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Association between vitamin D hypovitaminosis and severe forms of COVID-19

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Abstract. – OBJECTIVE: Hypovitaminosis D may be associated with an increased susceptibility to infection, more severe COVID-19 forms, and a higher risk of death. The objective of this study was to investigate any possible connections between vitamin D status [as measured by serum 25-hydroxyvitamin D (25(OH)D) levels] and COVID-19 severity.

PATIENTS AND METHODS: In 2021, a cross-sectional study of consecutive adult COVID-19 patients was conducted. Anthropometric data, comorbidities, hospital setting, length of stay, respiratory support, outcome data, and vitamin D status were all evaluated.

RESULTS: The length of hospitalization among participants (n = 74; mean age 57.64 ± 17.83 years, 55.4% male) was 18.58 ± 10 days, the majority of the hospital setting was a medical ward (67.6%), and the respiratory support in the form of mechanical ventilation was represented by 12.2%. Hypertension (54.1%), obesity (64.9%), and overweight (64.9%) were the most common cardiometabolic risk factors. In the study group, 44.6% of participants had severe vitamin D deficiency (< 30 nmol/l), while 8.1% had vitamin D insufficiency (50 - 74.9 nmol/l). Furthermore, patients with severe COVID-19 (semi-intensive care unit, intensive care unit) had significantly lower serum 25(OH)D levels (32.9 *vs*. 20.5 nmol/l; *p* = 0.007). Participants with severe vitamin D deficiency were older and had more prevalent hypertension, requiring mechanical ventilation; 24.2% experienced a fatal outcome.

CONCLUSIONS: Severe vitamin D deficiency may contribute significantly to the influence of other cardiometabolic risk factors in COVID-19.

Key Words:
COVID-19, Vitamin D deficiency, ICU, Cardiovascular risk.

Introduction

In December 2019, a new microbiological agent was suspected of being the source of a cluster of pneumonia cases. WHO (World Health Organization) declared a pandemic following the isolation of a novel coronavirus (2019-nCoV, later renamed severe acute respiratory syndrome coronavirus 2 - SARS-CoV-2), a member of the beta coronavirus subgroup. The manifestation of coronavirus disease 2019 (COVID-19) is highly diverse, ranging from asymptomatic to life-threatening infectious diseases[1]. Coronaviruses belong to the family of viruses called *Coronaviridae*. Humankind became aware of the potential severity of respiratory illnesses caused by beta coronaviruses, one of the four genera of coronaviruses, during the epidemics of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), with mortality rates of 10% and 37%, respectively, and now the pandemic of SARS-CoV-2 (alpha-, beta-, gamma-, delta-)[2]. According to WHO data, as of January 16th, 2023, there have been 662,445,150 confirmed cases of COVID-19 worldwide, with 6,704,827 confirmed deaths, with Europe lead-

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ing the list of the most affected regions. As of the same date, the most recent COVID-19 data confirms 2,460,387 cases in the Republic of Serbia, with 17,619 deaths and a mortality rate of 0.72%[3]. COVID-19 is a systemic disease, and viral presence has been demonstrated in tissues other than the lungs, such as the heart and kidneys[4].

Vitamin D is responsible for regulating 3% of the human genome. Vitamin D receptors (VDR) are widely distributed in human tissues[5]. Several mechanisms for vitamin D's protective role in COVID-19 have been proposed, including the following: reduced lung permeability *via* increased angiotensin-converting enzyme 2 (ACE2) protein levels and subsequent downregulation of bradykinin 1 and 2 receptors, inhibition of cytokine storm *via* immunomodulating effects, and reinforcement of multiprotein junctional complexes[6,7]. A meta-analysis of 11,321 participants found that vitamin D supplementation reduced respiratory tract infections[8]. Hypovitaminosis D (serum 25(OH)D < 75 nmol/l) may be associated with increased susceptibility to infection, more severe forms of COVID-19, and an increased risk of death[5,6,9].

This study aimed to examine the possible links between vitamin D status (as measured by serum 25(OH)D levels) and COVID-19 severity.

Patients and Methods

A cross-sectional study was conducted on consecutive adult COVID-19 patients (aged ≥18, both sexes) admitted to our university medical center in 2021. During the study, each participant's demographic, and anthropometric data [age, sex, body mass index (BMI)], medical history data and clinical data (length of hospital stay, hospital setting, respiratory support, comorbidities), laboratory analysis data, and outcomes data (discharge/death) were collected from medical documentation. In addition, oxygen therapy, a high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), and mechanical ventilation (MV) as respiratory support measures were evaluated. In addition, we collected information on the following comorbidities of interest: obesity, diabetes mellitus [insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM)], hyperlipoproteinemia (HLP), arterial hypertension (HTA), arrhythmia, cardiomyopathies (CMPs), coronary artery disease [myocardial infarction (MI), angina pectoris], anemia, cerebrovascular insult (CVI). The information presented above was obtained by reviewing electronic patient records. Two researchers collected data as a result of a double-checking process. Due to anonymous data collection and patient confidentiality, each patient was assigned an identification code. Patients with insufficient data were excluded from participation in the study. According to the current literature definition of severe vitamin D deficiency[10], patients were divided into two groups: those with serum 25(OH)D levels less than 30 nmol/l and those with serum 25(OH)D levels greater than 30 nmol/l. According to the most recent research[5,10], serum 25(OH)D levels less than 50 nmol/l (equivalent to 20 ng/ml) indicate vitamin D deficiency. In contrast, levels less than 30 nmol/l (equivalent to 12 ng/ml) indicate severe deficiency. Serum 25(OH)D levels of < 75 nmol/l (equivalent to 30 ng/ml) were used to define vitamin D insufficiency.

Patients were also divided into two subgroups for subgroup analyses based on disease form and the most intensive setting of care: mild form and severe form. Patients suffering from the mild form of the disease were cared for in medical wards. Those with moderately severe, severe, and very severe forms, on the other hand, were treated in semi-intensive care and intensive care units, respectively. The National Protocol for the Treatment of COVID-19 Patients [mild form - medical ward; moderately severe form - semi-intensive care unit (SICU); severe/very severe form - intensive care unit (ICU)] defines the disease form[11].

Furthermore, each subject's body mass index (BMI) was obtained using clinical charts. Patients were divided into four subgroups based on BMI values: normal weight (from 18.5 to 24.9 kg/m^2), overweight (from 25 to 29.9 kg/m^2), class 1 obesity (from 30 to 34.9 kg/m^2), class 2 obesity (from 35 to 39.9 kg/m^2), and class 3 obesity (BMI of 40 kg/m^2 or higher).

The study was conducted following the Helsinki Declaration and was approved by the Ethics Committees of the Clinical Center of Vojvodina, Novi Sad, Serbia (approval number: 00-153) and the Faculty of Medicine Novi Sad, Novi Sad, Serbia (approval number: 01-39/94/1). All subjects provided informed consent.

Study Protocol

Anthropometric measurements were made following standard procedure[12]. A Real-Time reverse transcription polymerase chain reaction (RT PCR) SARS-CoV-2 assay technique was used to

analyze nasopharyngeal swabs and detect SARS-CoV-2 infection (Gentier 96E/96R Real-time PCR system - Xi'an Tianlong Science & Technology Co. Ltd, Xi'an City, Shaanxi, China). The chemiluminescent microparticle immunoassay (CMIA) method was used to measure serum 25(OH)D levels (Alinity, ABBOTT Laboratories, Chicago, IL, USA).

Statistical Analysis

Statistical Package for the Social Sciences version 23 (IBM Corp., Armonk, NY, USA) and Jamovi software version 2.3 (available at: https://www.jamovi.org) were used for statistical data analysis. Continuous normally distributed variables were presented as mean ± standard deviation while continuous asymmetrical variables were presented as median with interquartile range. Categorical variables were presented as a percentage. Continuous variables normality was assessed using the Shapiro-Wilk test. The Independent-samples *t*-test was used for parametric variables, while Mann-Whitney and Kruskal-Wallis tests were used for non-parametric data. The χ^2 test and Fisher exact test were used for the categorical data. Statistical hypotheses are tested at the level of statistical significance (alpha level) of 0.05.

Results

In total, 74 patients with SARS-CoV-2 infection were included in this study. Table I summarizes participants' descriptive statistics. The participants were mostly men (55.4%), with an average age of 57.6 ± 17.8 (range 18 - 96). The mean BMI of our study group was a median 27.9 ± IQR 7.1 kg/m^2 (range 18.7 - 44.0 kg/m^2). The most common comorbidity was hypertension, followed by obesity. Chronic therapy was used by 67.6% of patients while angiotensin-converting enzyme (ACE) inhibitors were used by 23%. Tobacco use was present in 5.4% of patients. Regarding nu-

Table I. Participants' baseline characteristics.

Demographic and anthropometric data			Comorbidities	N (%)
Age (years)		57.6 ± 17.8 (18-96)	HTA	40 (54.1%)
BMI (kg/m^2)		27.9 ± 7.1 (18.7-44)	Obesity	25 (33.8%)
Normal weight		35.1%	IDDM	5 (6.8%)
Overweight		31.1%	NIDDM	3 (4.1%)
Obesity class I		23.0%	HLP	3 (4.1%)
Obesity class II		8.1%	CMPs	4 (5.4%)
Obesity class III		2.7%	Anemia	10 (13.5%)
			Arrhythmia	6 (8.1%)
			Angina pectoris	1 (1.4%)
			MI	2 (2.7%)
			CVI	4 (5.4%)
Sex	Male 41	(55.4%)		
	Woman 33	(44.6%)		
Hospital days		18.58 ± 10 (2-47)		
Respiratory support			**Hospital setting**	
Room air		26 (35.1%)	Medical ward	50 (67.6%)
OT		28 (37.8%)	SICU	4 (5.4%)
HFNC		1 (1.4%)	ICU	20 (27%)
NIV		10 (13.5%)	***Outcome***	
MV		9 (12.2%)	Discharge	65 (87.8%)
			Death	9 (12.2%)

Continuous variables are presented as mean ± SD or median (interquartile range). Categorical variables are presented as a percentage. BMI - body mass index; ICU - intensive care unit; SICU - semi-intensive care unit; OT - oxygen therapy; HFNC - high-flow nasal cannula; NIV - non-invasive ventilation; MV - mechanical ventilation; HTA - arterial hypertension; IDDM - insulin-dependent diabetes mellitus; NIDDM - non-insulin dependent diabetes mellitus; HLP -hyperlipoproteinemia; CMPs - cardiomyopathies; MI - myocardial infarction, CVI - cerebrovascular insult.

tritional status, 64.9% of the 74 patients included in the study were overweight (31.1%) or obese (33.8%). Only 2.7% of patients were classified as having class 3 obesity. The sample's mean 25(OH) D level was 35 nmol/l. Vitamin D deficiency (30 - 49.9 nmol/l) was found in 40.5% of patients, while vitamin D insufficiency (50 - 74.9 nmol/l) was found in 8.1%. Furthermore, 44.6% of participants had severe vitamin D deficiency (< 30 nmol/l) (Figure 1).

Serum 25(OH)D levels did not differ statistically between normal weight, overweight, and obese participants (32.7 *vs.* 33 *vs.* 26.1; $p = 0.6$), but serum 25(OH)D levels were lower in the obese group (Figure 2).

Serum 25(OH)D levels were significantly lower in patients with the severe form of COVID-19 (semi-intensive care unit, intensive care unit) (32.9 *vs.* 20.5; $p = 0.007$) (Figure 3).

Patients with severe vitamin D deficiency (< 30 nmol/l) and patients with serum 25(OH)D levels greater than 30 nmol/l had a statistically significant age difference (63.7 ± 17.8 *vs.* 52.8 ± 16.5; $p = 0.008$), along with hypertension as comorbidity ($p = 0.004$) (Table II).

All patients who received mechanical ventilation (MV) had 25(OH)D levels of < 30 nmol/l ($p < 0.001$, Fisher).

The mortality rate differed significantly between the vitamin D groups. As many as 97.6% of patients with 25(OH)D levels greater than 30 nmol/l survived, whereas 24.2% of patients with 25(OH)D levels 30 nmol/l or less died ($p = 0.009$) (Table III).

Table II. Participants' baseline characteristics according to the vitamin D status.

		Vitamin D			
		≤ 30 nmol/l	> 30 nmol/l		*p*
Age		63.7 ± 17.8	52.8 ± 16.5	57.6 ± 17.8	0.008[c]
BMI		29.4 (IQR 7.8)	27 (IQR 6.5)	27.7 (IQR 7.1)	0.521[d]
Comorbidities:					
HTA	Yes	24 (72.7%)	16 (39.0%)	40 (54.1%)	0.004[a]
	No	9 (27.3%)	25 (61.0%)	34 (45.9%)	
Obesity	Yes	14 (42.4%)	11 (26.8%)	25 (33.8%)	0.217[a]
	No	19 (57.6%)	30 (73.2%)	49 (66.2%)	
DM	Yes	4 (12.1%)	4 (9.8%)	8 (10.8%)	0.516[b]
	No	29 (87.9%)	37 (90.2%)	66 (89.2%)	
HLP	Yes	1 (3%)	2 (4.9%)	3 (4.1%)	0.582[b]
	No	32 (97%)	39 (95.1%)	71 (95.9%)	
CMPs	Yes	3 (9.1%)	1 (2.4%)	4 (5.4%)	0.230[b]
	No	30 (90.9)	40 (97.6%)	70 (94.6%)	
Anemia	Yes	5 (15.2%)	5 (12.2%)	10 (13.5%)	0.712[a]
	No	28 (84.8%)	36 (87.8%)	64 (86.5%)	
Arrhythmia	Yes	5 (15.2%)	1 (2.4%)	6 (8.1%)	0.059[b]
	No	28 (84.8)	40 (97.6%)	68 (91.9%)	
Angina pectoris	Yes	1 (3.0%)	-		
	No	32 (97.0%)	41		
MI	Yes	-	2 (4.9%)		
	No	33	39 (95.1%)		
CVI	Yes	4 (12.1%)	-		
	No	29 (87.9%)	41		
Total (%)		33 (100.0%) 44.6%	41 (100.0%) 55.4%	74 (100.0%) 100.0%	

[a]χ^2 test; [b]Fisher exact test; [c]independent-samples *t*-test; [d]Mann-Whitney test. BMI - body mass index; HTA - arterial hypertension; DM - diabetes mellitus (insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus); HLP - hyperlipoproteinemia; CMPs - cardiomyopathies; MI - myocardial infarction, CVI - cerebrovascular insult.

Table III. Differences in mortality according to vitamin D status.

		Vitamin D			
		≤ 30 nmol/l	> 30 nmol/l		*p*
Death	No	25 (75.8%)	40 (97.6%)	65 (87.8%)	0.009[b]
	Yes	8 (24.2%)	1 (2.4%)	9 (12.2%)	
		33	41	74	
		(100.0%)	(100.0%)	(100.0%)	

[b]Fisher's exact test.

Discussion

To the best of our knowledge, this is the first study in a Serbian tertiary medical center to investigate a possible link between vitamin D status and the clinical course of COVID-19. It is important to note that a group of researchers conducted a study[13] on 120 SARS-CoV-2 infected subjects in Serbia to investigate the genetic variation of lower bioavailability of micronutrients, including vitamin D, as a possible marker of COVID-19 severity. The main findings of the current study show that patients with a severe form of COVID-19 had significantly lower serum 25(OH)D. This finding is consistent with the findings of a previous meta-analysis[14] (1,368 patients) that revealed a causal role for vitamin D deficiency in COVID-19 severity, as well as the findings of a German study[15] that revealed a 6-fold increased risk of disease severity. According to a recent review of clinical studies and the study of Nimer et al[16,17], vitamin D sufficiency may reduce the clinical course of COVID-19, mortality, and general infection rates. Bassatne et al[18] conducted a systematic review and meta-analysis to determine the relationship between COVID-19 mortality and serum 25(OH) D levels. Above all, they discovered significantly lower serum 25(OH)D levels in SARS-CoV-2 positive patients compared to SARS-CoV-2 negative patients. Furthermore, in this study, lower serum 25(OH)D levels were associated with an increased risk of ICU admission, but mortality rates remained insignificant. We found a significant difference in COVID-19 mortality between groups with severe vitamin D deficiency and those with 25(OH)D levels greater than 30 nmol/l. This is consistent with the findings of Ilie et al[19] previous meta-analyses. In their study, they observed

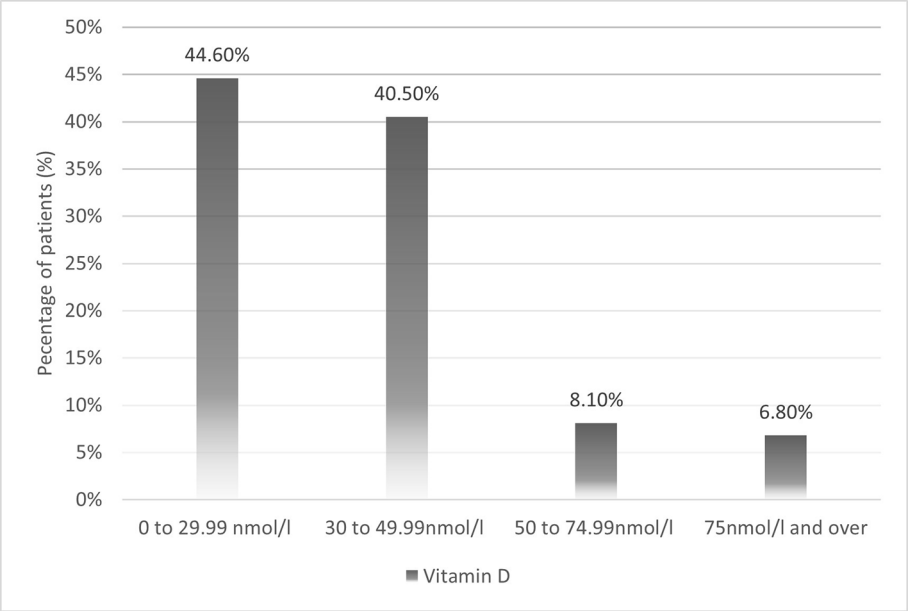

Figure 1. Vitamin D status of the study group (nmol/l).

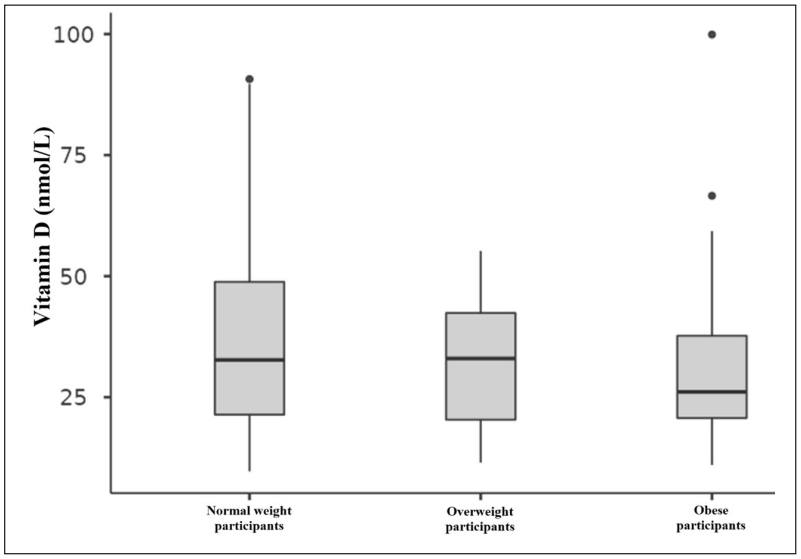

Figure 2. Vitamin D status of the study group according to the BMI classes.

a crude negative correlation between vitamin D levels and mortality rates in the populations of 20 European countries. In addition, a two-center (Boston, New York) cohort study[20] showed an independent relationship between vitamin D status and fatal outcomes in conjunction with MV usage. In our study, all patients who required MV had 25(OH)D levels less than 30 nmol/l. In the current study, we discovered that patients with severe vitamin D deficiency (< 30 nmol/l) were significantly older than patients with serum 25(OH) D levels greater than 30 nmol/l. Previous studies[21,22] showed that older vitamin D-deficient patients were more likely to develop a severe course of COVID-19. Similar to the findings of Ng et al[22] in a large meta-analysis of 375,000 subjects and one of the earliest comprehensive studies from New York City, our study found that hypertension and obesity were the most common comorbidities in COVID-19 patients[23]. Furthermore, our subgroup analysis confirmed that severely vitamin D deficient patients were more likely to have hypertension than patients with 25(OH)D levels above 30 nmol/l. Endothelial dysfunction has been linked to vitamin D deficiency and an increased risk of hypertension[24,25]. According to the most recent research, COVID-19 is a potentially endothelial disease with a pathophysiological concept of cytokine storm that may worsen initial pneumonitis, leading to destructive alveolitis and acute respiratory distress syndrome[26,27]. Endothelial dysfunction can cause thrombosis *in*

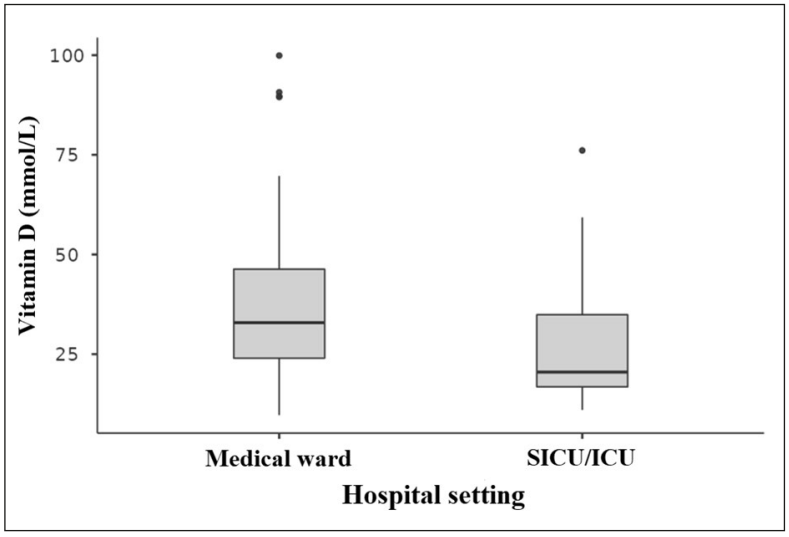

Figure 3. Vitamin D status of the study group according to the hospital setting.

situ in the pulmonary blood vessels, cerebral arteries, and peripheral veins. A lack of vitamin D may hasten the cytokine storm by interfering with the immune response. Baktash et al[21] discovered an increase in cytokine storm markers and significantly higher D-dimer levels in patients with 25(OH)D < 30 nmol/l. Endothelial dysfunction may be prevented by vitamin D-dependent inhibition of superoxide radical generation and preservation of functional cells in conjunction with nitric oxide release[24,26]. According to a group of researchers[28] who examined 1,739 subjects from the Framingham Offspring Study, a vitamin D level of 37 nmol/l correlates with a higher risk of cardiovascular events. Furthermore, vitamin D deficiency is widely accepted to be associated with cardiometabolic diseases, and a previous large meta-analysis (69,994 participants) confirmed the inverse relationship between 25(OH) D concentration and cardiovascular disease risk. A small pilot study in Spain[29] with 34.2% hypertension and 10.5% diabetes among COVID-19 patients found that subjects who did take vitamin D supplements spent less time in the intensive care unit. According to the current study, 64.9% of people were overweight or obese. An earlier pilot study discovered that obese subjects with true vitamin D deficiency (less than 37.5 nmol/l) had significantly higher levels of sE-selectin, hs-CRP (high-sensitivity C-reactive protein), and 2hPG (2-hour post-load plasma glucose)[24]. In our study, there was no significant difference in BMI between patients with severe vitamin D deficiency (≤ 30 nmol/l) and patients with serum 25(OH) D levels greater than 30 nmol/l. This could be due to prior abundant vitamin D supplementation in the obese population, based on previous data about synchronous epidemics of vitamin D deficiency and obesity[30]. In our study, 72.7% of patients with vitamin D deficiency (≤ 30 nmol/l) had pre-existing arterial hypertension, 15.2% had arrhythmia, 9.1% had cardiomyopathies, 12.1% had cerebrovascular insult, and 3% had angina pectoris. In comparison, the percentage of metabolic disorders for obesity was 42.4%, diabetes was 12.1%, and hyperlipoproteinemia was 3%. Because of the already present active inflammatory processes, these patients may be at a higher risk for a severe form of COVID-19. In light of the abovementioned, a recent review[28] emphasized the role of vitamin D levels in predicting illness severity and COVID-19 complications as clinical endpoints in this patient population. The study has some limitations, including a small number of enrolled participants, potential confounders such as age and comorbidities, and a low number of adverse clinical events (e.g., death, MV), in addition to unavailable information on prior consumption of vitamin D supplements and sunlight exposure.

Conclusions

According to the findings of this study, severe vitamin D deficiency may play a significant role in the synergy of the influence of other cardiometabolic risk factors in COVID-19. Due to the impossibility of determining the causality between vitamin D hypovitaminosis and adverse clinical outcomes in observational studies, more research and randomized controlled trials are urgently needed to validate this finding and provide evidence for the proper prevention and treatment of this modifiable risk factor in this pandemic era.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was conducted following the Helsinki Declaration and was approved by the Ethics Committees of the Clinical Center of Vojvodina, Novi Sad, Serbia (approval number: 00-153) and the Faculty of Medicine Novi Sad, Novi Sad, Serbia (approval number: 01-39/94/1).

Informed Consent

All subjects provided informed consent.

Data Availability

The data associated with the paper are available from the corresponding author upon reasonable request.

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Authors' Contributions

Mia Manojlovic contributed significantly to study conception and design, data acquisition, data interpretation, and manuscript writing; Branislava Ilincic contributed significantly to study conception and design and manuscript writ-

ing; Dragana Tomic Naglic contributed significantly to study conception and study design; Velibor Cabarkapa, Ivana Bajkin, and Aleksandra Plecas Djuric contributed significantly to study supervision and study design; Ivor Kolarski and Marko Bojovic contributed significantly to data acquisition and data analysis; Ivana Urosevic and Edita Stokic contributed significantly to study supervision; Esma R. Isenovic contributed significantly to manuscript writing and critical revision of the manuscript for important intellectual content; and in the final version of the manuscript was read and approved by all authors.

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