Original article

The Role of Serum Vitamin D Concentrations in Predicting COVID-19 Course and Outcome

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SUMMARY

Introduction/Aim. The coronavirus disease 2019 (COVID-19) pandemic had significant acute and long-term impact on people's health. As the available literature sources have shown that the premorbid conditions affect the course of COVID-19, we aimed to investigate the role of admission vitamin D concentration to predict the outcome of hospitalized COVID-19 patients.

Methods. An observational, prospective cohort study was conducted on 329 COVID-19 patients hospitalized at the University Clinical Centre Kragujevac, between October and December 2021. Within 24 hours of admission, vitamin D level was measured from the peripheral venous blood. Medical history data and socio-demographic characteristics were obtained anamnestically and using Health Information System (COMTRADE, Serbia). Lethal outcome and intensive care unit (ICU) admission were considered primary end-points.

Results. The prevalence of hypovitaminosis D on admission in our cohort was 27.7%. Both non-survivors and patients requiring ICU admission more frequently had hypovitaminosis D compared to survivors (42,9% versus 21,0%; p < 0,001) and patients on a standard level of care (31,5% verus 25,3%; p = 0,029). Our research showed that vitamin D concentration < 20 ng/mL was an independent predictor of mortality (aOR 2.142 [95% CI 1.226 – 3.744]). However, hypovitaminosis D upon hospital admission did not show a significant impact on ICU admission.

Conclusion. Low vitamin D concentration on admission could be a significant predictor of outcome in hospitalized COVID-19 patients.

Keywords: **coronavirus disease, intensive care unit, mortality, vitamin D**

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic was a major public health event affecting people's health and the economy worldwide (1). The disease manifestation varied from asymptomatic to life-threatening forms associated with extrapulmonary presentation (2).

According to the WHO's latest update, most people with COVID-19 developed a mild (40%) or moderate (40%) form of the disease. However, 15% of the infected patients developed a severe form and approximately 5% of patients were affected with a critical form, characterized by acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure with acute cardiac or kidney injury (3). Literature suggests that the elderly and patients with comorbidities were more frequently affected by COVID-19 and were more likely to develop severe forms (1). Therefore, it could be justified to explore possible links between the pre-existing conditions and outcome of the disease.

Besides age and comorbidities, low vitamin D concentrations is also recognized as a potential risk factor for adverse outcomes of COVID-19 (4). Vitamin D is a fat-soluble steroid and was primarily recognized for its role in regulating bone metabolism and calcium and phosphorus homeostasis. Recent researches have revealed new roles of vitamin D such as immunomodulation, impact on cardiovascular health, and even infection disease prevention. Vitamin D has an influence on more than 2500 genes affecting the pathophysiology pathways of diseases including cancer, autoimmune diseases, and acute respiratory tract infections (5). Experimental studies have shown that vitamin D stimulates the expression of the innate and adaptive immune system; also, vitamin D's immunomodulatory and anti-inflammatory role is particularly important in viral infections (6). Although studies about vitamin D and innate immunity were focused on its antibacterial mechanisms, it is shown that vitamin D also stimulates antiviral immunity through several mechanisms (4).

Previous publications revealed that age, sex, comorbidities, and certain laboratory parameters were associated with a higher risk of both disease onset and disease course (7, 8). Considering the fact the mechanisms of the disease progression and clinical deterioration are still not fully understood, we aimed to explore a potential link between vitamin D status and COVID-19. As a steroid hormone, vitamin D has multiple physiological roles, including immunomodulation and antiviral defence. Low values of vitamin D are associated with numerous diseases, which is especially significant when considering the estimated prevalence of hypovitaminosis D in different parts of the world. According to the Endocrine Society, a serum level of vitamin D below 20 ng/mL is designated as vitamin D deficiency, which compromises immunomodulatory functions and is associated with increased susceptibility to viral and bacterial infections (9).

However, literature data provides us with inconsistent results in regard to the relationship between vitamin D serum concentration and COVID-19 course and outcome (10 - 12). Therefore, our study aimed to investigate the predictive value of pre-admission vitamin D serum level on the course and outcome of COVID-19.

METHOD

The study was a part of the "COVID-19 admission PREDICTors of OUTCOME" (COVID-19 PREDICT OUTCOME) Registry, which was granted approval from the University Clinical Center Kragujevac (Serbia) Ethical committee. This clinical, observational, prospective cohort study included 329 adult COVID-19 patients hospitalized at the University Clinical Centre Kragujevac from October to December 2021. Patients were followed during hospital treatment, and ICU admission and in-hospital mortality were observed as the primary endpoints. Inclusion criteria were: adult age (≥ 18 years old), patient consent to participate in the study, and confirmed SARS-CoV-2 infection by RT-PCR or antigen test. Exclusion criteria were: underage (< 18 years old), patient refusal to participate in the study, pregnancy and postpartum period, chronic kidney disease grade 3 - 5 (based on pre-admission assessment using the Cockroft Gault index), initial hospitalization for non-COVID pathology, terminal phase of malignant disease, and continuation of treatment in another institution.

Data collection

Medical history regarding comorbidities was obtained from patients' electronic medical records (Health Information System, ComTrade, Serbia).

Within 24 hours of admission, vitamin D level was measured from the peripheral venous blood. According to our laboratory, low vitamin D serum level was referred to the value below 20 ng/ml.

Statistical analysis

Statistical analysis was performed using the SPSS statistical package, version 23.0 (IBM corporation, Armonk, NY). Categorical data were presented as the absolute and relative frequency, and continuous variables as median with interquartile range (IQR). Mann-Whitney U test was used to test differences in quantitative data. According to Kolmogorov-Smirnov test, non-normal distribution was found, so Spearman's correlation was used to test their relationship. The Chi-square test was used to analyze the counting data. Uni- and multivariable regression was performed. Odds ratio (OR) with the belonging 95% confidence interval (95% CI) shows the strength of the relationship between examined variables and outcomes for univariate and adjusted odds ratio (aOR) with the belonging 95% CI for multivariate analysis. "P" values < 0.05 were considered significant.

RESULTS

Three hundred twenty-nine COVID-19 patients hospitalized in the University Clinical Center Kragujevac were included in the study. Their demographic characteristics and medical history are presented in Table 1. The median age of participants was 69 years, and the most common comorbidities

Table 1. *Demographic and medical history characteristics of COVID-19 survivors and non-survivors*

| Cohort characteristics		Percentage (frequency) or median value (with interquartile range)
Sex	Male	59.3% (195)
	Female	40.7% (134)
Age (years)		Median: 69.0 (IQR 17)
COMORBIDITIES		
Arterial hypertension		67.7% (222)
Atrial fibrillation		7.3% (24)
Previous myocardial infarction		6.4% (21)
Diabetes mellitus (oral therapy)		60.9% (53)
Diabetes mellitus (insulin therapy)		39.1% (34)
COPD[1]		2.7% (9)
Asthma		1.5% (5)
Neurological condition[2]		11.3% (37)
Malignancy		7.3% (24)
Hypothyreosis		2.1% (7)
Charlson comorbidity index		Median: 3.0 (IQR 2)
DISEASE COURSE AND OUTCOME		
Hospital stay (days)		Median: 13.0 (IQR 10.5)
Duration between disease onset and hospital admission (days)		Median: 7.0 (IQR 4.25)
Duration between SARS-CoV-2 identification and hospital admission (days)		Median: 5.0 (IQR 5)
Oxygen support requirement		99.4% (327)
Mortality		30% (98)
ICU admission		32.8% (108)
Either primary endpoint[3]		43.2% (142)

Abbreviations: ICU - intensive care unit; IQR - interquartile range.

* - statistical significance level at < 0.05

1) Chronic obstructive lung disease

2) Neurological condition: history of stroke, brain tumor or malformation, vascular disease, dementia of any etiology, etc.

3) Either primary endpoint – lethal outcome and/or ICU admission
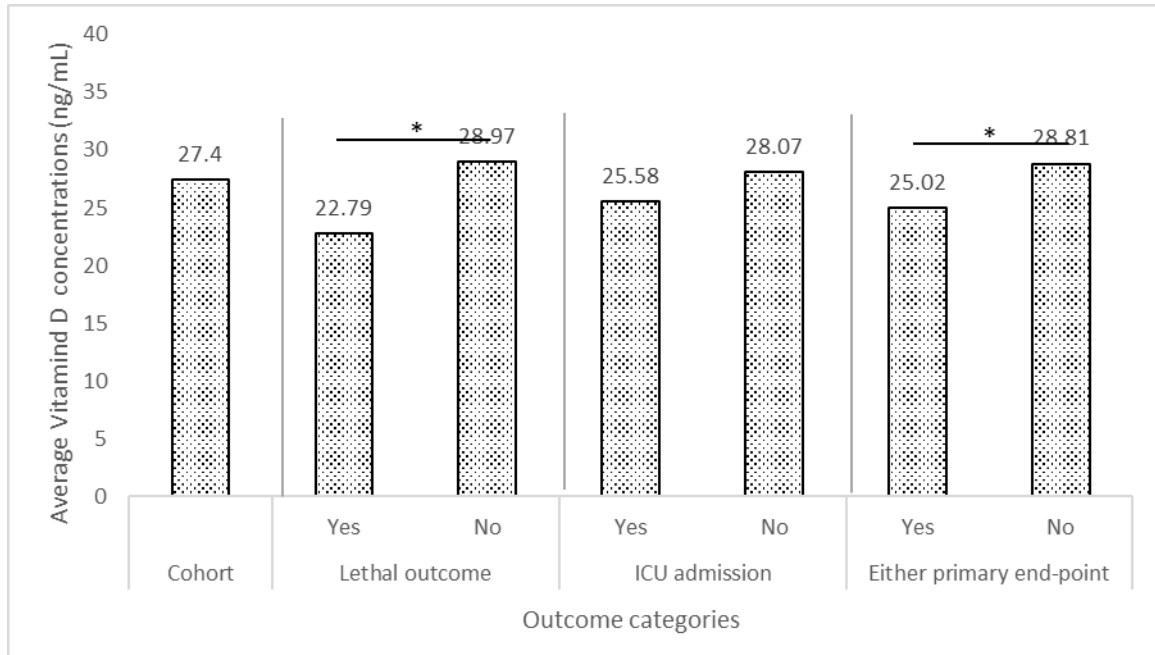
Figure 1. A*verage serum vitamin D concentrations by outcome groups*

Table 2. *Percentage representation of vitamin D serum concentration*

		Normal level[1]	**Low level[2]**	**„p" value**
Cohort		72.6%	27.4%	
Lethal outcome	**yes**	57.1%	42.9%	< 0.001
	no	79.0%	21.0%	
ICU admission	**yes**	68.5%	31.5%	0.029
	no	74.7%	25.3%	
Either primary end-point	**yes**	63.8%	36.2%	0.003
	no	79.3%	20.7%	

Abbreviations: ICU - intensive care unit

*statistical significance level at < 0.05

1) normal level: 20 – 40 ng/mL

2) low level: < 20 ng/mL

Table 3. *Crude and adjusted OR (with 95% CI and p values) for different outcomes with regard to primary end-points occurrence (mortality, ICU admission and composite outcome)*

Outcome	Vitamin D level	End-point occurrence (%)	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Lethal outcome	Vit D 20 – 40 ng/mL	23.6%	1		1	
	Vit D < 20 ng/mL	46.7%	**2.828** (1.696 - 4.715)	< 0.001	**2.142** (1.226-3.744)	0.007
ICU admission	Vit D 20 – 40 ng/mL	31%	1		1	
	Vit D < 20 ng/mL	37.8%	1.354 (0.816 - 2.247)	0.241	1.438 (0.814-2.541)	0.211
Either primary end-point	Vit D 20 – 40 ng/mL	37.7%	1		1	
	Vit D < 20 ng/mL	56.7%	**2.165** (1.323 - 3.542)	0.002	**1.868** (1.097-3.182)	0.021

Abbreviations: ICU - intensive care unit

* OR was adjusted for age, gender, days from symptom onset and comorbidities

were arterial hypertension and diabetes mellitus. Mortality in our cohort was 30% (n = 98), ICU admission requirement was 32.8% (n = 108), and either primary end-point was present in 43.2% of patients (n = 142).

Significantly lower vitamin D concentrations were noted in non-survivors and in patients who developed either primary end-point (Figure 1). Although patients who required ICU admission had lower vitamin D values on average, statistical significance was not found.

The prevalence of hypovitaminosis D on admission in our cohort was 27.7%. As seen in Table 2, both non-survivors and patients requiring ICU admission more frequently had hypovitaminosis D, compared to survivors and patients on a standard level of treatment.

Table 3 shows crude and adjusted OR for vitamin D levels in predicting primary end-points. We note that vitamin D concentration < 20 ng/mL was an independent predictor of mortality (OR 2.828 and aOR 2.142, respectively) and occurrence of either primary-end point (OR 2.165 and aOR 1.868, respectively), even after adjusting for other variables (including age, sex, days from disease onset, and comorbidities). However, hypovitaminosis D upon hospital admission did not show a significant impact on ICU admission.

DISCUSSION

Our cohort included 329 patients diagnosed with SARS-CoV-2 infection who were hospitalized at the University Clinical Center Kragujevac from September to December 2021. The study was a part of the "COVID-19 admission PREDICTors of OUTCOME" (COVID-19 PREDICT OUTCOME) Registry. The main goal was to examine the relationship between serum vitamin D concentration on admission and the course and outcome of COVID-19.

In the data collecting period, there was a presumable predominance of the delta SARS-CoV-2 variant in our country. The median age of our participants was 69 years, and the mortality rate was 30%. The median length between the onset of the disease and admission to the hospital was 13 days. Most patients required oxygen support (99.4%), 32.8% required ICU treatment, and 43.2% experienced either primary outcome (lethal outcome and/or ICU admission) (Table 1).

In our cohort, the prevalence of hypovitaminosis D was 27.7%. We note that hypovitaminosis D on admission was more frequent in non-survivors compared to survivors, and in those who required ICU admission compared to the standard care (Table 2). In addition, significantly lower concentrations of vitamin D on admission were found in those with

the lethal outcome and either primary endpoint (Figure 1).

Given the importance of vitamin D in overall health, especially in viral infections, we thought it was justified to interpret the values of this vitamin in the context of COVID-19. Low vitamin D serum concentration could be viewed as a pre-existing condition, but could also be a consequence of the negative impact of the virus on the immune defence (13). Therefore, we aimed to examine the link between vitamin D serum concentrations on admission and COVID-19 course and outcome, regardless of the mechanism of hypovitaminosis D at the time of admission. Given the results, the connection between low vitamin D values and unfavorable outcomes of COVID-19 could be hypothesized (Table 2 and 3). While the link between vitamin D serum concentration and COVID-19 mortality was found only in the part of the published studies, it is reasonable to assume that such a connection exists. In addition to the direct effect of vitamin D on antiviral immune defense (6), hypovitaminosis D is linked with other factors associated with poor outcome, such as older age (9) and certain comorbidities like chronic kidney disease (14).

We also aimed to examine the predictive power of admittance vitamin D serum concentration. After adjusting for other available variables (age, sex, comorbidities, days since disease onset), patients with hypovitaminosis D had more than two times higher risk of the lethal outcome than those with normal vitamin D serum levels on admission (aOR 2.142 [95% CI 1.226 – 3.744]). Also, these patients had approximately 1.9 times higher risk of either primary endpoint (aOR 1.868 [95% CI 1.097 – 3.182]), as shown in Table 3. However, there was no statistical significance in regard to predicting ICU admission.

Other authors have also tried to examine whether the value of vitamin D on admission could predict the course and outcome of COVID-19. However, literature data on this topic are inconsistent. Some meta-analyses suggest a link between hypovitaminosis D and a higher risk of acquiring SARS-CoV-2 infection and even developing severe clinical forms. While some publications reveal an association between hypovitaminosis D and lethal outcome, others do not implicate this connection (10, 11, 15). However, the results of our research indicate a possible relationship between hypovitaminosis D and mortality from COVID-19. The potential causes of conflicting data from the literature could be explained by the significant heterogeneity of the study population (socio-demographic characteristics, disease severity, vitamin D related genetic polymorphism, etc.), different methodological and statistical approach, predominance of different SARS-CoV-2 variants, and others. In addition, it is essential to consider the timing of vitamin D sampling.

LIMITATIONS

There are certain limitations of the study. Firstly, the number of patients included in the study could limit the generalization of the results. Secondly, the variables included in the multiple regression model is limited, as some potential predictors were not included. Also, we did not consider the possible vitamin D supplementation of patients before admission to hospital treatment.

CONCLUSION

Our results show that hypovitaminosis D is an independent predictive factor of mortality. However, the results of our study do not indicate an association between hypovitaminosis D and an increased risk of ICU admission. Sampling vitamin D on admission could make the physician expect a less favourable outcome if the values are below the reference range and adjust the treatment accordingly. Besides our topic, an open question is how could supplementing healthy individuals with hypovitaminosis D affect COVID-19 course and outcome, and that could be investigated in possible new waves.

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Uloga serumske koncentracije vitamina D u predikciji toka i ishoda COVID-19 infekcije

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S A Ž E T A K

Uvod/Cilj. Pandemija koronavirusne bolesti imala je akutni i dugoročni uticaj na zdravlje ljudi. S obzirom na to da, prema dostupnoj literaturi, premorbidna stanja utiču na tok COVID-19 infekcije, želeli smo da ispitamo ulogu koju koncentracija vitamina D izmerena prilikom prijema bolesnika ima u predikciji toka i ishoda njihove bolesti.

Metode. Ova opservaciona, prospektivna, kohortna studija sprovedena je na 329 konsekutivno hospitalizovanih COVID-19 bolesnika u Univerzitetskom kliničkom centru Kragujevac (Srbija) u periodu između oktobra i decembra 2021. godine. Unutar 24 časa od prijema, koncentracija vitamina D određivana je na osnovu uzoraka iz periferne venske krvi. Sociodemografski podaci i podaci u vezi sa istorijom bolesti prikupljeni su anamnestički i korišćenjem Zdravstvenog informacionog sistema (COMTRADE, Srbija). Kao najvažniji parametri razmatrani su potreba za intenzivnom negom i smrtni ishod u toku hospitalizacije.

Rezultati. Prevalencija hipovitaminoze D na prijemu bila je 27,7%. Bolesnici kod kojih je došlo do smrtnog ishoda i oni kojima je bilo potrebno lečenje u jedinici intenzivne nege imali su hipovitaminozu D značajno češće nego preživeli (42,9% nasuprot 21,0%; p < 0,001) i bolesnici sa standardnim nivoom nege (31,5% nasuprot 25,3%; p = 0,029). Ipak, koncentracija vitamina D < 20 ng/mL bila je nezavisan prediktor mortaliteta (aOR 2,142 [95% CI 1,226 – 3,744]), ali ne i potrebe za lečenjem u jedinici intenzivne nege.

Zaključak. Snižena koncentracija vitamina D prilikom prijema može biti važan prediktor mortaliteta hospitalizovanih COVID-19 bolesnika.

Ključne reči: vitamin D, jedinica intenzivne nege, koronavirusna bolest, mortalitet