REVIEW

Association of Vitamin D Status with SARS-CoV-2 Infection or COVID-19 Severity: A Systematic Review and Meta-analysis

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ABSTRACT

This systematic review was conducted to summarize and clarify the evidence on the association between 25-hydroxyvitamin-D [25(OH)D] concentrations and coronavirus disease 2019 (COVID-19) risk and outcomes. PubMed, Scopus, and Web of Science databases and Google Scholar were searched up to 26 November 2020. All retrospective and prospective cohort, cross-sectional, case-control, and randomized controlled trial studies that investigated the relation between 25(OH)D and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 severity were included. Thirty-nine studies were included in the current systematic review. In studies that were adjusted (OR: 1.77; 95% CI: 1.24, 2.53; I^2: 44.2%) and nonadjusted for confounders (OR: 1.75; 95% CI: 1.44, 2.13; I^2: 33.0%) there was a higher risk of SARS-CoV-2 infection in the vitamin D deficiency (VDD) group. Fifteen studies evaluated associations between VDD and composite severity. In the studies that were adjusted (OR: 2.57; 95% CI: 1.65, 4.01; $I^2 = 0.0\%$) and nonadjusted for confounders (OR: 10.61; 95% CI: 2.07, 54.23; $I^2 = 90.8\%$) there was a higher severity in the VDD group. Analysis of studies with crude OR (OR: 2.62; 95% CI: 1.13, 6.05; I^2: 47.9%), and adjusted studies that used the Cox survival method (HR: 2.35; 95% CI: 1.22, 4.52; I^2: 84%) indicated a significant association of VDD with mortality, while in adjusted studies that used logistic regression, no relation was observed (OR: 1.05; 95% CI: 0.63, 1.75; I^2: 76.6%). The results of studies that examined relations between VDD and intensive care unit (ICU) admission, pulmonary complications, hospitalization, and inflammation were inconsistent. In conclusion, although studies were heterogeneous in methodological and statistical approach, most of them indicated a significant relation between 25(OH)D and SARS-CoV-2 infection, COVID-19 composite severity, and mortality. With regard to infection, caution should be taken in interpreting the results, due to inherent study limitations. For ICU admission, inflammation, hospitalization, and pulmonary involvement, the evidence is currently inconsistent and insufficient. *Adv Nutr* 2021;00:1–23.

Keywords: COVID-19, vitamin D, severity, infection, SARS-CoV-2

Introduction

Vitamin D deficiency (VDD) and insufficiency in adults and children, as a global problem, is associated with several disorders, including metabolic disorders, autoimmune diseases, cardiovascular disease, diabetes, and infections, and has been widely considered by researchers and clinicians (1). In particular, several studies have investigated the link between the risk of respiratory tract infections and VDD (2). For instance, Mamani et al. (3) reported an association between incidence of community-acquired pneumonia and low serum concentrations of 25-hydroxyvitamin D [25(OH)D], and adverse outcomes were observed in acute respiratory distress syndrome (ARDS) patients with VDD (4).

Vitamin D is a fat-soluble vitamin that plays an important role in several physiological processes, such as bone metabolism, calcium and phosphorus absorption, and immune system function (5). It may reduce the risk of microbial infections through stimulating innate cellular immunity, inhibiting the cytokine storm, decreasing proinflammatory cytokine production, and modulating the adaptive immune response (6). Vitamin D3 and vitamin D2 are 2 primary metabolites of vitamin D (7). Unstable 7-dehydrocholesterol in the skin is transformed to pre-vitamin D3 and stable vitamin D3, respectively, when exposed to UV-B radiation (8). Vitamin D3, or cholecalciferol, can also be found in foods, such as dairy products, eggs, and fish (9). Vitamin D3 is subsequently converted to 25-hydroxyvitamin D3

($25(OH)D_3$) through 25-hydroxylase enzyme activity during the hydroxylation process in the liver. The $25(OH)D_3$ form then transfers to the kidney and converts to 1α,25-dihydroxyvitamin D3 via 1α-hydroxylase, otherwise known as calcitriol, the active form of vitamin D (8, 10).

Currently, the global community is involved in a novel pandemic named coronavirus disease 19 (COVID-19), a respiratory tract infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (11). The WHO reported the total global cases of SARS-CoV-2 infection and death as >61.8 and 1.4 million, respectively (weekly epidemiological update, 1 December 2020) (12). This novel coronavirus (SARS-CoV-2), like the other viruses of the β-coronavirus family, is extremely contagious, and COVID-19 symptoms vary from initially mild symptoms such as dry cough, fever, fatigue, and gastrointestinal symptoms, to severe situations requiring admission to an intensive care unit (ICU) or death in severe cases (13, 14). In some cases, inflammation can increase following both local and systemic immune responses generated by this virus and an increased number of leukocyte and concentrations of plasma proinflammatory cytokines have been reported in patients infected with SARS-CoV-2 (15).

Several studies have investigated the association of $25(OH)D_3$ concentrations and supplementation with the risk and severity of respiratory virus infections (16, 17). Indeed, Martineau et al. (18) conducted a meta-analysis that included 25 placebo-controlled clinical trials (total of 10,933 people) and concluded that vitamin D supplementation reduces the risk of acute respiratory infections, especially in people with the lowest 25(OH)D concentrations.

Recently, a growing body of evidence has emerged regarding potential factors affecting the incidence and severity of COVID-19 (19–21). Recent reports highlight that certain factors may be effective in controlling this pandemic or reducing the damage caused by it. Indeed, based on the global prevalence of VDD (22), it has attracted considerable attention as a potential factor associated with the risk or severity of COVID-19, and several studies have reported on this possible association (6, 23–25). However, results currently preclude a clear consensus. Thus, we conducted this systematic review to summarize and clarify the evidence on the association between 25(OH)D concentrations and COVID-19 risk and outcomes.

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Supplemental Tables 1–15 and Supplemental Figures 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ICU, intensive care unit; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TGF-β, transforming growth factor β; Th, T-helper; VDD, vitamin D deficiency; VDR, vitamin D receptor; WMD, weighted mean difference; 25(OH)D, 25-hydroxyvitamin-D.

Methods

The protocol of this study has been registered in PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/prospero/index.asp, identifier CRD42020203903). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used in developing and conducting this systematic review (26).

Search strategy and study selection

PubMed, Scopus, and Web of Science databases and the first 500 Google Scholar search results were searched up to 26 November 2020, with no restriction in language. Reference lists of included studies and relevant review articles were also scanned for additional relevant studies. The following search strategy was used for our search: (Coronavirus or COVID-19 or SARS-CoV-2) AND (vitamin D or 25-OH-D or cholecalciferol or 25-hydroxycholecalciferol or calcitriol or 25-hydroxyvitamin D or hydroxycholecalciferols or 25-hydroxyvitamin D3).

Two reviewers independently assessed the eligibility of studies. Studies that met the following criteria were included: *1*) study design as retrospective, prospective, or cross-sectional, or case-control studies reporting serum/plasma concentrations of 25(OH)D; *2*) participants as patients diagnosed with COVID-19 with no restriction on age; *3*) exposure/intervention as serum/plasma concentrations of vitamin D either reported as a continuous or categorical variable (deficiency vs. sufficiency); and *4*) outcome as SARS-CoV-2 infection or COVID-19 severity, with severity defined as at least 1 of the following outcomes—ARDS and/or mechanical ventilation, ICU admission, length of hospitalization, and death. The exclusion criteria were as follows: *1*) case reports, abstracts, and summaries of discussion; *2*) insufficient data on vitamin D measurement or COVID-19 outcomes; *3*) preprint studies without peer review; and *4*) studies that were not individual based (compared countries or regions).

Data extraction and quality assessment

The following data were extracted independently by 2 reviewers: first author, study design, start and completion date, geographical location, age and gender composition of patients, objective of the study [if the aim of the study was to assess association of 25(OH)D status with risk of SARS-CoV-2 infection or to assess the association with severity of disease], definition of VDD, time of serum 25(OH)D measurement, prevalence of VDD and insufficiency, definition of disease severity, the number of events and nonevents in the case and control groups, relative risk and 95% CIs for SARS-CoV-2 infection and disease severity, and adjustment factors.

Quality assessment of observational studies was assessed using the Newcastle–Ottawa Scale, which included 3 items: selection, comparability, and outcome (27). Studies with a score of $\geq$7 were defined as high quality. The Cochrane risk-of-bias tool was used to evaluate quality assessment

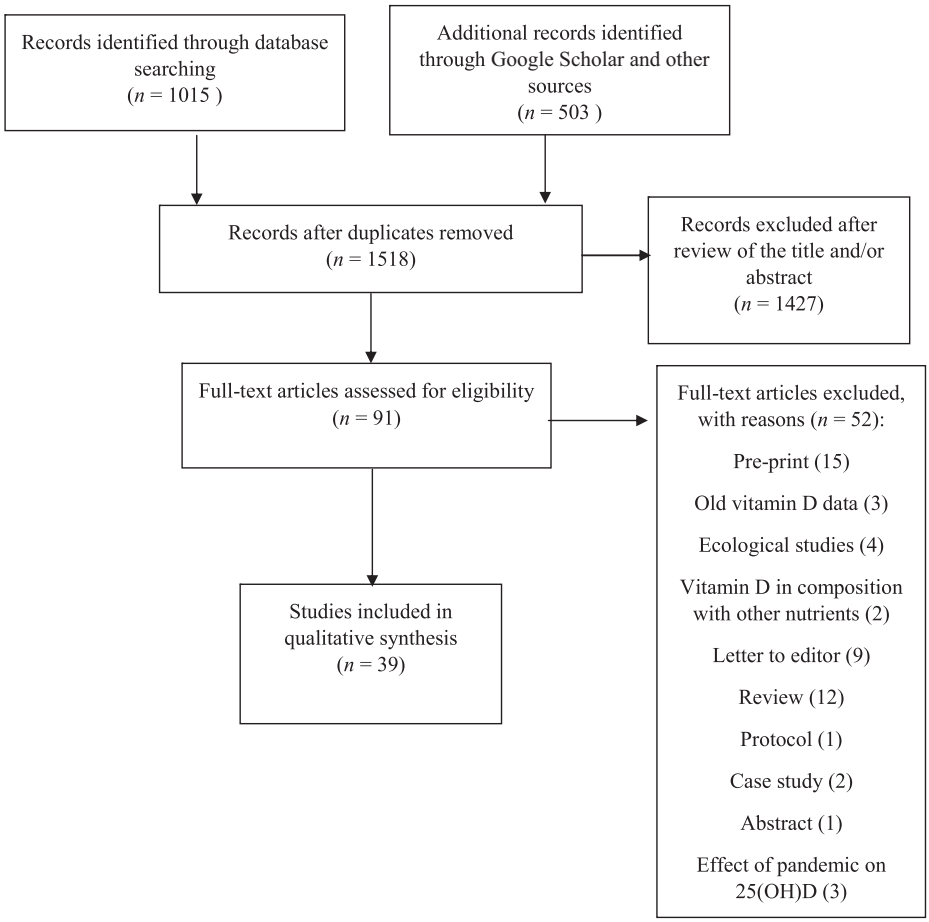

FIGURE 1 Summary of the process for selecting studies that investigated the association of vitamin D status with SARS-CoV-2 infection and COVID-19 severity. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 25(OH)D, 25-hydroxyvitamin-D.

of randomized trials. This tool included selection bias, performance and detection bias, attrition bias, reporting bias, and the other biases (28).

Statistical analysis

Wherever it was probable, we pooled data and conducted meta-analysis (SARS-CoV-2 infection, disease severity, ICU admission, and mortality). We used ORs to estimate the association between VDD and SARS-CoV-2 infection and COVID-19 severity. ORs with 95% CIs were obtained using a random-effects model. In studies that did not report relative risk, the OR was calculated by the number of events and nonevents in the case and control groups; these studies together with studies with crude ORs were analyzed separately from the studies that reported adjusted relative risk. To compare concentrations of 25(OH)D_3 between groups, we used the weighted mean difference (WMD) and its 95% CI. Heterogeneity was evaluated using Cochran's Q test, deriving its magnitude from the I^2. If at least 10 studies were available, we explored potential small-study effects, such as publication bias, using visual examination of the funnel plot and Egger's test (29). All analyses were conducted using Stata version 13 software (StataCorp).

Results

Characteristics of the study population

As described in **Figure 1**, 1518 records were obtained by the literature search. Of these, 57 articles met the inclusion criteria; however, 3 studies were excluded because they used old 25(OH)D data, and 15 papers were preprints (**Supplemental Table 1**). Finally, 39 studies were included, with different geographical locations and ethnic backgrounds, including Europe (n = 17 studies), North America (United States) (n = 2), South America (n = 2), West Asia (n = 9), South Asia (n = 4), East Asia (n = 4), and Africa (n = 1). Ten studies were of a case-control design, 19 cross-sectional, 2 retrospective cohorts, 2 randomized controlled trials (RCTs), 2 quasi-experimental design, and 4 studies were only descriptive. All studies were conducted in adults, except for 1 study in children and 1 study in pregnant women. All studies,

except for 2, included both male and female participants; in 1 study, participants were only male (30), and in another, only females were included (31). Nine studies were not included in the analysis because 4 of them were only descriptive [only reported concentration of 25(OH)D in patients; **Supplemental Table 2**] (31–34), 1 study was in children (35), and 4 were different in design from other studies [they assessed the effect of 25(OH)D_3 supplementation instead of 25(OH)D measurement] (14, 36–38).

Twenty-one studies examined the association of 25(OH)D concentrations with the severity, 14 studies with SARS-CoV-2 infection, whereas 10 of them assessed severity as a secondary outcome. Characteristics of studies that examined the association of vitamin D with SARS-CoV-2 infection are summarized in **Table 1**, and those examining COVID-19 severity are summarized in **Table 2**.

Association of 25(OH)D status with SARS-CoV-2 infection

Nine studies evaluated the relation between VDD and SARS-CoV-2 infection. Studies that were adjusted ($n = 3$) (39–41) (OR: 1.77; 95% CI: 1.24, 2.53; I^2: 44.2%; **Figure 2**A) and nonadjusted for confounders ($n = 5$) (42–45, 46) (OR: 1.75; 95% CI: 1.44, 2.13; I^2: 33%; Figure 2B) indicated higher risk of infection in the VDD group (Figure 2). The Blanch-Rubió et al. (37) study was not included in analysis, because of a different design. This study was a cross-sectional study including 2102 patients with noninflammatory rheumatic conditions and found that no association between intake of vitamin D supplement and COVID-19 (risk ratio: 0.91; 95% CI: 0.62, 1.34).

Twelve studies compared 25(OH)D concentration between COVID-19 patients and healthy subjects. The pooled analysis of 10 studies (41–49) revealed a lower concentration of 25(OH)D in cases compared with controls (WMD = −7.0 ng/mL; 95% CI: −9.49, −4.50; $I^2 = 92.4\%$; cases, $n = 1899$; controls, $n = 11{,}122$; **Supplemental Figure 1**). Subgroup analysis indicated a greater difference in the studies that measured 25(OH)D after a SARS-CoV-2 test (WMD = −10.28 ng/mL; 95% CI: −14.41, −6.16; $I^2 = 90.1\%$; $n = 6$ studies) compared with studies that used 25(OH)D data collected before a SARS-CoV-2 test (WMD = −3.0 ng/mL; 95% CI: −5.15, −0.86, $I^2 = 80.3\%$; $n = 4$ studies). Two studies were not included in the analysis (35, 50); both studies indicated that 25(OH)D concentrations were significantly lower in cases compared with controls. In 1 study, the participants were children (35); the other study only reported that COVID-19 patients had a significantly lower 25(OH)D concentration compared with healthy counterparts; however, the mean ± SD values of 25(OH)D were not provided (50). Results of studies are summarized in **Supplemental Table 3**.

Association of vitamin D status with COVID-19 severity

Twenty-one studies assessed the association of VDD with severity (composite severity or 1 feature of severity) as a primary outcome, and 10 studies as a secondary outcome.

Composite severity

Fifteen studies evaluated the association between VDD and composite severity. Studies that were adjusted (38, 41, 44, 46, 51, 52) (OR: 2.57; 95% CI: 1.65, 4.01; $I^2 = 0.0\%$; **Figure 3**A) and nonadjusted for confounders (42, 45, 53–55) (OR: 10.61; 95% CI: 2.07, 54.23, $I^2 = 90.8\%$; Figure 3B) revealed a higher severity in the VDD group. Four studies were not included in the analysis; one of these studies was conducted in children and found a negative correlation between fever symptom and 25(OH)D concentration ($P = 0.02$), while no significant correlations were found between other clinical parameters and 25(OH)D concentration (35). The other study had a quasi-experimental design and indicated that vitamin D3 supplementation was inversely associated with Ordinal Scale for Clinical Improvement (OSCI) score for COVID-19 ($\beta = -3.84$; 95% CI: −6.07, −1.62; $P = 0.001$) (56). The third study, which assessed vitamin D supplementation in patients with a past history of COVID-19, found that it reduces the risk of exacerbation and worsening of the disease (OR: 0.29; 95% CI: 0.10, 0.083; $P = 0.02$) (57). The last study did not provide sufficient data, and only reported that VDD was significantly associated with severity; however, no data were available to indicate this (58). Results of studies have been summarized in **Supplemental Table 4**.

ICU admission or stay

Four studies examined the relation between VDD and ICU admission and 1 study between VDD and ICU stay duration. Pooled analysis of 3 studies (38, 44, 59) with unadjusted ORs indicated no significant relation between VDD and ICU admission (OR: 1.17; 95% CI: 0.67, 2.03; $I^2 = 69.3\%$), while an RCT that was not pooled with these studies revealed a lower risk of ICU admission in the intervention group compared with the control group (OR: 0.03; 95% CI: 0.003, 0.25; $P = < 0.001$) (36). Carpagnano et al. (59) verified the association of VDD with ICU stay, highlighting that 10 patients with severe VDD had a median ICU stay of 8 d with the interquartile range (IQR) of 6 to 11.25., while 32 patients without VDD had a median stay of 12.5 d (IQ25 8, IQ75 20.5) (**Supplemental Table 5**).

Pulmonary complications

Eight studies investigated the association of VDD with one of the pulmonary complication indicators. In Abrishami et al. (60), an increase in 25(OH)D concentrations yielded a reduction in the development of severe lung involvement (OR: 0.96; 95% CI: 0.93, 0.98; $P = 0.04$). Pizzini et al. (61) found no significant difference between 25(OH)D concentrations in patients with or without computed tomographic (CT) abnormalities (22 vs. 21.6 ng/mL; $P = 0.83$). Three studies assessed the relation between 25(OH)D concentration and progression to ARDS. In a prospective study in 33 hospitalized patients, the patients who progressed to ARDS had a lower serum 25(OH)D concentration on presentation to the hospital compared with non-ARDS patients [mean (SD): 10.8 (4.8) ng/mL in ARDS and 16.4 (7.6) ng/mL in non-ARDS patients; $P = 0.03$] (30), while there was no difference

TABLE 1 Characteristics of studies investigated association of vitamin D status with SARS-CoV-2 infection[1]

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Definition of VitD deficiency	Time of VitD ascertainment	Objective/study question	Adjusting factors
Bahat (31)	April and June, 2020	A tertiary referral hospital, Turkey	Descriptive	44 SARS-CoV-2-positive (+) pregnant women who were hospitalized, >8 wk of gestation	Mean age: 28.57; female: 100%	Serum 25(OH)D <20 ng/mL	On the day of admission	To measure serum 25(OH)D concentration in SARS-CoV-2+ pregnant women	—
Baktash (47)	March 1 and April, 2020	General hospital in the UK	Prospective cohort	105 elderly (>65 y) participants, 70 SARS-CoV-2+, 35 SARS-CoV-2 negative (–)	Mean age: 81.28; patients: 60% male; healthy: 40%	Serum 25(OH)D ≤12 ng/mL	Concurrent with SARS-CoV-2 test	Relation between VDD and SARS-CoV-2 infection	No adjustment for confounders; another limitation is vitamin D intake after the acute phase of illness
Blanch-Rubió (37)	March 1 to May 3, 2020	Rheumatology service of hospital, Spain	Cross-sectional	2102 patients with noninflammatory rheumatic conditions	Mean age: 66.4; 80.5% female	—	—	Effect of vitamin D intake on COVID-19 incidence	Sex, age, comorbidities, treatment, and drugs
D'Avolio (48)	March 1 to April 14, 2020	Switzerland	Retrospective cohort	27 SARS-CoV-2+, 80 SARS-CoV-2–	Median age: 73, IQR (63 to 81); male: 54.2%	—	The vitamin D analysis was required to be conducted within 7 wk of the SARS-CoV-2 PCR result	Describing the 25(OH)D plasma concentrations in a cohort of patients from Switzerland	—
De Smet (42)	March 16 to April 16, 2020	General hospital in Belgium	Retrospective observational study	186 SARS-CoV-2+ hospitalized patients and 2717 diseased controls	Patients: median age, (IQR): 69 (52–80); male: 58.6%; controls: 68 (49–82); male: 36.8%	Serum 25(OH)D <20 ng/mL	Measured after SARS-CoV-2 test	Are lower 25(OH)D concentrations correlated with COVID-19?	—
Ferrari (43)	February to April, 2020	The San Raffaele Hospital, Milan, Italy	Retrospective cohort	128 SARS-CoV-2+, 219 SARS-CoV-2–	Patients: 64.8% males; male age: 62.7; female age: 69.3; healthy: 48.85% males; male age: 62.8, female age: 54.3	Serum 25(OH)D ≤30 ng/mL	The average time interval between SARS-CoV-2 test and their corresponding 25(OH)D measurements for the positive group was 33.9 and for the negative group was 33.33 d	—	—

(*Continued*)

TABLE 1 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Definition of VitD deficiency	Time of VitD ascertainment	Objective/study question	Adjusting factors
Hernández (44)	March 10 to March 31, 2020	University Hospital, Spain	Retrospective case-control study	216 SARS-CoV-2+ and 197 population-based controls; in COVID-19 patients: number of VDD: 35; number of non-VDD: 162	Cases: age, median (IQR): 61.0 (47.5–70.0); controls: 61.0 (56.0–66.0); male: 62.4% in both groups	Serum 25(OH)D <20 ng/mL	At admission	To assess serum 25(OH)D concentrations in hospitalized patients with COVID-19 and to analyze the possible influence of vitamin D status on disease severity	—
Im (45)	February to June, 2020	Inha University Hospital, South Korea	Case-control	50 patients with SARS-CoV-2+ and 150 controls	Mean age: 57.5 in case and 52.2 in control groups; male: 58%	Serum 25(OH)D_3 <20 ng/mL	Within 7 d of admis?sion	Prevalence of VDD among COVID-19 patients, comparing vitamin D status between COVID-19 patients and healthy individuals	Control group was matched for age and sex with the COVID-19 group
Kerget (50)	March 24, to May 15, 2020	University Hospital in Turkey	Case-control	88 SARS-CoV-2+, 20 SARS-CoV-2–	Mean age: cases: 49.1; male: 60%; controls: 35.2; male: 40%	—	Fifth day of admission to hospital	To determine the relation of serum vitamin D concentration between patients and healthy controls	—
Luo (46)	February 27 to March 21, 2020	Hospital in China	Cross-sectional	335 COVID-19 patients, age- and sex-matched population of 560 individuals	Patients: median (IQR) age: 56 (43–64); male: 44.2%; controls: age: 55 (49.0–60.0); male: 45.9%	Serum 25(OH)D <30 ng/mL	In control, serum 25(OH)D concentrations were measured during the same period from 2018–2019; in patients, serum 25(OH)D concentrations were measured on admission	To investigate whether VDD is associated with COVID-19 incidence	Age, sex, comorbidities, smoking status, and BMI
Mardani (49)	March, 2020	A general clinic, Iran	Case-control	63 SARS-CoV-2+, 60 SARS-CoV-2–	Median age of 39; male: 52%	Deficient [25(OH)D <10 ng/mL], insufficient [25(OH)D: 10–30 ng/mL]	At baseline of the study	Relation between VDD and SARS-CoV-2 infection	Not adjusted

(*Continued*)

TABLE 1 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Definition of VitD deficiency	Time of VitD ascertainment	Objective/study question	Adjusting factors
Meltzer (39)	March 3 to April 10, 2020	Academic hospital in USA	Retrospective cohort study	63 SARS-CoV-2+, 365 SARS-CoV-2−	Mean age: 45.7; male: 25.2%	VDD was defined by the most recent 25(OH)D <20 ng/mL or 1,25(OH)D <18 pg/mL	Within 1 y before SARS-CoV-2 test (subjects received treatment in this duration were excluded)	Is VDD associated with positive test for SARS-CoV-2?	Demographic and comorbidity
Merzon (40)	February 1 to March 30, 2020	Health Services in Israel	Retrospective cohort study	782 SARS-CoV-2+, 7025 SARS-CoV-2−	SARS-CoV-2+: mean age: 35.6; male: 49.23%; SARS-CoV-2−: mean age: 47.4; male: 40.6%	"Suboptimal" or "low": plasma 25(OH)D <30 ng/mL	At least 1 previous blood test for plasma 25(OH)D concentration	Is VDD risk factor for SARS-CoV-2 infection?	Demographic variables, psychiatric and somatic disorders
Sun (34)	February to February, 2020	Hospital University in Wuhan, China	Descriptive	241 patients with confirmed COVID-19	Median age: 65 (IQR: 55–72); male: 46.4%	—	Within 24 h of admission	25(OH)D concentration in SARS-CoV-2+ adults	—
Ye (41)	February to March, 2020	A Hospital in China	Case-control	62 SARS-CoV-2+, 80 healthy controls	Controls: median age (IQR): 42 (31–52); male: 40%; patients: age: 43 (32–59); male: 37%	25(OH)D <20 ng/mL	At admission	To examine the relation between serum 25(OH)D concentration and SARS-CoV-2 infection	Demographics and comorbidities
Yılmaz (35)	March to May, 2020	University Hospital in Turkey	Case-control	85 children (40 SARS-CoV-2+ and hospitalized, 45 healthy children in control group)	COVID-19 patients: 101.76 mo; male: 47.5%; controls: 75.68 mo; male: 60%	25(OH)D <12 ng/mL	From retrospective file records	Is VDD a risk factor for COVID-19 in children?	None

[1] COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; ref, reference; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VDD, vitamin D deficiency; VitD, vitamin D; 25(OH)D, 25-hydroxyvitamin D; 25(OH)D3, 25-hydroxyvitamin D3; 1,25(OH)D, 1,25-hydroxyvitamin D.

TABLE 2 Characteristics of studies investigated association of vitamin D status with COVID-19 severity[1]

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Abrishami (60)	February to April, 2020	Academic hospital in Iran	Retrospective study	73 SARS-CoV-2–positive (+) patients	Mean age: 55.18; male: 46.4%	To evaluate the prognostic role of serum 25(OH)D_3 on the extent of lung involvement and final outcome in patients with COVID-19	Lung involvement and mortality; serum 25(OH)D <25 ng/mL	At admission	For mortality, multivariate linear regression analysis adjusted for potential confounders including sex, age, and comorbidity
Anjum (62)	March to June, 2020	A hospital in Pakistan	Prospective	140 SARS-CoV-2+ patients	Mean age: 42.46; age range: 15–75; male: 58.57%	To determine the association between severe VDD and mortality in patients with COVID-19	Severity was defined as mortality; severe VDD was defined as 25(OH)D <10 ng/ml	At admission	—
Annweiler (56)	March to April, 2020	Nursing home in France	Quasi-experimental study with mean follow-up of 36 d	66 frail elderly nursing-home residents: intervention, *n* = 57; comparator, *n* = 9	Experiment: mean age: 87.7; male: 21% Comparator: mean age: 87.4; male: 33%	To evaluate COVID-19 severity and the use of COVID-19 drugs; the primary and secondary outcomes were COVID-19 mortality and OSCI score in acute phase	OSCI score	The intervention group received VitD3 (single dose of 80,000 IU every 2–3 mo) during COVID-19 or in the preceding month; the comparator group corresponded to all other participants	Age, gender, drugs, functional abilities, albuminuria
Annweiler (51)	March to May, 2020	One geriatric acute care unit dedicated to COVID-19 patients in France	Quasi-experimental study	Group 1 (*n* = 29), group 2 (*n* = 16), group 3 (*n* = 32)	Mean age: 88; male: 51%	14-day mortality and highest (worst) score on the OSCI measured during COVID-19 acute phase	To determine whether vitamin D3 supplementation taken either regularly over the preceding year or after the diagnosis of COVID-19 was	Group 1 (*n* = 29): supplemented regularly with VitD over the preceding year Group 2 (*n* = 16): supplemented with VitD after	Potential confounders were age, gender, functional abilities, undernutrition, chronic

(*Continued*)

TABLE 2 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
							effective in improving survival among hospitalized frail elderly COVID-19 patients; severe COVID-19 defined as an OSCI score ≥5	COVID-19 diagnosis Group 3 ($n = 32$): comparator received no VitD	disease, drugs; the 3 groups were similar in the treatments used for COVID-19
Arvinte (63)	May, 2020	ICU of medical center in Colorado, USA	Cross-sectional, descriptive	21 critically ill COVID-19 patients hospitalized; 11 survived, 10 died	Median age 61; age range: 20–94; male: 71.4%	To measure serum $25(OH)D_{2,3}$ in patients with critical COVID-19 illness and to assess if VDD correlated with other illness risk factors	Severity was defined as mortality	At ICU admission	—
Baktash (47)	March to April, 2020	General hospital in the UK	Prospective cohort study	70 elderly SARS-CoV-2+ individuals (aged ≥65 y); VDD patients: ($n = 39$); non-VDD patients: ($n = 31$)	Mean age: 81.28; Male: 60% in COVID-19 patients and 40% in non–COVID-19 patients	Vitamin D status and outcomes for hospitalized older patients with COVID-19	Noninvasive ventilation and high-dependency unit; clinical markers of disease severity; 25(OH)D ≤12 ng/mL	Concurrent with SARS-CoV-2 test	Not adjusted for confounders; another limitation is the supplementation of VitD after the acute phase of illness
Bagheri (57)	March to May 2020	University hospital in Iran	Cross-sectional	103 outpatients and 28 hospitalized patients	Mean age: 43.74 in outpatients and 58.77 in inpatients	The vitamin D supplementation pattern in past history of patients with COVID-19 in a cross-sectional inquiry	Severity was considered as hospitalization	Supplemented or not supplemented with vitamin D	Adjusted for the factors affecting the severity of this disease
Carpagnano (64)	March 11 to April 30, 2020	Italy, hospital policlinic	Retrospective, observational study	42 patients with ARF due to COVID-19, treated in respiratory intermediate care unit, and no need of intubation or invasive ventilation	Mean age: 65; male: 71%	Assessing any correlations with disease severity and prognosis	Transfer to ICU, death; vitamin D insufficiency, moderate deficiency, and severe deficiency were defined as 25(OH)D concentrations of 20–29, 10–19, and <10 ng/mL, respectively	Measured after SARS-CoV-2 test	—

(*Continued*)

TABLE 2 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Entrenas Castillo (36)	May, 2020	University hospital, Spain	RCT	76 patients hospitalized with SARS-CoV-2 infection (50 in the intervention and 26 in the control)	Mean age: 53; male: 59%	Effect of calcifediol treatment on ICU admission and mortality rate among patients hospitalized for COVID-19	Admission to ICU, (0.53 mg VitD at admission, 0.26 mg at day 3 and 7, and then weekly until discharge or ICU admission)	Not measured	Adjusted for variables that were different between groups at baseline (HTN, DM); MLR analysis for probability of the ICU admission
Cereda (65)	March to April, 2020	Italian tertiary referral hospital	Single-center cohort study	129 COVID-19 patients: VDD group, $n = 99$; non-VDD, $n = 30$	Median age: 77 (IQR, 65.0, 85.0); male: 54.3%	To determine the prevalence of VDD in COVID-19 patients and explore its association with clinical outcomes of disease severity	Clinical outcomes (severe pneumonia, admission to ICU and in-hospital mortality) and biochemical markers of disease severity 25(OH)D <20 ng/mL	Within 48 h since hospital admission	Age, sex, CRP, IHD, and severe pneumonia
De Smet (42)	March 1 to April 7, 2020	Belgium, general hospital	Retrospective observational study	186 hospitalized SARS-CoV-2–infected patients	Age 68.5; male: 58.6%	Are lower 25(OH)D concentrations correlated with COVID-19 severity?	Patients were classified based on the radiological lesion as early stage 1 (ground-glass opacities), progressive stage 2 (crazy paving pattern), or peak stage 3 (consolidation), 25(OH)D <20 ng/mL	Measured after SARS-CoV-2 test	None
Haraj (33)	April 17 to May 26, 2020	Endocrinology service in Morocco	Descriptive observational study	41 patients admitted to the endocrinology service for additional care after a stay in ICU	Mean age: 55 <45 years (26.8%), 45–70 years (48.8%), >70 (24.4%); 51.2% male	To assess the vitamin D status of patients with COVID-19 after a stay in intensive care	—	At the beginning of the study	—

(*Continued*)

TABLE 2 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Faul (30)	During March, 2020	Ireland, Connolly Hospital Blanchardstown	Cohort	33 hospitalized for COVID-19–related pneumonia; cases: patients progressed to ARDS ($n = 12$); controls: those who did not progress to ARDS ($n = 21$)	Mean age: 60; male:100%	Does low 25(OH)D contribute to severe disease and progression to ARDS in some patients infected with SARS-CoV-2?	Progression to ARDS, require intubation and mechanical ventilation, death	Measured after admission to hospital	—
Ferrari (43)	February 20 to April 7, 2020	San Raffaele Hospital, Milan, Italy	Retrospective cohort	128 SARS-CoV-2+ patients: severe disease ($n = 16$), nonsevere ($n = 112$)	Mean age: 62.7; male: 64.8%	Association between COVID-19 severity and VitD concentrations	Severity classification was not explained; 25(OH)D <30 ng/mL	VitD concentration measured, at least once, between the 1st of January and the 31st of May, 2020; the average time interval between SARS-CoV-2 test and VitD measurements was 33.5 d	—
Gonçalves (32)	March to April, 2020	ICU in Brazil	Descriptive cross-sectional study	176 elderly (aged ≥60 y)	Mean age: 72.9; male: 54%	Prevalence of VDD in elderly patients admitted to the ICU due to SARS-CoV-2	—	In the first day of ICU admission	—
Hamza (58)	March to April, 2020	Medical college hospital in Pakistan	Descriptive cross-sectional study	168 SARS-CoV-2+ patients	Age ranged from 30 to 80; mean age: 42.26; male: 56%	To determine the VDD in COVID-19 patients and its association with the severity and fatality of COVID-19 disease	The COVID-19 patients were categorized into asymptomatic and symptomatic; the symptomatic patients were categorized into mild, moderate, and severe disease according to questionairre	At the beginning of the study	—

(*Continued*)

TABLE 2 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Hernández (44)	March 10 to March 31, 2020	University hospital in Spain	Retrospective case-control study	197 COVID-19 patients; cases were the patients with VDD ($n = 35$); control patients with non-VDD ($n = 162$)	Age, median (IQR): 61.0 (47.5–70.0) in cases, 61.0 (56.0–66.0) in controls; males in both group: 62.4%	To assess serum 25(OH)D_3 in hospitalized patients with COVID-19 and to analyze the possible influence of vitamin D status on disease severity	Admission to ICU, requirement for mechanical ventilation, or in-hospital mortality; 25(OH)D <20 ng/mL	At admission	Age, smoking, chronic disease, immunosuppression, BMI, serum-corrected calcium, GFR, and the month of vitamin D determination
Im (45)	February to June, 2020	University hospital, South Korea	Case-control	50 patients with COVID-19, 32 with pneumonia and 18 without pneumonia	Median age: 57.5 in cases and 52.2 in controls; male: 58%	Association of 25(OH)D_3 with disease severity (defined by pneumonia)	Progression to pneumonia includes cases with or without an oxygen supply, high-flow nasal cannula, mechanical ventilator, and ECMO/death was considered as severe; 25(OH)D_3 ≤20 ng/dL	Within 7 d of admission	—
Jain (53)	June 5 to July 20, 2020	Tertiary COVID-19 care center in India	Prospective observational	Study included both asymptomatic COVID–19 patients (group A, $n = 91$) and severely ill patients requiring ICU admission (group B, $n = 63$)	30–60 y: Group A: mean age: 42.34; male: 58.2% Group B: mean age: 51.41; male: 66.66%	Analysis of vitamin D concentration among asymptomatic and critically ill COVID–19 patients and its correlation with inflammatory markers	Asymptomatic vs. ICU patients; 25(OH)D <20 ng/dL	At the beginning of the study	Not adjusted

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TABLE 2 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Karahan (54)	April 1 to May 20, 2020	Training and research hospital, Turkey	Retrospective observational study	149 COVID-19 patients; moderate ($n = 47$), severe–critical ($n = 102$)	Mean age: 63.5; age range: 24–90; male: 54.4%	To investigate the role of serum 25(OH)D concentration on COVID severity and related mortality	The severity of COVID was classified according to the Chinese Clinical Guideline for classification of COVID-19 severity[2]; 25(OH)D ≤20 ng/dL	Data were retrieved from the hospital electronic database system	Confounding factors not mentioned
Šaronova (55)	April 1 to May 15, 2020	Hospital in Russia	Cross-sectional	80 COVID-19 patients; severe: ($n = 25$), moderate: ($n = 55$)	All patients: Age range: 18–94; mean age: 53.2; male: 53.8% Severe disease: mean age: 51.8; male: 48% Moderate disease: mean age: 53.7; male: 56.4%	Association of 25(OH)D concentration in patients with COVID-19 hospitalized with community-acquired pneumonia and compare serum 25(OH)D with clinical outcome	25(OH)D <20 ng/dL	—	—
Kerget (50)	March 24 to May 15, 2020	Two hospitals in Turkey	Case-control	88 COVID-19 patients; 20 patients developed MAS and 35 developed ARDS and 8 died	Mean age: MAS: 70.1; non-MAS: 43.4; ARDS: 67.9; non-ARDS: 38.3	To determine the relation of serum 25(OH)D to clinical course and prognosis	Developing MAS and ARDS, and death	Fifth day of admission to hospital	—
Luo (46)	February to March 2020	Wuhan Tongji Hospital	Cross-sectional	335 COVID-19 patients; 74 severe, 261 nonsevere	Severe: Median age: 62.5; IQR: 51.0–75.3 y; male: 58.1% Nonsevere: Median age: 54; IQR: 40–62 y; male: 40.2%	To investigate whether VDD is associated with COVID-19 disease severity	Severity of COVID-19 was determined based on the level of respiratory involvement; based on Commission and State Administration of Traditional Chinese Medicine[3]; 25(OH)D <30 ng/mL	For the control group, serum 25(OH)D data on the same period from 2018–2019 were used; for the COVID-19 patients, on admission to hospital	Age, sex, comorbidities, smoking status, and BMI

(*Continued*)

TABLE 2 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Macaya (52)	—	Tertiary hospital in Madrid, Spain	Retrospective	80 COVID-19 patients (nonsevere, $n = 49$; severe, $n = 31$)	Nonsevere: Median age: 63; IQR (50–72); male: 29% Severe: Age: 75 (66–84); male:21%	The association of VDD with a composite of adverse clinical outcomes	Death, admission to the ICU, and/or need for higher oxygen flow than that provided by a nasal cannula; 25(OH)D <20 ng/mL	At admission or within the 3 previous months	Obesity, cardiac disease, and age
Maghbooli (38)	Until May 1, 2020	A hospital in Tehran	Cross-sectional	235 COVID-19 patients; mild–moderate severity: $n = 64$; severe–critical severity: $n = 172$	Mean age was 58.7; age range: 20–90; male: 61.3%	To investigate the association between serum 25(OH)D and clinical outcomes, parameters of immune function and mortality	CDC criteria[4] were used for the disease severity and prognosis; 25(OH)D <30 ng/mL	At admission to the hospital	Age, sex, BMI, smoking, and history of a chronic medical disorder
Merzon (40)	February to March, 2020	Israel, Health Services	Retrospective cohort study	782 SARS-CoV-2+	SARS-CoV-2+: mean age: 35.6; male: 49.23% SARS-CoV-2– negative (–): age: 47.4; male: 40.6%	Is VDD a risk factor for COVID-19 hospitalization?	Hospitalization was considered as the marker of severity; 25(OH)D <30 ng/mL	At least 1 previous blood test for plasma $25(OH)D_3$ concentration	Demographic variables, psychiatric and somatic disorders
Panagiotou (59)	—	UK, local clinical care pathway	Retrospective interim audit	134 SARS-CoV-2+ patients; 42 admitted to ICU; deceased: 16	Mean age: 65.9; male: 48.7%	The prevalence of VDD among COVID-19 inpatients, and its associations with disease severity	Severe COVID-19 was defined as admission to ICU and mortality; 25(OH)D <20 ng/mL	Measured after COVID-19 testing	Age, gender, comorbidities, and CRP concentrations for mortality
Pizzini (61)	Began on April 29, 2020; ongoing	Several hospitals and care centers in Austria	Prospective multicenter observational study	22 non-hospitalized (mild) and 87 hospitalized patients (moderate: 34; severe: 53); 38% with VDD	Median age: 58; male: 60%	To investigate associations of vitamin D status to disease presentation	Disease severity was categorized as mild for patients in outward treatment; moderate for patients in inward treatment; and severe for patients requiring oxygen supply, respiratory support, or ICU; 25(OH)D <12 ng/mL	The $25(OH)D_3$ concentration was measured 2 times: the first days of hospital admission and 8 wk after the diagnosis	—

(*Continued*)

TABLE 2 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Pérez (66)	—	Hospital Central Military Mexico		172 patients with COVID-19; cases: those who died ($n = 35$); controls: those who survived	Mean age: 51.44; male: 77.3%	Determine the association between 25(OH)D concentrations and mortality in hospitalized patients with COVID-19	Mortality was considered as severe; 25(OH)D <20 ng/dL	—	—
Radujkovic (13)	March to June, 2020	Medical university hospital, Heidelberg, Germany	Cohort	185 patients; patients with VDD ($n = 41$); non-VDD ($n = 144$); outpatients: 92; inpatients: 93	Median age: 60, IQR (49–70); male: 51%	To explore possible associations of vitamin D status with disease severity and survival	Decision for inpatient vs. outpatient admission was based on spontaneous oxygen saturation, comorbidities, and the overall performance status; based on COVID-19 severity classifications, all inpatients had severe disease (defined as tachypnea, oxygen saturation <93% at rest, or ICU requirement); 25(OH)D <12 ng/mL	At the time of admission	Adjusted for age, gender, and comorbidities
Rastogi (14)	—	Tertiary care hospital in north India	RCT	40 Asymptomatic or mildly symptomatic SARS-CoV-2+ with VDD [$25(OH)D_3$ <20 ng/mL]	Median age in the intervention group: 50.0, IQR (36–51); male: 37.5% Control: 47.5 (39.3 to 49.2); male: 58.3%	Effect of high-dose oral cholecalciferol supplementation on SARS-CoV-2 viral clearance	—	At the beginning of study	—
Ye (41)	February to March, 2020	Guangxi People's Hospital, China	Case-control	80 healthy controls and 62 patients diagnosed with COVID-19	Median age in controls: 42, IQR (31–52); male: 40% Age in cases: 43(32–59); male: 37%	To examine the relation between serum $25(OH)D_3$ concentration and COVID-19 severity, and its clinical case characteristics	Severe COVID-19 case was defined according to the guidelines of the National Health Commission of China[5]; 25(OH)D <20 ng/dL	At admission	Demographics and comorbidities

(*Continued*)

TABLE 2 (*Continued*)

First author (ref)	Study date	Country, setting	Design	Sample size, *n*	Age (y); sex	Objective/study question	Severity definition/vitamin deficiency definition	Time of VitD ascertainment	Adjusting factors
Yılmaz (35)	March to May 2020	Turkey, Dicle University Faculty of Medicine	Case-control	85 children (40 patients who were diagnosed with COVID-19 and hospitalized, 45 healthy children in the control group)	COVID-19 patients: 101.76 ± 27.91 mo; male: 47.5% Controls: 75.68 ± 27.34 mo; male: 60%	To determine the prevalence and clinical importance of VDD in children and adolescent patients who were hospitalized with the diagnosis of COVID-19	Mild: cases with upper respiratory tract infection with normal respiratory system examination Moderate: pneumonia with fever and cough but without symptoms of dyspnea and hypoxemia or cases with findings of COVID-19 on CT scan without any symptoms Severe: fever and cough in the early period who develop dyspnea and central cyanosis Critical: develop ARDS or RF rapidly 25(OH)D < 20 ng/mL	From retrospective file records	None

[1] ARF, acute respiratory failure; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; GFR, glomerular filtration rate; HTN, hypertension; ICU, intensive care unit; IHD, ischemic heart disease; MAS, macrophage activation syndrome; MLR, multivariate logistic regression; OSCI, Ordinal Scale for Clinical Improvement; PaO_2, partial oxygen pressure; RCT, randomized controlled trial; ref, reference; RF, renal failure; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, oxygen saturation; VDD, vitamin D deficiency; VitD, vitamin D; 25(OH)D, 25-hydroxyvitamin D; 25(OH)D3, 25-hydroxyvitamin D3; 1,25(OH)D, 1,25-hydroxyvitamin D.

[2] Chinese Clinical Guideline for classification of COVID-19 severity. Moderate: fever and pulmonary symptoms along with pneumonia on radiologic imaging. Severe: the presence of any of the following criteria: *1*) respiratory distress (≥30 breaths/min), *2*) oxygen saturation ≤93% at rest, *3*) PaO_2/FiO_2 ≤300 mmHg or chest imaging shows obvious lesion progression >50% within 24–48 h.

[3] Commission and State Administration of Traditional Chinese Medicine: *1*) mild: mild symptoms with no signs of pneumonia on imaging; *2*) moderate: fever, respiratory symptoms with radiological evidence of pneumonia; *3*) severe [i.e., meeting any of the following: respiratory distress, respiratory rate ≥30 breaths/min, hypoxemia, SpO_2 ≤93% (at rest), or lung infiltrates of >50% within 24–48 h]; and *4*) critical (i.e., meeting any of the following criteria: respiratory failure requiring mechanical ventilation, shock, or multiple organ dysfunction requiring ICU monitoring and treatment).

[4] CDC criteria were used for the disease severity and prognosis, which includes mild–moderate (mild respiratory symptoms and fever on an average of 5–6 d after infection), severe disease (dyspnea, respiratory frequency ≥30 breaths/min, blood oxygen saturation ≤93%, and/or lung infiltrates >50% of the lung field within 24–48 h) and critical (respiratory failure, septic shock, and/or multiple-organ dysfunction/failure).

[5] Per Guidelines of the National Health Commission of China severe cases met at least 1 of the following criteria: *1*) respiratory rate >30 breaths/min, *2*) pulse oximeter SpO_2 ≤93% when breathing ambient air, *3*) ratio of PaO_2 to FiO_2 ≤300 mmHg (1 mmHg = 0.133 kilopascal), and *4*) lung imaging showing significant progression of >50% within 24 to 48 h. Critical cases were defined as having at least 1 of the following: *1*) respiratory failure (PaO_2 <60 mmHg when breathing ambient air), *2*) hemodynamic shock (persisting hypotension requiring vasopressors to maintain mean arterial pressure >65 mmHg and serum lactate concentration >2 mmol/L despite volume resuscitation, and *3*) organ failure or admittance to ICU.

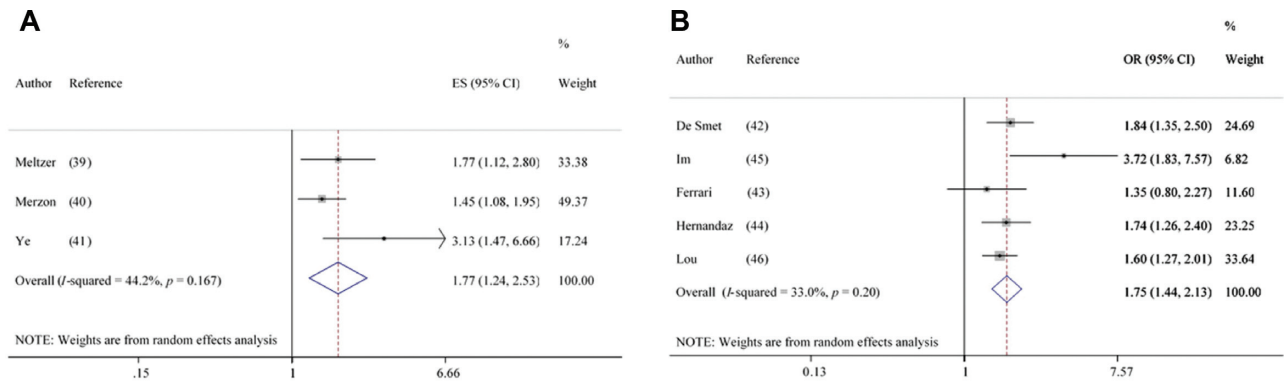

FIGURE 2 Relation between vitamin D deficiency and risk of SARS-CoV-2 infection in studies that adjusted for confounders (adjusted OR) (A) and studies that did not adjust for confounders (crude OR) (B). ES, effect size; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

between concentrations of 25(OH)D in ARDS [mean (SD): 16.8 (10.5) ng/mL) and non-ARDS [21.8 (15.8)] patients in Kerget et al. (50) ($P = 0.10$). Similarly, no significant association between VDD and ARDS was observed in the Maghbooli et al. (38) study (17.1% in VDD vs. 11.7% in non-VDD that progressed to ARDS; $P = 0.33$); moreover, bilateral lung involvement was observed in 33.3% in VDD versus 31.7% in non-VDD ($P = 0.86$) in this study. Three remaining studies evaluated the relation between VDD and risk of ventilation requirement. In a prospective study, VDD increased the risk of invasive mechanical ventilation and/or death (HR: 6.12; 95% CI: 2.79, 13.42; $P < 0.001$) (13). Consistently, another study indicated a significant relation between VDD and ventilation requirement (OR: 4.15; 95% CI: 1.05, 16.34; $P = 0.042$) (47), while one reported no relation (22.8% in VDD vs. 17.14% in non-VDD; $P = 0.58$) (44). Confounders were adjusted in the Radujkovic et al. (13) and Abrishami et al. (60) studies, while not adjusted in the Baktash et al. (47), Hernández et al. (44), Kerget et al. (50), Faul et al. (30), Maghbooli et al. (38), Pizzini et al. (61), and Im et al. (45) studies, respectively. Results of studies are summarized in **Supplemental Table 6**.

Hospitalization

Three studies investigated the relation between 25(OH)D and hospital admission and 2 with hospital stay. A significant association between VDD and risk of hospitalization was observed in Radujkovic et al. (13) (31% hospitalization in VDD vs. 69% in non-VDD, $P = 0.004$) and a marginally significant relation in Merzon et al. (40) (adjusted OR: 1.95; 95% CI: 0.98, 4.845; $P = 0.06$). The third study was a cross-sectional study that compared history of vitamin D3 supplement intake between inpatients and outpatients (57), where vitamin D3 intake was reported in 30% of outpatients versus 16.5% of hospitalized patients ($P = 0.001$).

Hernández et al. (44) found a significant relation between VDD and hospital stay [median (IQR) of 12.0 d (8.0–16.0) in patients with VDD vs. 8.0 d (6.0–14.0) in non-VDD patients; $P = 0.01$], while Luo et al. (46) failed to find a significant relation between serum 25(OH)D concentrations and length

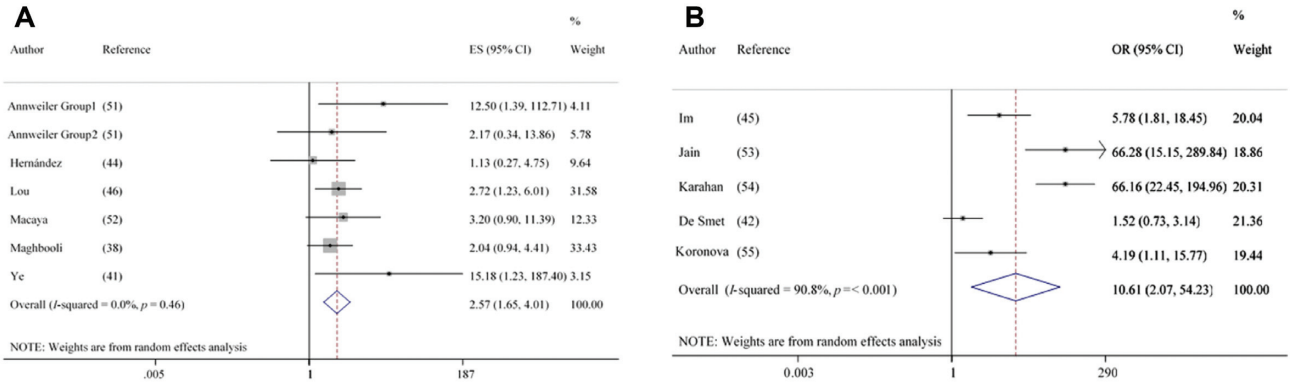

FIGURE 3 Relation between vitamin D deficiency and COVID-19 severity in studies that adjusted for confounders (adjusted OR) (A) and studies that did not adjust for confounders (crude OR) (B). COVID-19, coronavirus disease 2019; ES, effect size.

of hospital stay (B = −0.03, P = 0.64) (**Supplemental Table 7**).

Concentration of 25(OH)D between severe and less severe status of disease

Thirteen studies compared the serum concentration of 25(OH)D between patients with severe and nonsevere status of COVID-19 (either composite or 1 feature of severity). Analysis of 12 studies (13, 30, 41, 42, 43, 46, 50, 53–55, 59, 61), with 806 cases and 1024 controls, indicated that serum concentrations of 25(OH)D in patients with severe status of disease was lower (WMD = −7.17 ng/mL; 95% CI: −9.99, −4.34; I^2 = 87.6%) compared with less-severe counterparts (**Supplemental Figure 2**). In all of the studies except for one (43), 25(OH)D was measured after SARS-CoV-2 testing. One study was not included in the analysis, since the sample size according to hospitalization was not reported. Indeed, in this retrospective study, mean concentrations of 25(OH)D were 18.38 ng/mL (95% CI: 16.79, 19.96) in hospitalized and 20.45 ng/mL (95% CI: 20.22, 20.68) in nonhospitalized individuals (P < 0.001) (40) (**Supplemental Table 8**).

Inflammatory markers

We assessed the association of VDD with C-reactive protein (CRP), IL-6, D-dimer, and ferritin in COVID-19 patients. Nine studies examined the association of at least 1 of these markers with VDD. In an RCT in 40 COVID-19 patients, cholecalciferol supplementation did not significantly reduce CRP and D-dimer (14). A retrospective study in 42 patients with acute respiratory failure due to COVID-19 (64) revealed no statistically significant differences in inflammation indices among the 4 vitamin D groups (normal, insufficiency, deficiency, severe deficiency). Another retrospective study in 197 COVID-19 patients revealed that only ferritin, but not CRP, IL -6, and D-dimer, was significantly higher in VDD compared with non-VDD (44). In a prospective multicenter observational study in 109 patients, the correlation between 25(OH)D concentrations at follow-up and CRP, IL-6, ferritin, and D-dimer was not significant. The same was true for 25(OH)D concentrations measured at disease onset and CRP (r = 0.152, P = 0.45), IL-6 (r = 0.050, P = 0.80), and ferritin (r = 0.070, P = 0.73). In contrast, D-dimer concentrations were moderately associated with 25(OH)D concentrations (r = 0.437, P < 0.05) (61). Karahan and Katkat (54) in their retrospective study in 149 COVID-19 patients found a significant negative relation between serum 25(OH)D concentration and CRP (r = −0.253, P = 0.002). Kerget et al. (50) found a significant negative correlation only with CRP (r = −0.297, P = 0.01), but not IL-6, ferritin, and D-dimer. In a prospective study in 70 elderly individuals, it was reported that the VDD group demonstrated higher peak CRP, lactate dehydrogenase (LDH), and ferritin concentrations (47). Maghbooli et al. (38) in a cross-sectional study in 235 patients indicated that a relative risk of CRP >40 mg/L (inpatient mortality serum concentrations) was significantly higher in VDD. In Radujkovic et al. (13), IL-6 concentration was significantly higher in VDD versus non-VDD [median (IQR): 70.5 pg/mL (32.0–326.3) vs. 29.7 pg/mL (14.3–59.9); P = 0.01]. Only Maghbooli et al. and Radujkovic et al. adjusted for confounders, whereas the other studies did not report any adjustment. Results of studies are listed in **Supplemental Table 9**.

Mortality

Among 15 studies that assessed the relation between mortality and VDD, 13 studies were included in the analysis. Pooled analysis of 4 adjusted studies that used the Cox survival method (13, 51, 56, 60) (HR: 2.35; 95% CI: 1.22, 4.52; I^2: 84%; **Figure 4**A) and 5 studies (44, 47, 53, 55, 62) with crude OR (OR: 2.62; 95% CI: 1.13, 6.05; I^2: 47.8%; Figure 4B) indicated a significant association of VDD with mortality, while in adjusted studies that used logistic regression (54, 59, 65), no relation was observed (OR: 1.05; 95% CI: 0.63, 1.75; I^2: 76.6%). Two studies were not included in the analysis since 1 study had an RCT design (36) and another one used different statistical methods (64). In the RCT, 2 deaths in the control group versus no deaths in the intervention group were observed (36). In the other study, which had a retrospective design, patients with serum 25(OH)D <10 ng/mL had a 50% probability of mortality, while those with 25(OH)D ≥10 ng/mL had a 5% mortality risk after 10 d of hospitalization (P = 0.02) (64).

Moreover, 6 studies compared serum concentrations of 25(OH)D between deceased patients and those who survived (50, 54, 55, 60, 63, 66); pooled analysis of studies indicated lower concentrations of 25(OH)D in patients who died compared with those who survived (WMD: −9.05 ng/mL; 95% CI: −13.86, −4.23; I^2: 87.8%; **Supplemental Figure 3**). Results of studies are summarized in **Supplemental Table 10**.

Publication bias and quality assessment

Assessment of publication bias was conducted for 25(OH)D concentration between SARS-CoV-2–positive and –negative subjects as well as between severe and less-severe COVID-19 groups. Based on Egger's test, publication bias was evident in comparison of SARS-CoV-2–positive with –negative subjects (P = 0.002) and the funnel plot was asymmetric (**Supplemental Figure 4**A). The probable reason for publication bias may be that the studies with 25(OH)D data collected before SARS-CoV-2 testing had larger sample sizes and detected smaller differences compared with the studies that measured 25(OH)D after SARS-CoV-2 testing. There was no publication bias in the comparison of severe and less-severe COVID-19 patients (P = 0.60); however, a small deviation towards an WMD ∼ −5 and an SE ≈2 was observed in a funnel plot (Supplemental Figure 4B); this implies that studies with a smaller SE (more precision) indicate less difference in 25(OH)D concentration compared with the pooled WMD. Therefore, it should be considered that a small overestimation is probable. The quality of most of the studies was classified as poor (**Supplemental Tables 11–14**). Moreover, the strength and limitations of studies are summarized in **Supplemental Table 15**.

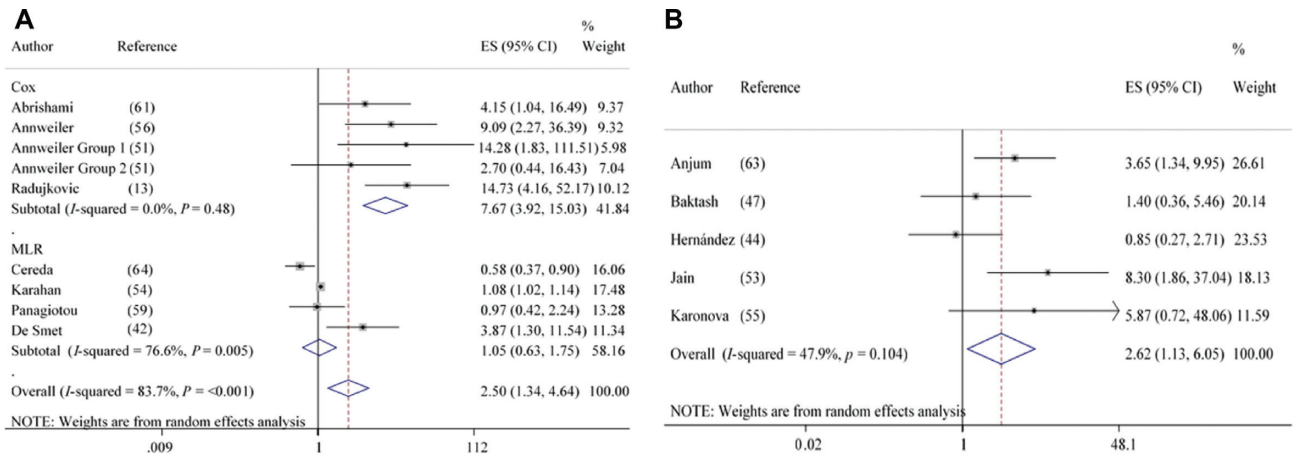

FIGURE 4 Relation between vitamin D deficiency and risk of mortality from COVID-19 in studies that adjusted for confounders (adjusted HR) (A) and studies that did not adjust for confounders (crude OR) (B). COVID-19, coronavirus disease 2019; ES, effect size; MLR, multiple logistic regression.

Discussion

In this systematic review, we investigated the relation between 25(OH)D concentrations and risk of SARS-CoV-2 infection and COVID-19 severity. For this purpose, we systematically reviewed and, where appropriate, meta-analyzed the related retrospective, cohort, cross-sectional, and clinical trial studies that assessed the association of 25(OH)D concentrations and the risk of SARS-CoV-2 infection, composite severity, or 1 feature of severity.

Higher risk of SARS-CoV-2 infection was observed in VDD and serum concentrations of 25(OH)D were lower in COVID-19 patients compared with healthy counterparts, as indicated by pooled results of both adjusted and nonadjusted studies. Among the 3 adjusted studies, 2 measured 25(OH)D in the preceding year before SARS-CoV-2 infection (39, 40); the sample sizes in one of these studies were sufficiently powered (case/control: 782/7025) (39). The nonadjusted studies measured 25(OH)D at admission and the sample sizes were sufficient in 4 studies (186/2700, 197/197, 128/219, 335/560) (39, 43, 39, 39). Moreover, concentrations of 25(OH)D were lower in COVID-19 patients compared with healthy subjects. Based on the findings, VDD is associated with increased risk of SARS-CoV-2 infection; however, caution should be made in interpreting these results, since the studies have inherent limitations.

All of the studies indicated a lower concentration of 25(OH)D with more severe status (composite severity) of disease. Furthermore, VDD was associated with composite severity in studies that were both adjusted and not adjusted for confounders. The significant relation between VDD and composite severity was evident in all of the primary studies, except for the Hernández et al. (44) and De Smet et al. (42) studies, where De Smet et al. revealed such a relation only in males but not in females. Zero heterogeneity was estimated for adjusted studies based on the I^2 statistic. It should be noted that the heterogeneity I^2 statistic can be biased in small meta-analyses and so an I^2 of 0.0% does not necessarily reflect perfect homogeneity (67).

Pooled results from the studies that were unadjusted and adjusted studies using Cox survival analysis indicated a higher risk of mortality in VDD; however, the adjusted studies that used logistic regression failed to find a significant relation. The Cox model estimates the instantaneous probability of death at a particular time, while logistic regression estimates the cumulative probability; instantaneous risk could be important as the cumulative probability can be conditioned by a complex clinical outcome. Moreover, it is noteworthy to mention that the Cox model tends to have greater statistical power to detect a significant exposure effect than logistic regression (68). Among the 4 adjusted studies that used logistic regression, 1 study indicated higher risk of mortality in VDD, 2 revealed no significant relation, and 1 study unexpectedly found a lower risk of mortality in VDD. In this study, the prevalence of $\geq$2 comorbidities was higher in the non-VDD (46.7%) versus the VDD group (30.3%). Although this difference between groups was not statistically significant, it could be important because of the small sample size ($n = 30$ in non-VDD and $n = 99$ in VDD). The authors adjusted for some confounders (age, sex, CRP, ischemic heart disease, and severe pneumonia), but the effects of other chronic diseases that were more prevalent in the non-VDD versus VDD groups (albeit nonsignificant) were not adjusted. Moreover, the population in this study was old (mean age of 77 y) and so at high risk for other nutrient deficiencies. The 2 studies that were not included in the analysis also indicated a significant relation, in which 1 study was an RCT (36, 64). Consistently, pooled results indicated a higher concentration of 25(OH)D in patients who survived versus those who died. Overall, evidence indicates that VDD greatly increases the risk of mortality.

Pooled analysis of unadjusted studies failed to detect any significant relation between 25(OH)D concentration and

ICU admission, although an RCT indicated a significant association (36).

For pulmonary complications, results of studies were inconsistent; 4 studies found a significant relation between 25(OH)D concentration and an increased risk of pulmonary involvement, while 4 studies failed to find any relation. Among them, only Radujkovic et al. (13) and Abrishimi et al. (60) were adjusted for confounders, and both found a significant association between VDD and risk of pulmonary involvement. Radujkovic et al. had some other strengths, such as a cohort design and larger sample size, as compared with the other studies. Although this study indicated a very large risk in VDD, the HR in this study was for the combination of both ventilator requirement and death. In Abrishami et al., increases in 25(OH)D concentration led to only a 4% reduction in severe lung involvement. Therefore, it seems pragmatic to suggest that no conclusion can be drawn regarding the relation between 25(OH)D and pulmonary complications.

All 3 studies that examined the association between VDD and hospitalization indicated a significant relation (13, 40, 57). One study adjusted for confounders and had a good quality design (13); another study adjusted for confounders and had a large sample size but the authors used vitamin D data that were measured in the past (40), while the third study did not adjust for confounders and had a poor design (57). With regard to the relation between 25(OH)D concentration and hospital length of stay, 1 study found a significant relation (44), while the other failed to find any relation (46). In total, the evidence is not adequate to draw a conclusion with regard to the association of vitamin D with hospitalization admission and length of stay.

We assessed CRP, D-dimer, ferritin, and IL-6 as the inflammatory markers. Five studies indicated a positive association between 25(OH)D concentration and inflammation. In 2 studies peak CRP and CRP >40 mg/L were evaluated in related to VDD (38, 47). In 1 study, only IL-6 was measured, and in the other 2 studies, the relation was examined using Pearson correlation coefficients (50, 54). Four studies failed to detect a significant relation (14, 44, 64, 61); among them, the highest-quality study was a clinical trial that failed to discern the effect of cholecalciferol supplementation on CRP and D-dimer (14), although it does not appear that 25(OH)D concentration is correlated with inflammation in nonacute phases, given that the evidence is currently not sufficient.

Several mechanisms are involved in elucidating the relation between VDD and SARS-CoV-2 infection risk and outcomes. Vitamin D improves cellular immunity and can decrease the plasma concentrations of proinflammatory cytokines, such as TNF-α and IFN-γ, that have been produced as part of the cytokine storm by the innate immune system in viral infections such as COVID-19, in addition to increasing concentrations of anti-inflammatory markers (69). Furthermore, vitamin D can regulate adaptive immunity response by stopping the T-helper (Th) cell type 1 (Th1) reaction, elevating production of cytokine by Th2, and increasing the induction of T-regulatory cells (70–72).

In addition, due to the highly expressed concentrations of vitamin D receptors (VDRs) in B- and T-lymphocytes (73), vitamin D can affect immune system function. VDR is a member of the nuclear hormone receptor (NHR) family, which is a known transcription factor (74); indeed, VDR is present in both T and B immune cells and regulates a variety of metabolic pathways, such as those involved in the immune response and cancer (75). High concentrations of transforming growth factor β (TGF-β) have been reported in the acute phase of COVID-19, where TGF-β signaling is closely related to SARS-CoV-2 and is suppressed by VDR via genomic competition with Mothers against decapentaplegic homolog 3 (Smad3) occupancy on proinflammatory (e.g., IL-6) genes and therefore creating a stable physiologic situation (76).

Another probable mechanism is that vitamin D can induce cathelicidin, IL-37, and defensins as antimicrobial peptides, and promote cellular innate immunity and reduce virus replication (77–79).

It has been posited that vitamin D can enhance the expression of some genes related to antioxidant systems, such as the glutathione reductase gene (80); accordingly, some studies have reported that vitamin D metabolites have vascular-related functions including anticoagulant effects through modifying the expression of thrombomodulin and tissue factor in monocyte and aortic cells (81, 82).

Because of the worldwide increasing prevalence of COVID-19 as a novel pandemic, it is important to research potential antiviral treatments or preventions. Therefore, we conducted this systematic review to investigate the association of vitamin D concentration with SARS-CoV-2 infection and various clinical outcomes.

Some systematic reviews have investigated the association between vitamin D3 and COVID-19 risk and severity (83, 84), in addition to a meta-analysis by Pereira et al. (85), which included 27 studies. The priority of the present study was to include a higher number of studies and exclude preprint articles that had not been peer reviewed and studies with high risk of bias. Moreover, problematically, studies that did and did not adjust for confounding variables were pooled together in the Pereira et al. study, while we analyzed these studies separately.

The main limitation of the present systematic review is the inclusion of studies that were heterogeneous in design, methodology, and statistical approach, and since most of the studies were observational, causality cannot be inferred. Sex and age are important factors that have been shown to be related to both COVID-19 and 25(OH)D concentrations independently. Thus, it is of high importance that the relation between COVID-19 and vitamin D be verified in different subgroups of age and sex. Indeed, we were unable to do so due to the results not being reported separately in the included studies.

In conclusion, although studies were heterogeneous in methodological and statistical approach, and some inherent

limitations were present, the findings of the present study indicated a significant relation between 25(OH)D concentration and SARS-CoV-2 infection, COVID-19 composite severity, and mortality. For infection, caution should be taken in interpreting the results due to inherent limitations of studies. For ICU admission, inflammation, hospitalization, and pulmonary involvement, the evidence is currently inconsistent and insufficient. Moreover, future studies should investigate the association of COVID-19 with vitamin D in subgroups of age and sex.

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