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Association of vitamin D status with COVID-19 and its severity

Vitamin D and COVID-19: a narrative review

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Abstract
Vitamin D is associated with biological activities of the innate and adaptive immune systems, as well as inflammation. In observational studies, an inverse relationship has been found between serum 25-hydroxyvitamin D (25(OH)D) concentrations and the risk or severity of coronavirus disease 2019 (COVID-19). Several mechanisms have been proposed for the role of vitamin D in COVID-19, including modulation of immune and inflammatory responses, regulation of the renin–angiotensin–aldosterone system, and involvement in glucose metabolism and cardiovascular system. Low 25(OH)D concentrations might predispose patients with COVID-19 to severe outcomes not only via the associated hyperinflammatory syndrome but also by worsening preexisting impaired glucose metabolism and cardiovascular diseases. Some randomized controlled trials have shown that vitamin D supplementation is beneficial for reducing severe acute respiratory syndrome coronavirus 2 RNA positivity but not for reducing intensive care unit admission or all-cause mortality in patients with moderate-to-severe COVID-19. Current evidence suggests that taking a vitamin D supplement to maintain a serum concentration of 25(OH)D of at least 30 ng/mL (preferred range 40–60 ng/mL), can help reduce the risk of COVID-19 and its severe outcomes, including mortality. Although further well designed studies are warranted, it is prudent to recommend vitamin D supplements to people with vitamin D deficiency/insufficiency during the COVID-19 pandemic according to international guidelines.

Keywords Vitamin D · COVID-19 · Immunomodulation · Inflammation · Renin–angiotensin–aldosterone system

Acronyms and abbreviations

$1,25(OH)_2D$	1,25-Dihydroxyvitamin D
25(OH)D	25-Hydroxyvitamin D
ACE2	Angiotensin-converting enzyme 2
AMP	Antimicrobial peptide
ARDS	Acute respiratory distress syndrome
CD	Cluster of differentiation
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular disease
DM	Diabetes mellitus
ICU	Intensive care unit
IFN	Interferon
IL	Interleukin
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OR	Odds ratio
RAAS	Renin–angiotensin–aldosterone system

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RANKL	Receptor activator of nuclear factor-κB ligand
RCT	Randomized controlled trial
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIRS	Systemic inflammatory response syndrome
TGF-β	Transforming growth factor-β
Th1	Type 1 helper T
TLR	Toll-like receptor
TNF	Tumor necrosis factor
VDR	Vitamin D receptor
VITAL	VITamin D and OmegA-3 Trial

1 Introduction

The prevalence of vitamin D deficiency, estimated at a serum concentration < 20 ng/mL of 25-hydroxyvitamin D (25(OH)D), as defined by the Endocrine Society's Practice Guidelines on Vitamin D [1], varies according to age, region, and ethnicity [2]. However, vitamin D deficiency is relatively common [3], especially among the elderly [4, 5]. A study of 191,779 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive patients found a strong inverse relationship between SARS-CoV-2 positivity rates and serum 25(OH)D concentrations determined in the preceding 12 months (Supplementary Fig. S1) [6]. Compared with patients who had serum 25(OH)D concentrations < 20 ng/mL, those with concentrations of 30–34 ng/mL were at a lower risk of SARS-CoV-2 infection (12.5% vs. 8.1%) [6]. This relationship persisted across sexes, races/ethnicities, latitudes, and age ranges and continued its downward trend in infectivity until the serum concentration reached 55 ng/mL (5.9%; 95% confidence interval (CI) 5.5%–6.4%) [6]. Another study of 489 individuals who had 25(OH)D concentrations measured in the year before COVID-19 testing found that the relative risk of testing positive for COVID-19 was 1.77 times greater for those who were deficient in vitamin D than for those in whom it was sufficient ($P = 0.02$) [7].

There is a considerable overlap between risk factors for vitamin D deficiency and COVID-19, including older age, obesity, dark skin tone, being Black, Asian, and minority ethnic groups, or living in northerly latitudes [8–10]. These factors are significantly associated with increased morbidity and mortality in patients with COVID-19 [10–14]. A systematic review found that low serum concentrations of 25(OH)D were associated with increased mortality and severity of COVID-19 [15]. Thus, vitamin D deficiency appears to be associated with severe COVID-19 outcomes (Table 1). From a different context, several studies have investigated whether vitamin D supplementation could reduce COVID-19 susceptibility or severity. In a pilot randomized controlled trial (RCT), including 76 patients hospitalized for COVID-19, oral administration of high-dose calcifediol (25(OH)D3; 0.532 mg on the day of admission and 0.266 mg on days 3 and 7 and weekly thereafter) reduced intensive care unit (ICU) admission [16]. In another study of SARS-CoV-2 RNA-positive patients in India, 10 (63%) participants in the intervention group and 5 (21%) in the control group became SARS-CoV-2 RNA-negative after 60,000 IU of vitamin D3 (cholecalciferol) supplementation for 14 days ($P < 0.018$) [17]. These data suggest that vitamin D sufficiency might have protective effects against COVID-19.

SARS-CoV-2 infection causes cellular and tissue damage and triggers innate and adaptive immune responses [18]. Vitamin D is associated with immunological activities by regulating important components of the innate and adaptive immune systems and inflammation [19]. Thus, several mechanisms have been proposed for the role of vitamin D in COVID-19, including modulation of immune and inflammatory responses [20] and regulation of the renin–angiotensin–aldosterone system (RAAS) [21, 22]. Given these pleiotropic effects, vitamin D could have beneficial effects on the prevention and treatment of COVID-19 [23, 24]. Here, we review the current evidence suggesting a role for vitamin D and its therapeutic potential in the management of patients with COVID-19.

2 Pathophysiological relationships between vitamin D and COVID-19

Vitamin D is synthesized in the skin after exposure to ultraviolet B radiation or is obtained from food and supplements. It undergoes 25- and 1α-hydroxylation sequentially in the liver and kidney, respectively, thereby converting it to 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), its biologically active form [25]. Vitamin D and its metabolites can affect SARS-CoV-2 infection and the severity of COVID-19 in several ways (Table 2). These include their effects on the immune system, inflammation, fibrosis, RAAS, acute lung injury, glucose metabolism, and cardiovascular risk.

2.1 Role of vitamin D in the immune system

Vitamin D metabolic enzymes and the vitamin D receptor (VDR) are present in most cells involved in the innate and adaptive immune system [26]. Importantly, these immune cells produce 1,25$(OH)_2$D locally, which has an immunoregulatory action against invading pathogens [27]. In addition,

Table 1 Selected studies evaluating the role of vitamin D status or vitamin D supplementation in patients with COVID-19

Author	Study region	Study design	Study population	Sample size (women/men)	Age in years*	Vitamin D status	Results (RR, OR, or HR; 95% CI)
Observational studies							
Ilie et al. [127]	20 European countries	Ecological study	Populations with data on mean 25(OH)D concentrations and COVID-19	NA	NA	25(OH)D: 22.7 ± 4.2 ng/mL	Negative correlation between 25(OH)D concentrations and • COVID-19 cases: $r = -0.44$ ($P = 0.05$) • COVID-19 mortality: $r = -0.44$ ($P = 0.05$)
Meltzer et al. [7]	USA	Retrospective cohort study	Individuals with 25(OH)D or $1,25(OH)_2D$ concentrations	489 (366/123)	49.2 ± 18.4	Vitamin D deficiency (< 20 ng/mL): 35%	Increased risk of test (+) for COVID-19 when vitamin D likely deficient vs likely sufficient (RR, 1.77; 1.12–2.81)
Kaufman et al. [6]	USA	Retrospective cohort study	Individuals tested for COVID-19 with matching 25(OH)D results from the preceding 12 months	191,779 (130,473/61,306)	54.0 (40.4–64.7)	Mean seasonally adjusted 25(OH)D: 31.7 ± 11.7 ng/mL	Association of vitamin D concentrations with SARS-CoV-2 positivity rates • 25(OH)D < 20 ng/mL (39,190 patients): 12.5%; 12.2%–12.8% • 25(OH)D 30–34 ng/mL: 8.1%; 7.8%–8.4% • 25(OH)D ≥ 55 ng/mL: 5.9%; 5.5%–6.4%
Merzon et al. [12]	Israel	Population-based retrospective study	Individuals tested for COVID-19 with plasma 25(OH)D concentrations	7,807 (4,573/3,234)	COVID-19 test (+): 35.6 (34.5–36.7); (–): 47.4 (46.9–47.9)	25(OH)D < 20 ng/mL: 13%; 25(OH)D 20–29 ng/mL: 72%	In patients with vitamin D < 30 ng/mL, • Likelihood of COVID-19: aOR, 1.50; 1.13–1.98 • Likelihood of hospitalization for COVID-19: aOR, 1.95; 0.99–4.78
Radujkovic et al. [13]	Germany	Consecutive case series with prospectively collected data	Hospitalized patients with symptomatic COVID-19	185 (90/95)	60 (49–70)	25(OH)D: 16.6 (12.4–22.5) ng/mL	Association of low vitamin D (< 12 ng/mL) with IMV and/or death (HR, 6.12; 2.79–13.42) and death (HR, 14.73; 4.16–52.19)

Table 1 (continued)

Author	Study region	Study design	Study population	Sample size (women/men)	Age in years*	Vitamin D status	Results (RR, OR, or HR; 95% CI)
Jain et al. [56]	India	Prospective observational study	(A) Asymptomatic patients with COVID-19 or (B) COVID-19 patients requiring ICU admission	154 (69/95)	(A) 42.3 ± 6.4; (B) 51.4 ± 9.1	(A) 25(OH)D: 27.9 ± 6.2 ng/mL; (B) 25(OH)D: 14.4 ± 5.8 ng/mL	Markedly low vitamin D concentrations in patients with severe COVID-19 In patients with vitamin D deficiency • Higher levels of IL-6, ferritin, and TNF-α • Higher fatality rate (21% vs 3%)
Hastie et al. [129]	UK	Retrospective study	UK Biobank participants	NA	NA	NA	No association with 25(OH)D concentrations with severe COVID-19 or mortality
Hernandez et al. [151]	Spain	Retrospective case–control study	Patients hospitalized for COVID-19	216 (86/130); 19 were on vitamin D supplementation	Vitamin D supplementation (+): 61.0 (47.5–70.0); (–): 60.0 (59.0–75.0)	Vitamin D < 20 ng/mL: 82%	Higher prevalence of vitamin D < 20 ng/mL than population-based controls (82.2% vs 47.2%, $P < 0.01$) 25(OH)D concentrations • Inverse correlation with ferritin ($P = 0.01$) and D-dimer levels ($P = 0.03$) • No relationship with COVID-19 severity
Angelidi et al. [152]	USA	Retrospective cohort study	Patients hospitalized for COVID-19	144 (80/64)	66 (55–74)	25(OH)D: 30.4 ± 17.0 ng/mL	Association with mortality • 25(OH)D < 30 ng/mL vs ≥ 30 ng/mL: 9.2% vs 25.3%, $P = 0.02$ • Association of increased vitamin D concentrations with in-hospital mortality (OR, 0.94; 0.90–0.98) and IMV (OR, 0.96; 0.93–0.99)
Abdollahi et al. [153]	Iran	Prospective case–control study	Hospitalized patients tested (A) positive or (B) negative for COVID-19	402 (132/270)	(A) 48.0 ± 17.0; (B) 46.3 ± 13.5	(A) 25(OH)D: 24 (19–29) ng/mL; (B) 25(OH)D: 26 (21–35) ng/mL	Association of low vitamin D concentrations with COVID-19 infection ($P = 0.02$)

Table 1 (continued)

Author	Study region	Study design	Study population	Sample size (women/men)	Age in years*	Vitamin D status	Results (RR, OR, or HR; 95% CI)
Reis et al. [131]	Brazil	Prospective cohort study	Patients hospitalized for moderate-to-severe COVID-19	220 (103/117)	55.1 ± 14.6	25(OH)D < 10 ng/mL: 16 (7%); > 10 ng/mL: 204 (93%)	Hospital length of stay • 25(OH)D < 10 ng/mL vs ≥ 10 ng/mL: 9.0 days vs 7.0 days, $P = 0.057$ • No association with IMV and mortality
Experimental studies							
Castillo et al. [16]	Spain	Pilot RCT (intervention: high-dose oral calcifediol)	Patients hospitalized for COVID-19	76 (31/45)	53 ± 10	NA	Intervention vs control • Reduced requirements for ICU admission ($P < 0.001$)
Rastogi et al. [17]	India	RCT (intervention: 60,000 IU/day with therapeutic target of 25(OH)D > 50 ng/mL)	Asymptomatic or mild COVID-19 patients with 25(OH)D < 20 ng/mL	40 (20/20)	Intervention group: 50.0 (36.0–51.0); Control group: 47.5 (39.3–49.2)	25(OH)D: Intervention group 8.6 ng/mL; Control group 9.5 ng/mL*	Intervention vs control • Higher negative conversion of SARS-CoV-2 RNA (62.5% vs 20.8%; $P < 0.02$) • A significant decrease in fibrinogen levels (difference: 0.70 ng/mL, $P = 0.007$)
Annweiler et al. [154]	France	Quasi-experimental study (intervention: bolus vitamin D administration)	Frail elderly nursing-home residents with COVID-19	66 (15/51)	87.7 ± 9.0	NA	Intervention vs control • Survival rate: 82.5% vs 44.4%, $P = 0.023$ • Mortality: aHR, 0.11; 0.03–0.48, $P = 0.002$
Annweiler et al. [121]	France	Quasi-experimental study: vitamin D supplementation (A) over the preceding year or (B) after COVID-19 diagnosis	Patients hospitalized for COVID-19 in a geriatric unit	77 (38/39)	88 (85–92)	NA	Survival at day 14 • (A) vs (B): 93.1% vs 81.2%, $P = 0.33$ • (A) vs control: 93.1% vs 68.7%, $P = 0.02$ Mortality for 14 days • (A) vs control: aHR, 0.07; 0.01–0.61 • (B) vs control: aHR, 0.37; 0.06–2.21
Murai et al. [125]	Brazil	RCT (intervention: a single oral dose of 200,000 IU of vitamin D3)	Patients hospitalized for COVID-19 who were moderately to severely ill	237 (104/133)	56.2 ± 14.4	25(OH)D: 20.9 ± 9.2 ng/mL	Vitamin D3 vs placebo • Length of hospital stay: 7.0 days vs 7.0 days • In-hospital mortality: 7.6% vs 5.1%, $P = 0.43$ • ICU admission: 16.0% vs 21.2%, $P = 0.30$ • IMV: 7.6% vs 14.4%, $P = 0.09$

Table 1 (continued)

Author	Study region	Study design	Study population	Sample size (women/men)	Age in years*	Vitamin D status	Results (RR, OR, or HR; 95% CI)
Lakkireddy et al. [155]	India	RCT (intervention: 60,000 IU/day of vitamin D)	Patients hospitalized for COVID-19 and vitamin D < 30 ng/mL	87 (22/65)	45 ± 13	Intervention group 16 ± 6 ng/mL; Control group: 17 ± 6 ng/mL	Inflammatory markers (CRP, LDH, IL-6, ferritin, N/L ratio) • Significant reduction in the intervention group ($P < 0.01$) but not in the control group ($P > 0.05$) except CRP
Sánchez-Zuno et al. [122]	Mexico	RCT (intervention: 10,000 IU/day of vitamin D3)	Asymptomatic or mildly symptomatic patients with COVID-19	42 (22/20)	43 (20–74)	Vitamin D: 22.4 (12.1–45.9) ng/mL	• > 3 symptoms of COVID-19 vs control: 0% vs 4%, $P = 0.04$ • SARS-CoV-2 RNA positivity vs control: 0% vs 5%, $P = 0.47$ • SARS-CoV-2 seropositivity vs. control: 72.7% vs 75.0%, $P > 0.05$
Mendelian randomization study							
Butler-Laporte et al. [132]		Two sample Mendelian randomization study	Individuals of European ancestry	GWAS of genetic variants associated with vitamin D concentrations: 443,734 (including 401,460 from the UK Biobank); GWAS of COVID-19 susceptibility, hospitalization, and severe diseases: 1,299,010 (from the COVID-19 Host Genetic Initiative)			Genetically increased 25(OH)D concentrations by one SD (logarithmic scale) • No association with COVID-19 susceptibility: OR, 0.95; 0.84–1.08 • No association with hospitalization for COVID-19: OR, 1.09; 0.89–1.33 • No association with severe COVID-19: OR, 0.97; 0.77–1.22

*(mean ± SD or overall range), *1,25(OH)$_2$D* 1,25-hydroxyvitamin D, *25(OH)D* 25-hydroxyvitamin D, *aHR* adjusted hazard ratio, *aOR* adjusted odds ratio, *CI* confidence interval, *COVID-19* coronavirus disease 2019, *CRP* C-reactive protein, *GWAS* genome-wide association study, *HR* hazard ratio, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *IL-6* interleukin-6, *LDH* lactate dehydrogenase, *NA* not applicable, *N/L ratio* neutrophil/lymphocyte ratio, *OR* odds ratio, *RCT* randomized controlled trial, *RR* relative risk, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SD* standard deviation, *TNF-α* tumor necrosis factor-α

Table 2 Potential effects of vitamin D on the risks and prognosis for patients with COVID-19

Categories	Possible effects	Mechanisms
Immune system	Modulating the risk of infection, attenuating excessive immune response	*Innate immunity* • Monocytes and macrophages: ↑proliferation [28], ↑antimicrobial peptides production (cathelicidins, defensins) [156], ↑autophagy [29] • Dendritic cells: ↓maturation [45], ↓MHC class II [45], ↓co-stimulatory molecules (CD40, CD80, CD86) [45], ↑inhibitory molecules (PD-L1)[157] *Adaptive immunity* • T cells: ↓proliferation [158], ↓Th1 (IFN-γ) [159] and Th17 (IL-17) [160] responses, ↑Th2 (IL-4, IL-5) [161] and Treg (IL-10) [157] responses • B cells: ↓proliferation [162], ↓differentiation into plasma cell [162], ↓Ig production (IgG, IgM) [163]
Inflammation	Anti-inflammation	↓TLR signaling [164], ↓NF-κB [165], ↓prostaglandins [166], ↑MAPK phosphatases [59], ↓proinflammatory cytokines (IL-6, TNF-α) [167], ↑inhibitory cytokines (IL-10, TGF-β) [157]
Fibrosis	Antifibrotic effect	↓Epithelial–mesenchymal transition [168], ↓fibroblast differentiation [169], ↑profibrotic factors (TGF-β, SERPINE1) [170], ↑antifibrotic factors (BMP-7, MMP-8, follistatin) [170], ↓collagen expression [170], ↓MCP-1 [171]
RAAS	Alleviating lung injury, improving outcome of preexisting CVD or reducing incident CVD	Classic pathway (ACE2/angiotensin-(1–7)/Mas receptor): ↑ACE2[21] Counter-regulatory pathway (angiotensin II/AT1R): ↓renin expression [21], ↓ACE [21], ↓angiotensin II expression [21]
ARDS	Reducing the risk of ARDS, promoting the recovery from lung injury	Epithelial barrier integrity: ↓extravascular lung water index [172], ↓pulmonary vascular permeability index [172] Epithelial injury: ↓RAGE (bronchoalveolar lavage fluid) [172], ↓protein permeability index [172] Inflammation: ↓TNF-α [172], ↓VEGF [172], ↓CXCL1 [172] Apoptosis: ↓soluble Fas ligand-mediated cell death [172] ↑Scratch wound healing [172]
Glucose metabolism	Improving outcomes of COVID-19 associated with hyperglycemia	T1DM: ↓insulitis [173], ↑β-cell survival [173], ↓disease onset [173], ↓disease progression [174] T2DM: ↑β-cell function [175], ↓islet inflammation [175], ↓islet RAAS components [176], ↓hyperglycemia [175], ↓disease progression [175]
CVD	Improving the prognosis of COVID-19	RAAS inhibition [65], ↓cardiac hypertrophy [177], ↑myocardial contractility [177], ↑endothelial function [177], ↓mortality [178]

ACE angiotensin-converting enzyme, *ACE2* angiotensin-converting enzyme 2, *AT1R* angiotensin II type 1 receptor, *ARDS* acute respiratory distress syndrome, *BMP-7* bone morphogenic protein-7, *CD* cluster of differentiation, *COVID-19* coronavirus disease 2019, *CVD* cardiovascular disease, *CXCL1* chemokine ligand 1, *IFN* interferon, *Ig* immunoglobulin, *IL* interleukin, *MAPK* mitogen-activated protein kinase, *MCP-1* monocyte chemoattractant protein-1, *MHC* major histocompatibility complex, *MMP-8* matrix metalloproteinase-8, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *PD-L1* programmed death ligand-1, *RAAS* renin–angiotensin–aldosterone system, *RAGE* receptor for advanced glycation end products, *T1DM and T2DM* type 1 and type 2 diabetes mellitus, *Th* T helper cell, *TLR* toll-like receptor, *Treg* regulatory T cell, *TGF-β* transforming growth factor-β, *TNF-α* tumor necrosis factor-α, *VEGF* vascular endothelial growth factor

25(OH)D is metabolized to $1,25(OH)_2D$ in innate and adaptive immune cells [28]. This locally produced $1,25(OH)_2D$ acts on the immune cells in autocrine and paracrine manners, exerting immunomodulatory effects [28, 29].

The VDR is a regulator of innate and adaptive immunity [29]. A meta-analysis of case-controlled studies showed that *VDR* gene polymorphisms were associated with susceptibility to enveloped virus infection, such as Respiratory Syncytial Virus [30]. VDR can also act as a checkpoint regulating inflammatory responses after tissue injury [31]. VDR agonists silence transforming growth factor β (TGF-β) signaling [32], potentially

inhibiting proinflammatory and profibrotic changes [31]. Certain toll-like receptor (TLR) signals induce the expression of VDR [28]. However, a recent study found that the expression of VDR was lower in patients with COVID-19 than in controls [33], which requires further investigation.

2.1.1 Innate immunity

Innate immune cells can prevent infections by producing antimicrobial peptides (AMPs) such as cathelicidins and defensins [34]. AMPs are an important component of innate immunity and are induced upon recognition of pathogen-associated molecular patterns [35]. A consensus sequence for the vitamin D response element was identified in the promoter regions of human genes for cathelicidin antimicrobial peptide (*CAMP*) and β-defensin-2 (*DEFB4*), and its expression was strongly upregulated by $1,25(OH)_2D$ [36, 37]. $1,25(OH)_2D$ induced autophagy in monocytes and macrophages via cathelicidin *in vitro*, with antimycobacterial effects [38]. A preliminary study found that oral administration of human cathelicidin, LL-37, ameliorated systemic symptoms in 11 patients with mild COVID-19 [39]. These findings suggest that improvement in vitamin D status, by providing more substrate (i.e., 25(OH)D) to immune cells capable of converting it to $1,25(OH)_2D$, might be a crucial constituent of the early host defense against SARS-CoV-2 infection through the production of AMPs.

2.1.2 Adaptive immunity

The adaptive immune system in which vitamin D is involved can act as a 'double-edged sword' in patients with COVID-19 [40]. An appropriate immune response to SARS-CoV-2 infection is necessary for viral clearance and mitigates adverse outcomes in patients with COVID-19. However, overproduction of proinflammatory cytokines can contribute to an uncontrolled excessive immune response, known as a cytokine storm [41]. This dysfunctional immune response has detrimental consequences, such as systemic inflammatory response syndrome (SIRS) and multiorgan failure [18].

Vitamin D and its metabolites are associated with both T and B cell immunity. In general, T cell responses play a pivotal role in combatting viral infections. Dysregulated T cell responses can lead to a pathological response to such infections [42]. Emerging evidence suggests that patients with severe COVID-19 are characterized by the functional exhaustion of T cells [43] and that improvements in vitamin D status can alleviate this process through immunomodulation [29]. $1,25(OH)_2D$ impairs the maturation of dendritic cells in a paracrine manner and renders them tolerogenic [44]. Because tolerogenic dendritic cells feature phenotypes resembling immature dendritic cells, $1,25(OH)_2D$ reduces the differentiation of naïve T cells into cytotoxic effector T cells [29, 45]. In addition, $1,25(OH)_2D$ directly suppresses T cell activation by reducing the type 1 helper T cell (Th1) and type 17 helper T cell responses [46]. This is mediated by the binding of $1,25(OH)_2D$ to the VDR and subsequent translocation to the nucleus of T cells, which upregulates the expression of the gene for *cytotoxic T-lymphocyte antigen 4* (*CTLA4*), *cluster of differentiation 38* (*CD38*), and *interleukin-10* (*IL-10*) [47]. As $CD4^+$ T cells are Th1-skewed in the bronchoalveolar lavage fluid of SARS-CoV-2-infected patients, $1,25(OH)_2D$ might alleviate uncontrolled excessive immune responses by promoting a transition from proinflammatory interferon-γ (IFN-γ)-positive Th1 cells to inhibitory IL-10^+ Th1 cells [47]. Although T cell dynamics in COVID-19 need further investigation, the evidence suggests that improving vitamin D status can be beneficial in reducing dysregulated T cell responses.

Vitamin D is also associated with B cell immunity. VDR is expressed in B cells and $1,25(OH)_2D$ directly reduces the proliferation of these cells and promotes the secretion of IL-10, which in turn suppresses the activation of Th1 and subsequently reduces inflammation [29]. These properties of locally produced $1,25(OH)_2D$ might alter B cell responses in patients with COVID-19. Of note, B cells are also involved in immunological memory and viral clearance. More studies are needed to elucidate the additional role of improved vitamin D status on B cell function and immunity. On the other hand, alterations in adaptive immunity and vitamin D status can affect the prognosis of COVID-19 by affecting bone metabolism. Under inflammatory conditions, the release of cytokines, such as tumor necrosis factor (TNF), IL-6, and IL-1, can upregulate osteoclastogenesis and inhibit osteoblast activities [48]. Among these cytokines, TNF is a key factor in bone loss and might synergize with the receptor activator of nuclear factor kappa-B ligand (RANKL) to induce osteoclastic bone resorption [49]. Activated T and B cells serve as major sources of RANKL and TNF in inflammatory states [49]. In murine macrophage cells, 3a/X1, an accessory protein of SARS-CoV, promoted osteoclastogenesis by upregulating TNF-α [50]. From a different point of view, SARS-CoV-2 infection might be harmful to bone metabolism. The use of corticosteroids for the treatment of patients with COVID-19 is likely to have detrimental effects on bone health [51]. Increased numbers of vertebral fractures caused by vitamin D deficiency in such patients exacerbate the clinical outcomes [52]. In this regard, the role of vitamin D should be also evaluated from osteo-metabolic perspectives in patients with COVID-19.

2.2 Association of vitamin D with inflammation

SARS-CoV-2 infection elicits local and systemic inflammatory responses in humans [53]. Hyperinflammation,

accompanied by an excessive immune response, induces pyroptosis, tissue damage, and SIRS in patients with COVID-19 [18]. When SARS-CoV-2 infects the lungs, it causes alveolar epithelial cell death, endothelial disruption, increased lung permeability, and alveolar edema, and can lead to acute respiratory distress syndrome (ARDS) and multiorgan failure [54]. After SARS-CoV-2 infection, recognition of the virus by pattern-recognition receptors, such as TLRs, induces the production of proinflammatory cytokines such as IL-6, IL-12, IFN-γ, and TNF-α [53, 55]. Of these, elevations of IL-6 and TNF-α levels have been associated with hyperinflammatory status, procoagulant profiles, and worse disease severity in patients with COVID-19 [42].

An association of vitamin D deficiency with inflammation in patients with COVID-19 has been reported. In a prospective study of 154 COVID-19 patients, serum 25(OH)D concentrations were significantly lower in patients requiring ICU admission than in asymptomatic patients [56]. Inflammatory responses, along with IL-6, TNF-α, and ferritin levels, were increased in COVID-19 patients with serum 25(OH)D < 20 ng/mL [56]. Large-scale data analysis shows a possible link between vitamin D deficiency and high fatality rates with COVID-19 across countries, thereby suggesting the role of vitamin D in preventing hyperinflammation [57].

Vitamin D has been reported to have anti-inflammatory effects. In a systematic review of human-derived immune cell studies, vitamin D3, including $1,25(OH)_2D3$ used in most of the studies as well as 25(OH)D3, reduced the levels of inflammatory cytokines and reactive oxygen species (ROS) [58]. *In vitro* studies showed that when the monocyte and macrophages were preincubated with ≥ 30 ng/mL of 25(OH)D3, a significant inhibition of lipopolysaccharide (LPS)-induced IL-6 mRNA expression was observed ($P < 0.01$), whereas there was no such inhibition when the cells were cultured with 15 ng/mL of 25(OH)D3. The active form of vitamin D, $1,25(OH)_2D3$, also significantly inhibited LPS-induced IL-6 mRNA expression [59]. The degree of suppression of IL-6 mRNA expression by 30 ng/mL of 25(OH)D3 was similar to that achieved with 0.04 ng/mL of $1,25(OH)_2D3$ [59]. Similar effects of $1,25(OH)_2D3$ were also observed in LPS-induced TNF-α mRNA expression [59]. Therefore, these data support observations that when a patient with COVID-19 is vitamin D sufficient, the morbidity and mortality rates are lower, probably from the downregulated production of proinflammatory cytokines, while increasing the production of inhibitory cytokines in monocytes and macrophages [59]. Genome- and transcriptome-wide studies showed that $1,25(OH)_2D3$ exerted anti-inflammatory effects by modulation of prostaglandin, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and mitogen-activated protein kinase (MAPK) phosphatase 5 signaling pathways [60]. $1,25(OH)_2D3$ might reduce inflammation by promoting nitric oxide production, inhibiting ROS generation, and preventing endothelial cell dysfunction [61].

Dexamethasone is an anti-inflammatory agent that has demonstrated improved outcomes regarding mortality in patients with COVID-19 receiving respiratory support [62]. A structure–activity relationship of dexamethasone with SARS-CoV-2 spike protein has been unraveled recently; the binding of dexamethasone to the fatty acid binding site in the SARS-CoV-2 stabilizes the locked spike conformation, interfering with the angiotensin-converting enzyme 2 (ACE2) receptor binding [63]. As vitamin D and dexamethasone are structurally similar and share the same fatty acid binding site [63], vitamin D could be a potential adjuvant treatment for reducing inflammation, although careful assessment of who might benefit from this therapy is warranted.

2.3 Vitamin D and the RAAS

Dysregulation of the RAAS predisposes patients to severe COVID-19 after SARS-CoV2 infection [64]. Low circulating concentrations of 25(OH)D cause inappropriate activation of this system [65, 66]. This is linked to deterioration in the cardiovascular system, which is the main mechanism for mortality in patients with COVID-19 [67].

SARS-CoV-2 enters the human body by binding to ACE2, which serves as the host cell receptor. Upregulation of the angiotensin II/angiotensin type 1 receptor axis and downregulation of the angiotensin-(1–7)/Mas receptor or the ACE2 receptor axis can induce inflammation, oxidative stress, apoptosis, high blood pressure, vascular dysfunction, and cardiovascular remodeling in these patients [64, 68]. In a prospective cohort study conducted in Germany, low serum concentrations of both 25(OH)D and $1,25(OH)_2D$ were found to be independently associated with increased RAAS activity in individuals who were referred for coronary angiography [69]. In mice, chronic vitamin D deficiency induced lung fibrosis through activation of the RAAS [70]. By contrast, administration of calcitriol ($1,25(OH)_2D3$), the active metabolite of vitamin D, alleviated LPS-induced acute lung injury by regulating the RAAS in rats [21]. This also increased the expression of ACE2 [21]. Initially, there were concerns on whether increased expression of ACE2 might increase the risk of SARS-CoV-2 infection. However, studies now claim that expression of ACE2 upregulates the angiotensin-(1–7)/Mas receptor axis, which alleviates acute lung injury and ARDS during COVID-19. These findings suggest that improvement in the circulating concentrations of 25(OH)D and locally produced $1,25(OH)_2D$ might have different effects depending on the stage of COVID-19, although the overall effects are considered beneficial [71]. Further studies are required to clarify the role of vitamin D in the RAAS among patients with COVID-19.

2.4 Relationship between vitamin D and glucose homoeostasis

Increased severity of COVID-19 in patients with diabetes mellitus (DM) has been reported [72]. Interacting with other risk factors, hyperglycemia might modulate immune and inflammatory responses, thus predisposing patients to severe COVID-19 and possible lethal outcomes [68]. Vitamin D insufficiency, defined as a 25(OH)D concentration of 20–29 ng/mL, is associated with impaired glucose homoeostasis, an established risk factor for COVID-19 [73]. Several studies have reported that optimal vitamin D homoeostasis is essential for pancreatic β-cell function and insulin sensitivity [74–76]. $1,25(OH)_2D3$ and calcium regulate the transcription of calcium transporter genes [77]. *VDR* gene suppression results in a decrease of intracellular Ca^{2+} concentrations [78]. Thus, vitamin D deficiency/insufficiency is likely to contribute to impaired glycemic control by disturbing calcium balance [79]. In some mouse models, vitamin D deficiency inhibits insulin secretion, resulting in hyperglycemia [80, 81]. Clearly, ancillary analysis from The VITamin D and OmegA-3 TriaL (VITAL) [82] and future clinical trials of higher-dose vitamin D supplementation are warranted to clarify any beneficial effects of vitamin D on the primary prevention of type 2 DM.

Vitamin D plays a role in controlling both gene transcription and cell signaling pathways and alleviates the onset of insulin resistance, especially in adipose tissue [83]. Of note, pulmonary lipofibroblasts, such as adipocytes and adipocyte-like cells, might play an important role in the pathogenic response to SARS-CoV-2 infection [84]. Expression of ACE2 is upregulated in the adipocytes of patients with DM, which renders adipose tissue a potential viral reservoir [68]. This may explain why patients with DM are at a high risk of contracting COVID-19 [68]. Furthermore, pulmonary lipofibroblasts located in the lung interstitium can transdifferentiate into myofibroblasts that play an integral part of pulmonary fibrosis [84]. An *in vitro* study reported that low concentrations of vitamin D was linked to adipocyte differentiation by the MAPK signaling pathway [85]. Vitamin D acts to inhibit apoptosis of adipocytes by reducing expression of the mitochondrial uncoupling protein 2 [86]. Mitochondrial dysfunction caused by vitamin D deficiency is particularly critical in debilitated conditions because it decreases adenosine triphosphate formation and increases ROS generation [87], which might be crucial for COVID-19. In addition, vitamin D regulates the expression of adiponectin, which has insulin-sensitizing and anti-inflammatory actions [88]. Taken together, alterations in cellular and systemic systems caused by vitamin D deficiency might impair mitochondrial function, contributing to the progression and severity of COVID-19 [89].

Uncontrolled glycemic status at admission and during a hospital stay are associated with worse clinical outcomes in patients with COVID-19 [90–92]. In turn, COVID-19 predisposes infected individuals to hyperglycemia [93]. Improving glycemic control in patients presenting with hyperglycemia with the assistance of vitamin D supplementation might help in reducing the risk of life-threatening metabolic complications.

2.5 Vitamin D and cardiovascular and thromboembolic risks

Vitamin D insufficiency is associated with increased cardiovascular disease (CVD) and thromboembolic risks [94, 95]. Animal and human studies suggest that serum 25(OH)D concentrations are inversely correlated with the prevalence of hypertension [96, 97]. High serum concentrations of 25(OH)D are considered to suppress renin formation in juxtaglomerular cells [98]. We found that participants with low 25(OH)D concentrations had a higher risk of significant coronary artery stenosis (odds ratio (OR) 2.1 for 25(OH)D concentrations of 15–29.9 ng/mL and 3.1 for < 15 ng/mL vs. at least 30 ng/mL, respectively; both $P < 0.05$) [95]. Of note, patients with DM and low vitamin D concentrations, as defined by a 25(OH)D concentration of ≤ 20 ng/mL, showed a worse outcome after myocardial infarction [99]. One study found that both total 25(OH)D and its metabolites were associated with cardiovascular risk factors in patients with type 2 DM [94]. However, in the VITAL study, vitamin D supplementation did not result in a lower incidence of adverse cardiovascular events than did placebo [100]. However, it should be noted that only 12.7% of the participants in the VITAL study were vitamin D deficient at baseline [101].

Of note, vitamin D deficiency/insufficiency is associated with an increased risk of stroke. The neuroprotective mechanisms by which vitamin D operates to mitigate stroke onset and outcomes have yet to be fully elucidated. However, several pathways, including the production of certain neuroprotective growth factors, reduction of arterial pressure through vasodilation, and inhibition of ROS, can be involved [102].

Thrombotic complications are a common and major cause of death among patients with COVID-19 [103]. Intriguingly, vitamin D is also involved in the regulation of thrombotic pathways, and vitamin D insufficiency/deficiency is associated with an increase in thrombotic episodes [104]. Clearly, the protective effect of vitamin D supplementation on thrombosis should be investigated.

2.6 Association between vitamin D and respiratory infection

In a study using the US National Health and Nutritional Examination Survey data, serum 25(OH)D concentrations

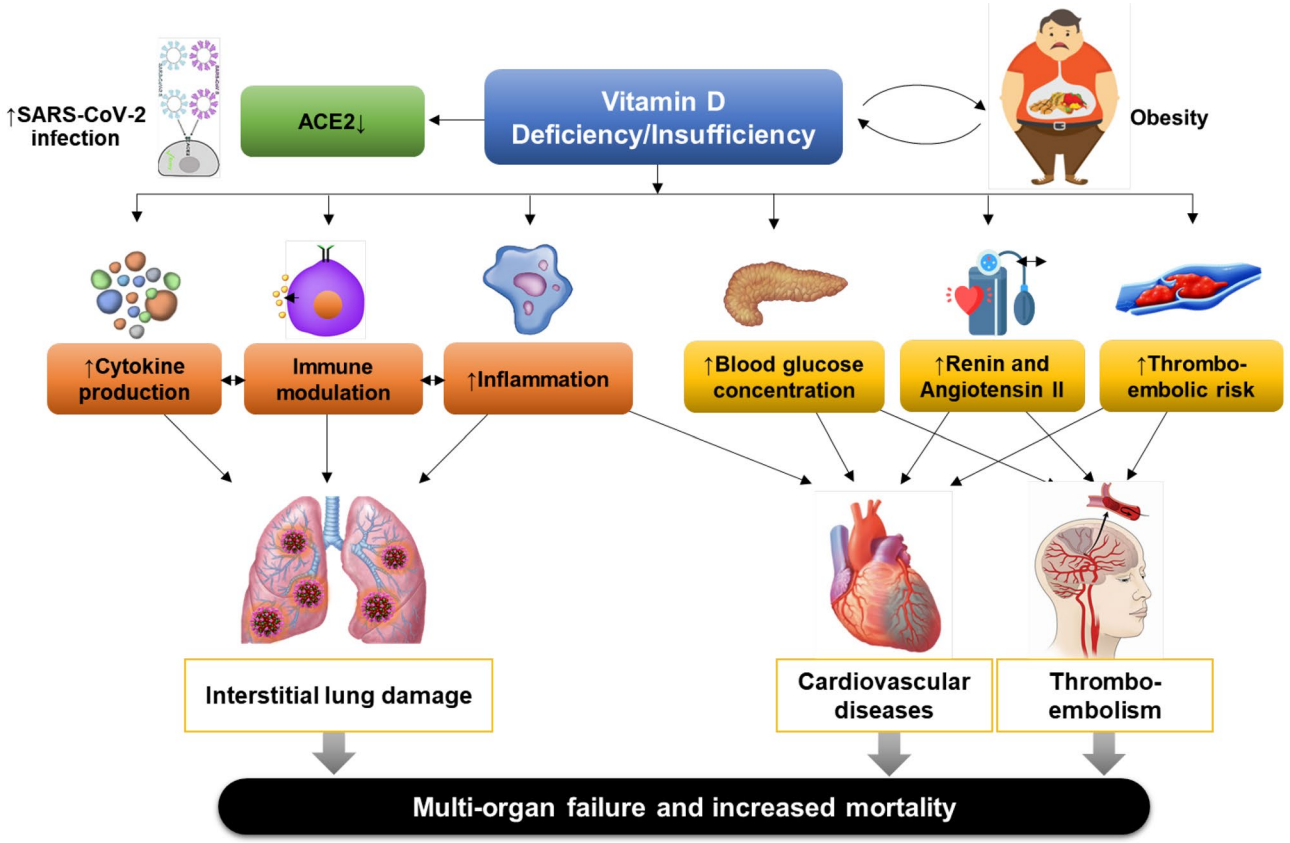

Fig. 1 Proposed pathogenic mechanisms leading to severe COVID-19 outcomes in individuals with vitamin D deficiency or insufficiency. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. References for evidence: cytokine production [41]; immune modulation [18, 29]; inflammation [53]; blood glucose concentration [149]; renin and angiotensin II levels [64]; and thrombo-embolic risk [104]

were inversely associated with recent respiratory tract infection [105]. This association seemed to be stronger in individuals with asthma and chronic obstructive pulmonary disease [105]. In a prospective cohort study, maintenance of serum 25(OH)D concentrations ≥ 38 ng/mL significantly reduced the incidence of acute viral respiratory tract infection in healthy individuals [106]. It has also been proposed that vitamin D deficiency might contribute to the development of seasonal influenza [107]. Proposed pathogenic mechanisms triggered by SARS-CoV-2 infection, leading to severe morbidity and mortality, in individuals with vitamin D deficiency/insufficiency are shown in Fig. 1.

2.7 Efficacy of vitamin D supplementation against respiratory infection

Vitamin D supplementation might play a beneficial role in combatting respiratory infections. In school children, vitamin D supplementation during the winter showed a 42% reduction in the incidence of influenza A, with a decrease in acute exacerbations of asthma, compared with placebo [108]. A meta-analysis of RCTs with individual participant data found that vitamin D supplementation reduced the risk of acute respiratory tract infection compared with placebo (adjusted OR 0.88; 95% CI 0.81–0.96) [109]. These protective effects were greater in those with vitamin D concentrations < 25 nmol/L (10 ng/mL; adjusted OR 0.30; 95% CI 0.17–0.53) than in those with ≥ 25 nmol/L (adjusted OR 0.75; 95% CI 0.80–1.20). A recent update of this meta-analysis, including 46 RCTs (75,541 participants), also showed protective effects of vitamin D administration with daily doses of 400–1000 IU for up to 12 months on acute respiratory infections [110]. In patients with active pulmonary tuberculosis, vitamin D supplementation increased the culture conversion rates and improved radiographic findings [111]. In another meta-analysis using individual participant data, vitamin D supplementation protected against acute respiratory infections, particularly in vitamin D deficient individuals and those not receiving bolus doses [112]. In a meta-analysis of nine trials involving 435 children and 658 adults, administration of vitamin

D reduced both the risk of severe asthma exacerbation and healthcare use [113]. However, several RCTs have reported conflicting results. In healthy individuals, administration of vitamin D (100,000 IU monthly) did not reduce the incidence or severity of upper respiratory tract infection [114]. High-dose supplementation with vitamin D did not prevent acute respiratory infections in older adults [115] or pneumonia in infants [116]. In 2021, the US Preventive Services Task Force reported that among community-dwelling populations with low vitamin D concentrations, treatment with vitamin D has no effect on mortality or the incidence of fractures, falls, depression, DM, CVD, cancer, or adverse events [117]. Overall, most but not all data support a role for vitamin D supplementation to prevent acute respiratory tract infections, especially in individuals with serum 25(OH)D concentrations < 10 ng/mL [110].

3 Effects of vitamin D supplementation on SARS-CoV-2 infection

The effects of vitamin D supplementation on acute respiratory tract infections, chronic lung disease, DM, and CVD are listed in Supplementary Table S1. Vitamin D deficiency is highly prevalent in patients hospitalized for COVID-19 [118]. Therefore, it is rational to anticipate the beneficial role of vitamin D supplementation in preventing this disease, reducing symptoms, or improving prognosis. Currently, more than 50 interventional studies are registered at ClinicalTrial.gov to investigate the effect of vitamin D on COVID-19. Among them, a few have found promising results (Table 1). In a pilot RCT, including 76 patients hospitalized for COVID-19, oral administration of high-dose calcifediol reduced ICU admissions. Concerns about the benefits of calcifediol administration have been raised because of imperfect blinding and uneven distribution of confounders [119]. An RCT of the oral administration of vitamin D3 (cholecalciferol; 60,000 IU daily), with a therapeutic target of serum 25(OH)D > 50 ng/mL, found that it significantly induced negative conversions of SARS-CoV-2-RNA and caused a decrease in fibrinogen [17]. Two quasi-experimental studies showed that vitamin D supplementation during or in the preceding month of SARS-CoV-2 infections was associated with less severe outcomes, including mortality, in frail elderly patients with COVID-19 [120, 121]. An RCT that gave vitamin D supplements to asymptomatic or mildly symptomatic patients with COVID-19 demonstrated amelioration of associated symptoms at day 14, although it did not significantly reduce the time for the negative conversion of the SARS-CoV-2 RNA virus [122]. In another RCT, a single high dose of vitamin D (200,000 IU) did not reduce hospital length of stay, mortality, ICU admission rates, or the need for mechanical ventilation in patients hospitalized for moderate-to-severe COVID-19 [123]. A recent meta-analysis found that 25(OH)D concentrations were weakly associated with COVID-19 severity when the threshold of 25(OH)D was set to 20 ng/mL [124]. In that study, thorough sensitivity analysis revealed a connection between a 25(OH)D concentration of < 30 ng/mL and increased mortality from COVID-19 [124].

Of note, we have conducted a meta-analysis with RCT data and found a positive impact of vitamin D supplementation on SARS-CoV-2 RNA positivity in asymptomatic or mildly symptomatic patients with COVID-19 [17, 122], but not in all-cause mortality or ICU admission in patients with moderate-to-severe COVID-19 [16, 125] (Fig. 2). The potential effects of optimum levels of vitamin D on critical pathways involved in the progress of COVID-19 are shown in Fig. 3.

4 Caveats in the interpretation of data on vitamin D and COVID-19

The role of vitamin D in the prevention and treatment of COVID-19 remains controversial. Several points should be considered to clarify this issue. Associations between vitamin D deficiency and the risk of SARS-CoV-2 infection or severe COVID-19 have been found in epidemiological studies [7, 56, 126–128], but several reports showed inconsistent results (Table 1). A retrospective study from the UK Biobank showed that both circulating 25(OH)D concentrations and vitamin D deficiency were not associated with the risk of COVID-19 [129]. In a retrospective case–control study, although 82.2% of hospitalized patients with COVID-19 had vitamin D deficiency, no relationship was found between serum 25(OH)D concentrations or vitamin D deficiency and severe outcomes [130]. A multicenter prospective cohort study showed that vitamin D deficient (25(OH)D < 10 mg/mL) patients hospitalized for moderate-to-severe COVID-19 tended to have a longer hospital stay compared with patients with higher 25(OH)D concentrations, with no significant association with invasive mechanical ventilation or mortality rates [131]. However, most of these studies used historic 25(OH)D measurements or did not evaluate vitamin D status at the time of SARS-CoV-2 infection. Moreover, unmeasured or residual confounders might influence vitamin D deficiency, as independent risk factors for COVID-19.

One RCT showed that oral administration of a single high dose of vitamin D after diagnosis of COVID-19 did not reduce the hospital length of stay or improve clinical outcomes in hospitalized patients with moderate-to-severe COVID-19 [123]. This observation is not unexpected because the virus takes hold and initiates its damaging

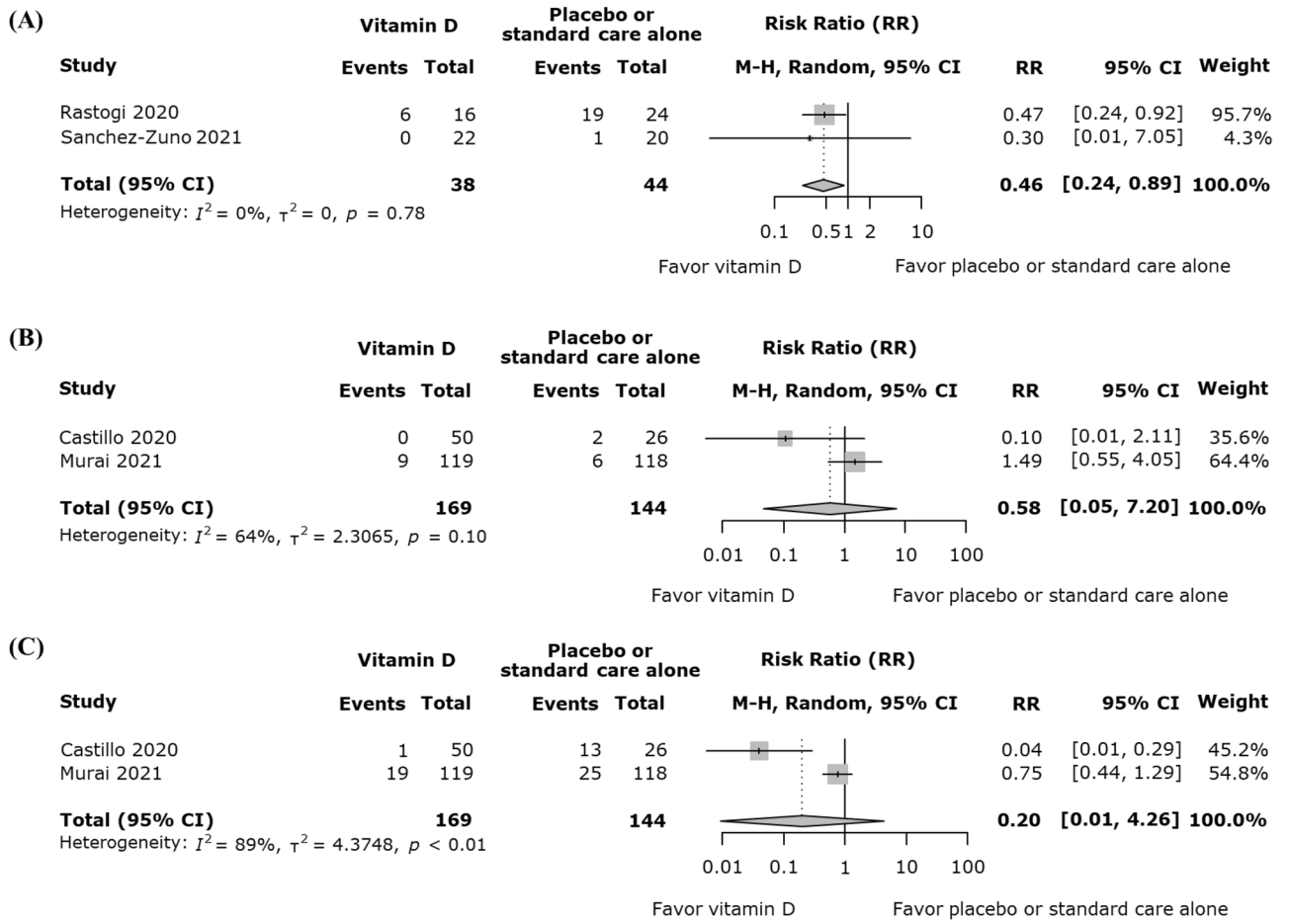

Fig. 2 The effects of vitamin D supplementation on (**A**) SARS-CoV-2 RNA positivity in asymptomatic or mildly symptomatic patients with COVID-19 [17, 122] and (**B**) all-cause mortality [16, 125] or (**C**) ICU admission [16, 125] in moderate-to-severe COVID-19 patients. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CI, confidence interval; ICU, intensive care unit; M-H, Mantel–Haenszel method

consequences on the respiratory epithelium and an exaggerated immune response, leading to a cytokine storm [123]. A recent Mendelian randomization study also failed to show the protective role of vitamin D supplementation in terms of COVID-19 susceptibility [132]. Thus, the evidence is very limited on the role of vitamin D treatment and how it can be involved in preventing or mitigating the development of COVID-19 and its clinical outcomes.

Studies linking vitamin D status with the degree of SARS-CoV-2 infectivity have suggested a significant inverse relationship between them, along with the modulation of the immune system. Although there are some reports that do not advocate vitamin D supplementation over placebo [100, 133–135], it would be prudent to correct vitamin D deficiency/insufficiency not only in patients with COVID-19 but in all individuals to reduce the risk for many acute and chronic illnesses.

Despite possible synergistic effects on immunomodulation and anti-inflammation [136, 137], the relationship between vitamin D and COVID-19 therapies, such as remdesivir, monoclonal antibodies (casirivimab/imdevimab, sotrovimab, and bamlanivimab/etesevimab), and immune modulators (baricitinib and tocilizumab), has not yet been evaluated (see https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 24 November 2021). Medications, such as dexamethasone, can complicate the effects of vitamin D supplementation in patients with COVID-19 [138]. Whether improving vitamin D status in symptomatic and asymptomatic patients with COVID-19 reduces the risk for long-term sequelae from COVID-19 (long COVID or post-acute COVID syndrome) also remains unknown.

COVID-19 vaccination programs have been initiated widely [139]. Interestingly, vitamin D supplementation promoted TGF-β levels in response to influenza vaccination in elderly individuals with vitamin D deficiency [140]. These effects were accompanied by changes in the degree of lymphocyte polarization towards a tolerogenic immune

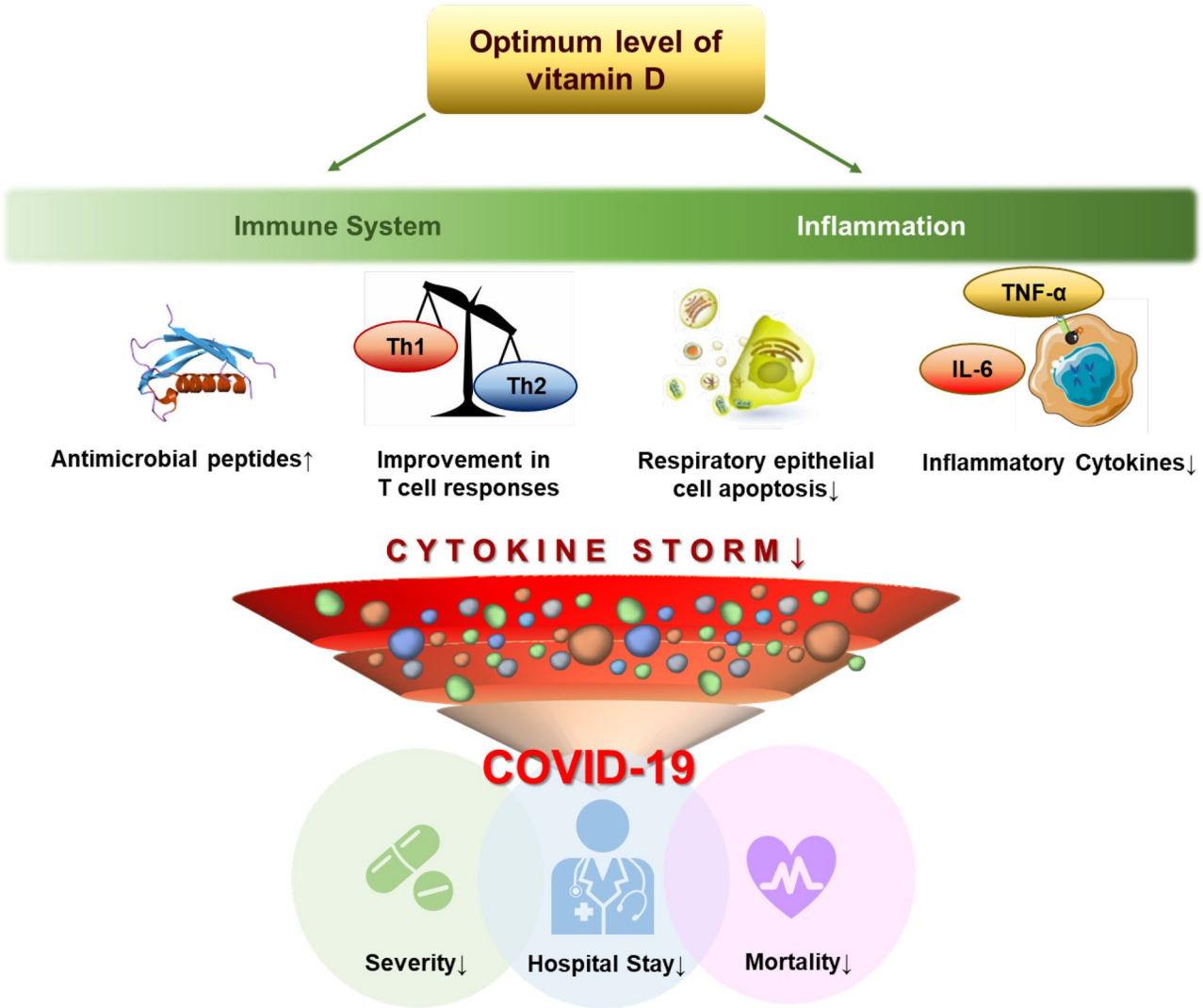

Fig. 3 Potential effects of optimum levels of vitamin D on critical pathways involved in the progress of COVID-19. COVID-19, coronavirus disease 2019; IL-6, interleukin-6; Th1, type 1 helper T cell; Th2, type 2 helper T cell; TNF-α, tumor necrosis factor-α. References for evidence: antimicrobial peptides [36]; T cell responses [43]; apoptosis of infected respiratory epithelial cells [150]; and inflammatory cytokines [58]

response [140]. Improvement in vitamin D status might also enhance immunity associated with vaccination [29]. Thus, vitamin D status might affect the immune response to vaccines against COVID-19. Further studies regarding vitamin D status and vaccination efficacy are warranted.

5 Practical considerations in vitamin D supplementation against COVID-19

To date, there are no consensus guidelines suggesting an adequate concentration of serum 25(OH)D in preventing COVID-19 or in reducing its morbidity and mortality. However, based on the available data, it is prudent to aim at vitamin D sufficiency with a serum concentration of 25(OH)D of at least 30 ng/mL with a preferred range of 40–60 ng/mL as recommended by the Endocrine Society's Practice Guidelines on Vitamin D [1].

In modern societies, it is difficult to obtain an adequate amount of vitamin D from sun exposure daily. It has been reported that a normal weight adult in a bathing suit exposed to one minimal erythema dose (which is defined as the amount of sunlight that causes a slight pinkness to skin in 24 hours) produces an amount of vitamin D that is equivalent to ingesting between 10,000 and 20,000 IU [141]. Time of day, season, latitude, weather conditions, altitude, and skin pigmentation all influence the effectiveness of the sun in producing vitamin D in the skin.

Similarly, proper sunscreen with a sun protection factor of 30 reduces the efficiency of sun exposure to produce vitamin D in the skin by more than 97% [141]. The preventive measures against the COVID-19 outbreak implemented in many countries include recommending social distancing, telecommuting, remote class activities, and closure of exercise facilities. These measures are likely to contribute to vitamin D deficiency/insufficiency in the general public.

To prevent vitamin D deficiency, we propose following the Endocrine Society's Practice Guidelines on Vitamin D [1]. To treat vitamin D deficiency, 50,000 IU of weekly vitamin D (equivalent to ~ 6,600 IU daily) for 8 weeks was shown to be effective in raising serum 25(OH)D concentrations above 30 ng/mL without any untoward toxicity [142]. In the Short Term, High-Dose Vitamin D Supplementation for COVID-19 (SHADE) study, an RCT in which 60,000 IU of oral vitamin D3 was provided in the intervention arm, 75% of the patients with COVID-19 achieved a 25(OH)D concentration of > 50 ng/mL by day 14 [17]. In that study, fibrinogen levels in patients who attained this status were significantly lower than in those with vitamin D deficiency, implying that adequate serum 25(OH)D concentrations might exert antithrombotic effects.

To maintain vitamin D sufficiency, the Endocrine Society recommends 400–1,000, 600–1,000, and 1,500–2,000 IU of vitamin D2 or vitamin D3 daily for infants aged up to 1 year, children, and adults aged ≥ 18 years, respectively [1]. For those patients hospitalized with moderate COVID-19, rapid augmentation with 25(OH)D is imperative when the patient is found to be vitamin D deficient or insufficient. This can be achieved by giving pharmacological doses of vitamin D in the range of 50,000–100,000 IU on admission. It has been demonstrated that 50,000 IU of vitamin D given once every 2 weeks (equivalent to approximately 3,300 IU daily) is effective for up to 6 years in maintaining circulating concentrations of 25(OH)D in the preferred range of 40–60 ng/mL [1]. However, obese adults need 2–3 times more vitamin D to satisfy their requirement because of the dilutional effect of the fat-soluble vitamin D in the large body fat reservoir. Under such circumstances, we advocate a loading dose of 10,000 IU, followed by a maintenance dosage of 3,200–4,000 IU daily as used in an ongoing trial of Vitamin D for COVID-19 (VIVID) [143].

Oral vitamin D supplementation is generally preferred to intramuscular injection. Intravenous administration of vitamin D is usually not recommended because of variable bioavailability. However, parenteral administration of vitamin D might be necessary for severely affected patients admitted to an ICU. Considering the minimal harm and potential benefits of vitamin D supplementation, an oral dosage of 50,000 IU daily or an intramuscular dosage of 100,000–200,000 IU daily could prove advantageous. This recommendation of the oral dosage is based on a prospective study that demonstrated that administration of 50,000 IU of vitamin D for 10 days effectively and rapidly normalized serum 25(OH)D concentrations in vitamin D deficient individuals without notable adverse events [144]. A systematic review suggested that 200,000–600,000 IU as a single oral dose was effective in raising circulating concentrations of 25(OH)D to > 30 ng/mL [145]. Transient hypercalciuria was observed in some patients who received 600,000 IU, but no other untoward toxicity was observed at any of these doses [145].

We do not recommend giving patients $1,25(OH)_2D3$ (calcitriol) to treat vitamin D deficiency. Not only does this hormone have a very short half-life (~ 4 h), but it can cause a marked increase in intestinal calcium absorption, resulting in transient hypercalciuria and hypercalcemia. Animal studies have also demonstrated that $1,25(OH)_2D3$ can cause vascular calcification [146, 147]. The dosing interval might be critical in vitamin D supplementation for patients with COVID-19. A systematic review and meta-analysis of individual participant data from 25 RCTs concluded that vitamin D supplementation was safe and provided modest protection against acute respiratory tract infections (adjusted OR 0.88; 95% CI 0.81–0.96) [109]. Notably, a subgroup analysis showed that beneficial effects were observed in patients receiving daily or weekly doses (adjusted OR 0.81; 95% CI 0.72–0.91), but not in those receiving a single bolus dose (adjusted OR 0.97; 95% CI 0.86–1.10). These findings were consistently observed in the recently published update of this study [110].

6 Conclusions

There is now substantial evidence suggesting a significant association between vitamin D insufficiency/deficiency and COVID-19 susceptibility and its severity. Several RCTs have suggested the beneficial effects of vitamin D supplementation on ameliorating respiratory infections and COVID-19, although its efficacy was rather modest. Targeting the host's metabolism might be a viable strategy to protect against pathogenic signals induced during SARS-CoV-2 infection and to limit tissue susceptibility to damage signals [148]. Based on this evidence, it is advisable to avoid vitamin D deficiency in the general population to maximize innate and adaptive immunity [19] and prevent adverse cardiovascular outcomes [27], particularly during the COVID-19 pandemic. Current evidence suggests that taking a vitamin D supplement at doses recommended by the Endocrine Society to maintain a serum concentration of 25(OH)D of at least 30 ng/mL

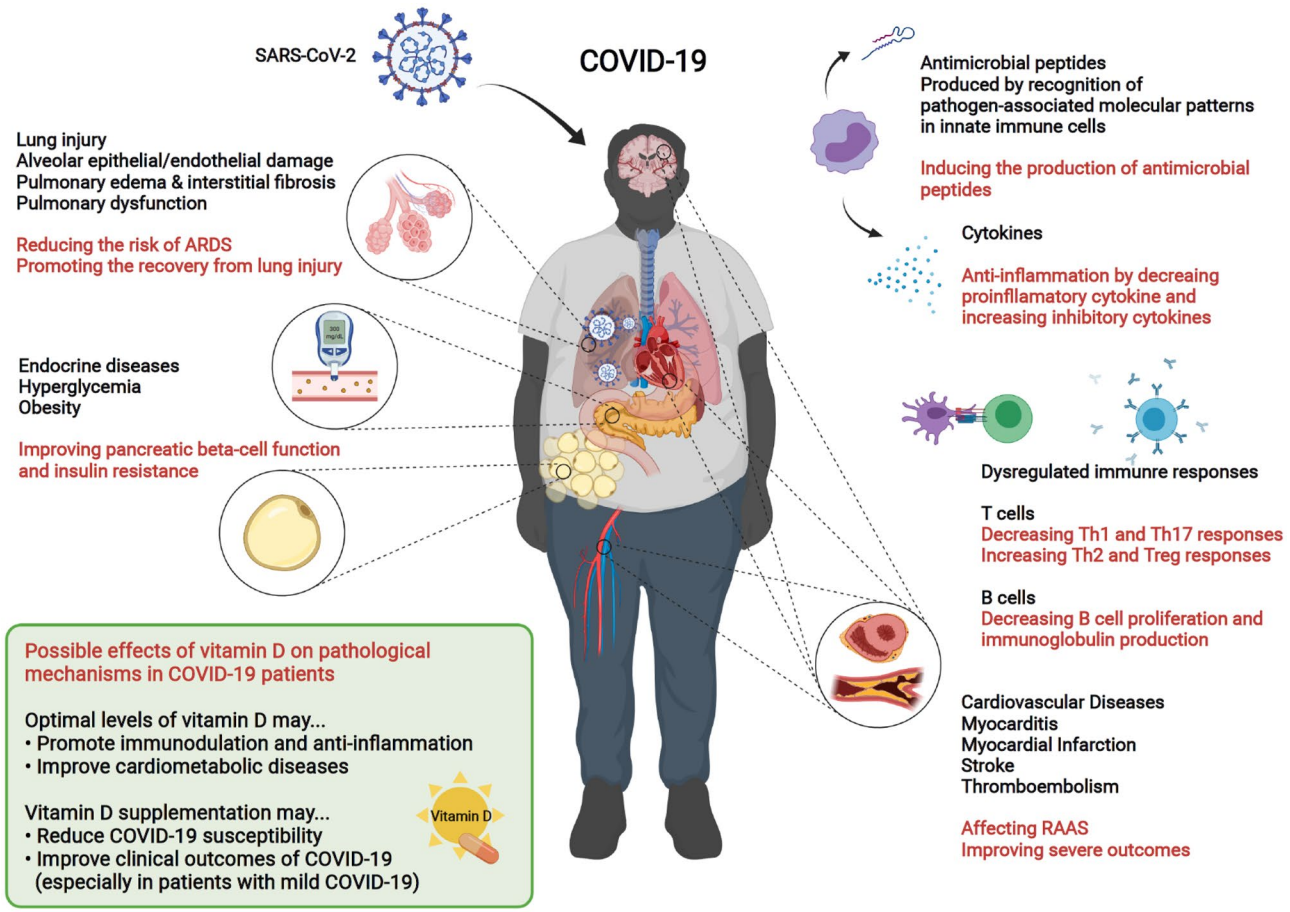

Fig. 4 Impacts of SARS-CoV-2 infection on human biological systems and proposed favorable effects of vitamin D on pathogenic processes involved in COVID-19. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; RAAS, renin–angiotensin–aldosterone system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th1, type 1 helper T cell; Th2, type 2 helper T cell; Th17, type 17 helper T cell; Treg, regulatory T cell

can help reduce the risk of SARS-CoV-2 infection and its severe outcomes, including mortality (Fig. 4). Ongoing well-designed interventional studies should provide conclusive information on the effects of vitamin D supplementation on the prevention and treatment of COVID-19 (Supplementary Table S2).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11154-021-09705-6.

Authors' contributions J.H.B. and H.J.C. conceived and designed the review, researched the literature, and wrote the manuscript. S.L. and M.F.H. reviewed, edited the manuscript, and were responsible for supervision. All authors read and approved the final manuscript.

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