REVIEW

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Association of vitamin D deficiency with COVID-19 infection severity: Systematic review and meta-analysis

Zhen Wang[1] | Avni Joshi[2,3] | Kaitlin Leopold[4] | Sarah Jackson[5] |
Stephanie Christensen[4] | Tarek Nayfeh[1,6] | Khaled Mohammed[7] | Ana Creo[5] |
Peter Tebben[5,8] | Seema Kumar[5]

[1]Division of Health Care Delivery Research, Robert D. and Patricia E. Kern Center for the Science of Health Care Division of Health Care Delivery Research, Mayo Clinic, Rochester, Minnesota, USA

[2]Division of Allergic Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

[3]Division of Pediatric Allergy and Immunology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

[4]Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

[5]Division of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

[6]Mayo Clinic Evidence-based Practice Center, Rochester, Minnesota, USA

[7]Community Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

[8]Division of Endocrinology and Metabolism, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Seema Kumar, Division of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA.
Email: kumar.seema@mayo.edu

Abstract

Background: We sought to evaluate the association between vitamin D deficiency and the severity of coronavirus disease 2019 (COVID-19) infection.

Methods: Multiple databases from 1 January 2019 to 3 December 2020 were searched for observational studies evaluating the association between vitamin D deficiency and severity of COVID-19 infection. Independent reviewers selected studies and extracted data for the review. The main outcomes of interest were mortality, hospital admission, length of hospital stay and intensive care unit admission.

Results: Seventeen observational studies with 2756 patients were included in the analyses. Vitamin D deficiency was associated with significantly higher mortality (odds ratio [OR]: 2.47, 95% confidence interval [CI]: 1.50–4.05; 12 studies; hazard ratio [HR]: 4.11, 95% CI: 2.40–7.04; 3 studies), higher rates of hospital admissions (OR: 2.18, 95% CI: 1.48–3.21; 3 studies) and longer hospital stays (0.52 days; 95% CI: 0.25–0.80; 2 studies) as compared to nonvitamin D deficient status. Subgroup analyses based on different cut-offs for defining vitamin D deficiency, study geographic locations and latitude also showed similar trends.

Conclusions: Vitamin D deficiency is associated with greater severity of COVID-19 infection. Further studies are warranted to determine if vitamin D supplementation can decrease the severity of COVID-19.

KEYWORDS
COVID-19, hospital admission, mortality, vitamin D

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) was initially identified in Wuhan, China in late 2019 and subsequently became a global pandemic.[1] The illness varies widely in severity with affected individuals being asymptomatic or developing mild, moderate or severe illness, which can be fatal. The case fatality rates have been different between geographic regions and countries.[2] The specific risk factors for a severe illness identified so far include older age, male sex, obesity, cardiovascular disease, chronic lung disease, diabetes mellitus and cancer.[1,3] Additionally, race is an important factor as several studies have shown that Black, Hispanic and Asian individuals accounted for a disproportionately higher number of hospitalisations and deaths due to COVID-19 in the United Kingdom and the United

States.[4] Many of the abovementioned risk factors are not modifiable, hence it is important to identify modifiable factors that might contribute to COVID-19 infection severity. Diet and nutrition have important implications in immune functioning and infection risk, especially vitamin D level.[5] Vitamin D may be one potentially modifiable risk factor postulated to modulate COVID-19 infection severity.[6]

Vitamin D, in addition to its role in skeletal health, may modulate immune regulation.[7] The vitamin D receptor is present in a variety of cells involved in immune regulation, including monocytes, activated T and B lymphocytes and dendritic cells. Vitamin D has been shown to impact cytokine synthesis, lymphocyte proliferation, antibody production, monocyte activation and cell-mediated immunity.[7] A systematic review and meta-analysis of 25 randomised, double-blind placebo-controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration found that vitamin D supplementation was beneficial in reducing the risk of acute respiratory tract infection.[8] There is a conflicting opinion on the role of vitamin D in impacting the risk of COVID-19, with some studies suggesting that vitamin D deficiency increases the risk of COVID-19 infection[9,10] while others did not find a significant association.[11] Similarly, there is conflicting evidence on whether vitamin D deficiency is associated with greater severity of COVID-19 infection.[12–17]

To further investigate this relationship and obtain greater clarity on this issue, we conducted this systematic review and meta-analysis to evaluate the association between vitamin D deficiency and the severity of COVID-19 infection.

2 | METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed to report this systematic review and meta-analysis.[18]

2.1 | Data sources and searches

We conducted a comprehensive database search, including MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Scopus, from 1 January 2019 to 3 December 2020. Reference mining of existing systematic reviews/meta-analyses, preprint medical literature from medRxiv. org, and relevant primary studies were conducted to identify additional studies. An experienced medical librarian, with input from the study investigators, developed the search strategy (Figure 1) and conducted the literature search.

2.2 | Study selection

Eligible studies (1) included patients with laboratory-confirmed COVID-19 diagnosis (polymerase chain reaction [PCR]); (2)

documented evaluation of total serum 25-hydroxyvitamin D (25(OH)D) level within 3 months of COVID-19 diagnosis; (3) availability of a comparison group: comparing vitamin D deficiency to nondeficiency (includes normal vitamin D status and insufficiency); and (4) reported outcomes of interest (mortality, hospital admission, length of hospital stay and intensive care unit [ICU] admission). As the 25(OH)D cut-offs for defining vitamin D deficiency are controversial,[19] we used the 25(OH)D cut-offs defined by each study. We included observational studies without restrictions on publication language, study location, or patient population. Studies were excluded if they evaluated vitamin D supplements, vitamin D insufficiency only, or suspected COVID-19 cases (including those evaluated by radiology only, without confirmatory PCR or antigen-based testing). We also excluded in vitro studies, and studies without original data (e.g., opinion, editorial and narrative review).

Pairs of reviewers, working independently, screened titles and abstracts of all references. Studies included by either reviewer were included for full-text screening. Pairs of independent reviewers screened the full text of the eligible studies. Conflicts between the reviewers were resolved by a third investigator.

2.3 | Data extraction and quality assessment

A pilot-tested standardised data extraction form was developed to extract study characteristics and outcomes of interest. Reviewers worked independently to extract study details. A second reviewer reviewed data and resolved inconsistencies.

We evaluated the risk of bias of the included studies using the modified Newcastle–Ottawa Scale, in terms of representativeness of study cohort, ascertainment of exposure, comparability between groups, outcome data source and assessment of outcome (Appendix Table S1).[20]

2.4 | Data synthesis and analysis

Odds ratio (OR) or hazard ratio (HR) for binary outcomes (mortality, hospital admission, ICU admission) and mean difference for the continuous outcome (length of hospital stay) were extracted or calculated. The DerSimonian–Laird random-effects model with Hartung–Knapp–Sidik–Jonkman variance correction was used to combine studies if the number of studies included in the analysis was larger than 3.[21] The fixed-effect model based on the Mantel and Haenszel method was adopted when the number of studies was 3 or less. Treatment arm continuity corrections were used to adjust double-zero-event studies (i.e., 0 event in both groups).[22] Heterogeneity across studies was measured using the I^2 indicator, in which $I^2 > 50\%$ suggests substantial heterogeneity. To further explore heterogeneity, we conducted prespecified subgroup analyses based on serum 25(OH)D cut-off levels used to define vitamin D deficiency (12, 20 and 25 ng/ml) and geographic regions (Europe, Asia, Middle East and North America). The latitudes of the study areas were

evaluated, which were identified as the latitudinal coordinates of the geographic centroid of the study areas extracted from Google Map and categorised based on 5° increments from the equator. Publication bias was evaluated quantitatively using the asymmetry test of funnel plots and Egger's regression test when the number of studies included in a meta-analysis was larger than 10. Two-sided p-value less than .05 was deemed to be statistically significant. All statistical analyses were conducted using Stata version 16.1 (Stata LLP Corp).

3 | RESULTS

Our literature search identified 560 citations. Seventeen observational studies with 2756 eligible patients who met our inclusion criteria were included in the analyses (Figure 1 and Table 1).[12-17,23-33] The studies included only adult patients; and the majority (70.6%) evaluated only hospitalised COVID-19 cases. Vitamin D deficiency was defined as total 25(OH)D level less than 12 ng/ml (seven studies), less than 20 ng/ml (eight studies) and less than 25 ng/ml (one study). Mendy et al.[16] did not specify the 25(OH) D levels used to classify vitamin D deficiency and instead based the diagnosis on the International Classifications of Diseases 10 code for

deficiency. Nine studies were conducted in Europe, one in the United States, five in Asia and two in the Middle East. Details of study characteristics can be found in Table 1.

The overall risk of bias of the included studies was high due to a lack of control of confounding variables (Appendix Table S1). We did not find potential publication bias for mortality, though we were unable to statistically evaluate publication bias for the other outcomes.

Of the 17 included studies, 14 compared vitamin D deficiency with normal vitamin D status, while the remaining 3 studies quantified vitamin D status qualitatively, which was categorised as deficiency, insufficiency and normal. For these three studies, outcomes in those with vitamin D deficiency were compared with the normal and insufficiency group combined. Vitamin D deficiency was associated with significantly higher mortality (OR: 2.47, 95% CI: 1.50–4.05; $I^2 = 30.5\%$; 12 studies; HR: 4.11, 95% CI: 2.40–7.04; $I^2 = 11.6\%$; 3 studies), higher rates of hospital admission (OR: 2.18, 95% CI: 1.48–3.21; $I^2 = 0\%$, 3 studies) and longer hospital stays (+0.52 days; 95% CI: 0.25–0.80; $I^2 = 89.6\%$; 2 studies) (Table 1 and Figure 2). We found no significant difference in ICU admissions (Table 2).

We examined the difference in the severity of COVID-19 infection based on different 25(OH)D cut-offs used for defining
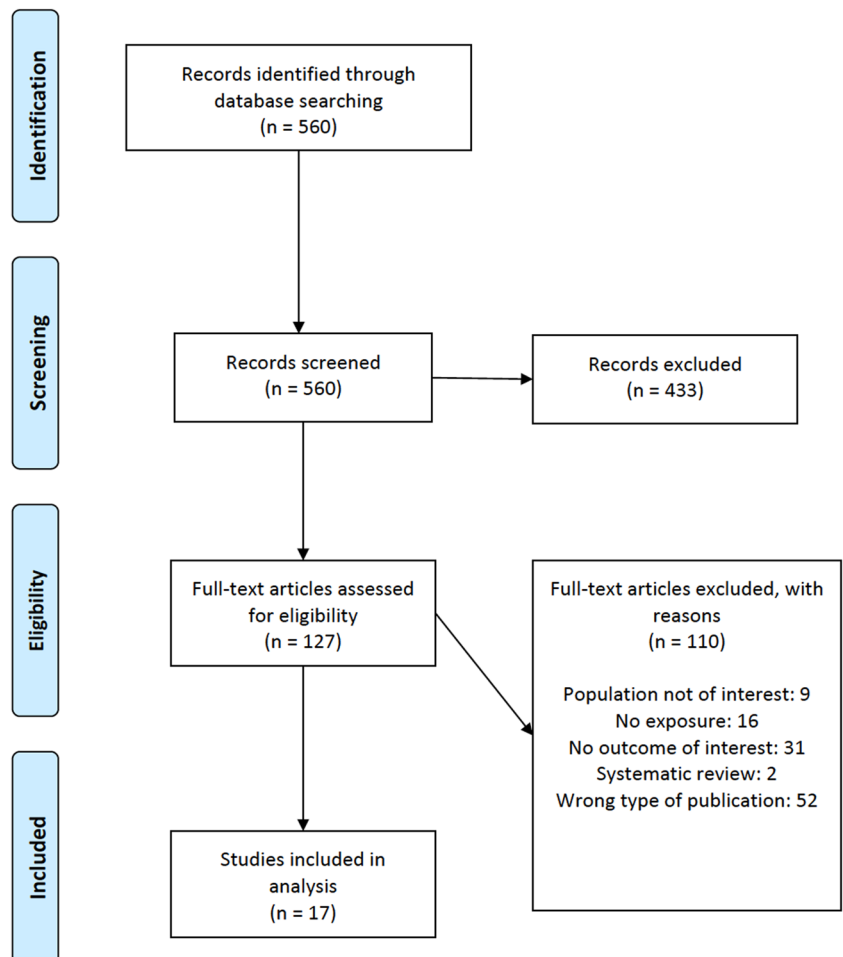

FIGURE 1 Flowchart outlining the protocol adopted in this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines

TABLE 1 Study characteristics

Author, year (country)	Study period	Methods used for confirmation of COVID-19	Comparisons	Patients characteristics
De Smet, 2020[1] (Belgium)	1 March 2020 to 7 April 2020	RT-PCR	≥20 ng/ml	109 Patients, aged 73 years (IQR: 53–81), 53.2% female, 100% Caucasian, 100% inpatients
			<20 ng/mL	109 Patients, aged 67 years (IQR: 52–79), 33.0% female, 100% inpatients
Carpagnano, 2020[2] (Italy)	11 March 2020 to 30 April 2020	RT-PCR	All groups	42 Patients, aged 65 ± 13 years, 28.6% female, BMI: 28.5 ± 5, 26.2% DM, 100% inpatients
Jain, 2020[3] (India)	5 June 2020 to 17 July 2020	RT-PCR	All groups	154 Patients, aged 46.1 ± 7.6 years, 44.8% female, BMI: 27.1 ± 4.6, 4.56% obese, 100% inpatients
Hars, 2020[4] (Switzerland)	13 March 2020 to 14 April 2020	RT-PCR	All groups	160 Patients, aged 85.9 ± 6.6 years, 59.4% female, 100% Caucasian, 100% inpatients
Cereda, 2020[5] (Italy)	March 2020 to April 2020	RT-PCR	≥20 ng/ml	30 Patients, aged 77.5 years (IQR: 65–86), 56.7% female, 100% Caucasian, BMI: 24.4 (IQR: 20.8–26.2), 36.7% DM, 100% inpatients
			<20 ng/ml	99 Patients, aged 77 years (IQR: 64–85), 42.4% female, 100% Caucasian, BMI: 24.7 (IQR: 22.9–27.9), 28.9% type 2 DM, 100% inpatients
Luo, 2020[6] (China)	Technology, 7 February 2020 to 21 March 2020	RT-PCR	All groups	335 Patients, aged 56 years (IQR: 43.0–64.0), 55.8% female, 100% Chinese, BMI: 23.5 ± 3.1, 100% inpatients
Hernandez, 2020[7] (Spain)	10 March 2020 to 31 March 2020	RT-PCR	≥20 ng/ml	35 Patients, aged 58 years (IQR: 45–69), 51.4% female, BMI: 29.8 ± 4.1, 17.1% DM, 100% inpatients
			<20 ng/ml	162 Patients, aged 62 years (IQR: 48–70.3), 34.6% female, BMI 29 ± 4.9, 17.3% DM, 100% inpatients
Abrishami, 2020[8] (Iran)	28 February 2020 to 19 April 2020	RT-PCR	All groups	73 Patients, aged 55.2 ± 15.0 years, 36.0% female, 15.1% DM, 100% inpatients
Ye, 2020[9] (China)	16 February 2020 to 16 March 2020	PCR	All groups	62 Patients, aged 43 years (IQR: 32–59), 63.0% female, 100% Chinese, 8.3% DM, 100% inpatients
Baktash, 2020[10] (United Kingdom)	1 March 2020 to 30 April 2020	RT-PCR	≤12 ng/ml	39 Patients, aged 79.4 ± 9.5 years, 38.5% female, 74.4% Caucasian, BMI: 25 (IQR: 23–32), 43.6% DM, 100% inpatients
			>12 ng/ml	31 Patients, aged 81.2 ± 7.2 years, 41.9% female, 67.7% Caucasian, BMI: 24 (IQR: 20–27), 29.0% DM, 100% inpatients
Mendy, 2020[11] (United States)	13 March 2020 to 31 May 2020	PCR	All groups	689 Patients, aged 49.5 ± 34.1 years, 47.0% female, 29.2% Caucasian, 25.5% Black, 32.5% Hispanic, 18.6% obese, 24.7% DM
Im, 2020[12] (Korea)	February 2020 to June 2020	RT-PCR	≤20 ng/ml	38 Patients, 57.9% female, 100% inpatients
			>20 ng/dl	12 Patients, 58.3% female, 100% inpatients
Mardani, 2020[13] (Iran)	March 2020	RT-PCR	All groups	63 Patients, aged 43.3 ± 14.5 years, 44.4% female
Macaya, 2020[14] (Spain)	5 March 2020 to 31 March 2020	RT-PCR	All groups	80 Patients, aged 67.7 years, 56.3% female, BMI: 27, 28.8% obese, 40.0% DM
Pizzini, 2020[15] (Austria)	From 29 April 2020	RT-PCR	All groups	109 Patients, aged 58 ± 14 years, 40.0% female, BMI: 27 ± 14, 18.0% DM, 80% inpatients
Radujkovic, 2020[16] (Germany)	18 March 2020 to 18 June 2020	RT-PCR	<12 ng/ml	41 Patients, aged 66 years (IQR: 53–78), 43.9% female, 19.5% DM, 100% inpatients
			≥12 ng/ml	144 Patients, aged 58 years (IQR: 47–67), 50% female, 19.4% DM, 100% inpatients
Anjum, 2020[17] (Pakistan)	March 2020 to July 2020	RT-PCR	All groups	140 Patients, aged 42.5 ± 14.7 years, 41.4% female, BMI: 23.5 ± 3.6

Abbreviations: COVID-19, coronavirus disease 2019; DM, diabetes mellitus; IQR, interquartile range; RT-PCR, real-time reverse transcription-polymerase chain reaction.
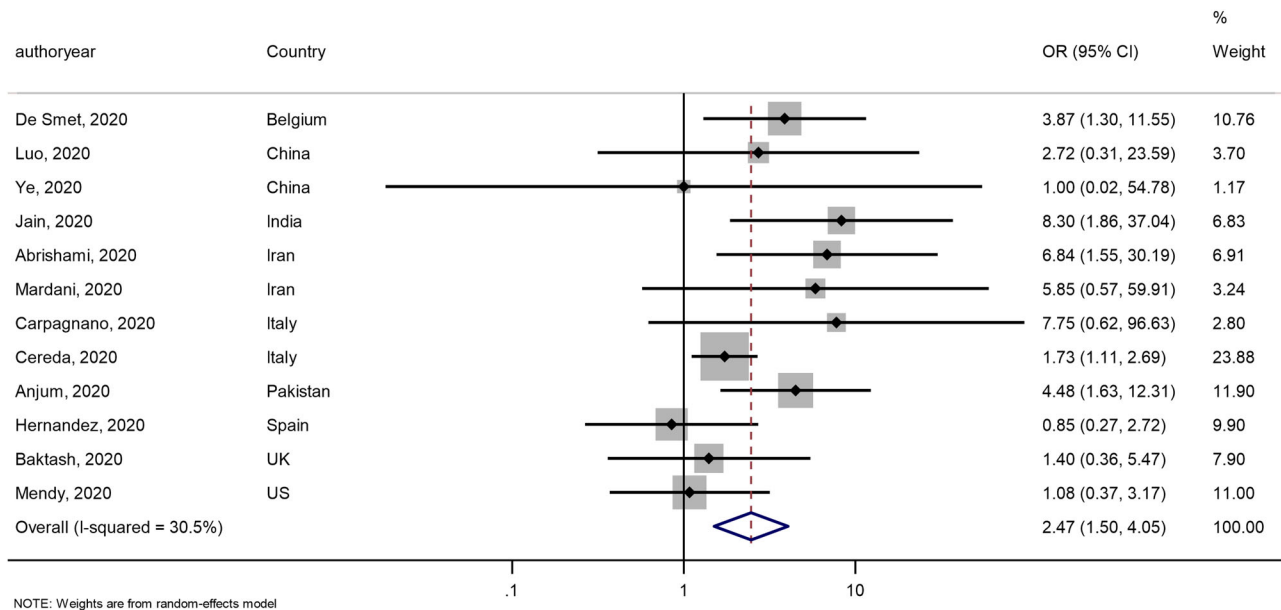
FIGURE 2 Forest plot showing odds ratio (OR) and 95% confidence interval (CI) for mortality for each of the 12 studies that reported this outcome

TABLE 2 Comparison of vitamin D deficiency versus nondeficiency

Outcome	Number of studies	Findings
Mortality	12	OR: 2.47, 95% CI: 1.50–4.05; $I^2 = 30.5\%$
	3	HR: 4.11, 95% CI: 2.40–7.04; $I^2 = 11.6\%$
Hospital admission	3	OR: 2.18, 95% CI: 1.48–3.21; $I^2 = 0\%$
Length of hospital stay	2	0.52 days; 95% CI: 0.25–0.80; $I^2 = 89.6\%$
ICU admission	4	OR: 5.44, 95% CI: 0.38–78.42; $I^2 = 83.1\%$

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

vitamin D deficiency, geographical location and latitude (Appendix Tables S2–S4). Findings on subgroup analyses are listed in Appendix Tables S2–S4. The significant difference between patients with vitamin D deficiency and nondeficiency levels remained in most of the subgroup analyses (25(OH)D cut-offs for the definition of vitamin D deficiency, geographic location and latitude).

4 | DISCUSSION

In this systematic review and meta-analysis of 17 studies, we found that vitamin D deficiency was associated with higher mortality and higher rates of hospital admissions with longer hospital stays in adult patients with COVID-19. These findings need further validation as our findings represent an association, not causation, which may have far-reaching implications for public health initiatives.

The association between vitamin D deficiency and COVID-19 infection severity as reflected by greater mortality, higher rate of hospital admissions and longer hospital stay are hypothesised to be due to the immunomodulatory effect of vitamin D.[7,34] These effects may be mediated in part by vitamin D reducing the 'cytokine storm,' which has been implicated in severe COVID-19 infection. Vitamin D decreases the production of Th1 cells[35] and suppresses the progress of inflammatory cascade by altering the proinflammatory cytokine signatures. Calcitriol (1,25(OH)2D3), the active metabolite of vitamin D, has been shown to inhibit the production of proinflammatory cytokines, such as interferon gamma, tumour necrosis factor alpha, interleuki-2 (IL-2), IL-17, nuclear factor-κB and IL-21 and toll-like receptors on monocytes and lead to upregulation of IL-4, IL-5 and IL-10.[36] In human umbilical vein cord cells, calcitriol also decreased the expression of adhesion molecules, as well as lipopolysaccharide-induced expression of receptor of the advanced glycation end product and IL-6.[36] 1,25(OH)D has been shown to result in upregulation of IkBalpha (an NF-κN inhibitor) in alveolar A549 cells infected with respiratory syncytial virus and in primary human tracheobronchial epithelial cells.[37] Additionally, vitamin D upregulates the expression of angiotensin-converting enzyme 2 (ACE2), the main host cell receptor of COVID-19 and also downregulates renin at the transcriptional level.[38–40] The combination of vitamin D's effects on the inflammatory pathway and ACE2 expression may be uniquely applicable to the disease pathogenesis and severity of COVID-19.[39]

Our findings are largely in agreement with two recent systematic reviews on this topic.[41,42] but differ from findings from a recent review by Bassatne et al.[43] who reported a statistically nonsignificant trend between serum 25(OH)D level less than 20 ng/ml and an increased risk of mortality and ICU admission. These differences are related to very different criteria used for the selection of studies in the review by Bassatne et al.[43] We included studies with PCR-confirmed positive COVID-19 with 25(OH)D levels drawn within 3 months of COVID-19 diagnosis and a comparison group (vitamin D deficiency vs. nondeficiency). As a result, more studies were included in the meta-analyses reported in the current study.

Our study has several strengths. We included only studies with laboratory confirmation of COVID-19 infection. We were able to examine the associations between vitamin D deficiency and severity in COVID-19 using different cut-offs for defining vitamin D deficiency. We found that these associations were noted at both 25(OH)D cut-offs (<12 and <20 ng/ml). We also conducted additional analysis on any variation in the association between vitamin D deficiency and COVID-19 infection severity among different latitudes, as the mortality from COVID-19 has been noted to be lower in countries south of latitude 35° North.[6] We also examined the relationship between vitamin D deficiency and COVID-19 severity in different geographic and cultural regions as ethnic and cultural factors likely play a role independent of latitude.

A limitation of our study is the inability to independently assess the impact of associated confounding variables, such as obesity, dark skin colour, non-White race, diabetes and advancing age, all of which are risk factors for both greater severity of COVID-19 infection and vitamin D deficiency. Most of the included studies did not adjust for any confounding variables, including weight status, race and age and therefore these results mainly represent an association and may not predict causality. Another limitation is that the age range in our study was limited as most studies included middle age and elderly patients. Children were not included in our study, as there were not enough studies assessing COVID-19 infection severity and vitamin D levels. Hence, our results may not be generalisable to the pediatric population. The cut-offs used to define vitamin-D deficiency varied among the studies due to a lack of consensus on optimal levels of 25(OH)D.[19] However, subgroup analyses suggested these associations remain regardless of the 25(OH)D concentration used for the definition for deficiency.

Therapies currently aimed at decreasing COVID-19 severity, such as monoclonal antibodies and remdesivir, may not be accessible in low-income regions and therefore further studies are warranted to determine if a low-cost intervention, such as vitamin D supplementation, can decrease COVID-19 infection severity. Multiple ongoing clinical trials are evaluating the efficacy of vitamin D supplementation early in the course of COVID-19 infection (https://clinicaltrials.gov/ct2/show/NCT04536298, https://clinicaltrials.gov/ct2/show/NCT04449718). Vitamin D deficiency may also have implications for Post-Acute Sequelae of SARS-CoV-2 infection and this would be an area of future research.

5 | CONCLUSION

Vitamin D deficiency is associated with greater COVID-19 infection severity as measured by rates of mortality, hospital admission and duration of hospital stay. Longitudinal interventional studies are warranted to determine if vitamin D supplementation can decrease COVID-19 infection severity.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. All authors have given final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. ZW, SK and AJ participated in conception and design of the study; ZW, AJ, KL, SJ, SC, AC, PT and SK were involved in data acquisition; ZW, TN and KM performed data analysis; ZW, AJ, KL, SJ. SC, TN, KM, AC, PT and SK were involved in drafting the manuscript or revising it critically for important intellectual content.

ORCID
Ana Creo http://orcid.org/0000-0002-4513-1800
Seema Kumar http://orcid.org/0000-0001-8004-4924

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.