

Clinical and Prognostic Significance of Baseline Serum Vitamin D Levels in Hospitalized Egyptian Covid-19 Patients

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Background and Aim: Vitamin D is a hormone with essential roles in both cellular metabolism and immunity. It controls calcium homeostasis and modulates innate and adaptive immune system responses. Many studies suggested an association between vitamin D deficiency and clinical outcomes of covid-19 infection, while others failed to document such a relation. The present study aimed to evaluate the clinical and prognostic significance of baseline vitamin D levels in hospitalized Egyptian covid-19 patients.

Patients and Methods: The present retrospective study included 300 hospitalized covid-19 patients. Patients were submitted to standard clinical, laboratory, and radiological assessment. According to vitamin D levels, patients were classified to have normal levels (≥ 30), insufficient levels (20–29) or deficient levels (< 20).

Results: According to their vitamin D levels, patients were classified into those with normal vitamin D ($n=135$), others with vitamin D insufficiency ($n=114$), and a third group with vitamin D deficiency ($n=51$). Patients with normal vitamin D levels and vitamin D insufficiency are significantly younger [median (IQR): 49.0 (39.0–57.0) versus 51.0 (40.0–61.0) and 55.0 (43.0–62.0) years, respectively, $p=0.012$] and had less frequency of severe disease (24.4% versus 40.4% and 51.0%, respectively) when compared with those with vitamin D deficiency. Moreover, they had significantly lower levels of D dimer [median (IQR): 1.5 (0.9–2.5) versus 1.8 (0.9–3.1) and 2.0 (1.0–3.2)], CRP [median (IQR): 58.0 (30.0–120.0) versus 76.0 (42.5–160.0) and 105.0 (74.0–208.0), respectively, $p<0.001$], ferritin [median (IQR): 458.0 (240.0–759.0) versus 606.0 (433.8–897.8) and 820.0 (552.0–1087.0), respectively, $p<0.001$], and procalcitonin [median (IQR): 290.0 (152.0–394.0) versus 372.5 (227.0–530.5) and 443.0 (272.0–575.0), respectively, $p<0.001$]. Only lower vitamin D levels were significant predictors of mortality in multivariate analysis [OR (95% CI): 0.88 (0.84–0.92), $p<0.001$].

Conclusion: Low vitamin D levels are related to exaggerated inflammatory response, disease severity, and poor clinical outcome in hospitalized covid-19 patients.

Keywords: covid-19, vitamin D, vitamin D deficiency

Introduction

More than 30 months after the initial reports of covid-19 infections, the unprecedented threats created by the pandemic are still in the focus of global interest despite the significant achievements in the fields of diagnosis, prevention, and treatment. This is chiefly attributed to the fast-evolving nature of the virus.¹

Until recently, five major variants (Alpha, Beta, Gamma, Delta, and Omicron) have been identified,² and more are expected in the upcoming years. There is always tremendous need to identify clinical and biochemical factors related to covid-19 severity and prognosis.³ In the absence of definitive therapeutic options, supplementary and complementary treatments are also welcome.⁴

Vitamin D is a hormone with essential roles in both cellular metabolism and immunity. It controls calcium homeostasis and modulates innate and adaptive immune system responses.⁵ Vitamin D status remains a significant health issue

worldwide. However, there has been no clear consensus on vitamin D deficiency and its measurement in serum, and the clinical practice of vitamin D deficiency treatment remains inconsistent.⁶

Many studies suggested an association between vitamin D deficiency and clinical outcomes of covid-19 infection, while others failed to document such a relation.⁷ Other studies investigated the role of vitamin D supplementation on infection severity and outcome.^{8,9}

The present study aimed to evaluate the clinical and prognostic significance of baseline vitamin D levels in hospitalized Egyptian covid-19 patients.

Patients and Methods

The present retrospective study was conducted at Al-Azhar University Hospitals. Patients included in the study were admitted during the period from November 2020 to December 2021. Access to patients' data was approved by the ethical committee of Al-Azhar Faculty of Medicine in accordance with the Helsinki Declaration on clinical research involving human subjects. The study included 300 hospitalized covid-19 patients with positive reverse-transcriptase polymerase chain reaction (RT-PCR) of a nasopharyngeal swab and a median age of 51 years. Patients were excluded ($n=37$) if they had associated malignancy, chronic infection, or immunocompromised state. Also, patients with specific comorbidities or receiving medications that can affect vitamin D levels were excluded from the study. None of the included patients were vaccinated.

Included patients had severe covid-19 infection in the presence of at least one major or three minor criteria. Major criteria included: (1) septic shock with need for vasopressors, and (2) invasive mechanical ventilation. Minor criteria included: (1) respiratory rate ≥ 30 breaths/min, (2) $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 250 , (3) multilobar infiltrates, (4) confusion/disorientation, (5) uremia (BUN level ≥ 20 mg/dL), (6) leukopenia as a result of infection alone (WBC count < 4000 cells/mL), (7) thrombocytopenia (platelets count $< 100,000$ /mL), (8) hypothermia (core temperature $< 36^\circ\text{C}$), (9) hypotension requiring aggressive fluid resuscitation).¹⁰

For laboratory assessment,

1. 3 mL of venous blood was drawn on EDTA tube for CBC analysis on routine automated K X21Nhaematology cell counters (Sysmex, Kobe, Japan).
2. 1 mL of venous blood was drawn on heparinized tube for D dimer analysis on Cobas h232 (Roche Diagnostics, Germany).
3. 5 mL of venous blood was drawn on admission and allowed (within 10–20 minutes) to coagulate at room temperature then centrifuged for 20 minutes at 2000–3000 rpm to extract the serum that had been aliquoted, and stored at -80°C . Serum was divided into three parts using suitable tubes: one used for assessment of urea, creatinine, ALT, AST, albumin, bilirubin, lipid profile tests, and CRP using the automated clinical analyzer Cobas Integra 400 plus (Roche Diagnostics, Germany). Second and third parts were stored at -80°C to be used for procalcitonin analysis using Human Procalcitonin ELISA Kit (Cat. no. E0977Hu) and for vitamin D and ferritin assessment via a chemiluminescence-based immunoassay technique on Cobas 411 (Roche Diagnostics, Germany). According to vitamin D levels, patients were classified to have normal levels (≥ 30), insufficient levels (20–29), or deficient levels (< 20).¹¹

Data obtained from the present study were presented as number and percent for categorical data or median and interquartile range (IQR) for numerical data. Categorical data were compared using Fisher's exact or chi-square tests as appropriate, while numerical data were compared using Mann–Whitney *U*-test. Correlation analysis was achieved using Spearman correlation coefficient. Receiver operating characteristic (ROC) curve analysis was used to identify sensitivity and specificity of investigated markers. Logistic regression analysis was utilized to identify predictors of disease severity or mortality in the studied patients. All statistical operations were processed using SPSS 25 (IBM, USA) with *p* value < 0.05 considered statistically significant.

Results

The present study included 300 patients with covid-19 infection. They included 172 men and 128 women. According to their vitamin D levels, patients were classified into those with normal vitamin D ($n=135$), others with vitamin D insufficiency ($n=114$), and a third group with vitamin D deficiency ($n=51$). Comparison between the three groups regarding clinical and laboratory data revealed that patients with normal vitamin D levels and vitamin D insufficiency are significantly younger [median (IQR): 49.0 (39.0–57.0) versus 51.0 (40.0–61.0) and 55.0 (43.0–62.0) years, respectively, $p=0.012$] and had less frequency of severe disease (24.4% versus 40.4% and 51.0%, respectively) when compared with those with vitamin D deficiency. Moreover, they had significantly lower levels of D dimer [median (IQR): 1.5 (0.9–2.5) versus 1.8 (0.9–3.1) and 2.0 (1.0–3.2)], CRP [median (IQR): 58.0 (30.0–120.0) versus 76.0 (42.5–160.0) and 105.0 (74.0–208.0), respectively, $p<0.001$], ferritin [median (IQR): 458.0 (240.0–759.0) versus 606.0 (433.8–897.8) and 820.0 (552.0–1087.0), respectively, $p<0.001$], and procalcitonin [median (IQR): 290.0 (152.0–394.0) versus 372.5 (227.0–530.5) and 443.0 (272.0–575.0), respectively, $p<0.001$] when compared with the other two groups. Also, patients with normal vitamin D levels had significantly lower rates of ICU admission (6.7% versus 22.0% and 70.6%, respectively, $p<0.001$), MV (3.0% versus 16.3% and 58.8%, respectively, $p<0.001$), and mortality (3.0% versus 11.4% and 41.2%, respectively, $p<0.001$) (Table 1).

Table 1 Clinical, Laboratory, and Outcome Parameters in the Studied Patients ($n=300$)

	All Patients N=300	Vitamin D Levels Status			p value
		Normal n=135	Insufficiency n=114	Deficiency n=51	
Age (years) median (IQR)	51.0 (40.0–60.8)	49.0 (39.0–57.0)	51.0 (40.0–61.0)	55.0 (43.0–62.0)	0.012
Male/female n	172/128	81/45	61/53	30/21	0.57
Disease severity n (%)					
Mild	195 (65.0)	102 (75.6)	68 (59.6)	25 (49.0)	0.001
Severe	105 (35.0)	33 (24.4)	46 (40.4)	26 (51.0)	
Laboratory findings median (IQR)					
Hb	11.3 (9.8–12.5)	11.3 (9.8–12.5)	11.3 (9.9–12.5)	10.8 (9.1–11.8)	0.11
WBCs	8.5 (4.9–13.2)	8.7 (4.9–13.3)	8.3 (4.7–12.9)	9.0 (5.0–13.5)	0.77
Platelets	210.5 (164.3–264.5)	201.0 (163.0–266.0)	201.0 (164.8–258.5)	232.0 (166.0–268.0)	0.4
Creatinine	1.0 (0.7–1.6)	1.0 (0.7–1.6)	1.0 (0.7–1.6)	1.2 (0.7–1.7)	0.86
Urea	49.5 (36.3–90.0)	49.0 (35.0–90.0)	49.5 (37.0–90.8)	51.0 (37.0–100.0)	0.61
Albumin	3.3 (2.9–3.7)	3.3 (2.9–3.7)	3.3 (2.8–3.7)	3.2 (2.8–3.6)	0.47
ALT	19.5 (13.0–33.0)	19.0 (12.0–33.0)	20.5 (13.0–34.0)	25.0 (14.0–34.0)	0.57
AST	32.5 (20.0–47.3)	30.0 (19.0–42.0)	32.5 (19.0–49.3)	37.0 (22.0–55.0)	0.35
Na	137.0 (133.0–140.8)	136.0 (133.0–140.0)	136.5 (133.0–140.0)	138.0 (133.0–141.0)	0.68
K	4.0 (3.6–4.5)	4.0 (3.6–4.5)	3.9 (3.6–4.5)	4.2 (3.6–4.8)	0.97
Glucose	145.0 (93.8–221.3)	145.0 (93.0–225.0)	147.5 (97.5–226.5)	137.0 (92.0–202.0)	0.53
D dimer	1.8 (0.9–2.8)	1.5 (0.9–2.5)	1.8 (0.9–3.1)	2.0 (1.0–3.2)	0.033
CRP	73.5 (40.8–157.0)	58.0 (30.0–120.0)	76.0 (42.5–160.0)	105.0 (74.0–208.0)	<0.001
Ferritin	572.0 (351.0–836.0)	458.0 (240.0–759.0)	606.0 (433.8–897.8)	820.0 (552.0–1087.0)	<0.001

(Continued)

Table 1 (Continued).

	All Patients N=300	Vitamin D Levels Status			p value
		Normal n=135	Insufficiency n=114	Deficiency n=51	
Procalcitonin	335.0 (202.3–472.0)	290.0 (152.0–394.0)	372.5 (227.0–530.5)	443.0 (272.0–575.0)	<0.001
Outcome parameters n (%)					
ICU admission	76 (25.3)	9 (6.7)	31 (22.0)	36 (70.6)	<0.001
MV	57 (19.0)	4 (3.0)	23 (16.3)	30 (58.8)	<0.001
Mortality	41 (13.7)	4 (3.0)	16 (11.4)	21 (41.2)	<0.001

Correlation analysis showed significant inverse correlation between vitamin D levels and age ($r=-0.23$, $p<0.001$), D dimer ($r=-0.20$, $p<0.001$), CRP ($r=-0.31$, $p<0.001$), ferritin ($r=-0.28$, $p<0.001$), procalcitonin ($r=-0.29$, $p<0.001$), MV days ($r=-0.17$, $p=0.012$), and ICU stay ($r=-0.2$, $p=0.007$) (Table 2). Multivariate logistic regression analysis identified age [OR (95% CI): 1.9 (1.06–1.12), $p<0.001$], male sex [OR (95% CI): 2.71 (1.35–5.41), $p=0.005$], D dimer levels [OR (95% CI): 1.43 (1.16–1.77), $p=0.001$], CRP [OR (95% CI): 1.006 (1.003–1.010), $p=0.001$], ferritin [OR (95% CI): 1.002 (1.001–

Table 2 Correlation Between Vitamin D Levels and Clinical and Laboratory Data

	Vitamin D	
	r	p
Age	-0.23	<0.001
Hb	0.08	0.18
WBCs	0.07	0.20
Platelets	-0.02	0.78
Creatinine	-0.08	0.89
Urea	-0.04	0.47
Albumin	0.05	0.35
ALT	-0.08	0.15
AST	-0.08	0.16
Na	-0.06	0.3
K	0.009	0.88
Glucose	-0.01	0.82
D dimer	-0.20	<0.001
CRP	-0.31	<0.001
Ferritin	-0.28	<0.001
Procalcitonin	-0.29	<0.001
MV duration	-0.17	0.012
ICU stay	-0.2	0.007

Table 3 Predictors of Disease Severity in the Studied Patients

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	1.1	1.07–1.13	<0.001	1.9	1.06–1.12	<0.001
Sex	3.1	1.85–5.22	<0.001	2.71	1.35–5.41	0.005
D dimer	1.76	1.44–2.14	<0.001	1.43	1.16–1.77	0.001
CRP	1.008	1.005–1.011	<0.001	1.006	1.003–1.010	0.001
Ferritin	1.001	1.001–1.002	<0.001	1.002	1.001–1.003	0.004
Procalcitonin	1.002	1.001–1.003	<0.001	1.002	1.001–1.003	0.004
Vitamin D	0.91	0.88–0.94	<0.001	0.96	0.92–0.99	0.043

Table 4 Predictors of Mortality in Patients with Severe Disease

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	1.03	1.00–1.06	0.054	1.007	0.98–1.04	0.65
Sex	0.84	0.43–1.63	0.61	–	–	–
D dimer	1.09	0.92–1.28	0.31	–	–	–
CRP	1.002	0.99–1.005	0.28	–	–	–
Ferritin	1.002	1.001–1.003	0.001	1.001	1.001–1.001	0.13
Procalcitonin	1.0	1.0–1.0	0.29	–	–	–
Vitamin D	0.87	0.83–0.91	<0.001	0.88	0.84–0.92	<0.001

1.003), $p=0.004$], procalcitonin [OR (95% CI): 1.002 (1.001–1.003), $p=0.004$], and vitamin D levels [OR (95% CI): 0.96 (0.92–0.99), $p=0.043$] as significant predictors of severe disease (Table 3). Only lower vitamin D levels were significant predictors of mortality in multivariate analysis [OR (95% CI): 0.88 (0.84–0.92), $p<0.001$] (Table 4).

Discussion

The present study recognized a significant association between low vitamin D levels and covid-19 severity in this cohort of hospitalized covid-19 patients. In addition, we found a relation between vitamin D levels and mortality in patients with severe covid-19 infection. Moreover, we could identify an inverse correlation between vitamin D levels and patients' age, inflammatory marker levels, MV days, and ICU stay.

Our conclusions are in harmony with the results of multiple reports. In the study of Takase et al¹² the authors found that low serum vitamin D levels are an independent risk factor for severe covid-19. Also, Hafez et al¹³ documented an association between vitamin D deficiency and poor clinical outcome parameters including ICU admission and mortality. In addition, Nguyen et al¹⁴ found that patients with vitamin D deficiency had increased risk-adjusted odds of in-hospital mortality while those with insufficient levels had significantly increased risk for mechanical ventilation during hospitalization. Moreover, Gholi et al¹⁵ noted that, in critically ill covid-19 patients, vitamin D levels are determinants of in-hospital mortality. Similar findings were reported by the other studies.^{16,17} The inverse correlation between vitamin D levels and longer ICU stay was reported by the study of Herrera-Quintana et al,¹⁸ while Notz et al¹⁹ recognized an association between lower vitamin D levels and longer duration of MV.

In the present study, significant inverse correlations were found between levels of vitamin D and D-dimer and other proinflammatory mediators including CRP, ferritin, and procalcitonin in accordance with previous works. In one meta-analysis of 22 observational studies comprising 7771 patients, the authors concluded that patients that were vitamin D sufficient had lower levels of IL-6, CRP, ferritin, LDH, fibrinogen, and D-dimer compared to vitamin D deficient counterparts.²⁰ Likewise, an association was found between vitamin D levels and anti-SARS-CoV-2 IgG levels as shown by one study.²¹

Importantly, the study of Povaliaeva et al²² found that severely ill covid-19 patients do not have only low levels of vitamin D but they also have profound abnormalities in the metabolism of vitamin D regardless of the clinical course of the disease. Also, the experimental study of Arora et al²³ provided evidence of the protective role of vitamin D against pulmonary viral infection.

On the other hand, Ozturk et al²⁴ found no significant relation between vitamin D levels and covid-19 severity nor with the other inflammatory markers. Of note, the study of Huțanu et al²⁵ concluded that low vitamin D levels are related to more severe forms of the disease but not with inflammatory markers or mortality. Also, the study of Bogliolo et al²⁶ failed to document a relation between vitamin D levels and mortality.

Noteworthy, the large study of Lin et al²⁷ that used UK Biobank data found no evidence of an association between historical vitamin D status and hospitalization or mortality due to covid-19. However, this study only used historical but not recent vitamin D levels. Interestingly, another large UK-based study found an association between covid-19 infection and mortality and percentage of households with access to total open space. They linked covid-19 incidence and mortality across London with environmental variables linked to vitamin D status.²⁸

In conclusion, low vitamin D levels are related to exaggerated inflammatory response, disease severity, and poor clinical outcomes in hospitalized covid-19 patients.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Consent for Publication

All authors reviewed the manuscript and approved its submission.

Ethics Approval and Consent to Participate

This article was approved by the ethical committee of Al-Azhar Faculty of Medicine in accordance with the Helsinki Declaration on clinical research involving human subjects. A written informed consent was obtained from all patients.

Informed Consent

Informed consent was obtained from all patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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