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Clinical Research Article

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Vitamin D Levels Are Associated With Blood Glucose and BMI in COVID-19 Patients, Predicting Disease Severity

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CRP, C-reactive protein; ED, emergency department; GLU, glucose; ICU, intensive care unit; IFN-γ, interferon gamma; IL-1β, interleukin 1beta; IL-6, interleukin 6; IL-18, interleukin 18; LDH, lactate dehydrogenase; NIV, noninvasive ventilation; N/L ratio, neutrophil to lymphocyte ratio; OW, overweight; PaO_2/FiO_2 ratio, ratio between arterial partial pressure of oxygen measured by arterial blood gas analysis and the fraction of inspired oxygen; VD, vitamin D.

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Abstract

Context: A high prevalence of vitamin D (VD) deficiency in COVID-19 patients has been reported and hypothesized to increase COVID-19 severity likely because of its negative impact on immune and inflammatory responses. Furthermore, clear associations between hypovitaminosis D and fat body mass excess and diabetes, factors associated with COVID-19 severity, have been widely recognized.

Objective: The aim of this study was to evaluate in COVID-19 patients the relationship between VD levels and inflammatory response, body mass index (BMI), blood glucose (GLU), and disease severity.

Methods: Patients admitted to San Raffaele-Hospital for COVID-19 were enrolled in this study, excluding those with comorbidities and therapies influencing VD metabolism. 25-Hydroxyvitamin D levels, plasma GLU levels, BMI, and inflammatory parameters were evaluated at admission.

Results: A total of 88 patients were included. Median VD level was 16.3 ng/mL and VD deficiency was found in 68.2% of patients. VD deficiency was found more frequently in male patients and in those affected by severe COVID-19. Regression analyses showed

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a positive correlation between VD and PaO_2/FiO_2 ratio, and negative correlations between VD and plasma GLU, BMI, neutrophil/lymphocyte ratio, C-reactive protein, and interleukin 6. Patients with both hypovitaminosis D and diabetes mellitus, as well those with hypovitaminosis D and overweight, were more frequently affected by a severe disease with worse inflammatory response and respiratory parameters, compared to those without or just one of these conditions.

Conclusion: We showed, for the first-time, a strict association of VD levels with blood GLU and BMI in COVID-19 patients. VD deficiency might be a novel common pathophysiological mechanism involved in the detrimental effect of hyperglycemia and adiposity on disease severity.

Key Words: vitamin D, plasma glucose, body mass index, COVID-19, SARS-CoV-2

COVID-19 clinical manifestations are characterized by widely varying respiratory and extrarespiratory features. Pulmonary manifestations range from asymptomatic forms to acute respiratory distress syndromes with high mortality risk, and extrarespiratory manifestations include cardiovascular, thrombotic, neurological, gastrointestinal, and endocrine features (1-5).

Risk factors recognized for COVID-19 severe forms characterized by hyperinflammatory response and dramatic pulmonary and systemic complications include older age, presence of concomitant comorbidities such as cardiovascular disease, diabetes, and cancer, male sex, and obesity (1-9). In addition, several findings have recently shown a novel role of an endocrine osteometabolic phenotype suggested to possibly influence COVID-19 severity and clinical outcomes (10-17). This phenotype is typically characterized by a widespread prevalence of acute hypocalcemia and chronic hypovitaminosis D and a highly prevalence of vertebral fractures (10-17).

A widespread prevalence of vitamin D (VD) deficiency in COVID-19 patients has been reported by several studies and, because VD is proved to be involved in immune response and immunocompetence, VD deficiency has been hypothesized to predispose individuals to SARS-CoV-2 infection and to increase COVID-19 severity, although not all research has confirmed these findings (18-25).

Furthermore, clear associations between hypovitaminosis D and overweight (OW), obesity, and diabetes mellitus, factors known to increase COVID-19 severity risks, have been widely recognized (26-29). Several pathophysiological mechanisms have been hypothesized to explain the associations between fat body mass excess and hypovitaminosis D, including lower dietary intake of VD, decreased outdoor physical activity with poorer skin exposure to sunlight, impaired hydroxylation in adipose tissue, VD accumulation in fat, and alterations in VD receptors in patients with body fat excess (26, 27).

It has been widely reported that patients with diabetes mellitus had low VD levels, likely due to impaired hepatic and renal metabolism of VD, decreased dietary VD intake, and reduced intestinal absorption of VD due to diabetic autonomic neuropathy (28-30). Moreover, low circulating VD levels have been reported to be associated with poor glycemic control in diabetic patients and large prospective studies have suggested that VD deficiency may predispose to a higher risk of developing impaired fasting glucose (GLU) and diabetes (31-33), although the influence of VD supplementation on diabetes onset risk is still unknown and, in a recent prospective randomized trial, VD supplementation did not result in a significantly lower risk of new-onset diabetes than placebo in prediabetic individuals (34).

To date, only a few studies have tried to investigate the impact of hypovitaminosis D on the inflammatory immune response in COVID-19 (19-21), and no data are available about the relationship between VD and blood GLU and body mass index (BMI) in these patients.

The aim of this study was to evaluate in COVID-19 patients the relationship between VD levels and inflammatory response, BMI, blood GLU, and disease severity.

Materials and Methods

Study Design

This was a retrospective substudy of the COVID-BioB study, a large prospective observational investigation performed at San Raffaele University Hospital, a tertiary health care hospital in Milan, Italy (35). The study protocol complies with the Declaration of Helsinki, was approved by the hospital ethics committee (protocol No. 34/int/2020), and was registered at ClinicalTrials.gov (NCT04318366). A full description of patient management and clinical protocols has been published previously (35). Signed informed consent was obtained from all patients participating in this study. Adult patients (age ≥ 18 years) admitted to San Raffaele University Hospital for COVID-19 during the first Italian wave of

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the pandemic (March 18 to May 5, 2020) were enrolled in the COVID-BioB study. Confirmed COVID-19 was defined as positive real-time reverse-transcriptase polymerase chain reaction from a nasal and/or throat swab together with signs, symptoms, and/or radiological findings suggestive of COVID-19 pneumonia. Patients admitted for other reasons and subsequently diagnosed with superimposed SARS-CoV-2 infection were excluded.

Data Collection

Data were collected from medical chart review or directly by patient interview and entered in a dedicated electronic case record form specifically developed for the COVID-BioB study. Before the analysis, data were cross-checked with medical charts and verified by data managers and clinicians for accuracy. As part of the COVID-BioB protocol, blood samples from all enrolled patients were collected and stored in the COVID-19 biobank of our institution according to appropriate quality control systems (35).

For this study the following variables were collected: age, sex, BMI (calculated as the ratio of weight in kilograms divided by height in meters squared), vitamin 25-OHD_3 (ng/mL), PaO_2/FiO_2 ratio (calculated as the ratio between the arterial partial pressure of oxygen measured by arterial blood gas analysis and the fraction of inspired oxygen), estimated glomerular filtration rate (as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation and expressed as mL/min/1.73 m^2), lymphocyte and neutrophil counts ($\times 10^9$/L), lactate dehydrogenase (LDH, U/L), high-sensitivity C-reactive protein (CRP, mg/dL), plasma GLU (mg/dL) on admission to the emergency department (ED), comorbidities (including history of hypertension, diabetes mellitus, coronary artery disease, and active malignancy), and clinical outcomes (discharge from ED or hospital ward, hospitalization, need for noninvasive mechanical ventilation (NIV), admission to intensive care unit [ICU], and mortality). Severe COVID-19 disease was defined as the need for high-flow oxygen therapy and/or NIV, admission to the ICU, and/or death from COVID-19 complications.

Patients with the following comorbidities and concomitant active therapies influencing VD metabolism were excluded from the study analyses: chronic kidney disease, osteoporosis, patients on glucocorticoids and antiepileptic drugs, VD/calcium, loop/thiazide diuretics, and patients with an estimated glomerular filtration rate of less than or equal to 30 mL/min/1.73 m^2 using creatinine levels at initial evaluation.

Definitions and Cutoffs

VD deficiency was defined as a 25(OH)D level below 20 ng/mL, according to the last consensus report by Sempos et al (36). OW was defined as a BMI greater than 25, accordingly to the World Health Organization classification (37). Hyperglycemia was defined as a plasma GLU greater than 125 mg/dL, according to American Diabetes Association cutoff values (38).

Assays

VD measurements were performed on a Roche COBAS 8000 using electrochemiluminescence immunoassays. Multiplex immunoassays (Bio-Rad) based on Luminex technology were used for the quantification of interleukin 1beta (IL-1β), interleukin 6 (IL-6), interferon gamma (IFN-γ), and interleukin 18 (IL-18) in human samples, according to the manufacturer's instructions. Data were measured on a Bio-Plex 200 System and calculated using Bio-Plex Manager 6.0 and 6.1 software.

Statistical Analysis

Descriptive statistics were obtained for all study variables. Categorical variables were summarized as counts and percentages. The Kolmogorov-Smirnov normality test was performed ($P < .05$) and continuous variables were expressed as medians and interquartile range (25th–75th percentile). The Fisher exact test or χ^2 test and the Wilcoxon signed rank test or the Kruskal-Wallis test were employed to determine the statistical significance of differences in proportions and medians, respectively. Linear regression analyses were used to correlate continuous variables. All statistical tests were 2-sided. A P value of less than .05 was considered statistically significant. Statistical analysis was conducted using IBM SPSS Statistics (IBM SPSS Statistics for Windows, version 23.0, IBM Corp).

Results

Clinical Presentations and Outcomes

A total of 111 patients were initially included in the study but, subsequently, 23 were excluded for the following exclusion criteria: 11 patients were affected by chronic kidney disease and 7 of them were on VD supplements; 3 patients were affected by osteoporosis and 3 by osteopenia, and were on VD supplements; and, finally, 6 patients were on VD supplements with not known diagnosis of osteoporosis/osteopenia.

Ultimately, a total of 88 COVID-19 patients were included in the study. Approximately two-thirds of the patients were male (67%), and the median age was 56.8 years (range, 49.2-67.5 years). Patient demographic, inflammatory, and disease characteristics on hospital admission are summarized in Table 1.

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Table 1. Baseline characteristics of COVID-19 patients

	No. (%), median (IQR)
Demographics	
Total patients	88
Age, y	56.8 (49.2-67.5)
Male	59 (67%)
BMI	27 (24.7-30.5)
Normal weight	16 (28.2%)
Overweight	43 (72.8%)
Missing	29
Comorbidities	
Hypertension	31 (35.2%)
Coronary artery disease	9 (10.2%)
Diabetes mellitus	18 (20.5%)
Malignancy	2 (2.3%)
Clinical and laboratory parameters at admission	
PaO_2/FiO_2 ratio	288 (190-366)
Neutrophil-lymphocyte ratio	5.3 (3.7-8)
CRP, mg/dL	102 (26-161)
LDH, U/L	403 (262-538)
eGFR, mL/min/1.73 m^2	96.5 (79.5-107)
IL-1β, pg/mL	3 (0.6-5.3)
IL-6, pg/mL	25.2 (6.9-77.4)
IFN-γ, pg/mL	11.6 (3.7-33.7)
IL-18, pg/mL	719 (521-1156)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IFN-γ, interferon gamma; IL-1β, interleukin 1beta; IL-6, interleukin 6; IL-18, interleukin 18; IQR, interquartile range; LDH, lactate dehydrogenase; PaO_2/FiO_2 ratio, ratio between arterial partial pressure of oxygen measured by arterial blood gas analysis and the fraction of inspired oxygen.

The main comorbidities were history of arterial hypertension (35.2%), followed by diabetes mellitus (20.5%) and coronary artery disease (10.2%). Sixty-two patients (70.5%) were hospitalized after initial evaluation and 28 (31.8%) were admitted to the ICU during hospitalization, and 17 (19.3%) patients died. Severe COVID-19 was found in 50 (56.8%) patients.

Vitamin D and Disease Severity

On initial hospital admission, median VD level was 16.3 ng/mL (range, 11.2-23.9 ng/mL) and VD deficiency was found in 60 (68.2%) patients.

VD deficiency was found more frequently in male patients compared to the female group (77% vs 48%, $P = .007$) and no differences regarding age and comorbidities distribution were found between VD deficiency patients and those without VD deficiency (see Table 2). Male patients presented with a median VD level of 15.9 ng/mL (range, 10.4-18.5 ng/mL) compared to female patients, who presented with a median VD level of 20.4 ng/mL (range, 13.2-27.8 ng/mL) ($P = .017$).

Linear regression analyses showed a positive correlation between VD levels and PaO_2/FiO_2 ratio ($P = .019$, $r = 0.25$), and negative correlations between VD levels and neutrophil to lymphocyte (N/L) ratio ($P = .04$; $r = –0.19$), CRP levels ($P = .047$, $r = –0.18$), and IL-6 levels ($P = .038$, $r = –0.22$) (see Fig. 1).

Lower VD levels were found in patients affected by severe disease than in nonsevere patients (13.4 ng/mL vs 18.45 ng/mL, $P = .007$). Moreover, patients with VD deficiency had higher levels of CRP, LDH, IL-6, IFN-γ ($P = .04$, $P = .01$, $P = .002$, $P = .04$; respectively), lower PaO_2/FiO_2 and higher N/L ratios ($P = .008$, $P = .004$; respectively), and higher rate of severe disease (65% vs 39%, $P = .02$), compared to patients without VD deficiency (see Table 2).

No differences regarding clinical outcomes were found between VD deficiency patients and those without VD deficiency (see Table 2).

Vitamin D and Glucose Levels

On initial hospital admission, median GLU level was 112.5 mg/dL (range, 97.2-137.5 mg/dL) and hyperglycemia, defined as a GLU level greater than 125 mg/dL, was found in 29 (32.9%) patients.

Linear regression analyses showed a negative correlation between GLU and VD levels ($P = .03$, $r = –0.23$) (see Fig. 2A).

In hyperglycemic patients we found lower levels of VD compared to normoglycemic patients (13.3 ng/mL vs 18.2 ng/mL; $P = .006$). Furthermore, VD deficiency patients were characterized by higher GLU levels compared to the normal VD group (118 mg/dL vs 100 mg/dL; $P = .004$) (see Table 2) and were more frequently hyperglycemic (41.6% vs 14.3%; $P = .01$).

Severe COVID-19 was found in 7 of 24 (29%) of patients with normal GLU and normal VD, in 24 of 39 (61%) of those with hyperglycemia or hypovitaminosis D, and in 19 of 25 (76%) of patients with both hyperglycemia and VD deficiency ($P = .003$) (see Table 3). No statistical differences were found regarding age in these 3 groups (see Table 3).

Higher PaO_2/FiO_2 and lower N/L ratio, LDH, CRP, IL-1β, and IL-6 levels were found in patients without hyperglycemia and VD deficiency compared to those with one or both conditions (see Table 3). Higher rates of hospitalization, ICU admission, and NIV requirement were found in patients with hyperglycemia and hypovitaminosis D compared to those with one or no conditions (see Table 3).

To evaluate the effects of hypovitaminosis D or hyperglycemia alone in patients with only one of these

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Table 2. Clinical biochemical parameters and disease outcomes in patients with vitamin D (VD) deficiency compared to patients without VD deficiency

	VD levels < 20 ng/mL (n = 60)	VD levels ≥ 20 ng/mL (n = 28)	P
Age, y	56 (50-67)	60 (48-70)	.75
BMI	29 (26-32)	25.6 (23.8-29.7)	**.043**
Hypertension	23 (38%)	8 (28%)	.37
Coronary artery disease	4 (6.6%)	5 (18%)	.13
Diabetes mellitus	12 (20%)	6 (21%)	.87
Malignancy	1 (1.6%)	1 (3.6%)	.54
PaO_2/FiO_2 ratio	271 (178-331)	356 (230-415)	**.008**
Neutrophil-lymphocyte ratio	6 (4.1-8.6)	3.7 (2-5.8)	**.004**
CRP, mg/dL	119 (44-172)	74 (8-153)	**.04**
LDH, U/L	444 (312-563)	307 (221-470)	**.01**
Plasma glucose, mg/dL	118 (106.2-143.5)	110 (90.2-112.5)	**.004**
IL-1β, pg/mL	3.3 (0.3-6.6)	2.1 (0.8-5)	.4
IL-6, pg/mL	32.4 (13.9-88)	8.2 (0.4-35.4)	**.002**
IL-18, pg/mL	847 (451-1222)	706 (533-1335)	.8
IFN-γ, pg/mL	13.8 (5.3-39.8)	6.8 (0.7-30.3)	**.04**
Hospitalized, No. (%)	45 (75%)	17 (60.7%)	.17
Severe disease, No. (%)	39 (65%)	11 (39%)	**.02**
NIV, No. (%)	25 (41.7%)	9 (31.1%)	.33
ICU, No. (%)	22 (36.7%)	6 (21.4%)	.15
Death, No. (%)	12 (20%)	5 (17.8%)	.8

P values reported in bold are statistically significant.

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; IFN-γ, interferon gamma; IL-1β, interleukin 1beta; IL-6, interleukin 6; IL-18, interleukin 18; LDH, lactate dehydrogenase; NIV, noninvasive ventilation; PaO_2/FiO_2 ratio, ratio between arterial partial pressure of oxygen measured by arterial blood gas analysis and the fraction of inspired oxygen.

conditions, we compared baseline characteristics, inflammatory parameters, and disease outcomes of patients with hypovitaminosis D and normoglycemia vs those with hyperglycemia and normal VD levels (see Table 4). Hyperglycemic patients were significantly older compared to hypovitaminosis D patients (age 73 [54-78] vs 52 [48-63] years; $P = .042$) (see Table 4) and required more frequently NIV support and ICU admission (see Table 4).

Vitamin D and Body Mass Index

BMI was available in 59 patients. In these patients median VD level was 16.4 ng/mL and VD deficiency was found in 66.1% of patients. Median BMI was 27 and OW was found in 43 of 59 (72.9%) patients, of whom 20 were obese (33.9%).

Linear regression analysis showed a negative correlation between BMI and VD levels ($P = .042$, $r = -0.26$) (see Fig. 2B).

In OW patients we found lower levels of VD compared to normal-weight patients (16.2 ng/mL vs 20.2 ng/mL; $P = .044$). Furthermore, VD deficiency patients were characterized by a higher BMI compared to the nondeficient VD group (28.4 vs 25.6; $P = .043$) and were more frequently OW (82% vs 55%; $P = .027$).

Severe COVID-19 was found in 3 of 9 (33%) patients with normal weight and normal VD, in 11 of 18 (61%) of those with OW or hypovitaminosis D, and in 23 of 32 (72%) patients with both OW and VD deficiency ($P = .1$) (see Table 5). In particular, comparing OW patients with hypovitaminosis D vs normal-weight patients with normal VD, severe COVID-19 was found more frequently in the first group (33% vs 72%; $P = .047$). Furthermore, a higher PaO_2/FiO_2 ratio and lower IL-6 levels were found in patients without OW and VD deficiency compared to those with one or both conditions (371 vs 243 vs 211; $P = .03$) (8.7 vs 24.3 vs 43.8 pg/mL; $P = .046$) (see Table 5).

To evaluate the effects of hypovitaminosis D or OW alone in patients with only one of these conditions, we compared baseline characteristics, inflammatory parameters, and disease outcomes of patients with hypovitaminosis D and normal weight vs those with OW and normovitaminosis D (see Table 6). Hypovitaminosis D patients were affected by a worse inflammatory response with higher levels of N/L, CRP, and LDH compared to OW patients (see Table 6); no statistically significant differences were found in baseline characteristics and disease outcomes (see Table 6).

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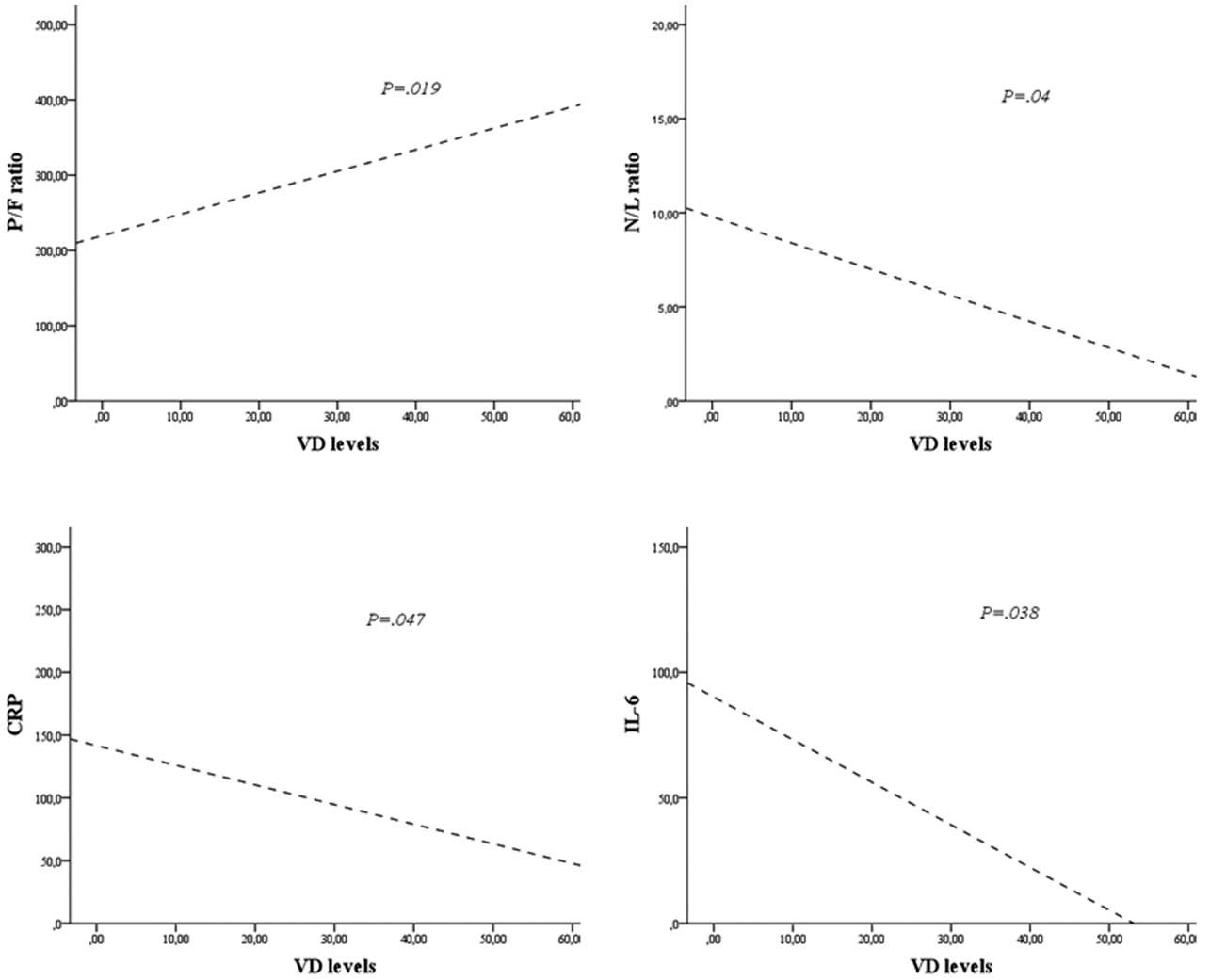

Figure 1. Vitamin D correlations with respiratory and inflammatory parameters. CRP, C-reactive protein; IL-6, interleukin 6; N/L, neutrophil-lymphocyte ratio; P/F, ratio between arterial partial pressure of oxygen measured by arterial blood gas analysis and the fraction of inspired oxygen; VD, vitamin D.

Discussion

From the beginning of the COVID-19 spread in Europe, we have proposed that VD deficiency could be involved in increased SARS-CoV-2 infection susceptibility and negative outcomes of COVID-19 (39).

The role of VD is well known to be crucial for the skeletal homeostasis in physiological and disease states, but it also has many systemic extraskeletal functions, including immunomodulation and immunocompetence both regarding innate and adaptive immunity (40). This immunomodulatory role is consistent with several findings showing low levels of VD in hospitalized patients with COVID-19 and with reported correlations between VD levels and disease clinical severity and outcomes (14).

Very recent systematic reviews and meta-analyses assessing the impact of VD status on COVID-19 infection and related mortality concluded that low VD levels seem associated with increased SARS-CoV-2 infection risk, COVID-19 severity, and associated mortality, although these analyses were conducted with available evidence to date obtained from largely not high-quality observational studies (41-43).

In our study we found clear associations between lower VD levels and worse inflammatory and clinical parameters in COVID-19 patients.

PaO_2/FiO_2 ratio, representing a reliable clinical indicator of hypoxemia, is one of the most useful parameters used in patients with respiratory diseases to identify those at higher risk of severe disease (44). In our study VD levels were found to be positively associated with PaO_2/FiO_2 ratio, and in VD deficiency patients lower PaO_2/FiO_2 ratio values were found. Moreover, inflammatory parameters, such as CRP and LDH, and cytokine immune markers, such as IL-6 and IFN-γ, typically increased and associated with severe COVID-19 (45), were found to be higher in VD deficiency patients, and some of these parameters were found to be negatively correlated with lower VD levels.

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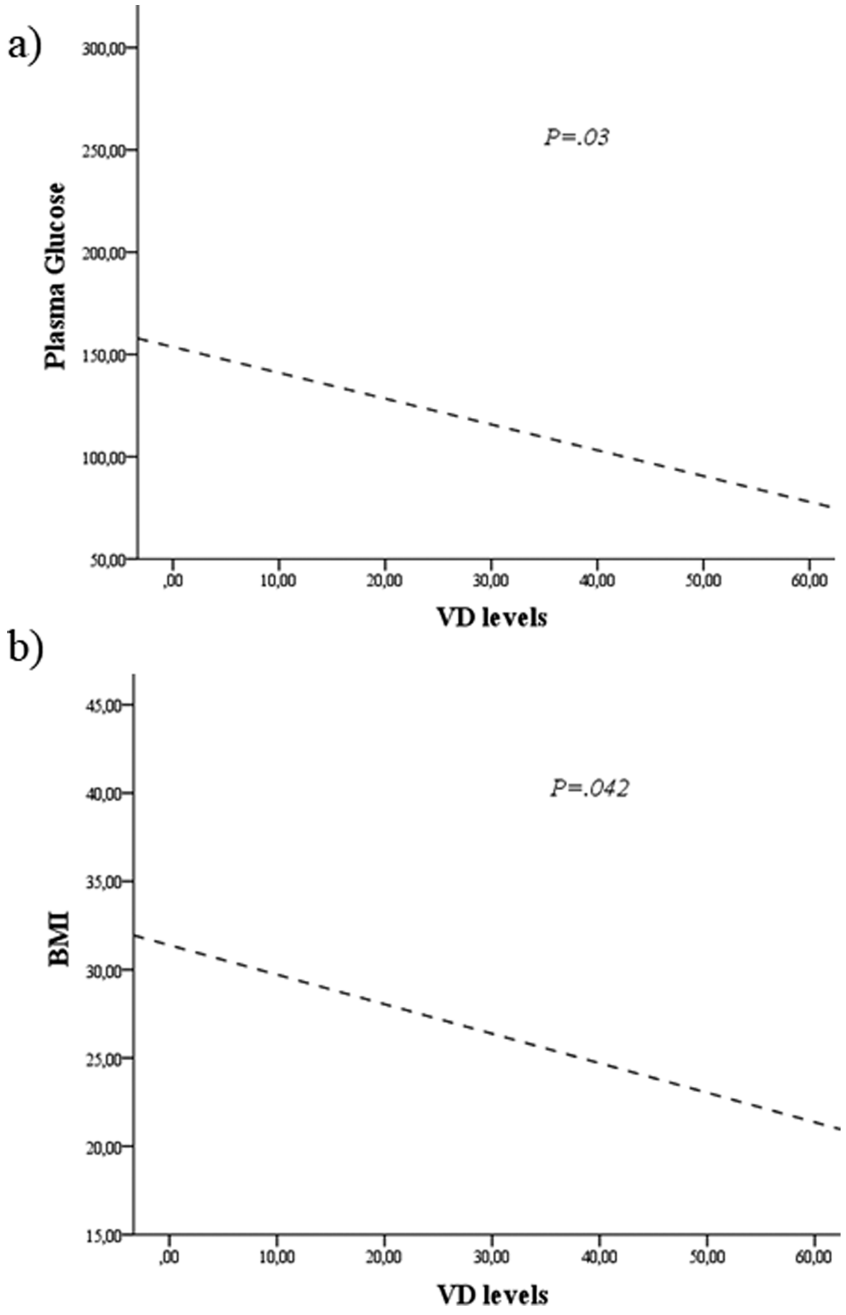

Figure 2. Vitamin D (VD) correlations with plasma glucose and body mass index (BMI).

Furthermore, the N/L ratio, which proved to be one of the most effective biochemical markers able to predict severe COVID-19 representing an immune-dysregulated response with lymphopenia and neutrophilia (46, 47), was found to be higher in VD-deficient patients and negatively associated with VD.

From the beginning of the COVID-19 pandemic, several studies showed clearly how male patients were at higher risk of a more severe disease compared to women with a similar pattern in different countries (9). In a recent study of patients with COVID-19, the majority of VD-deficient individuals on hospital admission were male (48), and our data are in agreement with these previous results. Therefore, these findings confirm that underdiagnosis of mineral metabolism diseases in male patients remains a critical medical issue with several systemic implications, including higher infectious risks and dysregulated inflammatory response.

History of or newly diagnosed diabetes mellitus and abnormalities of plasma GLU, including worsened hyperglycemia and euglycemic ketosis, rapidly emerged as one of the most relevant medical conditions negatively influencing

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Table 3. Clinical biochemical parameters and disease outcomes comparisons between patients with vitamin D deficiency and hyperglycemia and patients with one or no conditions

	Normo-GLU AND normo-VD (n = 24)	Hyper-GLU OR hypo-VD (n = 39)	Hyper-GLU AND hypo-VD (n = 25)	P
Age, y	58 (47-77)	65 (55-69)	57 (51-64)	.2
PaO_2/FiO_2 ratio	371 (288-413)	271 (164-316)	223 (147-310)	**.001**
Neutrophil-lymphocyte ratio	4.6 (2-8.5)	5.6 (3.7-9.8)	5.9 (3.9-7.8)	**.003**
CRP, mg/dL	100 (9.3-166)	103 (41-163)	109 (46-169)	**.019**
LDH, U/L	283 (195-610)	363 (327-535)	444 (312-581)	**.003**
IL-1β, pg/mL	2 (0.5-10.6)	1.3 (0.2-9.2)	2.9 (0.2-4.7)	**.045**
IL-6, pg/mL	8.7 (0.4-37.1)	24 (7.5-54.8)	38.9 (19.3-151)	**.002**
IL-18, pg/mL	876 (514-2048)	609 (456-1142)	702 (522-1036)	.4
IFN-γ, pg/mL	32 (2.2-42.8)	10 (4.8-30.5)	16.6 (6.9-43)	.09
Hospitalized, No. (%)	13 (54%)	28 (71.7%)	21 (84%)	.07
Severe disease, No. (%)	7 (29%)	24 (61%)	19 (76%)	**.003**
NIV, No. (%)	5 (20.8%)	15 (39%)	14 (58.3%)	**.026**
ICU, No. (%)	2 (8.3%)	14 (39%)	12 (48%)	**.009**
Death, No. (%)	3 (12.5%)	7 (17.9%)	7 (28%)	.37

P values reported in bold are statistically significant.
Abbreviations: CRP, C-reactive protein; GLU, plasma glucose; ICU, intensive care unit; IFN-γ, interferon gamma; IL-1β, interleukin 1beta; IL-6, interleukin 6; IL-18, interleukin 18; LDH, lactate dehydrogenase; NIV, noninvasive ventilation; PaO_2/FiO_2 ratio, ratio between arterial partial pressure of oxygen measured by arterial blood gas analysis and the fraction of inspired oxygen; VD, vitamin D.

Table 4. Clinical biochemical parameters and disease outcome comparisons between patients with vitamin D deficiency and hyperglycemia alone

	Hyper-GLU AND normo-VD (n = 4)	Hypo-VD AND normo-GLU (n = 35)	P
Age, y	73 (54-78)	52 (48-63)	**.042**
PaO_2/FiO_2 ratio	209 (53-316)	304 (228-333)	.07
Neutrophil-lymphocyte ratio	10.4 (5.4-11.8)	5.9 (3.9-8.1)	.4
CRP, mg/dL	160 (141-285)	98 (43-154)	.06
LDH, U/L	541 (411-610)	439 (299-505)	.14
IL-1β, pg/mL	1.6 (1.4-10.6)	3.7 (1.6-7.7)	.52
IL-6, pg/mL	35 (8.4-189)	34.8 (10-81)	≥ .1
IL-18, pg/mL	1962 (1053-2999)	676 (480-1160)	**.013**
IFN-γ, pg/mL	19 (2-80.6)	14 (4.7-42)	.9
Hospitalized, No. (%)	4 (100%)	24 (65%)	.3
Severe disease, No. (%)	4 (100%)	20 (57%)	.14
NIV, No. (%)	4 (100%)	11 (32%)	**.02**
ICU, No. (%)	4 (100%)	10 (29%)	**.01**
Death, No. (%)	2 (50%)	5 (14%)	.14

P values reported in bold are statistically significant.
Abbreviations: CRP, C-reactive protein; GLU, plasma glucose; ICU, intensive care unit; IFN-γ, interferon gamma; IL-1β, interleukin 1beta; IL-6, interleukin 6; IL-18, interleukin 18; LDH, lactate dehydrogenase; NIV, noninvasive ventilation; PaO_2/FiO_2 ratio, ratio between arterial partial pressure of oxygen measured by arterial blood gas analysis and the fraction of inspired oxygen; VD, vitamin D.

COVID-19 outcomes (49, 50). Several studies reported diabetic patients were at higher risk of hospitalization, severe pulmonary involvement, and mortality compared to nondiabetic individuals (49, 50). These findings suggest that glycemic control may improve outcomes in patients with COVID-19, although a potential caveat in this regard may be represented by the finding that in ICU patients with critical illness a too tight GLU control could be rather harmful, increasing mortality risk (51). Interestingly, it was previously reported that type 2 diabetic patients are characterized by low VD levels (52). In fact, postmenopausal diabetic women were cross-sectionally reported to have a significantly higher prevalence of severe hypovitaminosis D compared to controls (39 vs 25%, respectively) (53). Decreased circulating VD levels were also suggested to be involved in the pathophysiology of diabetes-related

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Table 5. Clinical biochemical parameters and disease outcomes comparison between patients with vitamin D deficiency and overweight and those with one or no conditions

	Normal weight AND normo-VD (n = 9)	Overweight OR hypo-VD (n = 18)	Overweight AND hypo-VD (n = 32)	P
Age, y	58 (46-67)	53 (49-65)	61 (53-68)	.3
PaO_2/FiO_2 ratio	371 (253-418)	292 (220-332)	211 (111-311)	**.03**
Neutrophil-lymphocyte ratio	3.2 (2-5.2)	5.9 (4.1-8.1)	6.8 (4.2-10.5)	.62
CRP, mg/dL	37 (6.4-118)	117 (46-159)	122 (38-236)	.9
LDH, U/L	275 (199-360)	440 (309-526)	495 (323-672)	.35
IL-1β, pg/mL	2.1 (0.4-5)	2.2 (0.3-3.5)	3.7 (1.6-7.7)	.84
IL-6, pg/mL	7.3 (0.4-24.7)	26.7 (18.4-177)	34.8 (10-81.4)	**.04**
IL-18, pg/mL	717 (433-1101)	693 (510-1229)	765 (641-1128)	.5
IFN-γ, pg/mL	13.8 (5.3-39.8)	6.8 (0.7-30.3)	16.1 (6.24-33.4)	.55
Hospitalized, No. (%)	5 (55%)	15 (83%)	27 (84%)	.14
Severe disease, No. (%)	3 (33%)	11 (61%)	23 (72%)	.1
NIV, No. (%)	3 (33%)	9 (50%)	14 (43.7%)	.71
ICU, No. (%)	2 (22%)	6 (33%)	11 (34%)	.78
Death, No. (%)	1 (11%)	3 (16.6%)	4 (12.5%)	.89

P values reported in bold are statistically significant.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; ICU, intensive care unit; IFN-γ, interferon gamma; IL-1β, interleukin 1beta; IL-6, interleukin 6; IL-18, interleukin 18; LDH, lactate dehydrogenase; NIV, noninvasive ventilation; PaO_2/FiO_2 ratio, ratio between arterial partial pressure of oxygen measured by arterial blood gas analysis and the fraction of inspired oxygen; VD, vitamin D.

Table 6. Clinical biochemical parameters and disease outcomes comparisons between patients with vitamin D deficiency and overweight alone

	Overweight AND normo-VD (n = 11)	Hypo-VD AND normal weight (n = 7)	P
Age, y	63 (48-69)	67 (57-79)	.25
PaO_2/FiO_2 ratio	253 (190-345)	178 (54-242)	.06
Neutrophil-lymphocyte ratio	4.3 (2.8-5.8)	9.1 (6.6-13)	**.02**
CRP, mg/dL	75 (28-113)	143 (100-293)	**.04**
LDH, U/L	344 (299-419)	508 (363-566)	**.04**
IL-1β, pg/mL	1.6 (0.3-5.5)	0.3 (0.27-14.6)	≥ .1
IL-6, pg/mL	10 (6.9-36.4)	45 (16-81)	.18
IL-18, pg/mL	603 (442-1145)	633 (461-1142)	.83
IFN-γ, pg/mL	7.4 (3.2-23.8)	16 (7-81.7)	.2
Hospitalized, No. (%)	9 (81%)	6 (86%)	.83
Severe disease, No. (%)	6 (54%)	5 (71%)	.6
NIV, No. (%)	4 (36%)	5 (70%)	.3
ICU, No. (%)	3 (27%)	3 (43%)	.62
Death, No. (%)	2 (18%)	1 (15%)	≥ .1

P values reported in bold are statistically significant.
Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; IFN-γ, interferon gamma; IL-1β, interleukin 1beta; IL-6, interleukin 6; IL-18, interleukin 18; LDH, lactate dehydrogenase; NIV, noninvasive ventilation; PaO_2/FiO_2 ratio, ratio between arterial partial pressure of oxygen measured by arterial blood gas analysis and the fraction of inspired oxygen; VD, vitamin D.

skeletal fragility (31), which is also prevalent in male patients (54) and very relevant to COVID-19 patients as we have recently shown (15).

Confirming these previous findings that showed strict relationships between glycemic status and VD levels, we found a negative correlation between GLU and VD levels in COVID-19 patients on admission to the ED. VD deficiency was found more frequently in hyperglycemic patients compared to normoglycemic individuals, and GLU levels were found to be significantly higher in patients with VD deficiency compared to those without VD deficiency.

Furthermore, for the first time, we showed that patients affected both by VD deficiency and hyperglycemia were at a higher risk of severe COVID-19 compared to those without or with only 1 of these 2 conditions; in particular, the VD deficient and hyperglycemic patient group

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was characterized by worse respiratory exchanges, higher inflammatory response, and worse disease outcomes, although hyperglycemia alone appears to have more severe negative consequences than hypovitaminosis D alone, at least in part due to the older age of the first vs the latter group. Because low VD also characterizes diabetic patients with retinopathy (55), it can be hypothesized that hypovitaminosis D may worsen the predisposition of patients with diabetes to the microvascular damage typical of COVID-19.

Interestingly, a recent critical analysis of randomized trials reported that supplementation with VD in diabetes may improve glycometabolic control, as assessed by fasting blood glucose and by glycated hemoglobin, likely through a decrease in insulin resistance and stimulated β-cell function (56, 57), particularly in patients with poor glycemic control at baseline (34). A very recent cross-sectional study showed that serum VD was statistically inversely associated with the homeostasis model assessment of insulin resistance, but this association was found only in the female population and not in males (58). The authors explained this sex-dependent correlation by the differential sex steroid hormone effects on pancreatic β cells and different distribution and metabolic effects of body fat tissue between men and women (58).

Moreover, some studies have suggested that VD treatment may slow the progression to diabetes in patients either at high risk of diabetes or with prediabetes, specifically in those with low baseline VD levels (59).

Based on the findings of our study, it can be hypothesized for the first time that low VD may be a predisposing detrimental or even causal factor in the bidirectional relationship between diabetes and COVID-19 increasing synergistically the vulnerability of diabetic patients to the infection as well as facilitating the diabetogenic action of COVID-19.

Furthermore, BMI and altered body composition with increased adiposity are reported as independent risk factors for greater disease severity and poor prognosis in COVID-19 patients (60, 61). Low levels of VD were frequently reported in obese and OW patients being inversely related to BMI and adiposity (26, 62), negatively influencing skeletal and muscle health with a resulting increased predisposition to an obese osteosarcopenic phenotype (63, 64). In fact, BMI has also been reported to predict resistance to VD (65).

A possible direct relationship between VD status, body fat, age, and SARS-CoV-2 infection and COVID-19 severity has been previously hypothesized. In fact, aging and fat accumulation may decrease VD bioavailability and action (66). In our cohort we found a very high prevalence of OW and hypovitaminosis D and, for the first time, we showed a negative correlation between BMI and VD values in COVID-19 patients. Furthermore, VD deficiency prevalence was found to be higher in OW patients, and those affected by both conditions presented more frequently with severe disease with higher IL-6 and lower PaO_2/FiO_2 ratio levels compared to those without VD deficiency and OW and those with 1 of the 2 conditions. Interestingly, among these latter groups we found that patients with hypovitaminosis D alone had worse biochemical inflammatory parameters compared to patients with OW alone, further underlining the importance of the synergistic negative impact of hypovitaminosis D and OW as unfavorable prognostic factors in patients with COVID-19.

Our data indicate that low VD levels in obese individuals may be associated with more severe COVID-19 and eventually worsen the prognosis in those patients admitted to the ICU likely because of an enhanced baseline inflammatory state. In fact, VD may exert a protective effect in obese individuals by reducing systemic inflammation (67). Moreover, VD has been suggested to play a role in modulating fat distribution and activity (68). Thus, adequate VD status may also be key in preserving body composition in post–COVID-19 recovery (69).

Limitations of this study are first its retrospective and cross-sectional nature, which did not allow us to evaluate the longitudinal modifications of biochemical and clinical parameters during disease progression and recovery; second, the relatively limited number of patients enrolled due to the strict and rigorous inclusion and exclusion criteria used that, on the other hand, allowed us to analyze our findings without the need to consider the potential impact of several confounding factors; third, we assessed 25(OH)D, which is universally accepted as the best marker of individual VD status (70, 71). In this specific setting, it could have been useful to also assess active or free VD (72, 73). However, because these parameters are not routinely available and because of the known methodological issues in their assays (36), they were not included in the study protocol.

To our knowledge, this is the first study providing evidence of a strict association of VD levels with male sex, GLU levels, and BMI in COVID-19 patients in predicting disease severity. Our study has limitations, and future larger studies and the results of ongoing interventional randomized clinical trials could be conclusive in clarifying the therapeutic role of VD supplementation in preventing SARS-CoV-2 infection and hard clinical end points including mortality in metabolically comorbid patients with COVID-19 (74-76). Moreover, because VD supplementation has been reported to be effective in preventing respiratory infections (77), it could be interesting to extend our observation to non–COVID-19 patients in order to understand if hypovitaminosis D may be associated with diabetes (78) and obesity in predisposing individuals to negative outcomes of pneumonia in the non–COVID setting.

In conclusion, in our cohort of COVID-19 patients admitted to the ED we found a high prevalence of low VD

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levels that was associated with an increased disease severity likely through an excessive immune inflammatory response. Moreover, we showed for the first time a significant association between VD levels and male sex, GLU levels, and BMI in COVID-19, and because male sex, hyperglycemia, and adiposity are largely recognized as risk factors for worse disease, VD deficiency might be identified as a novel pathophysiological mechanism involved as a common denominator of the endocrine phenotype (79, 80) that negatively influences COVID-19 patient outcome (14).

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