Original Article
Eurasian Journal of Critical Care

Relationship Between Vitamin D Level As An Independent Risk Factor and One-Year Mortality in Patients With Hospital-Acquired Pneumonia Followed Up in Intensive Care Unit

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Abstract

Background: Hospital-acquired pneumonia (HAP) is an important cause of mortality and morbidity among hospital-acquired infections. Vitamin D (25[OH] D) plays a role as an anti-inflammatory, immunomodulatory, and antimicrobial agent in infections. There are limited studies on the long-term mortality prediction of 25(OH)D deficiency in HAP and the findings are controversial. In this study, our primary aim was to investigate the role of 25(OH)D level measured during hospital admission as an independent risk factor for one-year mortality in HAP patients requiring intensive care.

Materials and Methods: The retrospective study included patients that were diagnosed with HAP and admitted to the intensive care unit (ICU) between 2014 and 2018. Relationship between pretreatment 25(OH)D level and one-year independent mortality was evaluated. Vitamin D deficiency was defined as a 25(OH)D level of <30 ng/ml. Patients were divided into two groups based on vitamin D level: (i) <20 ng/ml and (ii) >20 ng/ml.

Results: The study included 57 patients comprising 36 (63.2%) men and 21 (36.8%) women with a mean age of 75 years. One-year independent mortality occurred in 21 (36.8%) patients. Mean length of ICU stay was 16 days. Mean 25(OH)D level was 9.53 ng/ml, which was <20 ng/ml in 47 (82.5%) and >20 ng/ml in 10 (17.5%) patients. No significant relationship was found between 25(OH)D level and one-year independent mortality and the length of ICU stay (p=0.477 and p=0.941, respectively). Similarly, no significant relationship was found between 25(OH)D level and APACHE II, age, length of ICU stay, and one-year independent mortality (p=0.621, p=0.933, p=0.410, and p=0.933, respectively).

Conclusion: The study included 57 patients comprising 36 (63.2%) men and 21 (36.8%) women with a mean age of 75 years. One-year independent mortality occurred in 21 (36.8%) patients. Mean length of ICU stay was 16 days. Mean 25(OH)D level was 9.53 ng/ml, which was <20 ng/ml in 47 (82.5%) and >20 ng/ml in 10 (17.5%) patients. No significant relationship was found between 25(OH)D level and one-year independent mortality and the length of ICU stay (p=0.477 and p=0.941, respectively). Similarly, no significant relationship was found between 25(OH)D level and APACHE II, age, length of ICU stay, and one-year independent mortality (p=0.621, p=0.933, p=0.410, and p=0.933, respectively).

Key words: Hospital-acquired pneumonia, mortality, 25(OH)D, intensive care

Introduction

Vitamin D plays a role as a biomarker for cell proliferation and differentiation, hormone secretion, immune function regulation, and innate and acquired immune system. Vitamin D has also been shown to have inhibitory properties in T and B lymphocyte differentiation and in the acquired immune system. It transforms into 25 hydroxyvitamin D (25 OH D) in the skin, liver, and kidney and can be used to determine its pool and level since its half-life is two to three weeks.[1-3] Although there is no consensus in the literature regarding its optimal level, vitamin D deficiency is defined as a serum level of <20 ng/ml and vitamin D insufficiency is defined as level of 20-30 ng/ml. In recent studies, vitamin D deficiency has been shown to play a role in mortality associated with diabetes, hypertension, and inflammation-based diseases.[4]

Hospital-acquired pneumonia (HAP) is a pneumonia that develops 48 hours after hospital admission or discharge. HAP ranks second among all hospital-acquired infections worldwide. Moreover, it is an important cause of mortality and morbidity in patients followed up in intensive care unit (ICU).[5-7] Studies investigating community-acquired pneumonia (CAP) have shown that vitamin D plays has important anti-inflammatory, immunomodulatory, and antimicrobial properties. Additionally, it has been suggested that vitamin D deficiency in pneumonia patients is mostly caused by the deterioration of the oxidant/antioxidant balance. Therefore, it is important to detect and replace vitamin D levels during hospital admission. On the other hand, studies conducted on vitamin D level have shown that the risk of lower respiratory tract infection increases at 25(OH)D levels of 30-38 ng/ml.[1,8,9] In a study conducted on critically ill patients followed in ICU, vitamin D deficiency was found to be an independent risk factor for 30- and 90-day and 1-year mortality.[10,11] There is a limited number of studies on the relationship between vitamin D deficiency and long-term mortality in HAP and also there is no consensus regarding this relationship.[12] In the present study, our primary aim was to investigate the

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role of 25(OH)D level measured during hospital admission as an independent risk factor for one-year mortality in HAP patients requiring ICU care.

Materials and Methods

The retrospective study included patients who were diagnosed with HAP and admitted to ICU between 2014 and 2018. After obtaining an ethics committee approval (Date: June 18, 2020; No: 678), ICU observation charts, patient histories, and chest X-ray images were reviewed for each patient. Inclusion criteria were as follows: a diagnosis of HAP, admission to ICU according to the guidelines of the Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS), and one-year follow-up for independent mortality.[5-7] Additionally, patients whose HAP treatment was initiated after ICU admission, whose vitamin D levels were measured within the first hour of ICU admission, and those who were detected with vitamin D deficiency and received vitamin D replacement were included in the study.[4] Exclusion criteria were as follows: pregnancy, age below 18 years, prior vitamin D, calcium, and thyroid hormone replacement, a history of total thyroidectomy and parathyroidectomy, active malignancy, active infection other than HAP, and connective tissue disease (Table 1). Vitamin D level was studied with the immunoassay method using a Siemens ADVIA Centaur XPT Immunoassay System. Vitamin D deficiency was defined as a 25(OH)D level of <30 ng/ml. Patients were divided into two groups based on vitamin D level: (i) <20 ng/ml and (ii) >20 ng/ml.

Table 1: Flowchart of the study

Patients admitted to ICU during the study period (n=110)
Patients excluded due to exclusion criteria (n=3)
Patients with incomplete medical records (n=41)
Patients included in the study (n=57)

Statistical Analysis

Data were analyzed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptives were expressed as frequencies (n), percentages (%), median, and minimum-maximum values. Normal distribution of variables was assessed using Shapiro-Wilk test. Both dependent and independent variables with nonnormal distribution were compared using Chi-square test and Wilcoxon's signed-rank test. Continuous variables were compared using Student's t-test and Mann-Whitney U test. A p value of <0.05 was considered significant.

Results

The study included 57 patients comprising 36 (63.2%) men and 21 (36.8%) women with a mean age of 75 years. One-year independent mortality occurred in 21 (36.8%) patients. Mean 25(OH)D level was 9.53 ng/ml. Mean Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were 26 and 5, respectively. Table 2 presents demographic and clinical characteristics of the patients.

Table 2: Demographic and clinical characteristics

Variables	**All patients (N=57)**	**Mortality**		
	Median(Min-Max)	**No (N=36)** **Median (Min-Max)**	**Yes (N=21)** **Median (Min-Max)**	***P***
Age (years)	75 [20-92]	76.5 [20-92]	70 [48-90]	**0.011**
25(OH)D	9.53 [3.20-48.40]	10.20 [3.20-48.40]	8.54 [5.36-48.05]	0.477
SOFA	5 [2-18]	4 [2-12]	8 [3-18]	<0.001
APACHE II	26 [15-54]	26.5[15-42]	25 [16-54]	0.974
Variables	**All patients (N=57)** **N (%)**	**No (N=36)** **N (%)**	**Yes (N=21)** **N (%)**	***p***
Gender (male/female)	36 (63.2) / 21 (36.8)	23 (63.8) / 13 (36.2)	13 (61.9) / 8 (38.1)	0.882
Comorbidity	51 (89.5)	34 (94.4)	17 (81.0)	0.113
CAD	20 (35.1)	14 (38.9)	6 (28.6)	0.435
HT	24 (42.1)	18 (50.0)	6 (28.6)	0.117
DM	10 (17.5)	6 (16.7)	4 (19.0)	0.821
COPD	44 (77.2)	31 (86.1)	13 (61.9)	**0.037**
CKF	12 (21.1)	8 (22.2)	4 (19.0)	0.779
CHD	2 (40.4)	21 (58.3)	2 (9.5)	**<0.001**
Neurological disease	17 (29.8)	12 (33.3)	5 (23.8)	0.452
ICU stay (days)	16 [1-96]	17 [3-96]	15 [1-48]	0.941

APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CAD: Coronary artery disease, CHD: Coronary heart disease, HT: Hypertension, CKD: Chronic kidney disease, 25(OH)D: 25 25 hydroxyvitamin D, ICU: Intensive care unit

Table 3 presents the microbiological and radiological characteristics assessed at ICU admission. The type of microbiological culture samples established no significant relationship with radiological findings and one-year independent mortality (p=0.064 and p=0.355, respectively).

As an independent risk factor for one-year mortality, 25(OH)D level was found to be low (<30 ng/ml) in 18 (34.6%) and normal (>30 ng/ml) in 3% (60.0%) patients that died during the study.

Table 3 shows the relationship between 25(OH)D levels and demographic and clinical characteristics. No significant relationship was found between 25(OH)D level and one-year independent mortality and the length of ICU stay (p=0.477 and p=0.941, respectively). On the other hand, 25(OH)D level was found to be <20 ng/ml in 47 (82.5%) and >20 ng/ml in 10 (17.5%) patients. No significant relationship was found between 25(OH)D level and APACHE II, age, length of ICU stay, and one-year independent mortality (p=0.621, p=0.933, p=0.410, and p=0.933, respectively) (Table 4).

Discussion

The results indicated no significant relationship between vitamin D supplementation and one-year independent mortality and the length of ICU stay in HAP patients requiring ICU care.

Vitamin D is a steroid hormone that is vital for lung and bone health.[13] In infections, it decreases the production of inflammatory proteins with no elevation in viral replication in tracheobronchial cells.[14] Studies have shown that vitamin D receptors are available in various immune cells such as neutrophils, macrophages, and dendritic cells. It has also been shown that the secretion of proinflammatory cells such as interleukin-1 (IL-1), IL-6, IL-8, and IL-12, which occur with vitamin D replacement in the presence of inflammation, decreases in individuals with vitamin D deficiency. Based on this hypothesis, it is believed that vitamin D has immunoregulatory and immunomodulatory properties.[15] In recent years, there have been numerous studies conducted on the effect of vitamin D deficiency on the course of the disease, particularly in CAP, while studie evaluating HAP are relatively fewer. A study by Grant et al. [16] found that vitamin D replacement produced antimicrobial peptides and decreased the prevalence of pneumonia caused by influenza virus infection by reducing the production of proinflammatory cytokines. A randomized double-blind placebo-controlled study evaluated 46 ventilator-associated patients and reported that procalcitonin levels decreased significantly after vitamin D replacement in patients with vitamin D deficiency.[15] A prospective observational cohort study by Kempker et al.[17] evaluated vitamin D levels of 314 patients followed up in ICU and suggested that vitamin D deficiency predisposed patients to develop HAP. In our study, we evaluated 25(OH)

Table 3: Microbiological and radiological characteristics

Variables		N	%
Microbiological sample type	Sputum	23	52.6
	Endotracheal aspirate	30	40.4
	Blood	4	7.0
	Total	57	100
Microbiological culture growth	Pseudomonas Aerugionosa	13	22.8
	Acinetobacter Baumannii	34	59.6
	Acinetobacter Baumannii + Klebsiella Pneumoniae	9	15.8
	Acinetobacter Baumannii + Pseudomonas Aeruginosa	1	1
	Total	57	100
Chest X-ray infiltration	Consolidation	19	33.3
	Consolidation + ground glass opacity	24	42.1
	Ground glass opacity	6	10.5
	Consolidation + parapneumonic effusion	8	14.0
	Total	57	100

Table 4: Relationship between 25(OH)D levels and demographic and clinical characteristics

Variables	**All patients (N=57) Median (Min-Max)**	**Group 1 (N=47) Median (Min-Max)**	**Group 2 (N=10) Median (Min-Max)**	*p*
Age (years)	75 [20-92]	78 [61-82]	74 [20-92]	0.933
APACHE II	26 [15-54]	25 [20-39]	27 [15-54]	0.621
ICU stay (days)	18. 5 [4-96]	19 [4-96]	15.5 [5-33]	0.410
Variables	**All patients (N=57) N (%)**	**Group 1 (N=47) N (%)**	**Group 2 (N=10) N (%)**	***p***
One-year mortality	2136.8)	17(36.2)	4	0.933

ICU: Intensive care unit, Group 1: Vitamin D level <20 ng/ml, Group 2: Vitamin D level >20 ng/ml, APACHE II: Acute Physiology and Chronic Health Evaluation II

D levels in HAP patients with a high APACHE II score whose treatment was initiated in ICU. A control group could not be taken due to the retrospective nature of the study. Most of the studies in the literature have evaluated nonspecific hospital-acquired infections in medical ICUs and our study is one of the limited number of studies conducted in HAP patients.

In recent years, studies conducted on different diseases in the general population, different vitamin D deficiency rates have been reported with regard to the variation in ethnic origins, underlying diseases, genders, and seasonal characteristics.[14,18,19] In our study, the rate of additional diseases was 89.5% and additional diseases that may affect vitamin D level could not be standardized due to the retrospective nature of our study. The reference range to be used in the definition of vitamin D deficiency in the evaluation of immunological function remains unclear due to the lack of randomized controlled studies on the optimal dose for the treatment of deficiency.[12] Moreover, the optimal dose to be used in replacement, particularly the one that predisposes patients to bacterial and viral infections, has not been defined.[13] A study evaluated 4257 hospitalized adult patients and reported that the vitamin D level was below 50 nmol/L in 50% of the patients.[20] A retrospective study evaluated critically elderly patients followed up in ICU and found vitamin D deficiency in all (100%) patients.[19] Literature indicates that the cutoff value to be used in the definition of vitamin D deficiency and in the recommended optimal level to be achieved with replacement therapy remain uncertain.[21] In the majority of studies conducted in recent years, vitamin D deficiency has been defined as a 25(OH)D level of <30 ng/ml.[22] The present study evaluated ICU patients with a high APACHE II score and variable intra- and extra-vascular fluid volume due to sepsis. A previous study evaluated patients with sepsis followed up in ICU and reported that the fluid volume changed the level of vitamin D-binding protein by 6-13%.[21] Accordingly, the 25(OH)D levels in our study could be considered lower or higher than those reported in the literature since the hemodynamic status of the patients and the treatments administered could not be standardized and the study had a retrospective nature. Despite all these factors, the 25(OH)D deficiency rate in our patients was 91.2%, which was consistent with the rates reported by the studies conducted with ICU patients.[2,12] However, no statistical cut off value could be determined for 25(OH)D level since the sample size was relatively smaller and no control group of patients followed up in chest diseases clinic was included in the study. On the other hand, in line with the literature, vitamin D level was categorized as <20 ng/ml and >20 ng/ml.[4]

The relationship between 25(OH)D deficiency as a long-term independent risk factor and mortality remains unclear.[12] Graedel et al.[20] evaluated different disease groups and found prolonged hospitalization and increased 30-day in-hospital mortality in patients with 25(OH)D deficiency. In another study conducted in ICU patients, vitamin D deficiency was found to be an independent risk factor for 30- and 90-day and 1-year mortality.[10,11] Mrioliaee et al.[15] evaluated the effect of vitamin D supplementation in patients with ventilator-associated pneumonia and found that the decreased mortality rate achieved with replacement therapy in patients with vitamin D deficiency was independent of the type of microorganism. A study by Amrein et al.[23] evaluated critically ill patients followed up in ICU and found that the length of hospital stay and the rates of in-hospital and six-month mortality did not decrease after the replacement therapy in patients with vitamin D deficiency. Similarly, in our study, no significant relationship was found between 25(OH) D deficiency and one-year independent mortality and the length of ICU stay. To our knowledge, there are few studies in the literature specifically evaluating the relationship between pretreatment 25(OH)D deficiency and long-term independent mortality in HAP patients requiring ICU care, and their findings are controversial.[10,12,23] Nonetheless, our study had several limitations. First, it was not an observational study and was conducted retrospectively with a small number of patients. Second, vitamin D levels were not evaluated according to vitamin D-binding protein levels, which are likely to be affected by ICU care. Third, in patients who received replacement therapy due to vitamin D deficiency, the replacement therapy was not followed up after ICU discharge. Finally, vitamin D level was assessed with a single measurement.

Conclusion

We consider that multicenter, double-blind randomized controlled studies are needed to substantiate the definition of vitamin D deficiency and the optimal vitamin D level to be achieved with replacement therapy in order to evaluate the effect of the therapy on the course of the disease and long-term independent mortality in HAP patients followed up in ICU.

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