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Comparison of Length of Hospital Stay and Routine Laboratory Parameters in COVID-19 Patients with and without Serum Vitamin D Deficiency

Serum D Vitamini Eksikliği Olan ve Olmayan COVID-19 Hastalarında Hastanede Kalış Süresi ve Rutin Laboratuvar Parametrelerinin Karşılaştırılması

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Abstract

Aim: Although some recent studies have shown that serum 25-hydroxyvitamin D (25(OH)D) may be effective on the course of COVID-19 disease, the results obtained are still controversial. Therefore, in this study, it was aimed to examine whether there are differences in terms of age, gender, length of hospital stay, biochemical and hematological parameters between those with and without serum 25(OH)D deficiency in COVID-19 patients.

Material and Method: The data of 413 patients hospitalized in Ankara Pursaklar State Hospital whose COVID-19 positivity was revealed by PCR test were evaluated retrospectively. Those with less than serum 25(OH)D (<20 ng/mL) were considered as vitamin D deficient group.

Results: It was observed that there was a significant difference between the groups with and without serum 25(OH)D deficiency in terms of biochemical parameters total bilirubin (p=0.007), potassium (<0.05) and glucose (p=0.038) values. CRP (p=0.051) and fibrinogen (p=0.048) values, which are factors of inflammation and coagulation, were found to be significantly higher in the group with 25(OH)D deficiency. Similarly, hematocrit (p<0.05) and neutrophil count (p<0.001), which are hematological parameters, increased significantly in patients with 25(OH)D deficiency. There were no differences in age, gender and length of hospital stay between the groups with and without 25(OH)D deficiency.

Conclusion: Our findings showed that 25(OH)D deficiency in hospitalized COVID-19 patients was associated with some biochemical, hematological and inflammatory factors, but not with age, gender and length of hospital stay.

Keywords: COVID-19, 25(OH)D deficiency, blood parameters

Öz

Amaç: Son zamanlarda yapılan bazı çalışmalar serum 25-hidroksivitamin D (25(OH)D)'nin COVID-19 hastalığının seyri üzerinde etkili olabileceğini göstermiş olsa da elde edilen sonuçlar halen tartışmalıdır. Bu nedenle bu çalışmada COVID-19 hastalarında serum 25(OH)D eksikliği olan ve olmayanlar arasında yaş, cinsiyet, hastanede kalış süresi, biyokimyasal ve hematolojik parametreler açısından farklılık olup olmadığının incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Ankara Pursaklar Devlet Hastanesi'nde yatan ve PCR testi ile COVID-19 pozitifliği saptanan 413 hastanın verileri retrospektif olarak değerlendirildi. Serum 25(OH)D (<20 ng/mL)'den düşük olanlar vitamin D eksikliği olan grup olarak kabul edildi.

Bulgular: Biyokimyasal parametreler total bilirubin (p=0.007), potasyum (p=0.015) ve glukoz (p=0.038) değerleri açısından serum 25(OH)D eksikliği olan ve olmayan gruplar arasında anlamlı fark olduğu görüldü. Enflamasyon ve pıhtılaşma faktörleri olan CRP (p=0.051) ve fibrinojen (p=0.028) değerleri arasında 25(OH)D eksikliği olan grupta anlamlı fark bulundu. Benzer şekilde hematolojik parametrelerden hematokrit (p<0.05) ve Nötrofil sayısı (p<0.001) 25(OH)D eksikliği olan hastalarda anlamlı olarak farklıydı. 25(OH)D eksikliği olan ve olmayan gruplar arasında yaş, cinsiyet ve hastanede yatış süresi açısından fark bulunamadı.

Sonuç: Sonuç olarak hastanede yatan COVID-19 hastalarında 25(OH) D eksikliğinin bazı biyokimyasal, hematolojik ve inflamatuar faktörlerle ilişkili olduğu ancak yaş, cinsiyet ve hastanede yatış süresi ile ilişkili olmadığı bulgulandı.

Anahtar Kelimeler: COVID-19, 25(OH)D eksikliği, kan parametreleri

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INTRODUCTION

In addition to microbiological and radiological examinations, biochemical and hematological tests are also used for the diagnosis of the disease in COVID-19 infection. The biochemical and hematological tests will be useful in the diagnosis of tissue-organ damage related to infection, in identifying the patient with a poor prognosis and in monitoring the course of the disease.[1] Some biochemical and hematological parameters such as LDH, CRP, ALT and NEU are important in determining the severity and prognosis of COVID-19[2,3] and especially increased neutrophil lymphocyte ratio (NLO) is a marker of systemic inflammation in the severity of COVID-19 disease.[4] Moreover, meta-analysis studies reveal that AST, ALT and total bilirubin levels in COVID-19 patients are important parameters that determine the course of COVID-19 and should be included in routine tests.[5]

Vitamin D deficiency is a global health problem that concerns approximately 1 billion people worldwide[6] and a meta-analysis study conducted in Turkey shows that the prevalence of vitamin D deficiency varies between 58.9% and 66.6%. [7] Recent studies showing that vitamin D reduces the risk of respiratory tract infection also suggested that it may have an impact on the course of COVID-19 disease. Vitamin D, which has many pharmacological and physiological functions, plays an important role in the immune system by regulating antiviral mechanisms and inflammatory processes.[8] Vitamin D deficiency leads to the production of proinflammatory cytokines such as TNF-α, IL-1β and IL-6, resulting in increased CRP levels and inflammation.[9] It has been suggested that adequate vitamin D levels can prevent cytokine storms and reduce the severity of the disease by regulating inflammatory marker levels in COVID-19 patients.[10]

It has been observed that the serum vitamin D level is lower in COVID-19 positive patients than in negative patients.[10,11] Studies in different European countries[12-14] show that there is a relationship between the increasing number of COVID-19 cases, mortality and severity and vitamin D deficiency. In contrast, Chen et al.[15] showed that vitamin D deficiency or insufficiency, even vitamin D supplementation was not significant in the risk of COVID-19 or susceptibility to death in a meta-analysis study involving 536,105 patients. Similarly, Hastie et al.[16] demonstrated in a study of 341,484 UK Biobank participants that vitamin D deficiency or insufficiency was not associated with the severity or mortality of COVID-19 infection.

In short, studies examining the relationship between vitamin D and viral infections show conflicting results due to differences in methodology, demographics, vitamin D levels and supplement dosages in these studies.[17] From this point of view, in this retrospective study, we aimed to show the differences in age, gender, lenth of hospital stay, biochemical, hematological and inflammation parameters between COVID-19 positive patients with (≥20 ng/mL) and without vitamin D deficiency (<20 ng/mL).

MATERIAL AND METHOD

This single-center, retrospective study was conducted on 413 COVID-19 patients hospitalized in Ankara Pursaklar State Hospital, whose diagnosis was confirmed by real-time polymerase chain reaction (RT-PCR) between March 1, 2020 and January 31, 2021. The study was conducted only with patients who were discharged from the COVID-19 service, patients who were taken to intensive care or died were not included in the study. Serum 25(OH)D levels were processed by the Alinity i commercially available immunoassay kits in an Alinity i automated Analyzer (Abbott Laboratories, Illinois, United States). COVID-19 positive patients hospitalized in the ward were divided into vitamin D deficiency group [25(OH)D >= 20 ng/mL, n=374, 57.87±16.25 years old] and vitamin D deficiency group [25(OH)D]. <20 ng/mL, n=39, 62.87±12.00 years old].

The age, gender, length of hospital stay, routine blood tests (such as hemogram, biochemistry tests, coagulation parameters, biochemical, hematological and other laboratory data) of the patients were retrospectively scanned from the hospital information operating system. Also, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLT), and CRP/lymphocyte ratio (CLR) were calculated.

Ethical Consideration

The study was first approved by the Turkish Ministry of Health (28 February-2021). The study was carried out with the permission of Amasya University Non-interventional Clinical Researches Ethics Committee (Date: 08.04.2021, Decision No: 55). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

Data from research, IBM SPSS Version 22.0. (IBM Corp.) was analyzed using the program. The conformity of the data to the normal distribution was checked with the Kolmogorov-Smirnov / Shapiro Wilk test. Categorical variables are shown as numbers (n) and continuous variables as mean (mean). Chi-square test was used for group comparisons, Mann Whitney U Test was used for comparison of continuous data not suitable for normal distribution and two groups, and t test was used for comparison of continuous data suitable for normal distribution and two groups. Whether there is a significant relationship between biochemical parameters, inflammation and coagulation factors and hematological data and length of hospital stay was examined by looking at the correlation coefficients.

The effects of age, gender, and length of hospital stay on Vitamin D deficiency were investigated using binary logistic regression and the parameters that could be effective in predicting the diagnosis of vitamin D deficiency by Roc Curve Analysis.

RESULTS

A total of 413 COVID-19 positive hospitalized patients [male (n=233; 56.4%); female (n=180; 43.6%)] were included in the study. 25(OH)D levels were < 20 ng/ml in 39 of these patients and ≥20 ng/ml in 374 patients. There was no significant difference between the groups with and without vitamin D deficiency in terms of age (p=0.095), length of hospital stay (p=0.333) and gender (p=0.734) (**Table 1**). Similarly, as a result of Binary Logistic Regression Analysis, age(p=0.103), gender(p=0.995 and length of hospital stay (p=0.222) were not significantly associated with vitamin D deficiency, which is the dependent variable (p=0.103; p=0.995; p=0.222) (**Table 2**).

Table 1. Age, gender and length of hospital stay in groups with and without vitamin D deficiency

	Group vitamin D deficiency		Group without vitamin D deficiency		Statistics	p
	n	Mean± SD	n	Mean± SD		
Age	39	62.87±12.00	374	57.87±16.25	6110.000	0.095*
Length of hospital stay	39	11.59±7.87	374	10.03±5.58	6608.000	0.333*
Gender						
Male	21		212		0.734	
Famale	18		162	0.116**		
Total	39		374			

*Mann Whitney U test, ** Chi-Square Test Statistic, SD, Standard deviation

Table 2. Logistic Regression Analysis of the relationship between age, gender, length of hospital stay and vitamin D Deficiency

	S.E.	z	Exp(B)	95% C.I.for Exp(B)		p
				Lower	Upper	
Age	0.011	2.654	0.982	0.960	1.004	0.103
Gender	0.344	0.000	1.002	0.510	1.968	0.995
Length of hospitalization	0.024	1.490	0.972	0.928	1.018	0.222

There were significant differences in biochemical parameters such as total bilirubin (p=0.007), glucose (p=0.038) and potassium (p=0.015) between the groups with and without vitamin D deficiency. Although AST (p=0.251) and ALT (p=0.249) values were higher in the vitamin D deficient group, they were not statistically significant. Among the inflammation and coagulation factors, CRP (p=0.041) and fibrinogen (p=0.048) were found to be significantly higher in the vitamin D deficiency group. On the other hand, there were no significant differences between the levels of coagulation factor D-Dimer (p=0.332) and inflammation marker Ferritin (p=0.781), which are important parameters for COVID-19. It was observed that the levels of HCT (p=0.006) and NEU (p<0.0001) were significantly higher in the patient group with vitamin D deficiency. On the other hand, there was no significant difference between the groups in terms of NLR (p=0.119) and PLR rates (p=0.520), which are important inflammatory markers showing the severity of COVID-19 (**Table 3**).

Table. 3 Biochemical Parameters, Inflammation, Coagulation Factors and Hematological Data in the Groups with and without Vitamin D Deficiency

	Group Vitamin D Deficiency	Group Without Vitamin D Deficiency	t	p
	Mean ± SD	Mean± SD		
AST (U/L)	35.86±5.85	31.41±3.72	568.500	0.251**
ALT (U/L)	39.85±5.45	34.67±1.28	1.152	0.249*
AST/ALT	1.09±0.22	1.26±0.04	-0.713	0.486*
Total bilirubin (mg/dL)	0.63±0.02	0.47±0.03	2508.50	0.007**
Üric acid (mg/dL)	11.53±3.02	10.71±3.97	-0.464	0.643*
BUN (mg/dL)	27.63±3.18	20.86±1.15	1.518	0.131*
Creatinine (mg/dL)	7.57±0.65	7.98±0.14	4006.00	0.558**
EGFR (mL/dk/1.73 m²)	80.54±3.52	89.14±1.32	-1.882	0.061*
LDH (U/L)	340.75±40.12	266.13±8.17	1.822	0.078*
CK-MB (U/L)	16.8±3.28	20.10±2.17	211.500	0.557**
Glucose (mg/dL)	201.73±23.34	153.38±6.04	1.954	0.038*
Sodium (mmol/L)	123.91±5.63	121.72±1.91	6783.50	0.885**
Potassium (mmol/L)	4.39±0.09	4.17±0.027	2.448	0.015*
Calcium (mg/dL)	8.64±0.15	8.63±0.070	0.027	0.979*
Chlorine (mmol/L)	98.07±0.76	99.49±0.99	-0.502	0.619*
CRP (mg/dL)	19.69±2.15	15.67±0.58	1.967	0.041*
CLR (CRP/ LYM)	11.96±1.38	12.15±0.63	5521.00	0.338**
D-Dimer(mg/L)	1.28±0.38	1.33±0.17	6427.50	0.332**
Ferritin (ng/mL)	479.27±92.00	460.42±31.79	862.00	0.781**
Fibrinogen (mg/dL)	458.71±54.67	376.75±18.16	3961.50	0.048**
PCT (%)	0.24±0.017	0.21±0.004	5901.500	0.139**
INR	1.15±0.07	1.11±0.02	3799.500	0.969**
APTT (sn)	22.92±0.89	23.73±0.25	4112.000	0.085**
RBC (10^6/µL)	4.78±0.09	4.74±0.02	0.407	0.684*
HGB (g/dL)	13.83±0.29	13.50±0.08	1.108	0.268*
HCT (%)	169.74±24.41	97.13±4.02	2.934	0.006*
MCV (fL)	87.18±0.89	86.53±0.34	0.586	0.558*
MCH (pg)	28.98±0.32	28.57±0.13	0.964	0.336*
MCHC (g/dL)	33.24±0.12	32.99±0.055	5971.00	0.169**
RDW (%)	13.65±0.22	14.08±0.10	6223.500	0.313**
WCB (10^3/µL)	8.14±1.14	6.54±0.17	1833.500	0.117**
LYM (10^3/µL)	2.17±0.20	1.85±0.063	1.464	0.144*
NEU(10^3/µL)	5.27±0.37	4.21±0.14	4398.500	0.000**
NLR (NEU/ LYM)	3.35±0.43	3.27±0.17	5844.500	0.119**
MON (10^3/µL)	0.59±0.06	0.53±0.024	5670.000	0.070**
BAS(10^3/µL)	0.025±0.003	0.02±0.003	6417.000	0.453**
EOS(10^3/µL)	31.09±7.06	23.95±2.12	5836.000	0.194**
PLT (10^3/µL)	263.67±19.78	235.48±4.81	6157.500	0.269**
PLR (PLT/ LYM)	151.32±14.40	170.29±6.37	6475.500	0.520**
MPV (fL)	9.41±0.14	9.29±0.042	0.807	0.420*
PDW (%)	16.71±0.38	16.51±0.126	0.461	0.645*

*t Test, **Mann Whitney U Test

In the study, we also evaluated the correlations between laboratory parameters and length of hospital stay in patient groups with and without vitamin D deficiency. Although there was a correlation between some parameters and the length of hospital stay in the group without vitamin D deficiency, no correlation was observed with these parameters in the patient group with vitamin D deficiency. In the group without vitamin D deficiency, serum uric acid (r=0.126, p=0.027), CRP (r=0.128, p=0.014), fibrinogen (r=0.157, p=0.006) levels and length of hospital stay were found to be positively correlated at 0.05, 0.05 and 0.01 significance levels, respectively. As serum uric acid, CRP and fibrinogen levels increased, the length of hospital stay also increased. On the other hand, negative correlation were observed at 0.05 significance level between APTT (r=-0.118, p=0.27), RBC (r=-0.113, p=0.28) levels and the length of hospital stay; As APTT and RBC levels decreased, the length of hospital stay increased (**Table 4**).

Table 4. Correlations between Length of Hospital Stay and Uric Acid, CRP, Fibrinogen, APTT, RBC in the Group Without Vitamin D Deficiency

	Uric acid	CRP	Fibrinogen	APTT	RBC
r	0.126*	0.128	0.157	-0.118	-0.113
p	0.027	0.014	0.006	0.027	0.028
N	304	372	309	351	374

In the ROC analysis, it was observed that age, gender and length of hospital stay [AUC (area under curve) values of 0.514, 0.581 and 0.547, respectively] were not parameters explaining vitamin D deficiency with sufficient sensitivity. In addition, glucose, CRP and HTC (AUC values of 0.705, 0.620 and 0.682, respectively) were found to be parameters that explain vitamin D deficiency with poor sensitivity (**Figure 1**).

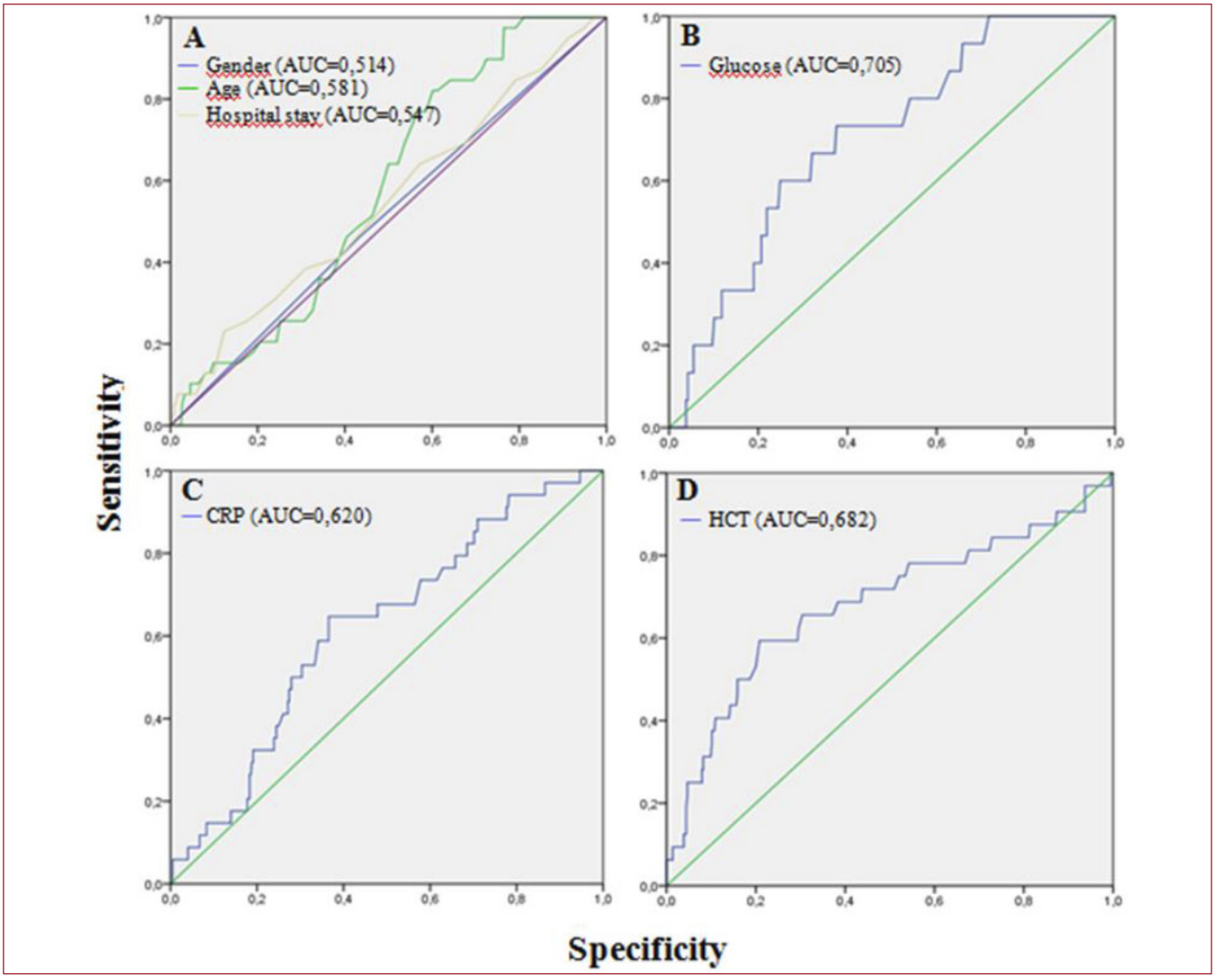

Figure 1. ROC curves analysis for vitamin D of Age, Gender, Length of Hospital Stay, Glucose, CRP and HCT Parameters in Predicting Vitamin D Deficiency in COVID-19 Patients.

ROC: receiver operating characteristic.

DISCUSSION

In our study, no significant difference was found between the groups with and without vitamin D deficiency in terms of age, length of hospital stay and gender. These findings supported by[18] suggest that COVID-19 patients with serum 25(OH)D < 20 ng/mL did not differ in age, gender, race, BMI or comorbidities compared with those with 25(OH)D ≥ 20 ng/mL. On the other hand, Demir et al.[19] stated in their study that COVID-19 patients with vitamin D >30 ng/ml had lower hospital stays than those with vitamin D levels <10 ng/mL and <20 ng/ml. Similarly, studies with COVID-19 patients serum 25(OH)D <20 ng/ml[20] and severe 25(OH)D deficiency (<10 ng/mL)[8] have found that these patients have longer hospital stays compared to patients with higher 25(OH)D concentrations.

Significant changes in heart and muscle damage (CK, CK-MB, Troponin-I, myoglobin increase), liver function (AST, ALT, total bilirubin increase and albumin decrease) and kidney function (BUN and creatinine increase) parameters in severe COVID-19 patients.[1] Similarly, higher levels of ALT, AST, GGT, and bilirubin were observed in patients with severe COVID-19 compared to those with mild.[5,22] Although not statistically significant in our study, it is seen that biochemical parameters such as ALT, AST, BUN and LDH increase in patients with vitamin D deficiency compared to patients without vitamin D deficiency. On the other hand, Demir et al.[19] showed that there was no difference between vitamin D levels of COVID-19 patients and biochemical and hematological parameters such as AST, ALT, Platelet, WBC, PLT, Urea, Creatinine, Na, K, Lymphocyte, neutrophil.

Bilirubin, which has antioxidant and anti-inflammatory effects, is the end product of heme catabolism. In our study, we observed higher bilirubin levels in the group with vitamin D deficiency compared to those without. This result is similar to studies showing that serum bilirubin levels are significantly higher in patients with severe COVID-19 symptoms such as pneumonia, ARDS, multiple organ damage, and septic shock.[22,23]

One of the statistically significant results of the current study is the presence of hyperkalemia in the vitamin D deficiency group. The serum potassium value, whose homeostasis is regulated by the kidneys, is important in the prognosis and management of COVID-19 patients. Hyperkalemia may occur in COVID-19 patients due to decreased urine output as a result of kidney failure or from acid/base imbalance caused by the side effects of the drugs that patients are treated.[24]

Vitamin D deficiency has been associated with increased infection formation, immunological disorders, cancers, obesity, insulin resistance, high fasting glucose concentrations and type 2 diabetes.[25] In our study, we observed a higher glucose level in COVID-19 patients with vitamin D deficiency compared to those without. Moreover, in ROC analysis, we determined that glucose level may be the most important parameter that can be used to predict vitamin D deficiency. In line with our findings, it was observed that blood glucose levels were high in COVID-19 emergency room patients with vitamin D deficiency and this situation increased the severity of the disease.[26] In relation to this, it has been reported that diabetic COVID-19 patients are at higher risk of hospitalization, severe lung involvement and mortality than non-diabetic patients.[27]

In our current study, in addition to biochemical parameters, hematological parameters such as CRP, fibrinogen, HCT and neutrophil count increased significantly in vitamin D deficient COVID-19 patients and these findings were found to be correlated with many studies in the literature. CRP is an acute phase protein synthesized in response to proinflammatory cytokines such as TNF-α, IL-1β and IL-6 and it appears to be elevated in COVID-19 positive cases. Similarly, vitamin D deficiency leads to the production of these proinflammatory cytokines, resulting in elevated CRP levels and inflammation.[9] Considering that C-reactive protein is an important marker for the severity of COVID-19 inflammation and cytokine storm, this result once again reveals the possible role of vitamin D in reducing the complications caused by cytokine storm.

It has been observed that COVID-19 patients with adequate vitamin D value have lower levels of inflammatory markers such as CRP and D-Dimer, have shorter hospital stays and better computed tomography results than those with low vitamin D value.[19] It has been reported that COVID-19 positive patients with serum vitamin D level >30 ng/ml have very low CRP levels moreover, vitamin D levels and ferritin, CRP and D dimer levels are inversely proportional.[10] In addition, it was found that vitamin D level was positively correlated with lymphocyte count and negatively correlated with CRP and fibrinogen levels in pediatric COVID-19 cases.[28] Compared to COVID-19 negative groups, COVID-19 patients were found to have higher levels of HCT, neutrophils and CRP but lower levels of Hb, monocytes, eosinophils and basophils.[29] Similarly, Bonetti et al.[3] reported that LDH, CRP, neutrophils, lymphocytes, albumin, APTT and age parameters are important determinants of hospital mortality in hospitalized COVID -19 patients. Pimentel et al.[30] observed that there was no significant change in CRP level but higher neutrophil count and neutrophil/lymphocyte ratio in COVID-19 intensive care patients with vitamin D deficiency compared to those who were not deficient.

In the current study, a negative correlation was observed between APTT and RBC levels and hospitalization time in the patient group without vitamin D deficiency, that is, as the level of these parameters decreased, the length of stay in hospital increased. Negative correlations between the severity of COVID-19 disease and the level of RBC can be explained in different ways. The decrease in the number of RBCs responsible for oxygen transport causes hypoxia,

which increases the severity of the COVID-19 disease or the COVID-19 virus damages the RBC structure. Thomas et al.[21] suggested that although there was no significant difference in hematological parameters such as RBC count and hematocrit between COVID-19 positive and healthy individuals, the COVID-19 virus could change the protein and lipid content of RBC membranes. Similarly, it has been reported that the virus may enter RBCs via spike and affect glycoprotein and hemoglobin function.[32] Significantly higher plasma D-dimer and APTT levels were observed in patients who died from COVID-19 infection, where APTT is one of the determining parameters in COVID-19 mortality.[33]

CONCLUSION

In the current study, higher total billurin, glucose, potassium, CRP, fibrinogen, HCT and neutrophil counts were observed in ward COVID-19 patients with serum vitamin D deficiency. In addition, in the group with a vitamin D level greater than 20 ng/ml, a positive correlation was observed with the length of hospital stay and Uric acid, CRP and fibrinogen levels and a negative correlation with APTT and RBC values. Serum vitamin D level has been effective on many biochemical, hematological and inflammation parameters in COVID-19 patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Amasya University Non-interventional Clinical Researches Ethics Committee (Date: 08.04.2021, Decision No: 55).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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