International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Vitamin D 25(OH)D_3 Levels in Patients Infected with SARS-CoV-2. The Effects on Hospital Admission Status, Hospital Length of Stay and COVID-19 Mortality Rate

Sylwia Serafińska[1,2], Krzysztof Simon [1,2], Marta Kucharska[1,2], Justyna Janocha-Litwin[1,2], Aleksander Zińczuk[2], Anna Nowicka[2], Monika Pazgan-Simon[2], Anna Szymanek-Pasternak[1,2]

[1]Department of Infectious Diseases and Hepatology, Wroclaw Medical University

[2]1st Department of Infectious Diseases of the J. Gromkowski Regional Specialist Hospital in Wroclaw

Abstract: ***Introduction: Several reports have found an effect of vitamin D on the course of certain infections, including COVID-19. Aim: Based on these reports, the present study measured serum vitamin D levels in COVID-19 adult patients and analysed the correlations between vitamin D levels and many aspects due to COVID-19. Materials and methods: This study involves a cohort of adult patients with COVID-19 interstitial pneumonia (n 301). The group was divided into subgroups based on baseline vitamin D levels (<30 ng/ml, 30-50, >50). The relationship of baseline vitamin D levels with patients' health status on admission, hospital length of stay, need for ICU transfer and in-hospital mortality rates was analysed. Results: There was a significant inverse correlation between baseline vitamin D levels and WHO COVID-19 severity on admission (p <0.001), especially if baseline levels were<30 ng/ml (p 0.006). Baseline vitamin D levels correlated with hospital length of stay (p 0.019). The group with low vitamin D levels<30 ng/ml alsohad a statistically significant higher risk of death (p 0.003). In both univariate and multivariate models, age and baseline vitamin D levels affected the hospitallength of stay (p <0.001). There was no association between baseline vitamin D levels and the need for transfer to the ICU. Conclusions: Older patients with baseline lower vitamin D levels<30 ng/ml have a more severe course of COVID-19, a longer hospital stay and present a significantly higher risk of death compared to younger patients with normal and high baseline 25(OH)D3 levels.***

Keywords: vitamin D levels, vitamin D deficiency, SARS-CoV-2 infection, COVID-19, primary prevention

1. Introduction

COVID-19 has become one of the most important causes of death worldwide, and there is still no effective, causal antiviral treatment for this infection. SARS-CoV-2 is, regardless of the variant, a highly infectious virus (to a greater extent than, for example, influenza virus), which contributes to the rapid spread of this infection worldwide [1]. The vast majority of SARS-CoV-2 infections are asymptomatic, mild or moderate, without the need to hospitalize patients. However, approximately 20% of infected individuals develop severe forms of COVID-19 with pneumonia, acute respiratory distress syndrome (ARDS) or other complications (thromboembolic, cardiovascular, neurological) that need specialized treatment, passive oxygen therapy or mechanical ventilation, often intensive care. Lymphopenia and thrombocytopenia are thought to be risk factors for the development of severe forms of COVID-19 [2]. Severe pneumonia, organ embolism, ARDS, septic shock, and multisystem organ failure are the main causes of death. Higher mortality rate was found to be associated with older age, pregnancy, obesity, chronic obstructive pulmonary disease (COPD), hypertension (HT), type 2 diabetes (DM2), cardiovascular disease, cancer and multimorbidity, as well as smoking or Down syndrome comorbidity [3].

The immune response to SARS-CoV-2 infection is complex and highly dependent on the viral variant, the viral load that enters the body and the individual fitness of the host immune system [4].

SARSCoV-2 uses angiotensin-converting enzyme 2 (ACE2) as an essential receptor to bind to and enter host cells. Therefore, ACE2 is a fusion receptor for the virus. Under the influence of the virus, ACE2 expression is reduced [5]. In addition to alveolar epithelial cells, the ACE2 receptor is found in many other tissues, such as the heart, vascular endothelium, kidney, intestine and brain, which overlaps with the SARS-CoV-2 tissue tropism and is responsible for various symptoms of COVID-19 disease, such as acute respiratory failure, acute cardiac injury, acute renal failure, diarrhea, and neurological disorders [6]. The role of ACE2 is to regulate the renin-angiotensin system (RAS). It plays an important role in the regulation of blood pressure and water balance in the human body, and its effects on lung injury include increased pulmonary vascular tone and permeability, reduced viability and apoptosis of epithelial cells and activation of fibroblasts via angiotensin-converting enzyme (ACE), angiotensin II (Ang II) and angiotensin receptor (AT1R). In other words, ACE2 can be considered a key factor for both the cellular fusion of the virus and its pathogenicity [7].

Vitamin D – 25(OH)D_3 – is a steroid hormone that binds to a specific receptor (VDRE) found in most human tissues, thus affecting more than 2,000 genes, hence its broad spectrum of action, known as pleiotropic [8]. It was revealed that vitamin D could prevent the adverse effects of COVID-19 by influencing the RAS system and innate and acquired cellular immunity, as well as the course of comorbidities [9]. Vitamin D was found to reduce pulmonary vascular endothelial permeability in ARDS by modulating RAS activity and increasing ACE2 expression [10]. In COVID-

Licensed Under Creative Commons Attribution CC BY

19, decreased ACE2 expression results in an inflammatory chain reaction and cytokine storm complicated by ARDS [11]. Many studies reported the vitamin D-mediated antiviral activity either through antimicrobial peptides with direct antiviral activity against both enveloped and non-enveloped viruses, or through immunomodulatory and anti-inflammatory effects [12]. Vitamin D may also prevent ARDS by decreasing the production of pro-inflammatory cytokines from Th1 helper cells, such as tumor necrosis factor (TNFα) and interferon gamma (IFN γ), and by increasing the expression of anti-inflammatory macrophage cytokines [13]. Vitamin D stabilizes barrier resistance by maintaining the functionality of cell junctions with E-cadherin, making it difficult for viruses to penetrate into host cells [14]. Numerous reports in the last decade also point to the role of hypovitaminosis D in the pathophysiology of comorbidities, including diabetes, hypertension, cardiovascular and respiratory diseases and cancer [8], which simultaneously increase the risk of COVID-19 progression and COVID-19-related death.

Vitamin D is naturally synthesized by the skin during exposure to solar UVB radiation. Residents of northern latitudes (above 20°, with low environmental sun exposure), and ethnic groups with high melanin content in UVB-protective skin (blacks, Asians, ethnic minorities) have a proven higher risk of death from COVID-19 [8, 1]. In the Polish population, vitamin D deficiency is a common phenomenon, affecting up to 90% of individuals, and is mainly due to the latitude of the country's location (low sun angle), climate (few sunshine days per year), and a diet that is insufficiently high in natural vitamin D [2]. A population-based vitamin D supplementation strategy appears to be a fairly straightforward and widely available solution, given its potential to balance and control immune and oxidative responses against SARSCoV-2 infection, and thus its preventive effect in COVID-19 [3, 4].

Aim

Given these facts, serum vitamin D levels were assessed in COVID-19 hospitalized patients and their possible association with the severity of the disease course, hospital length of stay and mortality rate due to COVID-19 was analyzed.

2. Materials and methods

A prospective cohort study was conducted in adult, Caucasian patients who were admitted to our center and were diagnosed with COVID-19 interstitial pneumonia (n 301). Blood serum Vitamin D status (a metabolite of $25(OH)D_3$, reflecting the vitamin D content of the body) was measured using the automated CLIA method on the LIAISON analyzer. Blood for testing was collected in the morning on an empty stomach on the first day after hospital admission. In all patients, the diagnosis of SARS-Cov2/COVID-19 was confirmed by the RT-PCR assay of nasal or pharyngeal swab specimens and chest radiology (X-ray/CT scan). The cohort was divided into age groups (≤50 years, 51-60, 61-70, >70) and by baseline vitamin D levels (<30 ng/ml, 30-50, >50) – according to local standards and laboratory norms. The subgroups were assessed for disease severity on admission using biochemical markers (saturation and capillary blood oxygen tension) and clinical markers (WHO COVID-19 severity scale). The relationship of baseline vitamin D levels with patients' health status on admission, hospital length of stay, need for ICU transfer and in-hospital mortality rates was analyzed.

Transfer to the ICU took place each time after consultation with an intensivist specialist, according to the current protocol of the Polish Society of Anesthesiology and Intensive Care (PTAiIT).

The hospital length of stay in both groups was determined solely by the patient's clinical status, not by the need for isolation for epidemic control (patients hospitalized for less than four days were excluded), and not by social conditions (patients hospitalized for lack of accommodation or home care were excluded).

All patients were treated with standard of care (SOC) therapy as recommended at the time by global, European and Polish expert groups, including the Polish Association of Epidemiologists and Infectiologists (PTEiLCHZ) and the J. Gromkowski Regional Specialist Hospital (procedure reference number PM51-37/20). The therapeutic regimen included the administration of prophylactic low-dose heparin, remdesivir and fresh frozen plasma (FFP) from convalescents (when the duration of disease was no longer than five days), as well as the administration of systemic glucocorticosteroids (when the patient had oxygen requirements), antibiotics (when markers of inflammation of bacterial infection were present), tocilizumab (when markers of cytokine storm were present).

Data were collected in the hospital's AMMS database, in accordance with European data protection legislation – GDPR.

All results were statistically analyzed using SAS 9.4 software.

Statistical methods

Descriptive statistics for continuous variables were presented as mean, standard deviation, median, first and third quartiles and minimum and maximum values, for categorical variables as counts and percentages.

Comparisons between groups defined by sex, age, BMI and vitamin D levels were made using the chi-squared test (categorical variables) and, in the case of continuous variables, using Student's tests or the analysis of variance (for variables with a normal distribution) and the Mann-Whitney test or the Kruskal-Wallis test (when the distribution is not normal). The normality of distribution was tested using the Shapiro-Wilk test.

The effects of selected factors on the odds of death or ICU transfer were analyzed using univariate and multivariate logistic regression methods. Factors influencing the hospital length of stay were analyzed using both univariate and multivariate linear regression methods.

The correlation of vitamin D3 levels with selected factors was described using the Pearson's correlation coefficient.

Licensed Under Creative Commons Attribution CC BY

The analysis was performed using SAS 9.4 software.

3. Results

The study group (n 301, 112 women; 37%, 179 men; 63%) had a mean age of 62.4 years (SD 14.7; Me 64.0; 21-94). The mean serum vitamin D levels of the patient cohort studied were below normal at 27.9 ng/ml (SD 15.6; Me 25.3; 4.0-93.0). The cohort was divided into 3 subgroups according to 25(OH)D_3 levels (<30 ng/ml, 30-<50, =>50). In terms of parameters assessed on admission, capillary blood oxygen saturation SatO2 averaged 89.7% (SD 6.7; Me 91; 53-100), capillary blood oxygen saturation PaO2 averaged 64.5 mmHg (SD 11.9; Me 63; 39-99), 48 (16%) patients had stage 3 of COVID-19, 235 (78.1%) – stage 4, 18 (6%) patients – stage 5. The hospital length of stay averaged 12.4 days (SD 7.4; Me 10; 4-50). Thirty-two people died (10.6%), including 15 patients (100%) after transfer to the ICU. Details on the characteristics of the study group and the parameters assessed on admission, as well as the aggregate hospital length of stay and the mortality rate are shown in Tables 1 and 2.

Table 1: Characteristics of the study group

Variable	Values
Sex F/M N, %	112, 37% 179, 63%
Age M, Me, range	62.4; 64; 21-94
Body weight M, Me, range	85; 85; 50-160
BMI M, Me, range	28.9; 28; 18.6-48.4
Presence ofHT N, %	164; 54.5%
Presence of DM2 N, %	75; 24.9%
Vitamin D levels ng/ml M, Me, range	27.9; 25.3; 4-93

Table 2: The characteristics of vital signs on hospital admission, hospital length of stay and mortality rate

Variable	Category	Stat.	Value
Health status on admission acc. to WHO *	3	N	48
		%	16.00%
	4	N	235
		%	78.10%
	5	N	18
		%	6.00%
O2 sat. ca [%]		N	301
		Mean	89.7
		SD	6.7
		Median	91
		Q1	88
		Q3	94
		Min	53
		Max	100
PaO2 ca [mmHg]		N	301
		Mean	64.5
		SD	11.9
		Median	63
		Q1	57
		Q3	69
		Min	39
		Max	99
Hospital length of stay [days]		N	301
		Mean	12.4
		SD	7.4
		Median	10
		Q1	7
		Q3	14
		Min	4
		Max	50
Treatment outcome	hospital discharge	N	269
		%	89.40%
	Death	N	17
		%	5.70%
	ICU transfer and death	N	15

Licensed Under Creative Commons Attribution CC BY

		%	5.00%
Treatment outcome – in-hospital death	no death	N	269
		%	89.40%
	Death	N	32
		%	10.60%
Treatment outcome – ICU transfer	no ICU transfer	N	286
		%	95.00%
	ICU transfer	N	15
		%	5.00%

* 3. No oxygen therapy, 4. Low-flow nasal oxygen therapy, 5. High-flow nasal oxygen therapy or non-invasive ventilation HFNOT / NIV

In the study group, there was a significant inverse relationship between baseline 25(OH)D_3 levels and WHO COVID-19 severity on admission (p <0.001), especially if baseline levels were lower than 30 ng/ml (p 0.006) – that group had the highest number of patients requiring HFNOT or NIV. Baseline vitamin D levels correlated with hospital length of stay (p 0.019) – patients in the <30 ng/ml subgroup had, on average, a four-day longer hospital stay compared to those in the >50 ng/ml subgroup (p 0.048). These data are summarized in Table 3.

Table 3: The characteristics of baseline parameters (PaO2, SatO2, WHO COVID-19 severity), hospital length of stay and mortality rate in subgroups determined by baseline vitamin D levels.

Variable	Category	Stat.	Subgroups by vitamin D levels [ng/ml]			p-value*
			<30.0	⩾30.0 &<50.0	⩾50.0	
Hospital length of stay [days]		N	159	69	20	**0.019****
		Mean	13.48	11.19	9.55	
		SD	8.56	6.28	5.32	
		Median	10	9	8	
		Q1	8	7	6	
		Q3	16	12	11.5	
		Min	5	5	4	
		Max	50	32	25	
O2 Sat. [%]		N	159	69	20	0.579
		Mean	88.9	89.8	89.8	
		SD	7.2	5.4	8.1	
		Median	90	90	92	
		Q1	86	88	88	
		Q3	94	93	95.5	
		Min	53	66	64	
		Max	100	98	98	
PaO2 [mmHg]		N	159	69	20	0.36
		Mean	63.8	63.99	67.45	
		SD	11.88	11.66	11.64	
		Median	63	63	66	
		Q1	56	56	58.5	
		Q3	70	67	73.5	
		Min	41	41	52	
		Max	99	99	95	
Treatment outcome – ICU transfer	no ICU transfer	N	151	63	19	0.555
		%	95.00%	91.30%	95.00%	
	ICU transfer	N	8	6	1	
		%	5.00%	8.70%	5.00%	
Treatment outcome – in-hospital death	no death	N	144	58	18	0.355
		%	90.60%	84.10%	90.00%	
	Death	N	15	11	2	
		%	9.40%	15.90%	10.00%	
Health status on admission acc. to WHO ***	3	N	17	10	8	**0.007**
		%	10.70%	14.50%	40.00%	
	4	N	128	55	12	
		%	80.50%	79.70%	60.00%	
	5	N	14	4	0	
		%	8.80%	5.80%	0.00%	

*p-value of the ANOVA test for continuous variables with normal distribution, the Kruskal-Wallis test for continuous variables with non-normal distribution, the chi-squared test for categorical variables

**pairwise comparisons for hospital length of stay in groups by baseline vitamin D status, the Mann-Whitney test:

- <30.0 ng/ml vs. ⩾30 &<50.0 ng/ml: p = 0.136
- <30.0 ng/ml vs. ⩾50.0 ng/ml: p = 0.048
- ⩾30 &<50.0 ng/ml vs. ⩾50.0 ng/ml: p = 0.442

Licensed Under Creative Commons Attribution CC BY

*** 3. No oxygen therapy, 4. Low-flow nasal oxygen therapy, 5. High-flow nasal oxygen therapy or non-invasive ventilation HFNOT / NIV

In both univariate and multivariate models (including also the presence of comorbidities, age and BMI), age was the strongest risk factor for death (p < 0.001, p 0.002, respectively). The subgroup with low vitamin D levels <30 ng/ml also had a higher risk of death compared to other subgroups (p 0.003). In both univariate and multivariate models, age and baseline vitamin D levels affected the hospital length of stay (p <0.001). Each additional 10 years of life was associated with 2 more days of hospitalization, and each 10 ng/ml of serum vitamin D loss contributed to an additional 1.5 days of hospitalization. There was no association between baseline vitamin D levels and the need for transfer to the ICU (p 0.555). Details of the analysis regarding the correlation of baseline vitamin D levels with hospital length of stay and mortality rates, as well as the effects of age, BMI, comorbidities (HT and DM2) are summarized in Tables 4-7.

Table 4: Correlation of vitamin D levels with selected parameters in the whole group and in the groups with low, normal and high vitamin D levels

Variable	Whole group		Low vitamin D levels (<30.0 ng/ml)		Normal vitamin D levels (⩾30.0 &<50.0 ng/ml)		High vitamin D levels (⩾50.0 ng/ml)	
	Correlation coefficient*	p-value	Correlation coefficient*	p-value	Correlation coefficient*	p-value	Correlation coefficient*	p-value
Hospital length of stay [days]	-0.217	<0.001	-0.216	0.006	0.232	0.055	-0.053	0.825
Sat. O2 [%]	0.085	0.185	0.07	0.379	0.038	0.756	0.402	0.079
PaO2 [mmHg]	0.045	0.484	0.048	0.545	-0.032	0.794	0.355	0.125

* Spearman's correlation coefficient

Table 5: The effects of vitamin D on incidence of death and ICU transfer in the whole group and in the groups with low, normal and high baseline vitamin D levels (univariate logistic regression)

Variable	Whole group		Low vitamin D levels (<30.0 ng/ml)		Normal vitamin D levels (⩾30.0 &<50.0 ng/ml)		High vitamin D levels (⩾50.0 ng/ml)	
	OR (95%P.U)	p-value	OR (95%P.U)	p-value	OR (95%P.U)	p-value	OR (95%P.U)	p-value
Incidence of death	0.987 (0.960-1.015)	0.36	0.880 (0.810-0.956)	0.003	0.899 (0.793-1.018)	0.094	0.977 (0.848-1.126)	0.748
ICU transfer	1.002 (0.969-1.036)	0.913	0.944 (0.855-1.042)	0.255	0.991 (0.864-1.137)	0.899	1.032 (0.880-1.210)	0.701

Table 6: The effects of hypertension, diabetes, BMI, and age on the occurrence of in-hospital death in the whole group (univariate logistic models and a multivariate logistic model}

Variable	Univariate models		Multivariate model	
	OR (95%P.U)	p-value	OR (95%P.U)	p-value
Hypertension (Yes vs No)	1.968 (0.898-4.313)	0.091	0.838 (0.303-2.321)	0.734
Diabetes (Yes vs No)	1.005 (0.431-2.343)	0.991	0.607 (0.207-1.783)	0.364
BMI [kg/m2]	1.046 (0.973-1.125)	0.222	1.082 (0.993-1.179)	0.073
Age [years]	1.071 (1.037-1.107)	<0.001	1.068 (1.025-1.112)	0.002
Vitamin D levels [ng/ml]	0.987 (0.960-1.015)	0.36	1.003 (0.974-1.032)	0.863

Table 7: The effects of hypertension, diabetes, BMI, and age on hospital length of stay in the whole group (univariate linear models and a multivariate linear model)

Variable	Univariate models		Multivariate model	
	Linear correlation coefficient (95%P.U)	p-value	Linear correlation coefficient (95%P.U)	p-value
Hypertension (Yes vs No)	2.906 (1.252-4.559)	0.001	0.690 (-1.540-2.919)	0.543
Diabetes (Yes vs No)	1.289 (-0.646-3.225)	0.191	-0.313 (-2.668-2.042)	0.793
BMI [kg/m2]	0.185 (0.008-0.362)	0.041	0.122 (-0.081-0.325)	0.237
Age [years]	0.148 (0.093-0.203)	<0.001	0.185 (0.108-0.262)	<0.001
Vitamin D levels [ng/ml]	-0.108 (-0.170- -0.046)	0.001	-0.118 (-0.185- -0.052)	0.001

4. Discussion

Three different studies [19, 20, 21], which included a total of 373 patients, revealed a significantly increased risk of death in COVID-19 patients with reduced 25(OH)D levels < 30 ng/ml (RR = 3.1, 95% CI [1.4-6.8]; I^2 = 0 %). One study found no significant association between 25(OH)D levels <30 ng/ml and risk of ICU admission (p = 0.3) [21]. Hernández et al. described the risk of a significantly longer hospital stay in COVID-19 patients with serum 25(OH)D levels <20 ng/ml (median = 12 days (IQR 8-17)) compared to patients with normal vitamin D levels (median = 8 days (IQR 6-14)) (p = 0,013) [22]. Two studies (N = 379) found no significant difference in terms of the hospital length of stay due to COVID-19 between patients with 25(OH)D levels < 30 ng/ml compared to the group with normal levels (MD = 0, 95% CI [-0.97, 0.97], I^2= 0%) [20, 21].

In our study, there were statistically significant differences in terms of both hospital length of stay and risk of death between the groups with normal and reduced vitamin D levels, in favor of the first group. However, the ICU transfer rate was comparable in both groups. In this study, age and

Licensed Under Creative Commons Attribution CC BY

baseline vitamin D levels had an effect on hospital length of stay (p <0.001) in both univariate and multivariate models. Each additional 10 years of life was associated with 2 more days of hospitalization, and each 10 ng/ml of serum vitamin D loss contributed to an additional 1.5 days of hospitalization. There was no association between baseline vitamin D levels and the need for transfer to the ICU (p=0.555).

A summary of the meta-analysis and systematic review [23], which analyses a much larger group of patients tested in a variety of conditions, including the risk of error, after adopting a cut-off point of normal vitamin D levels of 30 ng/ml, unequivocally revealed an increased risk of mortality and a positive result for SARS-CoV-2 in patients with reduced vitamin D levels. However, there was no association with the risk of disease severity and ARDS or length of hospital stay.

The above results, although not always consistent, support the assumption that an increase in serum 25(OH)D levels can significantly improve the prognosis of COVID-19, as proven in this study.

The analysis of the University of Cincinnati's COVID-19 patient data revealed that hospitalisation of those patients was associated with vitamin D deficiency (OR 1.77, 95% CI 1.07-2.93). Furthermore, disease severity was also associated with vitamin D deficiency (OR 1.95, 95% CI 1.07-3.56), and the odds of ICU admission were also higher in those with vitamin D deficiency (OR 2.55, 95% CI 1.28-5.08) [24]. Daneshkhah et al. found that the elimination of severe vitamin D deficiency most likely reduces the risk of severe COVID-19 cases [25]. Furthermore, a retrospective study in 20 European countries found a significant correlation between mean vitamin D levels and incidence rate of COVID-19 (p =0.033) but not with incidence of COVID-19-related death (p =0.123) [26]. In a review of the literature by Yisak et al., seven (77.8 %) publications found that baseline vitamin D levels were associated with SARS-CoV-2 infection, COVID-19 disease severity and COVID-19-related death [27].

Similarly, a study of Parkinson's disease patients living in Lombardy, Italy found that patients affected by COVID-19 were less likely to receive vitamin D supplementation than unaffected patients (OR 0.56, 95% CI 0.32-0.99; P = 0.048) [28]. A study conducted at the Policlinico di Bari, Italy, among adult hospitalised patients revealed that mortality rate was higher in patients with severe vitamin D deficiency (OR 5681, 95% CI 1114-28 974; P = 0.037) and after ICU admission (p = 0.019) compared to those with normal vitamin D levels [29].

Cross-sectional observational studies conducted in different parts of the world found that human populations with vitamin D deficiency (including the elderly) have a higher incidence rate of COVID-19 [30, 31, 32] as well as higher mortality rate and a higher proportion of severe and critical COVID-19-related cases [33, 34]. A review of the literature on the involvement of vitamin D in the pathogenesis of COVID-19 and the presumed benefit of vitamin D supplementation during the pandemic shows that reduced vitamin D levels appear to be more associated with the incidence rate, while age, sex and comorbidities appear to play a more important role in disease severity and mortality from COVID-19 [35].

Similar observations were made in our study, where, in both univariate and multivariate models (including also the presence of comorbidities, age and BMI), age was found to be the strongest risk factor for death (p < 0.001, p 0.002, respectively). The subgroup of patients with low vitamin D levels <30 ng/ml also had a higher risk of death compared to other subgroups (p 0.003).

D'Avolio et al. showed that COVID-19 cases had, on average, more than twice lower 25(OH)D levels than controls without COVID-19 (11.1 ng/ml versus 24.6 ng/ml, respectively, p = 0.004) [36]. Similarly, significant inverse correlations were found in 20 European countries between mean serum 25(OH)D levels and the number of COVID-19 cases, as well as mortality rate [37]. The severity of hypovitaminosis D appears to be associated with the prognosis of COVID-19, as COVID-19 cases with hypovitaminosis D were more likely to develop severe COVID-19 (relative risk 1.59 with P = 0.02 if vitamin D deficiency < 30 ng/ml) [21]. Finally, hypovitaminosis D was found to be associated with a higher risk of COVID-19 mortality (IRR = 1.56 with P< 0.001 for vitamin D deficiency;P= 0.404 after adjustment) [38].

Interestingly, previous meta-analyses found that high-dose prophylactic vitamin D supplementation was able to reduce the risk of respiratory tract infections. The optimal dose ranged from 1,000 to 4,000 IU/day, suggesting a benefit of high-dose vitamin D supplementation [39]. It is considered safe to take oral vitamin D supplements at a dose of up to 10,000 IU/day for a short period of time, especially in elderly people, in a population mainly affected by hypovitaminosis D, who should receive at least 1,500 IU/day of vitamin D to achieve the desired vitamin D status [40, 8, 9, 40].

The main findings of Baktash et al. and Alipio et al. imply that older patients with lower serum 25(OH)D levels compared to similarly aged patients with vitamin D deficiency may have significantly more severe COVID-19 consequences. Those patients were more likely to have elevated markers of cytokine release syndrome and were more likely to have hypoxia and the need for ventilator support in the ICU. There was no difference in terms of mortality between groups [42, 43]. Ilie et al. conducted a meta-analysis to investigate the association of vitamin D with COVID-19 morbidity and mortality in 20 European countries and proposed a possible negative correlation between vitamin D levels, incidence rate of SARS-CoV-2 infection and COVID-19 mortality rate [44].

Certainly, a limitation of this study is its single-centre nature, hence it is impossible to generalize these results to a larger population; nevertheless, the group represents a large, representative cohort of COVID-19 patients. The role of sunlight exposure, which may have influenced serum 25(OH)D levels, should also be recognized. Unfortunately, this could not be reliably measured in patients of this study,

Licensed Under Creative Commons Attribution CC BY

nor is there much data on this topic in other publications. It should be noted that this study was conducted in autumn and spring, which weakened the potential effect of weather on sunlight exposure. However, comparisons of the results of different studies from different parts of the world and conducted at different times of the year will always be subject to some error. Similarly, the different variants of SARSCoV-2, known for their different contagiousness and virulence, which is reflected in the different severity of the disease course, may significantly affect the final results of studies and bias attempts to compare scientific results.

It should also be emphasized that the hospital length of stay was reported for all patients of this study, was not dependent on the need for isolation for epidemic control, patients who were hospitalized for less than four days were excluded, and the hospital length of stay was determined solely by the patient's clinical status and not, for example, by social conditions. These data are not always available in publications, which also has an effect on errors when comparing study results.

Given all the above limitations, it must be concluded that the results of this study are largely in line with observations reported worldwide in the literature, so it is reasonable to draw the following conclusions.

5. Conclusions

1) Reduced baseline serum vitamin D levels in COVID-19 adult patients hospitalized at our center show a statistically significant positive correlation with more advanced disease stage at the time of hospital admission, according to WHO scale.
2) Reduced baseline serum vitamin D levels in COVID-19 adult patients are associated with significantly longer hospital length of stay and a higher risk of death compared to patients with normal baseline vitamin D levels.
3) 25(OH)D_3 levels below normal, i.e. < 30 ng/ml, may have a significant effect on the course and progression of COVID-19, the hospital length of stay and the risk of COVID-19-related death; hence, efforts should be made to maintain normal vitamin D levels in the population exposed to SARS-CoV2 infection.

Contribution to the Work

Design, analysis of results and preparation of the manuscript: Sylwia Serafińska; data collection, analysis of results, proofreading of the manuscript: Anna Szymanek-Pasternak, Marta Kucharska, Monika Pazgan-Simon, JustynaJanocha-Litwin, AleksanderZińczuk, Anna Nowicka; project supervision and manuscript revision: Krzysztof Simon; corresponding authors: Krzysztof Simon, Sylwia Serafińska.

References

[1] Chen JM. Novel statistics predict the COVID-19 pandemic could terminate in 2022. J Med Virol. 2022 Jun; 94(6):2845-2848
[2] PramathKakodkar, Nagham Kaka, M N Baig. A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19) Cureus. 2020 Apr 6; 12(4):e7560.
[3] de Lucena TMC, da Silva Santos AF, de Lima BR, de Albuquerque Borborema ME, de Azevêdo Silva J. Mechanism of inflammatory response in associated comorbidities in COVID-19. Diabetes MetabSyndr. 2020 Jul-Aug; 14(4):597-600.
[4] Zhou P, Xing-Lou Yang [# 1], Xian-Guang Wang [# 2], Ben Hu , et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar; 579(7798):270-273 [5].
[5] Han Q, Lin Q, Jin S, You L. Coronavirus 2019-nCoV: A brief perspective from the front line. J Infect. 2020 Apr; 80(4):373-377.
[6] Kuba K, Imai Y, Rao S, Jiang C, Penninger JM. Lessons from SARS: control of acute lung failure by the SARS receptor ACE2. J Mol Med (Berl). 2006 Oct; 84(10):814-20.
[7] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020 Apr; 46(4):586-590.
[8] Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective.Mayo ClinProc. 2013 Jul; 88(7):720-55.
[9] Annweiler C, Legrand E, Souberbielle JC. Vitamin D in adults: update on testing and supplementation.GeriatrPsycholNeuropsychiatrVieil. 2018 Mar 1; 16(1):7-22.
[10] Kong J, Zhu X, Shi Y, Liu T, Chen Y, Bhan I, Zhao Q, Thadhani R, Li YC. VDR attenuates acute lung injury by blocking Ang-2-Tie-2 pathway and renin-angiotensin system.MolEndocrinol. 2013 Dec; 27(12):2116-25.
[11] Zhang X, Li S, Niu S. ACE2 and COVID-19 and the resulting ARDS. Postgrad Med J. 2020 Jul; 96(1137):403-407.
[12] Fabbri A, Infante M, Ricordi C. Editorial - Vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections.Eur Rev Med Pharmacol Sci. 2020 Apr; 24(7):4048-4052.
[13] Dancer RC, Parekh D, Lax S, D'Souza V, Zheng S, Bassford CR, Park D, Bartis DG, Mahida R, Turner AM, Sapey E, Wei W, Naidu B, Stewart PM, Fraser WD, Christopher KB, Cooper MS, Gao F, Sansom DM, Martineau AR, Perkins GD, Thickett DR. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax. 2015 Jul; 70(7):617-24.
[14] Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020 Apr 2; 12(4):988.
[15] Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of covid-19? BMJ. 2020 Apr 20; 369:m1548.
[16] Płudowski P, Ducki C, Konstantynowicz J, Jaworski M. Vitamin D status in Poland. Pol Arch Med Wewn. 2016 Aug 9; 126(7-8):530-9.
[17] Bleizgys A. Vitamin D and COVID-19: It is time to act.Int J ClinPract. 2021 Mar;75(3): e13748

Licensed Under Creative Commons Attribution CC BY

[18] Hadizadeh F. Supplementation with vitamin D in the COVID-19 pandemic?Nutr Rev. 2021 Jan 9; 79(2):200-208.
[19] Karahan S., Katkat F. Impact of serum 25(OH) vitamin D level on mortality in patients with COVID-19 in Turkey. *J Nutr Health Aging.* 2020:1–8.
[20] Angelidi A.M., Belanger M.J., Lorinsky M.K., Karamanis D., Chamorro-Pareja N., Ognibene J. Vitamin D status is associated with in-hospital mortality and mechanical ventilation: a cohort of COVID-19 hospitalized patients. *Mayo Clin Proc.* 2021 Elsevier.
[21] Maghbooli Z., Sahraian M.A., Ebrahimi M., Pazoki M., Kafan S., Tabriz H.M. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. *PLoS One.* 2020;15(9)
[22] Hernandez J.L., Nan D., Fernandez-Ayala M., Garcia-Unzueta M., Hernandez-Hernandez M.A., Lopez-Hoyos M. Vitamin D status in hospitalized patients with SARS-CoV-2 infection. *J ClinEndocrinolMetab.* 2021;106(3):e1343. e135.
[23] AyaBassatne , Maya Basbous , Marlene Chakhtoura , Ola El Zein , Maya Rahme , Ghada El-Hajj Fuleihan. The link between COVID-19 and VItamin D (VIVID): A systematic review and meta-analysis. Metabolism 2021 Jun; 119:154753.
[24] Mendy A, Apewokin S, Wells AA, Morrow AL. Factors Associated with Hospitalization and Disease Severity in a Racially and Ethnically Diverse Population of COVID-19 Patients.medRxiv. 2020 Jun 27:2020.06.25.20137323.
[25] Ali Daneshkhah , Vasundhara Agrawal, Adam Eshein , Hariharan Subramanian, Hemant Kumar Roy, Vadim Backman. Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients. Aging ClinExp Res. 2020 Oct;32(10):2141-2158.
[26] Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. *J Infect Public Health*. 2020;13(10):1373–1380.
[27] HiwotYisak, Amien Ewunetei, BelaynehKefale, Melkalem Mamuye, Fentaw Teshome, Birhanie Ambaw, Getachew Yideg Yitbarek Effects of Vitamin D on COVID-19 Infection and Prognosis: A Systematic Review Risk ManagHealthc Policy. 2021; 14: 31–38.
[28] Fasano A, Cereda E, Barichella M, et al. COVID 19 in parkinson's disease patients living in Lombardy, Italy. *Mov Disorders*. 2020; 35(7):1089–1093.
[29] Carpagnano GE, Di Lecce V, Quaranta VN, et al. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. *J Endocrinol Invest*. 2020; 1–7.
[30] Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020; 80(6):639–645.
[31] Im JH, Je YS, Baek J, Chung M-H, Kwon HY, Lee J-S. Nutritional status of patients with coronavirus disease 2019 (COVID-19). *Int J Infect Dis*. 2020; 100:390–393.
[32] De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA. Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics. *MedRxiv*. 2020.
[33] Lau FH, Majumder R, Torabi R, et al. Vitamin D insufficiency is prevalent in severe COVID-19. *medRxiv*. 2020.
[34] Panagiotou G, Tee SA, Ihsan Y, et al. Low serum 25-hydroxyvitamin D (25 [OH] D) levels in patients hospitalized with COVID-19 are associated with greater disease severity. *ClinEndocrinol (Oxf)*. 2020.
[35] Ferrari D, Locatelli M, Briguglio M, Lombardi G. Is there a link between vitamin D status, SARS-CoV-2 infection risk and COVID-19 severity? *Cell BiochemFunct*. 2020.
[36] D'Avolio A, Avataneo V, Manca A, Cusato J, De Nicolò A, Lucchini R, et al. 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. *Nutrients.* 2020;12:1359.
[37] Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging ClinExp Res.* 2020;32:1195–1198.
[38] Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, Niedzwiedz CL, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes MetabSyndr*. 2020;14:561–565.
[39] Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017;356:i6583.
[40] Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J ClinNutr*. 1999;69:842–856.
[41] CédricAnnweiler, MélindaBeaudenon, Jennifer Gautier, Romain Simon, Vincent Dubée, Justine Gonsard, Elsa Parot-Schinkel. COvid-19 and high-dose VITamin D supplementation TRIAL in high-risk older patients (COVIT-TRIAL): study protocol for a randomized controlled trial. Trials. 2020; 21: 1031.
[42] Baktash V, Hosack T, Patel N, Shah S, Kandiah P, Van den Abbeele K, Mandal AKJ, Missouris CG.Vitamin D status and outcomes for hospitalised older patients with COVID-19. Postgrad Med J. 2021 Jul; 97(1149):442-447.
[43] Alipio M. Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-2019) *SSRN Journal*. 10.2139/ssrn.3571484.
[44] Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging ClinExp Res* 2020;32:1195–8. 10.1007/s40520-020-01570-8.

Licensed Under Creative Commons Attribution CC BY