7 [0.2–1.2]	0.036
	Day 4	3.9 [0.9–11.9]	0.4 [0.2–0.7]	0.004
	Day 7	1.9 [0.7–5.4]	0.3 [0.2–3.4]	0.166
Parathormon (pg/mL) β		60.2 [36–80]	51.6 [39.1–92]	0.530
Calcium (mg/dL)*		9.09 ± 0.52	9.20 ± 0.65	0.596
		n (%)	**n (%)**	
28-day mortality	Survivors	12 (34.3)	8 (100)	0.001
	Non-survivors	23 (65.7)	0 (0)	

* Data are expressed as mean ± standard deviation; β Data are expressed as median [interquartile range]; APACHE II: acute physiology and chronic health evaluation; CRP: C-reactive protein; SOFA: sequential organ failure assessment.

mortality [30]. SOFA scores in our study were significantly lower in survivors on days 1, 4, and 7 compared with the scores of non-survivors. There was also a negative correlation found between vitamin D levels and day 4 and day 7 SOFA scores.

A body of evidence showed that PCT, the pre-hormone of calcitonin, was a predictor of severity in sepsis, antimicrobial efficiency, and hospital mortality [31,32]. The level of PCT correlates with the severity of pneumonia [33,34]. Also, one small study found that procalcitonin levels increased over time in non-survivors but decreased in survivors [34]. Luyt *et al*. studied the prognostic value of PCT kinetics in patients with VAP and concluded that elevated serum levels of PCT on days 1, 3, and 7 of VAP were strong predictors of unfavorable outcomes [35]. CRP, an acute-phase protein produced by the liver, appears to be less sensitive than procalcitonin for the detection of bacterial pneumonia [34]. In our study, we showed a significant relationship between PCT and vitamin D levels but no correlation between 25(OH)D concentrations and serum CRP levels, consistent with the literature.

In terms of CPIS and cause of admission, the two groups were comparable. Similary to what we found in our study, Seligman *et al*. found that CPIS and the causes of admission were not significantly pronounced in both groups [36]. APACHE II scores on admission were also similar between survivors and non-survivors. In addition, we found no significant correlations between serum 25(OH)D and APACHE II and CPIS scores.

NT-proBNP has recently been used to predict sepsis outcomes. A recent meta-analysis suggested that elevated NT-proBNP levels could be a predictor of mortality in patients with sepsis [37]. Another study demonstrated that elevated serum NT-proBNP was an independent predictor for poor ICU outcomes in the presence of clinical severity scores [38]. In our study, the NT-proBNP levels in the non-survival group were higher than those in the survival group on days 4 and 7. Additionally, there was a negative correlation found between vitamin D levels and day 1, day 4, and day 7 NT-proBNP levels.

Underlying disease of patients has also been related with death as much as the infection sites and antibiotic susceptibility of pathogens [39]. Diabetes mellitus and cardiovascular diseases were negatively associated with mortality in our study. These susceptible populations may be considered for special follow-up of response to treatment.

There were some limitations to our study. First, the patient population was small and no control group was included. Second, this was not a prospectively designed study, so causal relationship could not be established. These limitations reduce the strength of the conclusions; thus, the results should be verified by larger scale, prospectively designed studies. Nevertheless, to our knowledge, this is the first study to investigate the clinical and microbiologic outcomes of patients with VAP caused by XDR *A. baumanii*, one of the most frequent and mortal VAP pathogens, and extremely low 25 (OH)D levels. Further studies are needed to address the benefits of rapid vitamin D replacement in this population.

Conclusions

Vitamin D deficiency is highly prevalent in patients with VAP caused by XDR *A. baumanii*. We confirmed that severe 25(OH)D deficiency was associated with adverse outcomes in patients with VAP associated with XDR *A. baumanii*. Vitamin D levels may be a significant predictor of 28-day mortality. It is also important to evaluate the effects of rapid vitamin D replacement on mortality.

Acknowledgements

The English in this document was checked by David Chapman, who is a professional editor and native English speaker.

References

1. American Thoracic Society; Infectious Diseases Society of America (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171: 388-416.
2. Chastre J, Fagon, JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165: 867-903.
3. Melsen WG, Rovers MM, Koeman M, Bonten MJ (2011) Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. Crit Care Med 39: 2736-2742.
4. Jiao J, Wang M, Zhang J, Shen K, Liao X, Zhou X (2015) Procalcitonin as a diagnostic marker of ventilator-associated pneumonia in cardiac surgery patients. Exp Ther Med 9: 1051-1057.
5. Seligman R, Seligman BG, Teixeira PJ (2011) Comparing the accuracy of predictors of mortality in ventilator-associated pneumonia. J Bras Pneumol 37: 495-503.
6. Chaari A, Mnif B, Bahloul M, Mahjoubi F, Chtara K, Turki O, Gharbi N, Chelly H, Hammami A, Bouaziz M (2013) *Acinetobacter baumannii* ventilator-associated pneumonia: epidemiology, clinical characteristics, and prognosis factors. Int J Infect Dis 17: e1225-e1228.

7. Ozgur ES, Horasan ES, Karaca K, Ersoz G, Nayci Atis S, Kaya A (2014) Ventilator-associated pneumonia due to extensive drug-resistant *Acinetobacter baumannii*: risk factors, clinical features, and outcomes. Am J Infect Control 42: 206-208.
8. Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, So TM, Yasin RM, Hsueh PR, Carlos CC, Hsu LY, Buntaran L, Lalitha MK, Kim MJ, Choi JY, Kim SI, Ko KS, Kang CI, Peck KR; Asian Network for Surveillance of Resistant Pathogens Study Group (2011) High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. Am J Respir Crit Care Med 184: 1409-1417.
9. Aranow C (2011) Vitamin D and the immune system. J Investig Med 59: 881-886.
10. Ginde AA, Mansbach JM, Camargo CA Jr (2009) Association between serum 25 hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 169: 384-390.
11. Berry DJ, Hesketh K, Power C, Hypponen E (2011) Vitamin D status has a linear association with seasonal infections and lung function in British adults. Br J Nutr 106: 1433-1440.
12. Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML (2010) Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. PLoS One 5: e11088.
13. Leow L, Simpson T, Cursons R, Karalus N, Hancox RJ (2011) Vitamin D, innate immunity and outcomes in community acquired pneumonia. Respirology 16: 611-616.
14. Remmelts HH, van de Garde EM, Meijvis SC, Peelen EL, Damoiseaux JG, Grutters JC, Biesma DH, Bos WJ, Rijkers GT (2012) Addition of vitamin D status to prognostic scores improves the prediction of outcome in community-acquired pneumonia. Clin Infect Dis 55: 1488-1494.
15. de Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A (2014) Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Crit Care 18: 660.
16. Moromizato T, Litonjua AA, Braun AB, Gibbons FK, Giovannucci E, Christopher KB (2014) Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill. Crit Care Med 42: 97-107.
17. Chastre J, Fagon JY, Bornet-Lecso M, Calvat S, Dombret MC, al Khani R, Basset F, Gibert C (1995) Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 152: 231-240.
18. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL (2012) Multidrug resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18: 268-281.
19. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE (1981) APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med 9: 591-597.
20. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL (2001) Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 286: 1754-1758.
21. Zagli G, Cozzolino M, Terreni A, Biagioli T, Caldini AL, Peris A (2014) Diagnosis of ventilator-associated pneumonia: a pilot, exploratory analysis of a new score based on procalcitonin and chest echography. Chest 146: 1578-1585.
22. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96: 1911-1930.
23. Turkoglu M, Aygencel G, Dizbay M, Tuncel AF, Arslan Candir B, Deligoz Bildaci Y, Pasaoglu H (2013) Is vitamin D deficiency associated with development of *Acinetobacter baumannii* infections in critically ill patients? J Crit Care 28: 735-740.
24. Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y, Giovannucci E, Christopher KB (2011) Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. Crit Care Med 39: 671-677.
25. Braun AB, Gibbons FK, Litonjua AA, Giovannucci E, Christopher KB (2012) Low serum 25-hydroxyvitamin D at critical care initiation is associated with increased mortality. Crit Care Med 40: 63-72.
26. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G (2016) Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev 96: 365-408.
27. Bikle D (2009) Nonclassic actions of vitamin D. J Clin Endocrinol Metab 94: 26-34.
28. Jeng L, Yamshchikov AV, Judd SE, Blumberg HM, Martin GS, Ziegler TR, Tangpricha V (2009) Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. J Transl Med 7: 28.
29. Seligman R, Papassotiriou J, Morgenthaler NG, Meisner M, Teixeira PJ (2008) Copeptin, a novel prognostic biomarker in ventilator-associated pneumonia. Crit Care 12: R11.
30. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 26: 1793-1800.
31. Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, Zimmerli W, Ritz R (2000) Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med 28: 977-983.
32. Pettila V, Hynninen M, Takkunen O, Kuusela P, Valtonen M (2002) Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive Care Med 28: 1220-1225.
33. Masia M, Gutierrez F, Shum C, Padilla S, Navarro JC, Flores E, Hernandez, I (2005) Usefulness of procalcitonin levels in community-acquired pneumonia according to the patients outcome research team pneumonia severity index. Chest 128: 2223-2229.
34. Boussekey N, Leroy O, Alfandari S, Devos P, Georges H, Guery B (2006) Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. Intensive Care Med 32: 469-472.
35. Luyt CE, Guerin V, Combes A, Trouillet JL, Ayed SB, Bernard M, Gibert C, Chastre J (2005) Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. Am J Respir Crit Care Med 171: 48-53.
36. Seligman R, Meisner M, Lisboa TC, Hertz FT, Filippin TB, Fachel JM, Teixeira PJ (2006) Decreases in procalcitonin and

C-reactive protein are strong predictors of survival in ventilator-associated pneumonia. Crit Care 10: R125.
37. Wang F, Wu Y, Tang L, Zhu W, Chen F, Xu T, Bo L, Li J, Deng X (2012) Brain natriuretic peptide for prediction of mortality in patients with sepsis: a systematic review and meta-analysis. Crit Care 16: R74.
38. Kotanidou A, Karsaliakos P, Tzanela M, Mavrou I, Kopterides P, Papadomichelakis E, Theodorakopoulou M, Botoula E, Tsangaris I, Lignos M, Ikonomidis I, Ilias I, Armaganidis A, Orfanos SE, Dimopoulou I (2009) Prognostic importance of increased plasma amino-terminal pro-brain natriuretic peptide levels in a large noncardiac, general intensive care unit population. Shock 31: 342-347.
39. Ozdemir H, Kendirli T, Ergun H, Ciftci E, Tapisiz A, Guriz H, Aysev D, Ince E, Dogru U (2011) Nosocomial infections due to *Acinetobacter baumannii* in a pediatric intensive care unit in Turkey. Turk J Pediatr 53: 255-260.

Corresponding author

Dr. Murat Haliloglu
Marmara University School of Medicine
Department of Anestesiology and Reanimation Fevzi Çakmak Mah
Mimar Sinan Cd. No: 41, Üst Kaynarca
Pendik, Istanbul, Turkey
Phone: +090 (533) 4746808
Fax: +90 (216) 657 0606
Email: mrt.haliloglu@gmail.com

Conflict of interests: No conflict of interests is declared.