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Association between Vitamin D Status and Risk of Developing Severe COVID-19 Infection: A Meta-Analysis of Observational Studies

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ABSTRACT

Objective: The relationship between 25-hydroxyvitamin D3 (25(OH)D), the surrogate marker for vitamin D_3, serum concentration and COVID-19 has come to the forefront as a potential pathway to improve COVID-19 outcomes. The current evidence remains unclear on the impact of vitamin D status on the severity and outcomes of COVID-19 infection. To explore possible association between low 25(OH)D levels and risk of developing severe COVID-19 (i.e. need for invasive mechanical ventilation, the length of hospital stay, total deaths). We also aimed to understand the relationship between vitamin D insufficiency and elevated inflammatory and cardiac biomarkers.

Methods: We conducted a comprehensive electronic literature search for any original research study published up to March 30, 2021. For the purpose of this review, low vitamin D status was defined as a range of serum total 25(OH)D levels of <10 to <30 ng/ml. Two independent investigators assessed study eligibility, synthesized evidence, analyzed, critically examined, and interpreted herein.

Results: Twenty-four observational studies containing 3637 participants were included in the meta-analysis. The mean age of the patients was 61.1 years old; 56% were male. Low vitamin D status was statistically associated with higher risk of death (RR, 1.60 (95% CI, 1.10–2.32), higher risk of developing severe COVID-19 pneumonia (RR: 1.50; 95% CI, 1.10–2.05). COVID-19 patients with low vitamin D levels had a greater prevalence of hypertension and cardiovascular diseases, abnormally high serum troponin and peak D-dimer levels, as well as elevated interleukin-6 and C-reactive protein than those with serum 25(OH)D levels ≥30 ng/ml.

Conclusions: In this meta-analysis, we found a potential increased risk of developing severe COVID-19 infection among patients with low vitamin D levels. There are plausible biological mechanisms supporting the role of vitamin D in COVID-19 severity. Randomized controlled trials are needed to test for potential beneficial effects of vitamin D in COVID-19 outcomes.

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Vitamin D; COVID-19; association; meta-analysis; observational studies

Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic is undoubtedly one of the most unprecedented infectious diseases in the recent history. The first reported case of COVID-19 goes back to December 2019 with exponential proliferation of the cases within a very short time, as of April 7, 2021 there have been 131,837,512 cases and 2,862,664 deaths worldwide (1). COVID-19 is caused by a novel coronavirus, Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) and was first discovered in Wuhan, Hubei Province, China (2). Based on phylogenetic analysis, it is postulated that this SARS-like virus originated in bats and subsequently transmitted via an intermediate carrier into humans (3). SARS-CoV-2 differs from other coronaviruses of the past due to its very high rate of transmission and its relatively high mortality (2, 4–6). Although geographical variability exists, it is worth recognizing that SARS-CoV-2 appears to have a lower case-fatality rate compared to other coronaviruses (7, 8). COVID-19 has a variety of symptoms ranging from asymptomatic to severe outcomes such as respiratory failure and death (9). There are also strong association between COVID-19 infection and the presence of preexisting comorbidities such as hypertension, diabetes, obesity, chronic obstructive pulmonary disorder, cardiovascular disease, malignancy, human

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Supplemental data for this article is available online at here.

immunodeficiency virus, and renal disease. These conditions are not only associated with higher risk of infection but also increased risk of severe disease and mortality (10). Age has been found to be one of the most prominent risk factors for severity of COVID-19 where children specifically are less frequently and less severely affected than adults and geriatric patients (11).

Vitamin D3 is often recognized for its role in calcium and phosphorous homeostasis, however it is also a key hormone in myriad diverse biological processes (12). There are two main ways to acquire vitamin D3, either through synthesis within the body or by ingestion via food or dietary health supplements. The primary source of vitamin D in the body is the epidermis where 7-dehydrocholesterol transformed into vitamin D3 under ultraviolet B (UVB) light from sunlight (13). Vitamin D status has been linked to many factors including seasonal variation (increase in summer and decrease in winter) or latitude (greater in latitudes close to the equator) (14). Vitamin D3 is biologically inactive and requires further cytochrome P450 (CYP)-mediated hydroxylation for activity. Vitamin D3 is first converted to 25-hydroxyvitamin D3 (25(OH)D3) by CYP2R1 (25-hydroxylase) in hepatocytes (15). The second hydroxylation occurs in the kidney where 25(OH)D3 is converted by CYP27B1 to its biologically active form, 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), also known as calcitriol (16). It is important to recognize that due to technological convenience and circulating levels, 25(OH) D3 is measured as the surrogate marker of vitamin D levels and activity in humans, whereas calcitriol is the most potent vitamin D derivative (13, 17).

Though calcitriol has multiple functions, it is now known as a cornerstone immunomodulatory hormone through its action at the vitamin D3 receptor (VDR). VDR is present in a multitude of different cell types throughout the body and is also present in many cells of the immune system such as neutrophils, T-lymphocytes, macrophages and dendritic cells (18). Calcitriol has multiple effects on both adaptive and innate immune system and consequently is a key regulator of inflammation. In the innate immune system, calcitriol has been shown to promote differentiating effects on monocytes and monocyte-derived cell lines, resulting in phenotypical features of macrophages (19). It also has the ability to improve the chemotactic and phagocytic capacity of macrophages (20). In the adaptive immune system, calcitriol targets both antigen-presenting cells (APCs), like dendritic cells, and T helper (Th) cells directly. In APCS, calcitriol inhibits the surface expression of MHC-II-complexed antigen, other co-stimulatory molecules and production of interleukin-12 (IL-12) and IL-23, which indirectly causes a shift in T cells to a Th2 phenotype (21). These key immunomodulatory and anti-inflammatory properties of calcitriol are potentially the reasons that it is widely researched for a variety of disease states and most recently for potential benefits in COVID-19.

The cases of COVID-19-related acute cardiac injury have become increasingly prevalent. The inflammatory response to COVID-19 leads to increased systemic inflammatory markers and potential abnormal function of vital organ systems, including pulmonary and cardiovascular. We have previously shown that there is significant association between elevated cardiac and inflammatory biomarkers and the severity of COVID-19 (22). To our knowledge, no meta-analysis has addressed the association between vitamin D levels with cardiac and inflammatory biomarkers. At the time of writing this article, there is very limited clinical trial data on vitamin D3 supplementation as a treatment for COVID-19. There are however some observational study reports showing the potential of vitamin D3 as a viable treatment option. The primary goal of this meta-analysis is to study the relationship between vitamin D_3 serum levels and the risk of developing COVID-19 infection in terms of mortality, severity, and inflammatory markers.

Methods

Study design

This review was designed to answer the following clinical research question: For adults age over 18 years old diagnosed with COVID-19 pneumonia, does vitamin D status impact the severity and outcomes of COVID-19 infection? The meta-analysis was performed based on the principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (23, 24). The primary outcomes of the study are all-cause mortality and COVID-19 severity including total number of severe cases, hospital duration, and the need for mechanical ventilation. Secondary outcomes of this study are laboratory markers of cardiac and inflammatory markers.

The primary objectives of this review were to evaluate the association between vitamin D level and risk of developing severe outcomes of COVID-19 infection and death. Data on total mortality at any stage of the illness, total number of severe patients, the need of invasive mechanical ventilation, and total days of hospital stay was sought and analyzed. The secondary focus of this review was to understand the relationship between low vitamin D (levels <30 ng/ml) and the inflammatory biomarkers such as C-reactive protein (CRP) and IL-6. We aimed to understand the potential mechanism behind cardiac injury with significant elevation of troponin and D-dimer. These biomarkers were found to be the most common in all the included studies.

Literature search strategy

We performed a comprehensive electronic search for any articles published up to March 30th, 2021, in the following databases: MEDLINE, EMBASE (through Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews. The combination of the following medical subheadings (MeSH) and key words was used for database searches: COVID-19 OR coronavirus disease 2019 OR SARS-CoV-2 OR severe acute respiratory syndrome coronavirus 2 OR 2019-nCOV

OR 2019 novel coronavirus OR coronavirus AND vitamin D OR ergocalciferol OR cholecalciferol. Alternative spellings and abbreviations of the above key words were also considered. The search results were limited to articles that were published in English language.

Inclusion criteria

Study titles and abstracts were reviewed, and publications were selected based on the following criteria: studies had to have a control group (sufficient vitamin D level), original study with COVID-19 patients, adults aged 18 years or older, serum 25(OH)D levels were reported. Reported serum 25(OH)D levels from the control and low vitamin D groups were needed for inclusion in our analysis. For the purpose of this review, low vitamin D level was defined as a serum total 25(OH)D level in the range from <10 to <30 ng/ml. Two investigators (MBE and RH) selected eligible trials according to the inclusion criteria independently. Disagreements were resolved by discussion until consensus was achieved or was discussed with another expert (JMW and SD) until consensus was achieved.

Exclusion criteria

Studies that are not conducted in humans, and adults <18 years of age were excluded. Abstracts were excluded if they were commentary, letter to editors, reviews (expert opinion, narrative, systematic review, or an overview), mechanistic papers, conference posters, non-COVID-19 patients, or had no control groups. Upon reading the full text, we excluded studies from further consideration if the patients were on active treatments for COVID-19 including vitamin D supplementations, lab reporting issues or if there was no mention of total number of subjects in each group. Studies were also excluded if they were focused on COVID-19 outcomes other than those listed above. We did not anticipate that any participants will be evaluated for vitamin D levels prior to COVID-19 infection. Therefore, it is unlikely that studies will select patients with deficient vitamin D levels, which is the group of individuals most likely to be affected by COVID-19.

Data extraction

The review authors (MBE, RH) independently performed the data extraction in duplicate. Discrepancies in data extraction were resolved by rechecking the data, discussing the outcome, and reaching to a consensus between the review authors and experts.

Data analysis

We used Review Manager (RevMan. version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) to perform data synthesis and meta-analysis. Studies were weighted according to their sample size and event rate to produce the final-pooled risks ratios (RR). We performed meta-analysis using the Mantel–Haenszel method for dichotomous outcomes RR with 95% CI using a random-effect model, and the inverse variance method for continuous outcomes as mean differences (MD) with 95% confidence interval (95% CI) using a random-effect model. For laboratory values, if only the median and interquartile range (IQR25, IQR75) were reported, then it was assumed that the median was equal to the mean and that the standard deviation (SD) was (Q75-Q25)/1.35.

Assessment of heterogeneity

The I^2 statistic test was performed to assess in-between study heterogeneity (I^2 of < 25%, 25–50%, 50–75%, and >75% indicating no, low, moderate, and high degree of heterogeneity, respectively). The statistical significance was set at 95% CI and p value < 0.05. Each laboratory parameter from the included studies was reported in different units, which were all converted into one common unit for the final analysis.

Results

Study characteristics

After screening of 543 citations, 474 studies were excluded, and a total of 24 observational studies were included in the final analysis (25–48). Sixteen studies were retrospective and eight studies were prospective in design. In total, 3637 patients were included. All were problematic with potential confounding as expected from non-randomized studies. Figure 1 shows the detailed selection process and Table 1 summarizes the characteristics of the included studies in this meta-analysis. The included studies represent broad geographic representation with mixed populations. Most studies were performed exclusively in hospital settings, mainly in Europe (UK, Italy, Germany, Belgium, Greece, and Spain), North America (USA), and Asia (China, Turkey, Iran, India, Pakistan). No studies were performed in Africa or in Australia.

Most of the patients were older with a pooled mean age of 61.1 years, predominately male (56%), and had multiple comorbid conditions. Various comorbidities were reported with hypertension being the most frequent, followed by cardiovascular diseases and diabetes. There were significant associations reported between low levels of vitamin D and severity of infection with cardiovascular diseases including hypertension being the most common. The definitions for vitamin D deficient were heterogeneous across studies. Low levels of 25(OH)D ranged from <10 to <30 ng/ml in low vitamin D group compared to the rest as the control group.

All-cause mortality

There is an association between low vitamin D levels and mortality. The meta-analysis of the 18 included studies

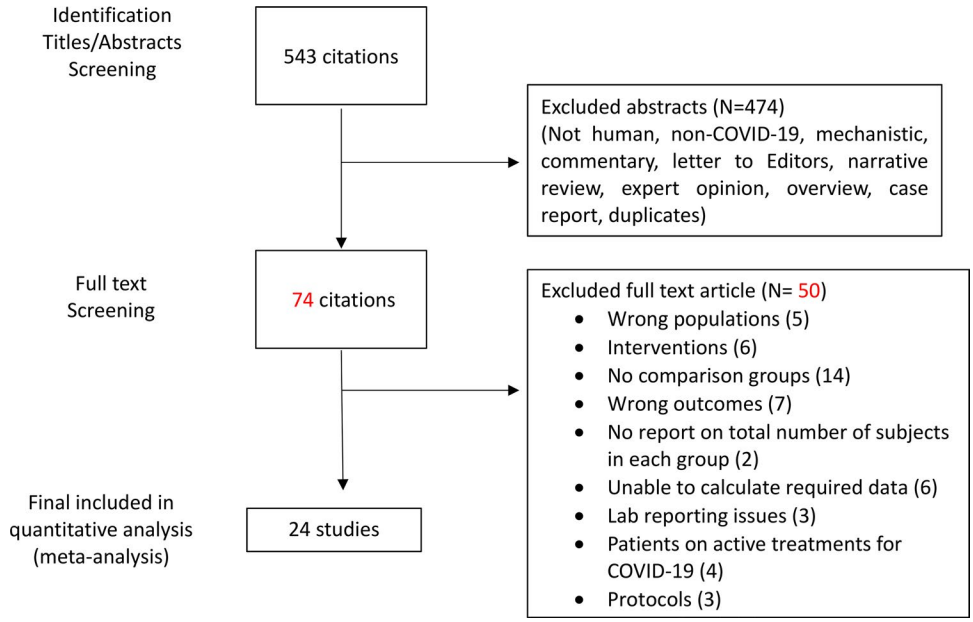

Figure 1. Flow chart of literature search and selection process.

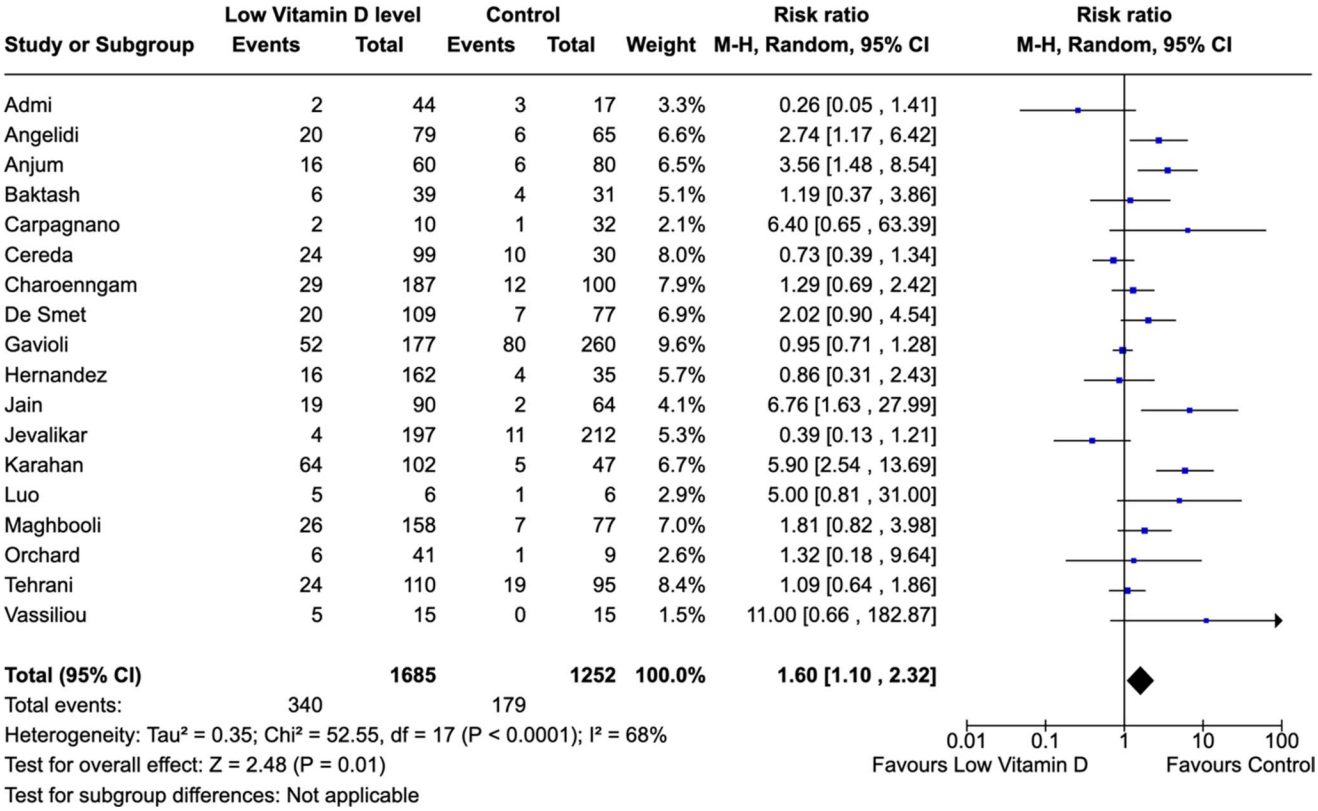

Figure 2. Association between vitamin D levels and all-cause mortality.

indicated that low vitamin D level, compared with controls, was associated with higher risk of death (RR, 1.60 [95% CI,1.10–2.32]; $P = 0.01$; I^2 = 68% (Figure 2). Data on total mortality was collected from a total of 2937 COVID-19 patients. Event rates were 340 per 1685 (20.17%) among COVID-19 patients with low vitamin D status versus 179 per 1252 (14.29%) in control group patients (Figure 2).

COVID-19 severity

The definitions for severe COVID-19 were heterogeneous across studies. There were significant associations between low vitamin D level with severe COVID-19 cases (Figures 3 and 4). The meta-analysis suggested a considerable higher risk of severe COVID-19 infection in individuals with low vitamin

Table 1. Summary characteristics of included studies.

First author country	Total *N*	Age Years	% Male	Low Vitamin D* cutoff	Study design	Comorbidity % >10%	Ref.
Abrishami Iran	73	55	64%	<25 ng/ml	Retrospective study	Hypertension (24.7%) Chronic kidney disease (21.9%)	(25)
Adami Italy	61	69.4	52.5%	<20 ng/ml	Retrospective observational study	Hypertension (59%) Cardiovascular diseases (27.8%) Diabetes. (18%) Cancer (18%) Chronic kidney disease (18%) Chronic obstructive pulmonary disease (18%)	(26)
Angelidi USA	144	66	44.4%	<30 ng/ml	Retrospective, observational, cohort	Hypertension (73.6%) Hyperlipidemia (54.9%) Diabetes. (43.8%)	(27)
Anjum Pakistan	140	42.5	58.6%	<10 ng/ml	Prospective cohort	NR	(28)
Baktash UK	70	80	70%	<30 ng/ml	Prospective cohort study	Hypertension (48.5%) Diabetes (37.1%)	(29)
Carpagnano Italy	42	65	71%	<30 ng/ml	Retrospective, observational single center study	Total: 86% Hypertension (26%)	(30)
Cereda Italy	129	77	54%	<20 ng/ml	Prospective cohort	Hypertension (70.1%) Ischemic heart disease (40.9%) Diabetes. (30.7%)	(31)
Charoenngam USA	287	62	52.6%	<30 ng/ml	Retrospective chart review cross-sectional study	Hypertension (79.9%) Diabetes (56%) Hyperlipidemia (58.2%) Chronic kidney disease (37.6%)	(32)
Demir Turkey	227	46.3	44.66%	<30 ng/ml	Retrospective cohort study	NR	(33)
De Smet Belgium	186	69	58.6%	<20 ng/ml	Retrospective observational trial	Coronary artery disease (61.5%)	(34)
Gavioli USA	437	67	48%	<30 ng/ml	Retrospective, observational cohort study	Hypertension (68%) Diabetes (45%) Coronary artery disease (30%) Malignancy (24%)	(35)
Hernandez Spain	197	61	62.4%	<20 ng/ml	Retrospective case-control study	Hypertension (38.6%)	(36)
Jevalikar India	409	54	68.9%	<20 ng/ml	Prospective observational study	Diabetes (46.1%) Hypertension (40%) Hypothyroidism (14.9%)	(37)
Karahan Turkey	149	63.5	54.4%	<20 ng/ml	Retrospective observational study	Hypertension (57%) Diabetes (40.9%) Dyslipidemia (26.2%) Coronary artery disease (21.5%) Chronic kidney disease (19.5%)	(38)
Luo China	74	62.5	58.1%	<30 ng/ml	Retrospective cross-sectional study	Total 67.6%	(39)
Maghbooli Iran	235	59	61.3%	<30 ng/ml	Retrospective cross-sectional study/ analysis	Hypertension (44.4%) Diabetes (36.6%)	(40)
Orchard UK	50	60	56%	<20.83 ng/ml	Prospective cohort	Hypertension (40%) Diabetes (28%) Asthma (10%)	(41)
Radujkovic Germany	185	60	51%	<12 ng/ml	Prospective cohort	Cardiovascular disease (31%)	(42)
Ricci Italy	52	68.4	48 %	<10 ng/ml	Cohort	Hypertension (42.3%) Obesity (23%)	(43)
Tehrani Iran	205	59.7	69%	<30 ng/ml	Descriptive retrospective study	Hypertension (44.4%) Diabetes (35.1%) Ischemic heart disease (24.9%) Chronic kidney disease (23.4%)	(44)
Vassiliou Greece	30	65	80%	<15.2 ng/ml	Retrospective observational study	Hypertension (50%) Hyperlipidemia (30%)	(45)
Ye China	60	43	37%	<12 ng/ml	Case control study	Hypertension (10%) Renal failure (26.6%) Diabetes (8.3%)	(46)
Kerget Turkey	88	49.1	46.6%	<20 ng/ml	Prospective cohort	Hypertension (11.36%) Diabetes (9%)	(47)
Jain India	154	46	48.5%	< 20 ng/ml	Prospective observational study	Diabetes Hypertension	(48)

*Low vitamin D = vitamin D levels ranges from <10 to <30 ng/ml, NR: not reported.

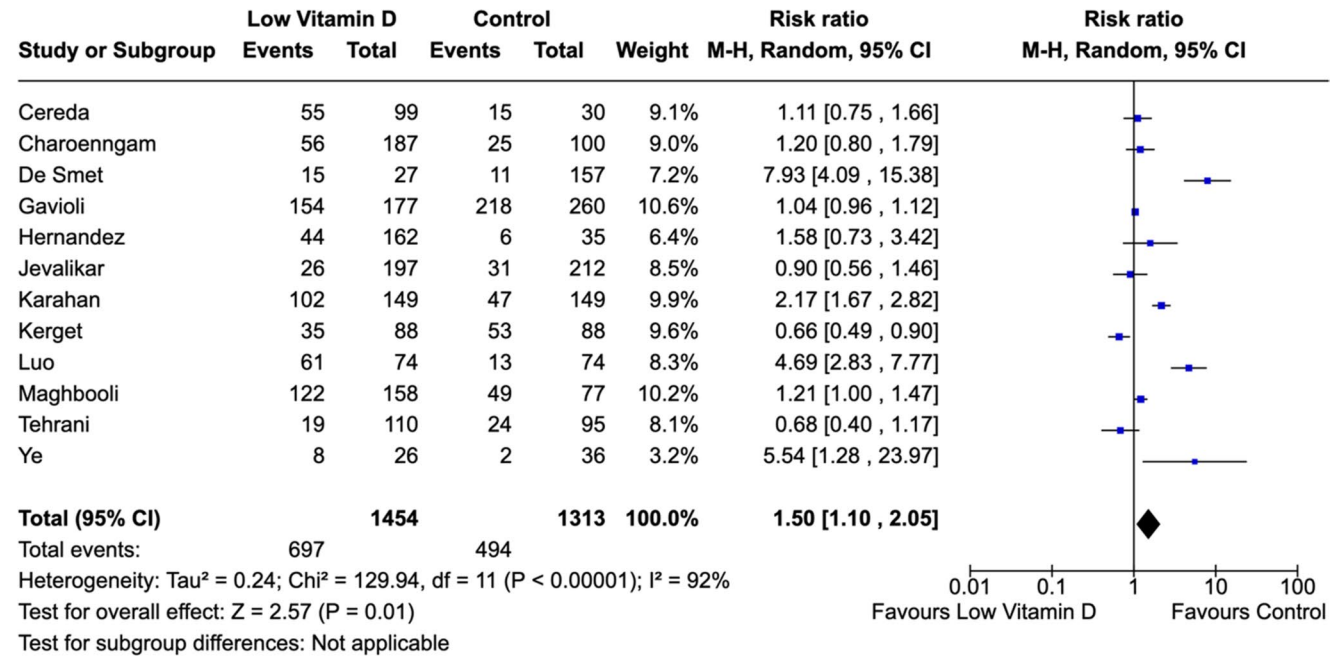

Figure 3. Association between vitamin D levels and COVID-19 severity.

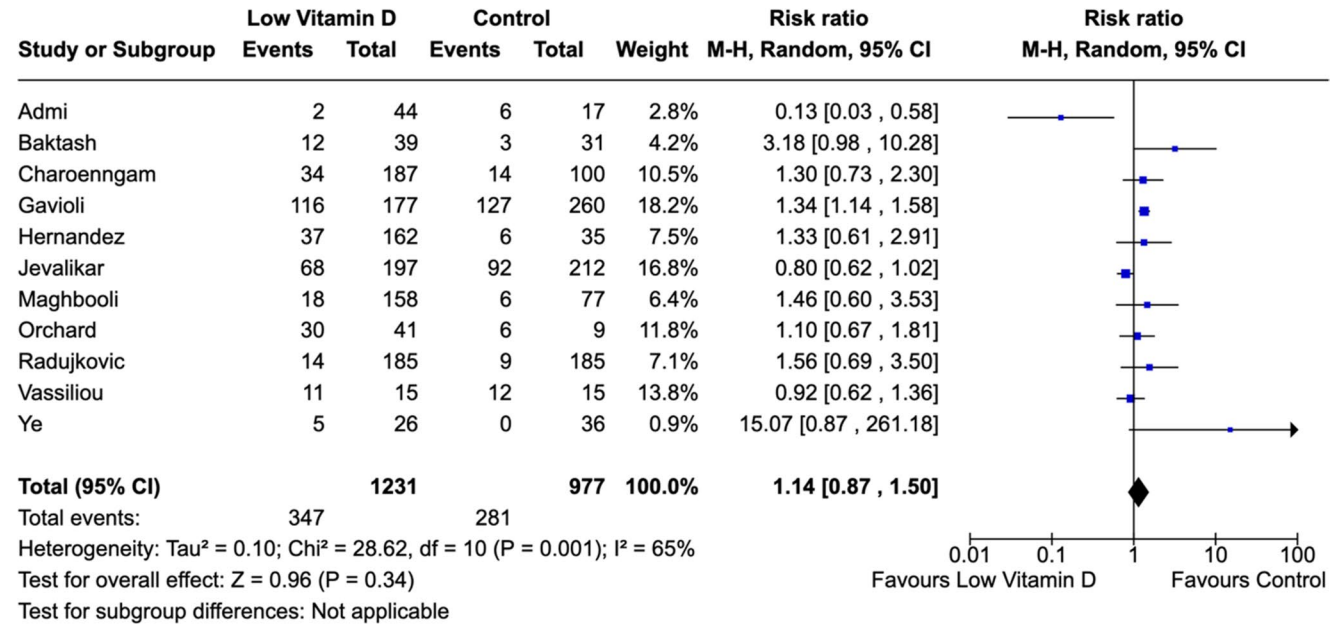

Figure 4. Association between vitamin D levels and need for mechanical ventilation.

D levels (RR: 1.50; 95% CI, 1.10–2.05) (Figure 3). Overall, 28.4% of COVID-19 patients required ICU admissions (628/2208). We found no difference in the need for mechanical ventilations in low vitamin D level ICU patients compared to control group patients (RR: 1.14; 95% CI, 0.87–1.50) (Figure 4).

Difference in biological markers and disease severity

All laboratory parameters, both cardiac (troponin and D-dimer) and inflammatory (CRP and IL-6) biomarkers, were found to have significant mean differences between low vitamin D group and the control group (Figures 5–8). The cardiac biomarkers were abnormally high at all times. The difference in CRP and IL-6 levels between low vitamin D and control groups were statistically significant in all patients. Heterogeneity of the studies were very high for all biomarkers.

Discussion

This meta-analysis underlines the potential benefits of sufficient vitamin D levels and serves as a comprehensive summation of the currently available research on various COVID-19 outcomes in relation to measured serum vitamin D levels. Our work has described the association between vitamin D levels and COVID-19 markers representing severity of the disease including mortality, use of mechanical

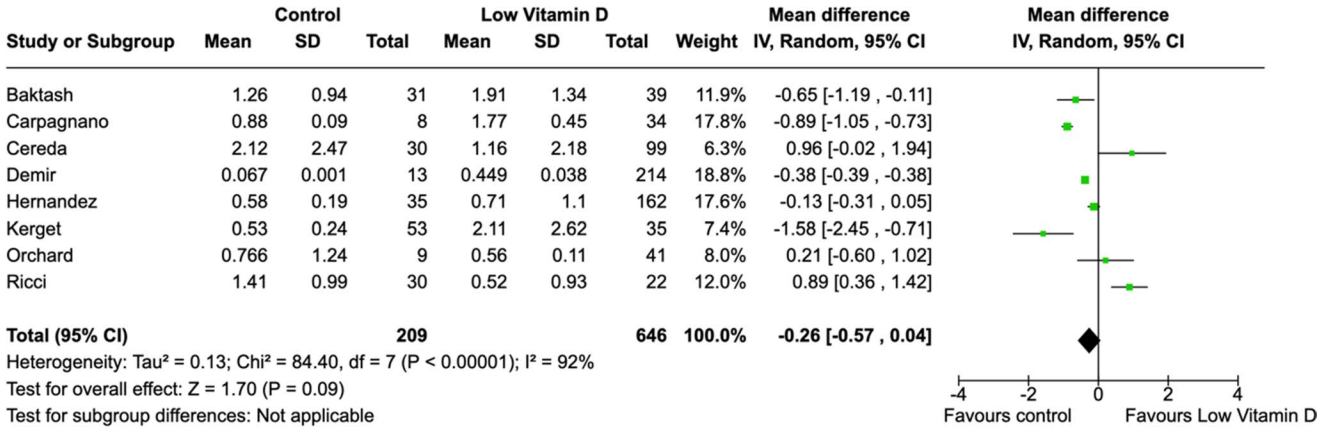

Figure 5. Association between vitamin D and D-dimer (μg/ml) levels.

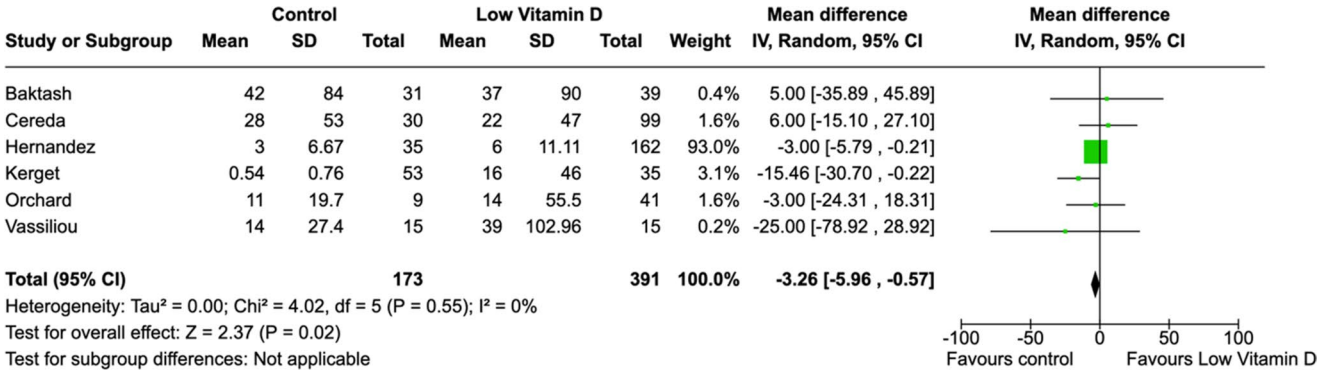

Figure 6. Association between vitamin D and troponin (ng/L) levels.

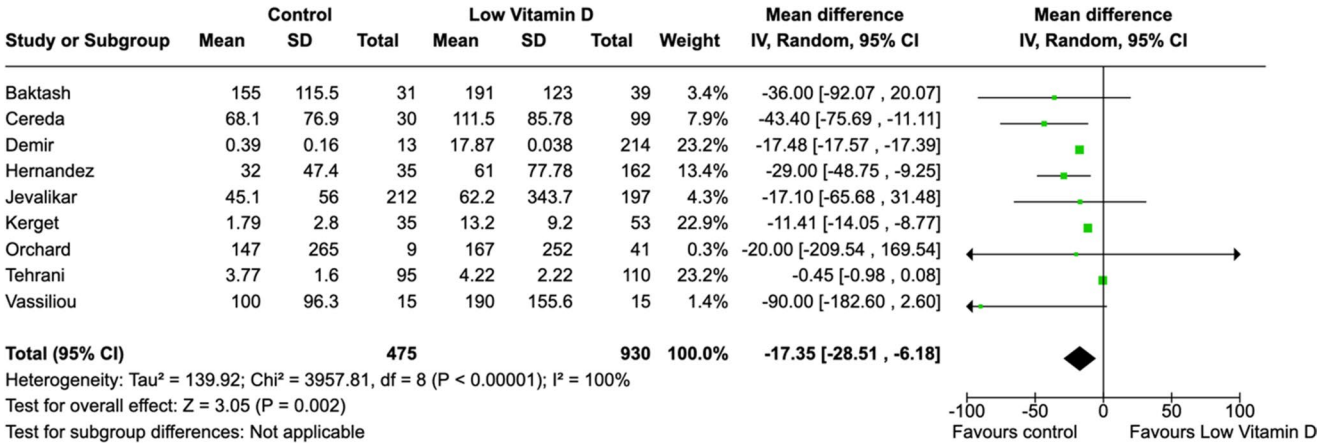

Figure 7. Association between vitamin D and C-reactive protein (mg/L) levels.

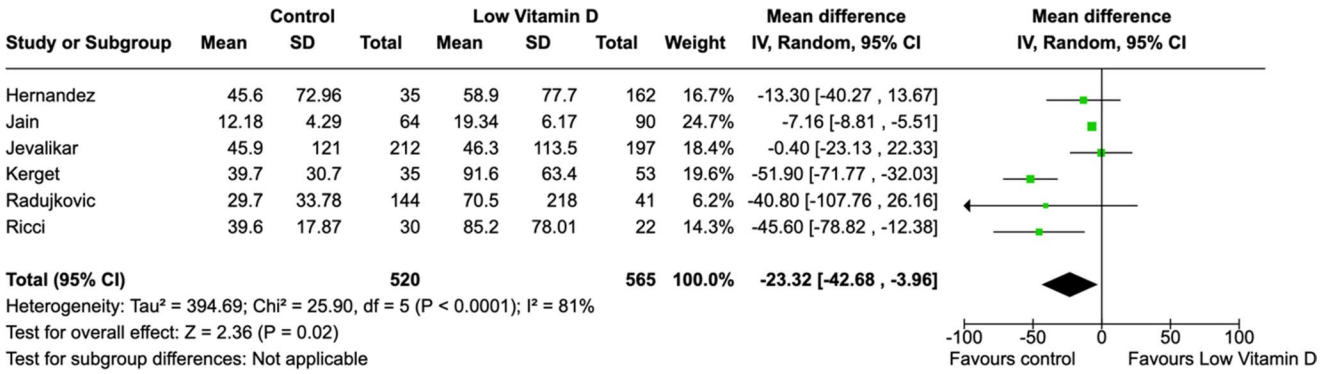

Figure 8. Association between vitamin D and interleukin-6 (pg/mL) levels.

ventilation, and inflammatory parameters. The connection between vitamin D levels and COVID-19 is a prevalent topic of discussion to predict disease outcomes such as mortality and disease severity. In recent times, vitamin D has been highlighted as one of the key immunomodulatory hormones both in the innate and adaptive immune systems that support routine immune functions through VDR-mediated actions. In addition, the role of vitamin D in the inhibition of Renin Angiotensin System (RAS) links the importance of adequate vitamin D status as a protective factor during COVID-19 pandemic. These non-classical actions of regulating immune cell differentiation and proliferation by vitamin D have sparked research interest to help combat the ongoing COVID-19 pandemic (49).

We found a significant increase in all-cause mortality and COVID-19 severity among people with low vitamin D levels and the risk of death increases in patients with preexisting cardiovascular diseases and older adults. Sufficient vitamin D levels (levels >20–30 ng/ml) were found to decrease all-cause mortality and COVID-19 severity with $p = 0.0001$ and $p < 0.00001$, respectively. Cardiac biomarker (troponin and D-dimer) levels tended to be lower in the vitamin D sufficient COVID-19 patients. Biomarkers of inflammation (CRP and IL-6) were significantly higher in patients with low vitamin D levels. Our findings are consistent with other reviews. The meta-analysis reported by Bassatne et al. (2021) included studies up to December 18, 2020, and demonstrated a positive trend of increased mortality risk in patients with vitamin D levels <20 ng/ml (RR = 2.09, 0.92-4.77). The work included data only from seven studies for mortality outcome, with insufficient evidence provided with data only from two to three studies on ICU admission or invasive mechanical ventilation requirement (50). A systematic review and meta-analysis conducted by Pereira et al. (2020) included studies up to October 9, 2020, and found similar results in terms of mortality where vitamin D levels of less than 75 nmol/L (approximately 30 ng/ml) were found to be inversely related with mortality (OR = 1.82, 95% CI = 1.06–2.58; I^2 = 59.0%), with a significant increased chance of hospitalization (OR = 1.81, 95% CI = 1.41–2.21; I^2 = 0.0%) (51). Munshi et al. (2021), with studies analyzed up to June 8, 2020, found further supporting results in which patients with poor prognosis had significantly lower vitamin D serum levels compared to those with good prognosis. Poor prognosis was defined as severe presentation and ICU admission. The adjusted mean difference was −0.58 (95% CI = −0.83 to −0.34, $p < 0.001$) and −0.84 (95% CI = −1.32 to −0.36, $p = 0.001$) between ICU and floor admission, respectively (52).

The biological mechanisms linking vitamin D deficiency and excessive deaths are plausible. The exact mechanism of the beneficial effects of vitamin D sufficiency found in this meta-analysis is a topic for future research. However, it can be postulated that these are the results of anti-inflammatory actions of vitamin D (53). Mortality from COVID-19 is typically caused by severe acute respiratory syndrome, uncontrolled release of pro-inflammatory cytokines alongside unbalanced immune response, which eventually lead to cytokine storm and diffuse micro and macrovascular thrombosis, the occurrence of new disease states (e.g., myocarditis) or worsening of preexisting diseases (e.g., cardiovascular and kidney disease) (53, 54). Thus, association of low vitamin D levels and increased cardiovascular and inflammatory markers could translate into increased risk of cardiovascular morbidity and mortality (55).

Vitamin D may potentially reduce severity of respiratory tract infections. In the adaptive immune system vitamin D causes a shift away from Th-1 responses and toward Th-2 responses therefore decreasing the viral induction of inflammatory genes (56). Furthermore, vitamin D inhibits the development of pro-inflammatory Th-17 cells as well as modulates pro-inflammatory cytokines such as IL-1, IL-6 and IL-10 which are heavily involved in cytokine storms (57). These anti-inflammatory properties of vitamin D provide a link between COVID-19 mortality and severity and vitamin D levels (48, 54). According to a meta-analysis by Ji et al. (2020), elevated levels of white blood cells, CRP, erythrocyte sedimentation rate, IL-6, and IL-10 showed more severe COVID-19 disease and higher risk of death during follow up (58).

Due to the fast onset and evolving nature of the COVID-19 pandemic, there is a lack of randomized control trials on sufficient vitamin D levels and its potential benefits in COVID-19. The best available data at this time is strictly observational and lacks the robustness to prove a causative relationship between vitamin D serum levels and COVID-19 outcomes. We cannot exclude the possibility of residual confounding and did not aim to assess the quality of the included studies as a part of this review. The limitations of these associations are that the overall quality of evidence is low. Unmeasured differences in baseline comorbidities in combination with other potential confounding is the reason for high heterogeneity among the studies. It is important to point out that low RRs should be interpreted with caution, since RRs of observational studies <2 fall into the gray area of potential bias where usually confounding factors are difficult to control. In addition, the obtained confidence intervals have a very wide interval which indicates the need for larger sample size to better estimate the true value in the population. There is a lack of data availability for race or ethnicity in the included studies which precluded us from evaluating any potential effect of genetics or diet on their vitamin D status. Similarly, the contribution of seasonal variations on vitamin D levels in these studies remains unknown. Also, we aimed to evaluate the association between vitamin D levels and total days of hospital stay. However, there are no accurate data reported on this outcome. There was no difference in the average length of stay between vitamin D subgroups with 10.9 days in controls versus 14.4 days in low vitamin D patients. The results for this specific endpoint have been reported only in eleven included studies, which represent a small sample size with several associated issues described in details by Baktash et al. (29).

There are no clinically established data yet on the range of vitamin D levels recommended to protect against COVID-19. In general, in non-COVID-19 situations, there is consensus that sufficient vitamin D status is defined as >30 ng/ml (59–62). However, there has been ongoing

debate regarding the definition of vitamin D deficiency as noted by different recommendations from various expert groups. The Institute of Medicine (United States) indicates that levels of <12 ng/ml are deficient, >20 ng/ml are sufficient and >50 ng/ml are potentially toxic (61, 62). In contrast, the Endocrine Society recognizes significantly higher levels for those categories: <20 ng/ml is deficient, and 21–29 ng/ml is insufficient (60, 62). Thus, there is disagreement on how to approach levels between 12 ng/ml and 30 ng/ml. Guidelines from certain agencies recommend a threshold value of 20 ng/ml, whereas others suggest a benefit for a higher threshold of 25(OH)D levels ≥30 ng/ml (60–62). For the purpose of this review, low vitamin D status was defined as a range of serum total 25(OH)D levels of <10 to <30 ng/ml. A sensitivity analyses were performed to evaluate the effect of each study's different 25(OH)D cutoff values on the overall pooled effects, which did not significantly change these findings (Supplementary Materials). The results of this meta-analysis found a significant increase in all-cause mortality and COVID-19 severity among people with vitamin D levels <30 ng/ml, and the risk of death increases in preexisting cardiovascular diseases in older adults. The strength of the present study is that twenty-four studies were included and serves as an exhaustive list of the most current research in vitamin D levels and COVID-19. Based on our review, the clinical aim should be to raise vitamin D levels >30 ng/ml which will likely be the range of protection by vitamin D against respiratory infections. However, adequate supplementation is necessary to achieve >30 ng/ml 25(OH)D levels. It is important to point out that there are significant differences in the guidelines across the health agencies for daily recommended intake of vitamin D. The standard supplementation of 600 IU/day (Institute of Medicine, United States) will likely not achieve the concentrations needed to offer protection from COVID-19 infection. Recommendations for higher vitamin D supplementation (at least 20–25 micrograms or 800–1000 IU per day) for COVID-19 treatment were provided by the European and American Societies for Clinical Nutrition and Metabolism, European Food Safety Authority, National Institute for Health and Care Excellence, and Australian high-priority guidelines (63–65). People with different physiological factors, for example, obesity, might need greater intake of vitamin D to achieve >30 ng/ml 25(OH)D levels compared to healthy individuals (66). However, during pre-COVID-19 situations Endocrine Society of United States had recommended 1500-2000 IU/day intake to achieve sufficient levels of vitamin D (62). It is critical to recognize that the current vitamin D supplementation guidelines for COVID-19 are not evidence based and there is an urgent need for more information to guide clinical decision-making for COVID-19 patients.

To our knowledge, no meta-analysis has addressed the association between vitamin D levels with cardiac and inflammatory biomarkers. Herein, we show that vitamin D status may influence the severity of responses to COVID-19 infection. The evidence appears to be enough that clinicians and patients should be aware that severe COVID-19 cases may occur in people with vitamin D deficiency. Since vitamin D deficiency is modifiable, identifying individuals most susceptible to severe infection and treating them for vitamin D deficiency may represent a practical way to minimize COVID-19-associated fatality. If a causal link is established, VDR could be a potential therapeutic target. Vitamin D might be able to protect patients against developing severe form of disease. It has been hypothesized that vitamin D supplementation potentially would reduce the risks of cytokine storm, myocarditis, or cardiac injury via inhibition of RAS (48, 53–55, 58). Vitamin D supplements would present relatively safer (wide therapeutic window) and economic low risk intervention. Although currently there are 44 registered trials on supplementation of vitamin D in COVID-19 (https://clinicaltrials.gov/), currently there is no evidence that supplements reduce the risk of COVID-19 infection. Limited interventional trials have investigated the role of vitamin D supplementation for the treatment COVID-19 infection (67, 68). A Cochrane meta-analysis using a living systematic review approach, which has included evidence up to 11 March, 2021, identified three randomized clinical trials with 356 participants, of whom 183 received vitamin D (68). According to this analysis, there is currently insufficient evidence to determine the benefits and harms of vitamin D supplementation as a treatment of COVID-19. Future research should focus on well-designed studies with robust methods, which will likely improve our understanding of the role of vitamin D and its clinical benefits in COVID-19. Further randomized control studies are needed to demonstrate whether vitamin D might be effective in reducing all-cause mortality and COVID-19 morbidly.

Conclusion

Vitamin D status may play a significant role in developing severe COVID-19 infection. In this study low vitamin D status was associated with higher risk of all-cause mortality in COVID-19 positive patients. There is a plausible anti-inflammatory biological mechanism supporting the protective role of vitamin D in COVID-19 severity. Further research is needed in this area, in the form of randomized control trials, to determine whether there is a cause-effect relationship between low vitamin D status and COVID-19 outcomes.

Disclosure statement

The authors declare that they have no conflicts of interest.

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