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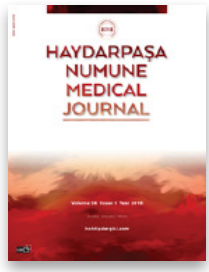

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ORIGINAL ARTICLE

The Effect of Serum Cortisol and Vitamin D Levels on Mortality in Covid-19 Patients Admitted to the Intensive Care Unit

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Abstract

Introduction: One of the ways to reduce deaths due to Coronavirus-19 disease is to identify the factors that increase the mortality of the disease. Deficiency of vitamin D, which supports the immune system, and corticosteroids administered to suppress excessive inflammatory response may be risk factors that may affect mortality.

Methods: In our study, we evaluated serum vitamin D and cortisol levels in Covid-19 patients during their admission to the intensive care unit, together with the demographic data and comorbidities of the patients, and examined their effect on mortality and their relationship with intensive care unit (ICU) scoring systems.

Results: In the study, 101 Covid-19 patients were examined. Serum vitamin D and cortisol levels did not affect mortality statistically. Intensive care unit admission was more common in patients with low vitamin D levels. Cortisol levels were also higher in patients who died.

Discussion and Conclusion: Vitamin D deficiency increased the risk of admission to the intensive care unit, and serum vitamin D and cortisol levels during admission to the intensive care unit had no effect on the prediction of mortality.

Keywords: Covid-19; Cortisol; Intensive Care Unit; Vitamin D.

The coronavirus (Covid-19) pandemic has affected many people today and caused deaths. Detection of factors that increase the risk of mortality will help to control the disease and reduce its prevalence. There are positive studies related to vitamin D, which supports the immune system, and corticosteroids applied to suppress excessive inflammatory response during the disease process. It is thought that low serum vitamin D and cortisol levels may be risk factors affecting mortality. The aim of this study is to examine the relationship between serum cortisol and vitamin D levels and mortality in patients admitted to the intensive care unit (ICU) due to Covid-19 pneumonia.

Materials and Methods

A total of 103 patients with positive reverse transcriptase-polymerase chain reaction (rt-PCR) test for Covid-19 in oropharyngeal or nasal swab samples, admitted to the anesthesia ICU of Health Sciences University Tepecik Training and Research Hospital between 01 November 2020 and 01 January 2021, were included in our study. One patient each with a history of corticosteroid use due to a known comorbid disease and using vitamin D supplementation was excluded from the study, as it may affect the basal serum cortisol level and vitamin D levels during admission to the

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ICU. A total of 101 patients covering these criteria were included in the study. Serum vitamin D and cortisol levels of the patients admitted to the intensive care unit were recorded. ADVIA Centaur® XP analyzer (Siemens Healthineers, Erlangen, Germany) was used to measure vitamin D levels and DxI immunoanalyzer (Beckman Coulter Inc., CA, USA) device was used for cortisol. Serum vitamin D (25-Hydroxy vitamin D) level was shown as µg/L and cortisol level as µg/dl. We evaluated serum vitamin D and cortisol levels together with the demographic data and comorbidities of the patients, and examined their effect on mortality and their relationship with intensive care unit (ICU) scoring systems. The study protocol was approved by the Health Sciences University Izmir Medical Faculty Tepecik Training and Research Hospital Clinical Research Ethics Committee (Ethics committee decision no: 2020/12-9). The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

In the study, as descriptive statistics, mean±standard deviation was given for numerical variables, and number (n) and percentage (%) were given for categorical data. Whether there was a significant difference between the groups in terms of numerical variables was analyzed with the Student's t test if the parametric test assumptions were met, and with the Mann-Whitney U test if they were not. Pearson's chi-square test or Fisher's exact test was used depending on the assumptions in the evaluation of categorical data. Binary logistic regression analysis was used to calculate the risk factors for death for the parameters found to be statistically significant, and given with Odds ratio and 95% confidence intervals. The analyzes of the study were made in IBM SPSS V22 program and $p<0.05$ was considered statistically significant.

Results

Of the 101 patients included in the study, 40 (40.4%) were female and 61 (59.6%) were male. While 34 (33.7%) of these people were discharged from the ICU (living patients), 67 (66.3%) died. The mean age of the patients was 67.4 (32–96). A statistically significant difference was found between discharged and patients who died in terms of gender, Sequential Organ Failure Assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (p=0.035; p=0.015; p=0.001, respectively). 21 (31.3%) of the patients who died were female and 46 (68.7%) were male. Males were 2.46 times more likely to die than females (p=0.037; OR=2.464 (95% CI (1.06-5.76)). The APACHE II and SOFA scores were found to be significantly higher in the patients who died, than in the survivors (APACHE II score was 14.79±6.328 in patients who survived and was 19.80±8.476 in patients who died (p<0.001); SOFA score was 4 (2-15) in patients who survived and 6 (3-15) in patients who died (p<0.015)). A 1-unit increase in SOFA score increased mortality by 1.17-fold (p=0.030; OR=1.174 (95% CI 1.02-1.36)), while 1-unit increase in APACHE II score by 1.09-fold (p=0.005; OR=1.092 (95% confidence interval) 1.03-1.16)). Table 1 shows the demographic data of the patients, their

Table 1. Statistical analysis of patients' demographic data, comorbidities, APACHE II and SOFA scores (CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease, CVD: Cerebrovascular Disease)

	All Patients	Discharged Patients n=34	Patients who died n=67	p
Age	67.43±13.89	63.71±17.20	69.66±11.596	0.075[d]
Gender (Female/Male)	39 (38.6)/62 (61.4)	18 (46.2)/16 (25.8)	21 (53.8)/46 (74.2)	0.035[a]
Diabetes	29 (28.7)	9 (31)	20 (69)	0.723[a]
Hypertension	41 (40.6)	12 (29.3)	29 (70.7)	0.440[a]
CAD	29 (28.7)	9 (31)	20 (69)	0.723[a]
COPD	9 (8.9)	1 (11.1)	8 (88.9)	0.266[b]
CVD	6 (5.9)	3 (50)	3 (50)	0.402[b]
Cancer	2 (2)	0 (0)	2 (100)	0.549[b]
Alzheimer's	2 (2)	0 (0)	2 (100)	0.549[b]
SOFA score	11.5 (2-15)	4 (2-15)	6 (3-15)	0.015[c]
APACHE II score	18.06±8.09	14.79±6.32	19.80±8,476	0.001[d]
Vitamin D	11.23 (4.20-35.47)	10.98 (4.20-34.46)	11.01 (4.20-35.47)	0.796[c]
Cortisol	16.9 (0.72-63.60)	15.43 (0.72-49.60)	18.10 (1.20-63.60)	0.275[c]

[a]: Pearson's Chi-square; n (%); [b]: Fisher's exact Test; n (%); [c]: Mann-Whitney U test; median (minimum-maximum); [d]: Student's t test; mean±standard deviation.

comorbidities and statistical analysis of disease severity scores such as APACHE II and SOFA.

The mean vitamin D level of the patients admitted to the intensive care unit was 11.23 µg/L. The mean serum vitamin D level was 10.98 µg/L (4.20-34.46) in survivors, and 11.01 µg/L (4.20-35.47; p<0.796) in patients who died. The mean cortisol level was found to be 16.9 µg/dl at the time of admission to the intensive care unit. While the mean cortisol level was 15.43 µg/dl (0.72-49.60) in surviving patients, it was 18.10 µg/dl (1.20-63.60; p<0.275) in patients who died. There was no statistically significant difference in serum vitamin D and cortisol levels of patients discharged from the ICU and those who died.

Discussion

Many studies are carried out to determine the factors that will reduce the severity and mortality of the Covid-19 infection. In epidemiological studies, it has been determined that some risk factors affecting the severity and mortality of the disease are inversely correlated with vitamin D levels[1]. In these epidemiological studies, it was determined that the mortality rate due to Covid-19 is low in the equatorial region, whixh is exposed to sunlight[2], and although Covid-19 infection is more common in young people, it has been determined that the death rate is higher in the elderly, where vitamin D deficiency is more common[3,4]. In addition, it has been reported that the severity of the disease is higher in patients with chronic renal failure (CRF), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD) and coronary artery disease (CAD) with severe vitamin D deficiency, where there is severe vitamin D deficiency[3,5]. Furthermore, it has been reported that after vitamin D supplementation in infected patients, vitamin D levels normalize, clinical status improves, oxygen demand and inflammatory markers are decreased, and hospital stays are shortened[6]. It has been reported that those with viral infections have lower vitamin D levels, compared to those without an infection[7,8]. In some studies, it has been observed that patients with low vitamin D levels have a high risk of hospitalization and that the use of calcifediol in patients with Covid-19 infection reduces the need for intensive care by reducing the severity of the disease[8,9]. All these epidemiological studies indicate that low vitamin D levels may increase the severity and mortality of the disease.

Vitamin D is a fat-soluble vitamin and sun exposure is required for synthesis of Vitamin D in the skin, and a small part is obtained from food[10]. Vitamin D is essential for bone metabolism. In addition, it has positive effects on the immune system and plays a role in the prevention of viral diseases. It protects against pathogens by acting as an immune modulator on the innate and acquired immune system[11-14]. A serum level of 25-hydroxyvitamin D higher than 30 µg/L is considered as sufficient for vitamin D, while a serum 25-hydroxyvitamin D level between 20 and 30 µg/L is considered insufficient, and a serum 25-hydroxyvitamin D level lower than 20 µg/L is considered a deficiency[15]. The prevalence of vitamin D deficiency is high in healthy individuals in our country, as worldwide[16]. According to the data of 2011-2014 in the National Health and Nutrition Survey-NHANES study in the United States, it is reported that one fifth of the population has vitamin D deficiency. In a study conducted in healthy individuals in our country, the average vitamin D level was 19.4 µg/L in men over 45 years old and 17.8 µg/L in women[17].

In the United States, it is reported that vitamin D deficiency is common among Hispanic and black people, and Covid-19 disease is more common in these people[18]. Although vitamin D levels are low in patients with CRF, COPD, CVD and hypertension, it has been reported that these diseases are associated with poor prognosis by increasing the possibility of admission to intensive care unit due to Covid-19 disease[3,5]. In a study involving the UK population, it was emphasized that those with low vitamin D levels in Covid-19 patients had a higher need for intensive care than those with normal levels[19]. In a study where vitamin D deficiency was defined as less than 12 µg/L, it was stated that vitamin D deficiency increased the severity and mortality rate of Covid-19, and no difference was observed between patients with vitamin D deficiency in outpatient treatment and patients with vitamin D levels of 12 ng/mL and above[20]. In our study, the mean serum vitamin D level was found to be 13.15 µg/L in Covid-19 patients admitted to the intensive care unit, and we can say that vitamin D deficiency is common in patients hospitalized in the intensive care unit.

There are also studies showing increased morbidity in elderly patients with vitamin D deficiency[4]. The mean age of the patients was 67.4 years in our study, and there was no statistically significant difference in vitamin D levels between those who died and those who survived. This study revealed that vitamin D deficiency has no effect on mortality in the elderly. Contrary to our study, correlation analysis involving the Indian population found a possible inverse relationship between vitamin D level and mortality due to Covid-19 disease. Recent reports of Covid-19 mortality data and the mean serum 25-hydroxyvitamin D level of 12

European countries provided similar observations[1,19]. It has been reported in these studies that low vitamin D levels increase the risk of viral infections.

Cortisol is secreted from the adrenal cortex within minutes in the case of acute illness as a protective response to stress. It is argued that cortisol levels increase according to the severity of the disease[21-23]. In a study that included patients with severe sepsis and septic shock admitted to the intensive care unit, free cortisol levels of surviving patients were found to be lower than those who died[24]. Tan et al.[25] compared serum cortisol levels in a study involving patients with Covid-19 pneumonia and other patients. They reported that patients with Covid-19 had higher serum cortisol levels (22.43, 18.81 µg/dl, respectively) than patients without Covid-19. In a similar study between Covid-19 patients and other patients in the intensive care unit, the mean serum cortisol level of Covid-19 patients was found to be higher[26]. In our study as well, serum cortisol levels of Covid-19 patients admitted to intensive care unit were found to be higher in patients who died. However, there was no statistically significant difference between living and patients who died, that would affect mortality. Some studies reported that serum cortisol level may be affected by the disease, which accelerates the admission of patients to the intensive care unit, and that this result may have an independent predictive effect on mortality[27-30].

The APACHE II score is a scoring system used in the gross estimation of the patient's mortality risks by evaluating the acute physiological and chronic health status of hospitalized critically ill patients. A one-point increase in risk on this score is associated with the risk of hospital death[31]. The SOFA score, on the other hand, is a score developed to evaluate organ failure in sepsis[32]. Although the SOFA score does not calculate the estimated mortality expectation, it shows a high correlation with mortality. In our study, the higher serum cortisol level in the patients who died, compared to the surviving patients may explain the more severe course of the disease in this group, and therefore the higher APACHE II and SOFA scores. Consistent with the literature, APACHE II and SOFA scores, which determine disease severity, were found to be higher in patients who died. However, the high serum cortisol level detected in the patients who died, did not contribute to the prediction of mortality.

There are some limitations in this study. The serum vitamin D level and cortisol level of the patients were checked at the time of admission to the intensive care unit, and a comparison could not be made with the levels of the patients when they were diagnosed with Covid-19. This situation reduces the efficiency of the study.

Conclusion

As a result, in this study, it was determined that vitamin D deficiency is common in Covid-19 patients admitted to intensive care unit. Vitamin D deficiency increases the risk of admission to intensive care unit. However, it was found that serum vitamin D and cortisol levels, which were checked simultaneously after admission to the intensive care unit, did not have an effect on the prediction of mortality. Further research is needed on this topic.

Ethics Committee Approval: The study protocol was approved by the Health Sciences University Izmir Medical Faculty Tepecik Training and Research Hospital Clinical Research Ethics Committee (Ethics committee decision no: 2020/12-9). The study was conducted in accordance with the Declaration of Helsinki.

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Authorship Contributions: Concept: U.U.; Desing: U.U., M.G.; Supervision: A.S., N.Ş.; Materials: F.D.A.; Data Collectionor Processing: İ.S.,T.Ç.; Analysisor interpretation: Ç.Z.; Literature Search: İ.K., U.U., M.G.; Writing: U.U.; Criticial Review: A.S., K.R.

Conflict of Interest: None declared.

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