ORIGINAL ARTICLE

The prognostic value of vitamin D level for in-hospital mortality in patients with acute pulmonary embolism

Akut pulmoner emboli hastalarında D vitamini değerlerinin hastane içi mortaliteyi öngörme değeri

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ABSTRACT

Objective: The aim of this study was to investigate the prognostic value of the serum vitamin D (Vit-D) level on admission in patients with acute pulmonary embolism (APE) to determine in-hospital mortality.

Methods: Ninety-nine patients who were diagnosed with APE between January 2015 and January 2018 and had a record of an admission serum Vit-D level were enrolled in the study. The serum Vit-D level was measured using an immune-based assay in all cases. The primary outcome of the study was in-hospital all-cause mortality.

Results: The study population was divided into 2 groups according to the median value of serum Vit-D level: Vit-D level ≤7.36 ng/mL in 49 patients and Vit-D level >7.36 ng/mL in 50 patients. The patients with a serum Vit-D level ≤7.36 ng/mL had a higher of incidence of in-hospital death compared with those whose serum Vit-D level was >7.36 ng/mL (6 [12.2%] vs. 1 [2%]; p=0.048). In Cox regression analysis, the serum Vit-D level (Hazard ratio: 0.82, 95% confidence interval: 0.68-0.98; p=0.043) was found to be independently associated with in-hospital mortality. The optimal value of serum Vit-D level for the prediction of in-hospital mortality was ≤6.47 ng/mL, with a sensitivity of 71.4% and a specificity 86.9% (area under the curve: 0.81, 95% CI: 0.72–0.88; p=0.004).

Conclusion: The findings demonstrated that the serum Vit-D level on admission may be an independent predictor for in-hospital mortality in patients with APE.

ÖZET

Amaç: Biz bu çalışmada, akut pulmoner embolisi (APE) olan hastalarda başvuru sırasındaki serum D vitamini (Vit-D) düzeylerinin hastane içi mortalitedeki öngörme değerini araştırmayı amaçladık.

Yöntemler: Ocak 2015'ten Ocak 2018'e kadar, APE tanısı konulan ve başvuru esnasında serum Vit-D değerleri bulunan toplam 99 hasta çalışmaya dahil edildi. Serum Vit-D değerleri tüm hastalarda immün temelli tahlil kullanılarak ölçüldü. Çalışmanın primer sonlanım noktası tüm nedenlere bağlı hastane içi ölümlerdi.

Bulgular: Çalışmaya alınan hastalar serum Vit-D ortanca değerine göre iki gruba ayrıldı (Vit-D değeri ≤7.36 ng/mL olan 49 hasta hasta ve Vit-D değeri >7.36 ng/mL olan 50 hasta). Serum Vit-D düzeyi ≤7.36 ng/mL olan hastalar, serum Vit-D değeri >7.36 ng/mL olanlara göre daha yüksek ölüm oranına sahipti [6 (%12.2) ve 1 (%2), p=0.048]. Cox regresyon analizinde; serum Vit-D düzeyi (Hazard oranı: 0.82, %95 Güven Aralığı [GA]: 0.68–0.98, p=0.043) hastane içi mortalite ile bağımsız olarak ilişkili bulundu. Hastane içi mortaliteyi ön geren en uygun Vit-D düzeyi %71.4 duyarlılık ve %86.9 özgüllük ile ≤6.47 ng/mL saptanmıştır (eğri altında kalan alan: 0.81, GA %95: 0.72–0.88; p=0.004).

Sonuç: Bu çalışma, başvuru sırasındaki serum Vit-D düzeylerinin APE hastalarında hastane içi mortalite için bağımsız bir belirleyici olabileceğini göstermiştir.

Vitamin D (Vit-D) deficiency is very common in the general population, and it is estimated that more than 1 billion people worldwide have a low serum level of Vit-D.[1] In addition to its crucial role in calcium absorption and bone metabolism, the discovery of Vit-D metabolizing enzymes in the heart and blood

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vessels suggests a role in the cardiovascular system. Several experimental studies have demonstrated that Vit-D may have a potentially protective role through modulation of the inflammatory and thrombotic pathways.[2] In addition to in-vivo studies, several large observational studies have shown a link between Vit-D deficiency and the development of hypertension and diabetes mellitus, as well as an increased risk of coronary artery disease and cardiovascular mortality.[3–5] Serum Vit-D deficiency has also been shown to be a risk factor for a first cardiovascular event, most likely due to increased inflammation, insulin resistance, or neurohumoral activation.[6,7] Although there are established data associating a low level of Vit-D with cardiovascular disease, the prognostic value of a low level of Vit-D in patients with acute pulmonary embolism (APE) has not been explored.

The objective of this study was to investigate the relationship between the serum Vit-D level measured on admission and the in-hospital mortality in APE patients.

METHODS

Study design and patient population

The medical records of our institution were retrospectively screened for patients who were diagnosed with APE between January 2015 and January 2018. Initially, a total of 200 subjects were selected for review. Patients with chronic renal failure or undergoing peritoneal dialysis or hemodialysis, acute or chronic infection, known calcium homeostasis or parathyroid hormone disorders, an auto-immune disease, use of any glucocorticoid therapy within 3 months, or hematological disease were excluded from the study. Cases where the serum Vit-D level was not measured on admission, and patients who had used active Vit-D supplementation within the previous 3 months were not included. After these exclusions, a total of 99 patients were found to be eligible for this analysis.

Patient characteristics upon admission were obtained, including baseline demographics, vital signs, and co-morbidities. The simplified Pulmonary Severity Index score was calculated for each subject in the study. All of the patients received the standard medical therapy in accordance with current guidelines. The protocol for this study was approved by the Clinical Research Committee of Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK-2018/KK/102), and it was conducted in keeping with the principles of the Declaration of Helsinki. The regulations in Turkey at the time the study was conducted did not require informed consent for retrospective studies.

Abbreviations:

APE	*Acute pulmonary embolism*
CI	*Confidence interval*
CRP	*C-reactive protein*
CTA	*Computed tomography angiography*
eGFR	*Estimated glomerular filtration rate*
HR	*Hazard ratio*
ROC	*Receiver operating characteristic*
Vit-D	*Vitamin D*
V/Q	*Ventilation/perfusion lung scan*

Laboratory analysis

Venous blood samples were obtained from all of the study patients upon admission to the emergency department. The immune-based Architect 25-OH Vitamin D assay (Abbott Laboratories, Lake Bluff, IL, USA) was used to assess the level of Vit-D and the serum Vit-D level was measured in ng/mL. C-reactive protein (CRP) was measured using the nephelometric method with an automated biochemical analyzer (Cobas 8000-c502; F. Hoffmann-La Roche Ltd., Basel, Switzerland). The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease formula.

Imaging data

Pulmonary computed tomography angiography (CTA) or ventilation/perfusion lung scan (V/Q) (in cases of contraindication) was used in order to confirm the diagnosis of APE. Two experienced radiologists who were blinded to patient clinical data confirmed the diagnosis of APE with CTA when there was a thrombus in the main pulmonary arteries or its branches. A high-probability V/Q scan was also accepted as diagnostic of APE.

All of the echocardiographic examinations were performed by an experienced cardiologist using an ultrasound machine (Vivid 7; GE Healthcare, Inc. Chicago, IL, USA) and a 3.5 MHz probe within 48 hours of hospitalization. The Simpson method was used to calculate the left ventricular ejection fraction. The pulmonary arterial peak systolic pressure was calculated using the simplified Bernoulli equation.

Definitions

The primary endpoint was the incidence of in-hospital all-cause mortality. In-hospital mortality was defined as death from any cause during hospitalization. In-

hospital mortality was determined by a trained study coordinator who evaluated the hospital files and computer records.

Statistical analysis

Continuous variables were expressed as mean±SD or median, and categorical variables were expressed as a percentage. A chi-square or the Fisher's exact test was used to compare the categorical data. Normal distribution of continuous variables was tested with the Kolmogorov-Smirnov test. Student's t-test or the Mann-Whitney U test was used to compare continuous variables between groups. All of the variables shown in Table 1 were included in a univariate analysis. In order to identify the independent predictors of in-hospital all-cause mortality, a multivariate Cox regression analysis was performed using variables that demonstrated statistically significant associations with in-hospital mortality in the univariate analysis. The Hosmer-Lemeshow statistic of the logistic regression model was 0.461 (x^2=7.71). Receiver operating characteristic (ROC) curve analysis was used to determine the best specificity and sensitivity of the serum Vit-D level in the prediction of in-hospital mortality. The effect size (Cohen's d) and power value (1-β) of the study were calculated using G*Power software (Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A.) The effect size and power value were 1.33 and 0.95, respectively. A 2-sided p value of <0.05 was considered significant. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The mean age of the patients in this study was 66±17 years, and the prevalence of female gender was 62.6%. The study population was divided into 2 groups according to the median value of serum Vit-D level: A Vit-D level of ≤7.36 ng/mL was observed in 49 patients and a Vit-D level of >7.36 ng/mL was seen in 50 patients. The baseline demographic characteristics, and the laboratory and echocardiographic results of all of the patients are provided in Table 1. There were no significant differences between the 2 groups regarding the presence of hypertension, diabetes mellitus, cardiopulmonary disease, current smoking status, deep vein thrombosis, or malignancy (p>0.05 for all). On admission, the patients' vital signs were similar between groups (p>0.05 for all). In terms of laboratory findings, only the serum Vit-D level was significantly different between the groups (7.04±2.35 ng/mL vs. 19.20±7.62 ng/mL; p<0.001). Comparison of echocardiographic findings revealed that the left ventricular ejection fraction and the pulmonary arterial peak systolic pressure were similar in both groups. Although the length of hospital stay was similar in the 2 groups, the patients whose serum Vit-D level was ≤7.36 ng/mL had a higher of incidence of death compared with those whose serum Vit-D level was >7.36 ng/mL (6 [12.2%] vs. 1 [2%]; p=0.048).

In univariate analysis, age, female gender, systolic blood pressure, fever, eGFR, and levels of serum albumin, CRP, and Vit-D were found to be correlated with in-hospital mortality. These parameters were included in multivariate Cox regression analyses. The results of the multivariate analysis indicated that age (hazard ratio [HR]: 1.12, 95% confidence interval [CI]: 1.07–1.27; p=0.048), CRP level (HR: 1.00, 95% CI: 1.00–1.01; p=0.041) and serum Vit-D level (HR: 0.82, 95% CI: 0.68-0.98; p=0.043) were found to be independently associated with in-hospital mortality in the study population (Table 2). ROC analysis revealed that the optimal value of serum Vit-D level for the prediction of in-hospital mortality was ≤6.47 ng/mL with a sensitivity of 71.4% and a specificity of 86.9% (area under curve: 0.81, 95% CI: 0.72–0.88; p=0.004) (Fig. 1).

DISCUSSION

These study findings showed that poor serum Vit-D status may be an independent predictor of in-hospital mortality in APE patients. To the best of our knowledge, this is the first study reporting an association between low serum Vit-D level and increased risk of in-hospital mortality in patients with APE.

In addition to its main role in bone metabolism and calcium hemostasis, serum Vit-D has several anti-inflammatory functions, which include the inhibition of pro-inflammatory cytokine expression, inhibition of adhesion molecules in endothelial cells, and the regulation of immune cell activity.[8,9] The data from some experimental animal studies indicated that Vit-D deficiency increased cardiovascular risk as result of vascular inflammation, insulin resistance, and activation of the renin-angiotensin-aldosterone system.[6,7] Based on these findings, we hypothesized that a low level

Table 1. Baseline demographic characteristics and laboratory and echocardiographic findings of all of the patients

	All patients (n=99)	Vitamin D level ≤7.36 ng/mL (n=49)	Vitamin D level >7.36 ng/mL (n=50)	*p*
Age (years), Mean±SD	66±17	66±19	66±15	0.711
Female gender, n (%)	62 (62.6)	34 (69.4)	28 (56)	0.171
History, n (%)				
Hypertension	49 (49.5)	28 (57.1)	21 (42)	0.134
Diabetes mellitus	23 (23.2)	15 (30.6)	8 (16)	0.087
Cardiopulmonary disease	33 (33.3)	16 (32.7)	17 (34)	0.888
Current smoking status	17 (17.4)	7 (14.3)	10 (20)	0.453
Deep vein thrombosis	6 (6.1)	4 (8.2)	2 (4)	0.388
Malignancy	6 (5.9)	4 (5)	2 (9.1)	0.637
At admission, Mean±SD				
Systolic blood pressure (mm Hg)	116.0±23.0	118.0±22.0	115.0±23.0	0.324
Diastolic blood pressure (mm Hg)	72±14	72±14	71±15	0.366
Fever, °C	36.6±0.4	36.7±0.3	36.6±0.4	0.977
Heart rate, beats per minute	98±15	98±16	98±15	0.883
O_2 saturation (%)	89±5	90±5	89±5	0.284
Respiratory rate, beats per minute	20±3	20±3	20±3	0.322
Admission laboratory variables, Mean±SD				
Admission glucose (mg/dL)	143±109	148±109	139±107	0.151
Admission D-dimer (ng/mL)	2968±1188	2773±1113	3403±1753	0.246
Admission troponin I (ng/dL)	0.10±0.01	0.12±0.01	0.10±0.01	0.677
Creatinine (mg/dL)	1.02±0.3	1.02±0.36	1.03±0.23	0.513
Estimated glomerular filtration rate (mL/min)	61.7±20.3	62.6±22.9	60.8±17.5	0.967
White blood cell count (cells/μL)	11.2±8.0	11.5±8.6	10.95±8.0	0.295
Hemoglobin (g/dL)	12.66±2.4	12.35±2.5	12.96±2.3	0.278
Platelet count (cells/μL)	247±98	246±81	247±113	0.629
Alanine aminotransferase (u/L)	19.0±13.0	19.0±14.0	19.0±12.0	0.716
Serum albumin (g/dL)	3.29±0.63	3.20±0.60	3.37±0.66	0.188
Brain natriuretic peptide (pg/mL)	7760±3762	8253±4266	7334±3673	0.484
C-reactive protein (mg/dL)	70.2±30.3	77.9±38.4	59.6±20.4	0.287
25-hydroxyvitamin D levels (ng/mL)	13.18±8.31	7.04±2.35	19.20±7.62	<0.001
Echocardiographic parameters				
Left ventricular ejection fraction (%)	58.0±9.0	56.0±10.0	59.0±7.0	0.381
Pulmonary artery systolic pressure (mmHg)	39.0±18.0	40.0±19.0	37.0±18.0	0.486
Simple PESI score	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (2.0–3.0)	0.736
Length of hospital stay, days	8.0 (7.0–11.0)	8.0 (7.0–11.0)	8.0 (7.0–11.0)	0.476
In-hospital mortality, n (%)	7 (7.1)	6 (12.2)	1 (2)	0.048

Continuous variables are presented as mean±SD or median, nominal variables are presented as frequency (%). PESI: Pulmonary Embolism Severity Index.

of Vit-D might result in a deficiency in some anti-inflammatory functions in APE patients. As a result, this decreased anti-inflammatory capacity could contribute to poor outcomes in APE patients. Several studies

Table 2. Independent predictors of in-hospital mortality

Univariate analysis	*p*	HR (95% CI)	B	Wald	Multivariate analysis	*p*	HR (95% CI)	B	Wald
Vit-D level	0.036	0.78 (0.62–0.98)	-0.23	4.39	Vit-D level	0.043	0.82 (0.68–0.98)	-0.18	3.69
Age	0.018	1.14 (1.02–1.28)	0.13	5.59	Age	0.048	1.12 (1.07–1.27)	0.12	3.59
CRP	0.014	1.00 (1.00–1.01)	0.08	6.01	CRP	0.041	1.00 (1.00–1.01)	0.08	3.50

All clinically relevant parameters were included in the model.*

*Includes baseline demographic characteristics of gender, hypertension, diabetes mellitus, current smoking etc.; hemodynamic status data from admission, such as systolic and diastolic blood pressure, heart rate, fever, etc.; and laboratory and echocardiographic parameters, such as levels of D-dimer, troponin I, brain natriuretic peptide, left ventricle ejection fraction, and pulmonary artery systolic pressure.

CI: Confidence interval; CRP: C-reactive protein; HR: Hazard ratio; Vit-D: Vitamin D.

have reported the prognostic value of some inflammatory markers such as interleukin 6 and CRP with adverse outcomes in APE.[10] Consistent with these earlier studies, our finding was that CRP, a well-known inflammatory marker, was independently associated with in-hospital mortality.

In addition to its anti-inflammatory functions, several experimental studies have shown that Vit-D may exert some antithrombotic effects, which include the upregulation of the anticoagulant glycoprotein thrombomodulin and downregulation of thrombospondin-1 and plasminogen activator inhibitor-1 in human aortic smooth cells.[11,12] This might be another explanation for low Vit-D levels and poor outcomes in APE patients.

Various studies have demonstrated that a low level of Vit-D was linked to a risk of endocrine, neurological, and cardiovascular disorders.[8,13–15] In a prospective study conducted with heart failure patients, the researchers demonstrated that Vit-D supplementation was related to improved survival.[16] Similarly, it has been reported that Vit-D supplementation was also associated with improved survival among patients with end-stage renal failure.[17] Moreover, 2 recent observational studies demonstrated a significant association between a low level of Vit-D and the development of venous thromboembolism.[18,19] To the best of our knowledge, there has been no previous report exploring a relationship between serum Vit-D level and poor outcomes in APE patients. This may be the first study to demonstrate that APE patients with a low serum Vit-D level had a significantly elevated rate of in-hospital mortality.

Our study findings may be useful in terms of clinical applicability. As a simple and easily obtained laboratory parameter, the serum Vit-D level may have an additive prognostic value for in-hospital mortality in APE patients. In addition, our findings provided compelling evidence that treatment or correction of a low serum Vit-D level may decrease in-hospital mortality among these patients, though this needs further research. As this was a retrospective study, definitive recommendations based on the study findings cannot be made. Our study findings deserve further investigation with multi-center and prospective studies to clarify the precise role of serum Vit-D in patients with APE.

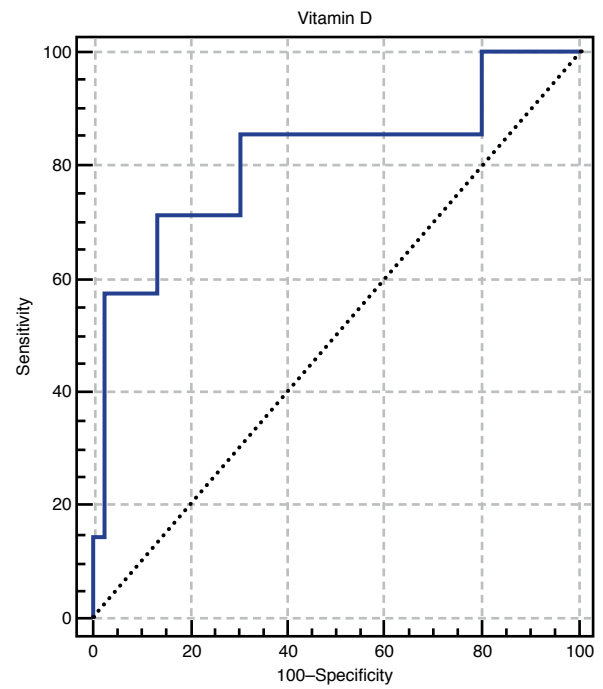

Figure 1. Receiver operating characteristic analysis showed that the optimal cut-off value of the serum vitamin D level in predicting in-hospital mortality was ≤6.47 ng/mL with a sensitivity 71.4% and a specificity 86.9% (area under the curve: 0.81, 95% confidence interval: 0.72–0.88; p=0.004).

Limitations

Our findings were based on a single-center population and need to be verified with larger cohorts. This study had a small sample size, though it did employ consecutive APE patients. In addition, although multivariate logistic regression analysis was used, some residual unmeasured confounders of in-hospital mortality might not have been fully evaluated. Furthermore, a spot laboratory value was used to estimate in-hospital mortality in the study. Finally, some well-known inflammatory markers, such as fibrinogen, interleukin 6, etc., were not evaluated in this study.

Conclusion

In the present study, we observed that a low serum Vit-D level was an independent predictor of in-hospital mortality in APE patients. Consequently, serum Vit-D levels may have an additive prognostic value for in-hospital mortality in APE patients.

Ethics Committee Approval: The protocol for this study was approved by the Clinical Research Committee of Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK-2018/KK/102).

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