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## Co-evaluation of magnesium and 25-hydroxyvitamin D<sub>3</sub> in predicting the severity of COVID-19 disease

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### Abstract

The severity of COVID-19 disease ranges from asymptomatic to severe, life-threatening symptoms. The aim of our study was to co-evaluate magnesium and 25-hydroxyvitamin D<sub>3</sub> in predicting the severity of this disease.

This study included 232 inpatients with COVID-19 and 250 healthy individuals (control group). Magnesium and 25-hydroxyvitamin D<sub>3</sub> levels were compared. ROC curve analysis was performed by co-evaluation of magnesium and 25-hydroxyvitamin D<sub>3</sub> levels. Correlation analysis was performed between co-evaluation of magnesium and 25-hydroxyvitamin D<sub>3</sub> levels together and the laboratory parameters used in the prognosis of COVID-19 disease.

Magnesium and 25-hydroxyvitamin D<sub>3</sub> levels of the group with COVID-19 were lower than the control group ( $p < 0.001$ ). AUC value was found to be 0.924 in ROC curve analysis ( $p < 0.001$ ). In the ROC curve analysis, the cut-off value for magnesium was found to be 2.20, and the cut-off value for 25-hydroxyvitamin D<sub>3</sub> was found as 25.80. Co-evaluation of magnesium and 25-hydroxyvitamin D<sub>3</sub> levels were negatively correlated with D-dimer, C reactive protein, procalcitonin, neutrophil lymphocyte ratio and monocyte lymphocyte ratio ( $P < 0.05$ ).

Co-evaluation of magnesium and 25-hydroxyvitamin D<sub>3</sub> may be useful in predicting the severity of the disease in patients with COVID-19. Low magnesium and 25-hydroxyvitamin D<sub>3</sub> levels can be considered a risk factor in patients with COVID-19. People with magnesium and 25-hydroxyvitamin D<sub>3</sub> deficiencies may be considered at risk for COVID-19 disease. We recommend monitoring of magnesium and 25-hydroxyvitamin D<sub>3</sub> levels to predict the prognosis of the COVID-19 disease. Individuals may be offered prophylactic magnesium and 25-hydroxyvitamin D<sub>3</sub> supplementation.

**Keywords:** COVID-19, SARS-Cov-2, Magnesium, 25-hydroxyvitamin D<sub>3</sub>, disease severity

### Introduction

The coronavirus disease (COVID-19), which emerged in late 2019 and caused a outbreak in a short time, has become an important public health problem [1]. The severity of this disease is associated with the effect of viral load in patients and the immune system response to this effect. The response of the immune system against the viral load may be insufficient. In the face of this situation, it causes a devastating inflammatory response with increased levels of certain inflammatory biomarkers [2]. The destructive inflammatory response leads to a hyper-reaction of the immune system. Hyper reaction of the immune system and cytokine storm is one of the most harmful effects of COVID-19 disease [3]. COVID-19 disease can cause depletion of cellular adenosine triphosphate and dysfunction of immune cells. Replenishment of cellular adenosine triphosphate is necessary to increase the effectiveness of the immune system [4].

25-hydroxyvitamin D<sub>3</sub> is a vitamin that has many effects on the immune system. 25-hydroxyvitamin D<sub>3</sub> deficiency has been associated with the severity of acute viral infections. It has been stated that 25-hydroxyvitamin D<sub>3</sub> levels should be sufficient in individuals for the antiviral effectiveness of the immune system [5, 6]. The immune modulatory role of 25-hydroxyvitamin D<sub>3</sub> is based on its receptors on many immune cells and the synthesis of active metabolites from these cells [5]. It has been reported that 25-hydroxyvitamin D<sub>3</sub> has a protective effect on alveolar epithelial cells, preserves endothelial integrity and also induces the expression of angiotensin converting enzyme 2 (ACE2) [7]. On the other hand, expression of ACE2 plays an important role in the pathophysiological mechanisms of COVID-19 disease [8].

Magnesium is necessary to move 25-hydroxyvitamin D<sub>3</sub> in the bloodstream and activate 25-hydroxyvitamin D<sub>3</sub>. Magnesium deficiency may also reduce the levels of 25-hydroxyvitamin D<sub>3</sub> [9]. Therefore, optimal magnesium levels are required for optimal 25-hydroxyvitamin D<sub>3</sub> activity [10]. Magnesium is required for adenosine triphosphate synthesis and regeneration [11]. Intracellular adenosine triphosphate depletion increases cytokine release and catabolism, which may inhibit the immune system [12].

In this study, it was aimed to examine 25-hydroxyvitamin D<sub>3</sub> and magnesium levels in COVID-19 disease, in which cytokine storm is associated with the severity of the disease. Co-evaluation of 25-hydroxyvitamin D<sub>3</sub> and magnesium levels in predicting the severity of COVID-19 disease was examined.

## Materials and Methods

### Study design

The type of study was a case-control and a single-center study. The ethics committee approval required for the study was obtained from the human research ethics committee of the hospital where the study was conducted. The number of patients was determined by Gpower analysis. 232 inpatients with COVID-19 who came to Samsun Training and Research Hospital were included in the study. In addition, 250 healthy individuals were included as a control group. Patients and healthy individuals were randomly selected. The data of the patients were obtained retrospectively from the "Hospital Information Management System" of the hospital where the study was conducted. 25-hydroxyvitamin D<sub>3</sub> and magnesium levels of the patients and individuals included in the study were compared. Regression and ROC curve analysis was performed on the 25-hydroxyvitamin D<sub>3</sub> and magnesium levels of the patients.

In addition, D-dimer, C reactive protein, ferritin, procalcitonin, neutrophil lymphocyte ratio, monocyte lymphocyte ratio levels of the patients were obtained. The relationship between these parameters and the 25-hydroxyvitamin D<sub>3</sub> and magnesium levels of the patients was investigated.

### Patients

Patients with positive COVID-19 polymerase chain reaction test were included in the patient group. In addition, the

patient group consisted of patients hospitalized in the intensive care and inpatient clinics of the hospital where the study was conducted.

### Main outcome variable

Serum 25-hydroxyvitamin D<sub>3</sub> levels were determined by chemiluminescence immunoassay method using Roche Cobas 8000 (Basel, Switzerland) device. Magnesium levels were determined using Beckman Coulter AU5800 (Brea, California, USA) device with appropriate kits.

### Other variables

C reactive protein levels with Beckman Coulter AU5800 (Brea, California, USA) device, D-dimer levels with SYSMEX CS-5100 (Siemens Healthcare Diagnostics, Erlangen, Germany) device, ferritin and procalcitonin levels with Roche Cobas e 411 (Basel, Switzerland) device, neutrophil, lymphocyte and monocyte levels were determined with SYSMEX XN-1000 (Siemens Healthcare Diagnostics, Erlangen, Germany) device and appropriate kits.

### Statistical methods

The sample size was calculated using the G\*Power 3.1.9.7 program. The Minitab 21 program was used for the analysis of the variables. Continuous variables were defined as the median (25-75th percentile). The main outcome variables of the groups were compared using the Mann-Whitney U test. Regression analysis of the main outcome variables was performed. The regression equation was calculated to evaluate the main outcome variables together. ROC curve analysis was performed, in which the main outcome variables were evaluated together. Spearman correlation analysis was used for the correlation analysis between the main outcome variables and other variables.

## Results

### Descriptive information

This study was included 232 inpatients with COVID-19 and 250 healthy individuals. Of these inpatients, 198 were in the inpatient clinics and 34 were in the intensive care unit. The descriptive information and laboratory findings of the groups were given in table 1 as the median (25<sup>th</sup>-75<sup>th</sup> percentile).

**Table 1:** The descriptive information and laboratory findings of the groups

Parameters	COVID-19 (n=232)	Control (n=250)
Male n (%)	117 (50.43)	78 (31.20)
Female n (%)	115 (49.57)	172 (68.80)
Age	65 (49-73)	48 (36-61)
25-hydroxyvitamin D <sub>3</sub> (ng/ml)	10.40 (7.23-10.60)	29.20 (27.60-32.50)
Magnesium (mg/dl)	2.10 (1.90-2.30)	2.20 (2.10-2.20)
D-dimer (µg/ml)	0.96 (0.31-2.68)	-
C reactive protein (mg/L)	58.60 (18.58-114.00)	-
Ferritin (ng/mL)	305.00 (144.50-866.50)	-
Procalcitonin (mg/L)	0.11 (0.04-0.31)	-
Neutrophil (10 <sup>9</sup> /L)	5.30 (3.65-8.95)	-
Monocyte (10 <sup>9</sup> /L)	0.50 (0.30-0.60)	-
Lymphocyte (10 <sup>9</sup> /L)	1.00 (0.70-1.35)	-
Neutrophil lymphocyte ratio	5.60 (2.84-10.43)	-
Monocyte lymphocyte ratio	0.42 (0.31-0.70)	-

### Analysis of the main outcome variables

The 25-hydroxyvitamin D<sub>3</sub> and magnesium levels of the patients with COVID-19 were found to be lower than the

control group ( $p < 0.001$ ). The results of the regression analysis of 25-hydroxyvitamin D<sub>3</sub> and magnesium levels were given in table 2.

**Table 2:** Regression analysis of 25-hydroxyvitamin D<sub>3</sub> and magnesium levels

Parameters	Odds ratio	%95 CI	p
25-hydroxyvitamin D <sub>3</sub>	0.78	(0.75-0.81)	<0.001
Magnesium	0.20	(0.05-0.86)	0.031

**Table 3:** ROC curve analysis results

Parameters	AUC (95% CI)	Cut Off	p	SEN (%)	SPE (%)	PPV (%)	NPV (%)
25-hydroxyvitamin D <sub>3</sub> , Magnesium	0.924 (0.893-0.955)	25.80, 2.20	<0.001	91.40	91.60	36.41	99.58

AUC: area under the curve, SEN: sensitivite, SPE: specifity, PPV: positive predictive value, NPV: negative predictive value,

### Correlation analysis of main outcome variables with other variables

The correlation of the data obtained by co-evaluation the 25-hydroxyvitamin D<sub>3</sub> and magnesium levels with some laboratory findings was given in table 4.

**Table 4:** Correlation of 25-hydroxyvitamin D<sub>3</sub> and magnesium levels with some laboratory findings

Parameters	Correlation coefficient	p
D-dimer	-0.200	0.032
C reactive protein	-0.259	0.005
Ferritin	-0.150	>0.05
Procalcitonin	-0.289	0.002
Neutrophil lymphocyte ratio	-0.192	0.039
Monocyte lymphocyte ratio	-0.253	0.006

### Discussion

COVID-19 disease varies greatly in patients, from asymptomatic infections to severe life-threatening symptoms [13]. Increases in pro-inflammatory cytokines and changes in various laboratory findings, as well as possible complications, may indicate that COVID-19 disease has progressed to a serious and critical level [14]. Overproduction of pro-inflammatory cytokines leads to multiple organ failures and systemic inflammation [15].

25-hydroxyvitamin D<sub>3</sub> has been found to play a role in many-body systems, including the immune system [16]. It is recognized as an immune modulatory agent that regulates both innate and adaptive immune systems [17]. 25-hydroxyvitamin D<sub>3</sub> suppresses T helper 1 cell function and also reduces the production of pro-inflammatory cytokines such as interleukin 6 and interferon-gamma, and provides anti-inflammatory cytokine release from T helper 2 cells. It also plays a role in the regulation of the immune response [18]. Therefore, it is thought that 25-hydroxyvitamin D<sub>3</sub> can prevent cytokine storm and multi-organ failure in COVID-19 patients thanks to these effects [17]. Studies conducted in various parts of the world show that 25-hydroxyvitamin D<sub>3</sub> levels are low in COVID-19 patients [19]. In a systematic review published by Liu *et al.*, it is stated that 25-hydroxyvitamin D<sub>3</sub> levels in COVID-19 patients were lower than in other patients. Low 25-hydroxyvitamin D<sub>3</sub> levels may also be associated with an increased risk of COVID-19 [20]. It was determined by Yisak *et al.* that 25-hydroxyvitamin D<sub>3</sub> deficiency was associated with an increase in disease severity [21]. A meta-analysis evaluating 27 studies reported a significant relationship between 25-hydroxyvitamin D<sub>3</sub> deficiency and disease severity, hospitalization, and mortality rates in COVID-19 patients [22]. A recent another study reported that a statistically significant correlation was found between 25-hydroxyvitamin D<sub>3</sub> deficiency and prolongation of disease duration, increased lung involvement, and increased risk of

The regression equation was obtained by co-evaluation 25-hydroxyvitamin D<sub>3</sub> and magnesium levels. ROC curve analysis was performed with the data obtained as a result of this equation. ROC curve analysis results were given in table 3.

death in elderly patients with SARS-CoV-2 [23]. On the other hand, in a study conducted with 1326 cases, it is determined that there is no significant relationship between COVID-19 disease and 25-hydroxyvitamin D<sub>3</sub> levels [24]. Likewise, in another study with 449 cases, it is determined that there is no relationship between COVID-19 disease and 25-hydroxyvitamin D<sub>3</sub> levels [25].

In our study, 25-hydroxyvitamin D<sub>3</sub> levels of COVID-19 patients were found to be lower than healthy individuals. A 25-hydroxyvitamin D<sub>3</sub> level of less than 20 ng/ml is considered severe deficiency [26]. In our study, the median 25-hydroxyvitamin D<sub>3</sub> levels of COVID-19 patients were at the level of severe deficiency.

Magnesium is the main cation concentrated in human cells, especially in the mitochondria. It is one of the crucial ions required as a cofactor for ATP, enzymatic reactions, and other biological processes. Low magnesium concentration causes disruption of CD8+ T-cell response to virus infection, reduces T-cell activation and exacerbates morbidity [27]. A study on asthma-chronic obstructive pulmonary disease showed that serum magnesium level may have a protective effect against loss of lung function [28]. On the other hand, magnesium deficiency promotes inflammation by priming phagocytes to increase granulocyte oxidative burst, activate endothelial cells, and increase cytokine levels [29]. In a study on the importance of magnesium homeostasis in COVID-19, it is stated that there is a relationship between COVID-19 and unbalanced magnesium homeostasis. Magnesium supplementation may also contribute to protecting against SARS-CoV-2 infection, reducing the severity of COVID-19 symptoms and facilitating recovery after the acute phase [30]. Magnesium is necessary to activate 25-hydroxyvitamin D<sub>3</sub>. Magnesium and 25-hydroxyvitamin D<sub>3</sub> are crucial for both immune function and cellular stability. Adequacy of both is essential to counter the detrimental effects of the COVID-19 disease [31].

In our study, magnesium levels of COVID-19 patients were found to be lower than healthy individuals. The AUC value was also found to be 0.924 in the ROC curve graph obtained by co-evaluation of magnesium and 25-hydroxyvitamin D<sub>3</sub> levels.

It has been reported that D-Dimer values are very high in patients followed up in COVID-19 services, especially in COVID-19 patients hospitalized in intensive care units [32]. In addition, in many studies conducted with COVID-19 patients, some inflammatory indicators (C reactive protein, procalcitonin, neutrophil lymphocyte ratio and monocyte lymphocyte ratio) were found to be high [33-36]. It was stated that inflammatory, hematological and D-dimer values were also high in patients with COVID-19 with different variants [37].

In our study, 25-hydroxyvitamin D<sub>3</sub> and magnesium levels of COVID-19 patients were found to be lower than the control group. In addition, co-evaluation of magnesium and 25-hydroxyvitamin D<sub>3</sub> levels were negatively correlated with D-dimer, C reactive protein, procalcitonin, neutrophil lymphocyte ratio and monocyte lymphocyte ratio.

### Conclusion

In conclusion, co-evaluation of magnesium and 25-hydroxyvitamin D<sub>3</sub> may be useful in predicting the severity of the disease in patients with COVID-19. Low magnesium and 25-hydroxyvitamin D<sub>3</sub> levels can be considered a risk factor in patients with COVID-19. People with magnesium and 25-hydroxyvitamin D<sub>3</sub> deficiencies may be considered at risk for COVID-19 disease. We recommend monitoring of magnesium and 25-hydroxyvitamin D<sub>3</sub> levels to predict the prognosis of the disease in patients with COVID-19. Prophylactic magnesium and 25-hydroxyvitamin D<sub>3</sub> supplementation may be recommended to individuals considered at risk for COVID-19 disease. Magnesium and 25-hydroxyvitamin D<sub>3</sub> levels in COVID-19 patients can be evaluated for a predictive, preventive and personalized medical treatment.

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