Association Between Vitamin D Levels and Inflammatory Markers in COVID-19 Patients: A Meta-Analysis of Observational Studies

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ABSTRACT -- Purpose: Vitamin D has immunomodulatory properties that can be useful in COVID-19 patients. We performed a meta-analysis of observational studies to analyze the association of vitamin D levels with the inflammatory markers in COVID-19 patients. **Methods:** We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, and ClinicalTrial.gov for any relevant studies with comparison data reporting vitamin D levels and inflammatory markers in COVID-19 patients. A literature search was conducted from December 1, 2019, to January 14, 2022. Vitamin D deficiency was defined by each individual study and ranged from <9.9 ng/mL to <30 ng/mL. The inflammatory markers of interest were interleukin-6 (IL-6), C-reactive protein (CRP), ferritin, procalcitonin, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), fibrinogen and D-dimer. Weighted mean difference (WMD) and 95% confidence intervals (CIs) were pooled using random or fixed-effects models. Two independent investigators assessed study eligibility and synthesized the evidence. **Results:** Thirty-two observational studies were included comprising of 7,771 patients ranging from 40-81 years of age with 57.1% being male. Meta-analysis showed that patients that were vitamin D sufficient (levels >30ng/mL) had statistically significant lower levels of IL-6, CRP, ferritin, LDH, fibrinogen, and D-dimer compared to vitamin D deficient group. With the highest mean difference found in ferritin (95.62; 95% CI, 33.14-158.10); P=0.003; I^2=99%). No significant reductions were found in ESR (P=0.97). All inflammatory markers analyzed were higher than the normal healthy reference ranges in both groups. **Conclusions:** Our results suggest that low vitamin D levels are associated with increased inflammatory marker levels. Vitamin D deficiency may potentially serve as an early identifier for COVID-19 patients at high risk of developing severe inflammatory conditions as well as thrombotic complications. Randomized controlled trials should be conducted to establish a causal relationship.

INTRODUCTION

COVID-19 is the most devastating pandemic in recent history with more than 386 million confirmed cases and more than 5 million deaths worldwide as of February 4, 2022 (1). COVID-19 is caused by the highly infectious virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified in Wuhan, China in late 2019. SARS-CoV-2 has a structure similar to coronavirus responsible for previous pandemics, mainly SARS-CoV-1, with which it shares approximately 80% of the genome (2). The main route of COVID-19 transmission is through respiratory droplets and can be transmitted to a healthy individual if they come into contact with an infected person or their belongings (3). Symptoms usually present after an incubation time of five days. Infected individuals can present in a variety of ways, including but not limited to, being asymptomatic, mild gastrointestinal symptoms and fatigue, and respiratory failure in severe cases (4). A variety of risk factors have been identified to predict progression into severe stages of COVID-19 including older age, male gender, underlying hypertension, diabetes, obesity, chronic lung diseases, heart, liver, and kidney diseases, and immunodeficiencies (5). Additionally, socioeconomic status, diet, lifestyle, ethnicity, and geographical differences can impact disease outcomes (5).

Cytokine storm is defined as a potentially fatal immune syndrome identified by overactivation of immune cells and excessive production of inflammatory cytokines and chemical mediators (6). Cytokine storm has been identified as a predictor of COVID-19 severity and a crucial cause of death in patients due to high levels of cytokines, lymphopenia, thrombosis, and mononuclear cell infiltration into multiple organs (7). SARS-CoV-2 first enters respiratory cells through the interaction of the S proteins on the virion surface with the ACE2 receptor (8), resulting in an immune response and inflammatory cytokine production through downstream signalling of Th1 cells and intermediate CD14+ and CD16+ monocytes. Leading to infiltration of macrophages and neutrophils into lung tissue resulting in a cytokine storm (7). Systemic cytokine profiles in severe COVID-19 cases mirror profiles of cytokine release syndromes such as macrophage activation syndrome, with increased IL-6, IL-7, tumor necrosis factor α (TNFα), and inflammatory chemokines (9). Other inflammatory markers and end-organ related indices such as C-reactive protein (CRP), ferritin, procalcitonin, erythrocyte sedimentation rate (ESR) and LDH are shown to be elevated in severe COVID-19 patients and associated with the development of acute respiratory distress syndrome (ARDS) (10-12). Multiple meta-analyses have also demonstrated that CRP, procalcitonin, ESR and ferritin can be used to predict prognosis and severity of COVID-19 infection (13, 14). COVID-19 has been shown to have an association with thrombotic events because of the excessive inflammation, platelet activation, endothelial dysfunction, and stasis (12, 15). Furthermore, elevated fibrinogen and D-dimer levels are present in early stages of infection, with elevated D-dimer at admission being directly associated with increased mortality (16-18). Increased D-dimer levels were also shown to predict COVID-19 severity with high sensitivity and specificity, as well as venous thromboembolism (VTE) with high sensitivity, suggesting that it can be used to screen for patients with VTE (19).

Vitamin D is best known for its role in maintaining the balance of serum calcium and phosphate levels in the body. Active vitamin D (calcitriol) is synthesized within the body in various steps. The first step is the synthesis of vitamin D_3 (cholecalciferol) in the skin from 7-dehydrocholesterol when exposed to UV radiation. Cholecalciferol is then transported to the liver through the blood by attaching to vitamin D binding protein (DBP). In the liver, cholecalciferol is hydroxylated at C-25 to form calcifediol which is the major circulating form of vitamin D. Calcifediol can then be transported to the kidney by attaching to DBP in the blood where it is further hydroxylated at the C-1 position to form the active form known as calcitriol (20). During periods of sufficient serum calcium, calcitriol stimulates osteoclastogenesis and bone matrix mineralization, while in periods of low serum calcium can have opposite effects leading to bone resorption and reduced bone mineralization (21). Vitamin D has also become known as a key immunomodulatory hormone through its action at the vitamin D receptor (VDR). VDR is abundantly expressed in vital immune cells such as B cells, T cells and antigen presenting cells and it has been shown that VDR activation can modulate various immune system responses (22). VDR activation can have significant anti-inflammatory effects by prevention of T-cell and B-cell immune response (23, 24). VDR activation in dendritic cells leads to a less mature phenotype with changes in morphology and cytokine production resulting in increased inhibitory molecules (IL-10, TNF-α, programmed death-ligand 1, immunoglobulin-like transcript-3) and decreased expression of MHC class II, co-stimulatory molecules, IL-12, and IL-23 (25). Activation of VDR in macrophages leads to reduction in pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, RANKL and COX-2, and increase in the anti-inflammatory IL-10 (26). The anti-inflammatory effects of VDR activation present a unique pathway to limit inflammation in variety of disease states, especially in those who are vitamin D insufficient.

Within the relatively short time of the COVID-19 pandemic there have been several studies to determine how serum vitamin D levels impact incidence and disease severity of COVID-19 patients (27). Majority of the current studies demonstrate a relationship between low vitamin D levels and poorer outcomes for COVID-19 patients. It should be noted that many of the current studies are observational and often retrospective due to the time sensitive manner of the pandemic. There have been multiple systematic reviews and meta-analyses suggesting a link between insufficient vitamin D levels and COVID-19 incidence and poorer outcomes such as severe presentations and ICU admission (20, 28-30). In contrast, a recent systematic review and meta-analysis by Hu et al. (2022) reported that vitamin D status had no significant effect on the severity of COVID-19 in

terms of mortality, hospitalization, and other similar parameters (31). However, further randomized controlled trials and more robust studies need to be conducted to provide solid evidence of a link between vitamin D levels and COVID-19 incidence and outcomes. There is some conflict about what vitamin D levels are most beneficial for patients, especially when levels are higher than 20 ng/mL (32). In fact, Rosen et al. (2011) argued that less than 3% of the general population is likely to have vitamin D needs that require levels to be higher than 20 ng/mL (32). It is important to consider this when looking at vitamin D levels that are much higher than recommended. This meta-analysis evaluated the relationship between vitamin D levels and inflammatory markers in COVID-19 patients because cytokine storm is a hallmark of severe COVID-19 cases.

METHODS

Study Design

The inflammatory markers of interest are interleukin-6 (IL-6), C-reactive protein (CRP), ferritin, procalcitonin, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), fibrinogen and D-dimer. These biomarkers were found to be the most reported across the available literature.

Search Strategy

An extensive literature search was conducted for articles published between December 1, 2019, and January 14, 2022, in the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews. The following combinations of medical subject headings (MeSH) terms and keywords were used for database searching: (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, variations and abbreviations of the key words were also considered, and the search results were limited articles published in the English language.

Inclusion Criteria

Study abstracts were reviewed, and publications were selected if they met the following criteria: COVID-19 patients, adults greater than 18 years of age, studies with a control group (cohort and case control) that reported vitamin D levels for a group with sufficient vitamin D level and compared with insufficient vitamin D level group, as well as inflammatory marker levels of interest reported in each group.

Exclusion Criteria

Observational studies were excluded if they were not conducted in humans or patients less than 18 years old. Abstracts were excluded if they were duplicates, letters to editors, commentary, narrative or systematic reviews, conference posters, probabilistic modeling, conducted in non-COVID-19 patients, studies with no control groups (cross sectional, case series, and case reports), or vitamin D supplementation. Upon analysis of the full text, further studies were excluded if patients were actively receiving treatment for COVID-19, number of patients in each control or experiment group were not reported, or levels of serum inflammatory markers were not reported. Studies were also excluded if they reported on inflammatory markers that were not of interest, or there were less than three total available studies reporting the inflammatory marker level. This resulted in some studies being excluded for insufficient data when there was two or less independent studies on an inflammatory marker.

Data Extraction

This meta-analysis was performed according to the Preferred Reporting Items for the Systemic Reviews and Meta-Analyses (PRISMA) guidelines (33, 34). Two separate investigators (MBE and RH) selected potential studies based on inclusion criteria independently. Disputes were resolved by discussion or consultation of another investigator (SD) until agreement was achieved. Data extraction was independently completed in duplicate by MBE and RH. Study characteristics such as primary author, country, setting, number of patients, age, percentage of males and females, comorbidities, serum vitamin D levels, and inflammatory markers levels were extracted. Discrepancies in extraction results were resolved by rechecking the data, discussing the outcome and reaching a consensus.

Data Analysis and Assessment of Heterogeneity

To perform data synthesis and meta-analysis, Review Manager (RevMan. version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used. All data used in this study were unadjusted in nature. The inverse variance method was used for continuous

outcomes represented by mean differences (MD) with a 95% CI. If only median values and interquartile range (IQR25, IQR75) were reported, it was assumed that the median was equal to the mean and the standard deviation (SD) was calculated using the equation: (Q75-Q25)/1.35). Inflammatory markers were converted into one common unit before analysis. The I^2 statistic test was performed to assess study heterogeneity. I^2 of <25% (no heterogeneity), 25-50% (low), 50-75% (moderate), and >75% (high heterogeneity). The statistical significance was set at 95% CI and p value <0.05. A fixed effects model was adopted without significant heterogeneity (I^2< 50% and P > 0.1), while a random effects model was employed in all other instances (I^2 > 50% or P < 0.1)

RESULTS

Study Characteristics

The initial literature search yielded 1039 potential studies with 931 studies excluded based on the previous defined exclusion criteria. 108 articles were left, and the full text articles were reviewed. Of the 108 articles, articles were excluded for the following reasons: wrong populations (9), no comparison groups (14), wrong outcomes (26), unable to calculate needed data (15), patients are already receiving active treatment for COVID-19 (12). Finally, 32 studies were included in our analysis. Figure 1 outlines the selection process for the included studies.

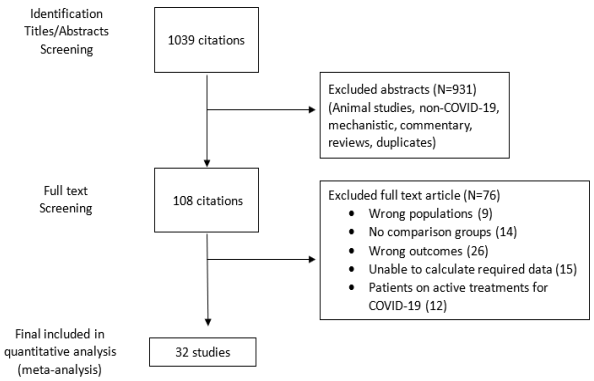

Figure 1. Flow chart of literature review and study selection process for studies including vitamin D levels and inflammatory marker levels.

7,771 patients were included across all studies with eighteen of the studies conducted retrospectively while eleven were conducted prospectively and three were conducted cross sectionally (35-66). Studies included were conducted in Europe (Greece, Italy, Cyprus, Spain, United Kingdom, Germany, and North Macedonia), North America (USA and Mexico), South America (Brazil), and Asia (Turkey, Iran, India, Oman, Saudi Arabia, Indonesia, and Russia). All included studies were conducted in hospital settings. All included studies had a mean patient age between 40 and 81 years of age and an overall percentage male of 57.1%. There were multiple comorbidities mentioned in each study, but the most common were hypertension, diabetes, cardiovascular diseases, and pulmonary disorders. Each study defined vitamin D deficiency differently, but the most common definition was <20 ng/mL. Low vitamin D groups ranged from <9.9 ng/mL to <30 ng/mL.

Vitamin D Levels and Systemic Inflammatory Markers (IL-6, CRP)

There was a significant association between the systemic inflammatory markers and vitamin D levels observed in this study. The analysis of IL-6 levels included 10 total studies and 1,761 patients. IL-6 levels were found to be significantly higher in vitamin D deficient groups (mean difference 7.23; 95% CI, 6.42–8.05; P>0.00001; I^2=41%) (Figure 2). In both the vitamin D deficient and vitamin D sufficient groups, IL-6 levels were higher than the normal reference range of <7 pg/mL (67). CRP levels were also found to be significantly higher in vitamin D deficient groups when compared to sufficient vitamin D groups (mean difference 18.42; 95% CI, 11.70-25.15; P<0.00001; I^2=99%) (Figure 3). Both groups had higher CRP levels than the normal reference range of <8.0 mg/L (68). A total of 28 studies were included in the CRP analysis including a total of 6,889 patients.

Relationship of Vitamin D Levels and Blood or Blood Cell Related Markers (Ferritin, Fibrinogen, ESR, D-dimer)

There was significant association between serum vitamin D levels and ferritin, in which higher levels of ferritin were found in low vitamin D groups (mean difference 95.62; 95% CI, 33.14-158.10; P=0.003; I^2=99%) (Figure 4). A total of 17 studies and 5814 patients were included in the ferritin analysis. The analysis of fibrinogen included 3,267 patients from 7 included studies and showed fibrinogen levels to be significantly higher in vitamin D deficient groups (mean difference 80.69; 95% CI, 7.17-154.20; P=0.03; I^2=83%) (Figure 5). D-dimer also showed to be significantly higher in low vitamin D groups

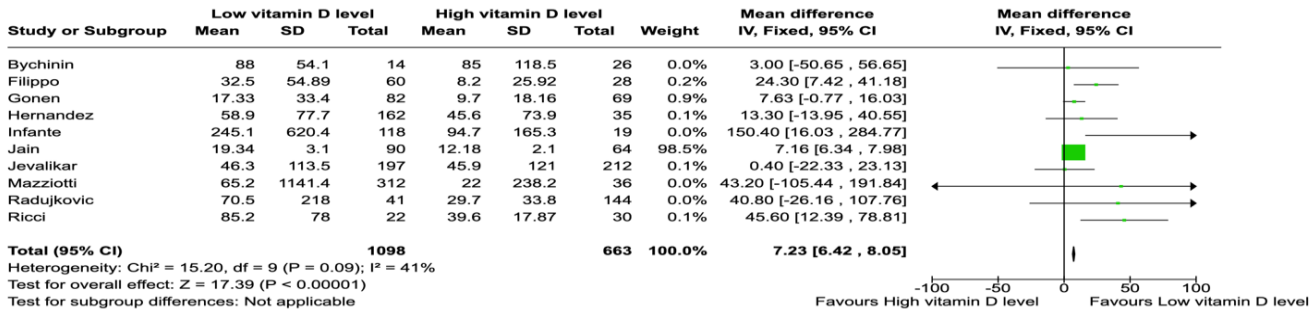

Figure 2. Forest-plot analysis for IL-6 serum levels in low and high vitamin D levels COVID-19 patients. Association between vitamin D (ng/mL) land IL-6 (pg/mL) levels.

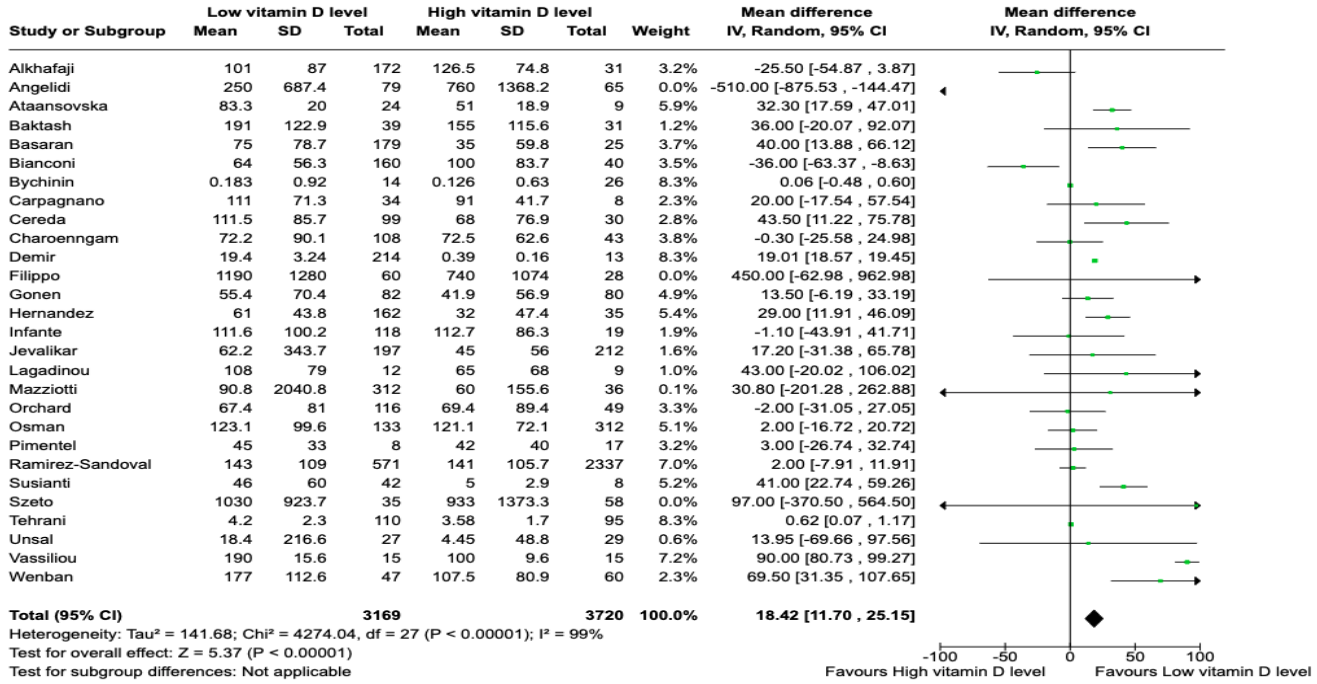

Figure 3. Forest plot between low and high vitamin D levels groups for levels of CRP in COVID-19 patients. Association between vitamin D (ng/mL) and CRP (mg/L) levels. Low vitamin D levels were defined by each individual study and ranged from <9.9 ng/mL to <30 ng/mL.

across 19 included studies (mean difference 0.72; 95% CI, 0.43-1.01; P<0.00001; I^2=91%) (Figure 6). No significant difference was found in ESR levels between low and high vitamin D levels. (Figure 7). All blood related markers in both the vitamin D deficient and vitamin D sufficient groups were higher than the normal reference ranges for healthy patients (ferritin 30-300 ng/mL; fibrinogen 150-350 mg/dl; ESR 0-20 mm/hr; D-dimer ≤500 ng/mL) (68).

Cellular Injury (LDH) in Low and High Vitamin D Status

LDH levels were observed in a total of 5,485 patients in 18 different studies. The LDH levels were found to be significantly higher in the low vitamin D groups (mean difference 60.87; 95% CI, 17.96-103.78; P=0.005; I^2=93%) (Figure 8). LDH levels in both 25(OH)D deficient and sufficient groups had LDH levels higher than the normal reference range for healthy patients of 60-160 U/L (68).

DISCUSSION

Cytokine storm has been found to be a critical cause of death in many COVID-19 patients while vitamin D is known as a key immunomodulatory hormone. The objective of this meta-analysis was to analyze the association between vitamin D levels with inflammatory cytokines and markers in COVID-19 patients. We believe that this may be the first

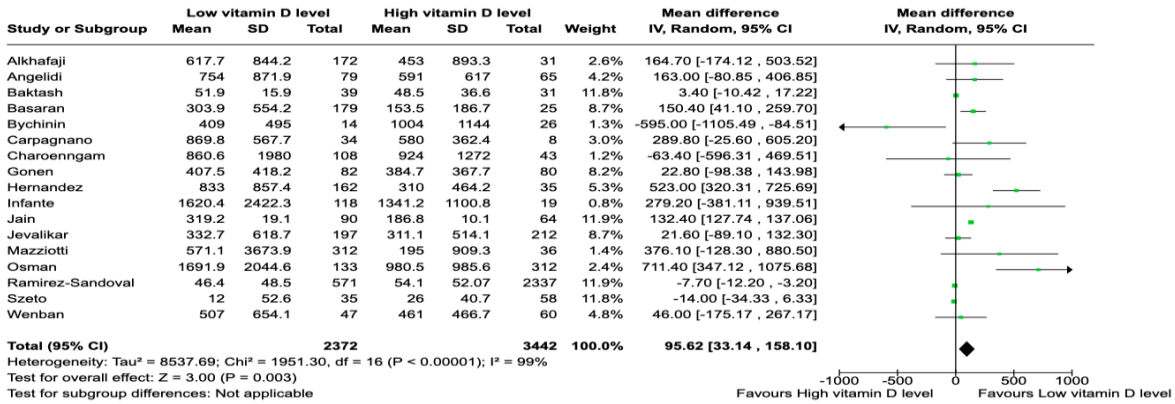

Figure 4. Forest-plot analysis for ferritin levels in low and high vitamin D levels COVID-19 patients. Association between vitamin D (ng/mL) and Ferritin(ng/mL) levels. Low vitamin D levels were defined by each individual study and ranged from <9.9 ng/mL to <30 ng/mL.

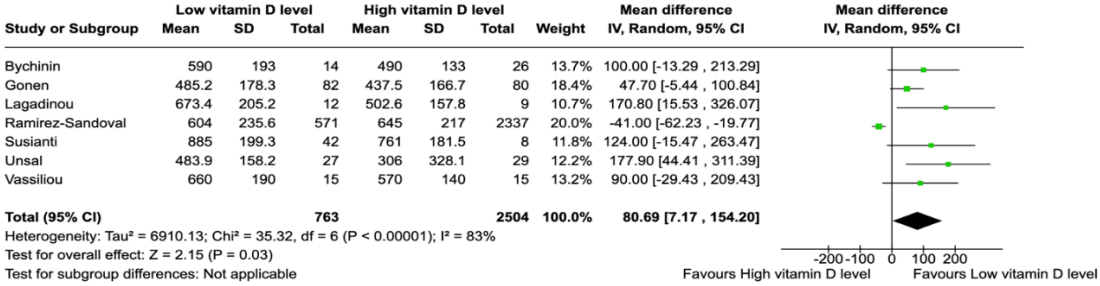

Figure 5. Forest-plot analysis for Fibrinogen levels in low and high vitamin D levels COVID-19 patients. Association between vitamin D (ng/mL) and Fibrinogen(mg/dL) levels. Low vitamin D levels were defined by each individual study and ranged from <9.9 ng/mL to <30 ng/mL.

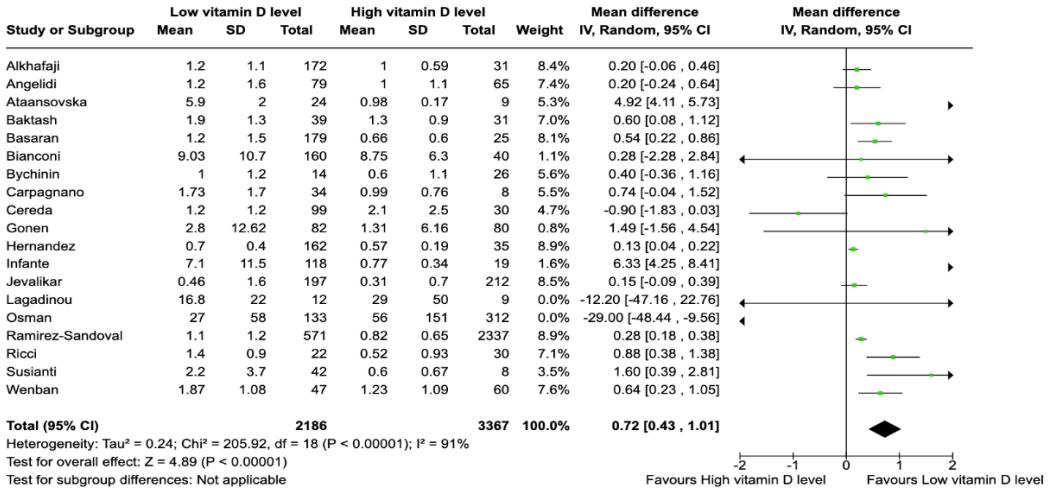

Figure 6. Forest-plot analysis for D-dimer levels in low and high vitamin D levels COVID-19 patients. Association between vitamin D (ng/mL) and D-dimer (mg/L) levels. Low vitamin D levels were defined by each individual study and ranged from <9.9 ng/mL to <30 ng/mL.

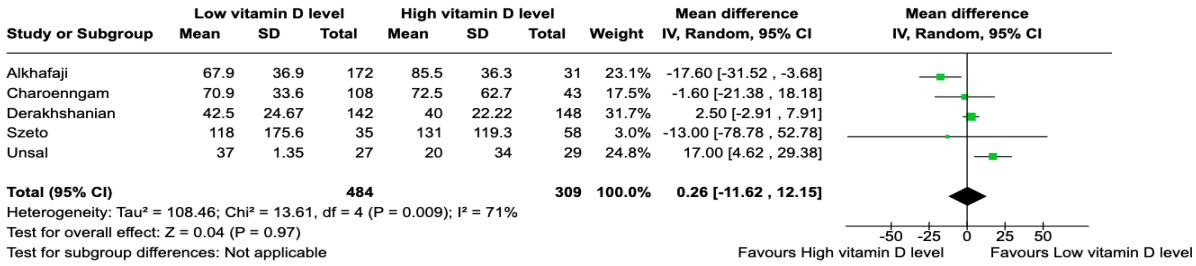

Figure 7. Forest-plot analysis for ESR levels in low and high vitamin D levels COVID-19 patients. Association between vitamin D (ng/mL) and ESR (mm/hr). Low vitamin D levels were defined by each individual study and ranged from <9.9 ng/mL to <30 ng/mL.

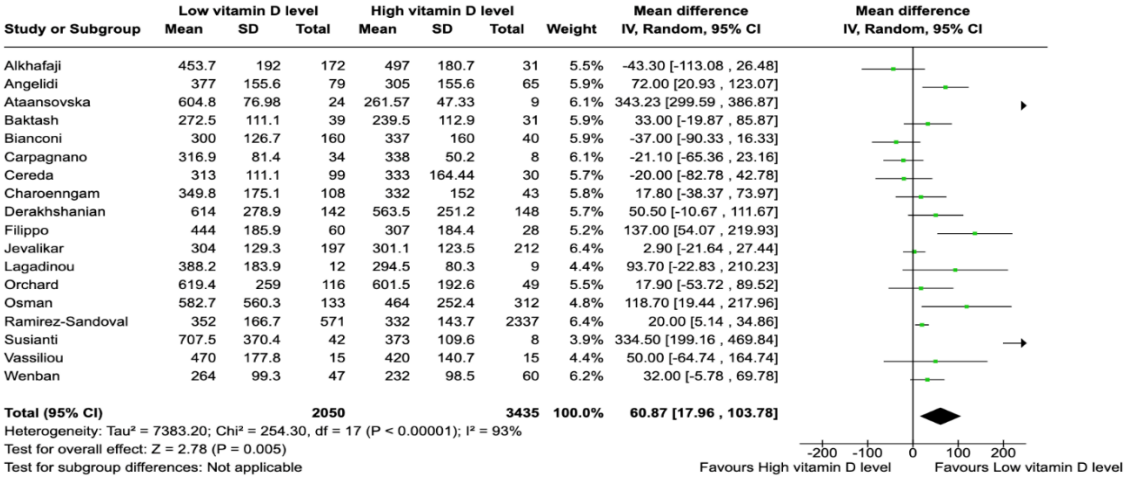

Figure 8. Forest-plot analysis for LDH levels in low and high vitamin D levels COVID-19 patients. Association between vitamin D (ng/mL) and LDH (U/L) levels. Low vitamin D levels were defined by each individual study and ranged from <9.9 ng/mL to <30 ng/mL.

meta-analysis to assess the relationship between vitamin D levels and inflammatory markers in COVID-19 patients. All included studies in this work are observational due to the evolving landscape of the pandemic. All patients were 18 years and older and each study used a different definition for low vitamin D which again decreased uniformity across included studies.

We found that there was a significantly higher level of IL-6, CRP, ferritin, LDH, fibrinogen and D-dimer in the vitamin D deficient groups compared to the control vitamin D groups across the included studies. The highest mean difference was found in ferritin (95.62; 95% CI, 33.14-158.10; P=0.003; I^2=99%). There was no significant relationship between vitamin D levels and ESR (P=0.97). Although not significant, the results showed a trend to be inversely related to vitamin D levels as well. In all patients included (both vitamin D deficient and sufficient groups) the levels of IL-6 CRP, ferritin, ESR, LDH, fibrinogen and D-dimer were much higher than the normal healthy reference ranges. Our results are consistent with other currently available meta-analyses looking at similar inflammatory outcomes. A meta-analysis by Zeng et al. (2020) highlighted the relationship between COVID-19 severity and its association with inflammatory markers. They found that CRP, procalcitonin, IL-6, ESR, serum amyloid A, and serum ferritin all had significantly lower levels in the non-severe group (14). Similarly, Coomes et al. (2020) conducted systematic review and meta-analysis on IL-6 specifically and found significantly higher serum IL-6 levels in severe COVID-19 cases, noting that patients with complicated COVID-19 cases had almost three times higher serum IL-6 than those with noncomplicated disease (69). It is very important to note here that each of these meta-analyses mention COVID-19 severity and inflammatory markers only and do not assess patients' serum vitamin D levels.

Our analysis presents a unique perspective because it is the first meta-analysis specifically examining the relationship between vitamin D status and inflammatory markers in COVID-19 patients.

Vitamin D levels and its relationship with COVID-19 outcomes has been extensively studied, but there is significantly more research needed. Due to the observational nature of the available data, there are some inconsistencies leading to debate on the effect of vitamin D levels and COVID-19 outcomes. However, many meta-analyses have found that higher serum vitamin D levels can significantly improve COVID-19 outcomes. Munshi et al. (2021) determined that patients with poor prognosis (N=150) had significantly lower levels of vitamin D compared to those with good prognosis (N=161) with an adjusted standardized mean difference of −0.58 (95% Cl = −0.83 to −0.34, p <0.001). Poor prognosis was defined as having a severe presentation, ICU admission, or death (29). Pereira et al. (2020) found that prevalence of vitamin D deficiency was 65% higher in those with severe vs mild covid cases (OR = 1.65; 95% CI = 1.30–2.09; I^2 = 35.7%). Vitamin D levels of less than 30 ng/mL also were shown to increase hospitalization and mortality related to COVID-19 (70). A meta-analysis by Bassatne et al. (2021) found conflicting results in which they found no significant relationship between vitamin D levels and COVID-19 mortality, ICU admission, Invasive mechanical ventilation, non-invasive mechanical ventilation or SARS-CoV-2 positivity status (71).

The relationship between vitamin D and CRP is also well researched but some studies fail to show a relationship between CRP and vitamin D levels (72, 73). However, a comparative observational study by Kruit et al. (2016) found that increasing serum vitamin D levels are negatively correlated with CRP levels in elderly patients with inflammatory and non-inflammatory diseases. A stronger correlation was found in the inflammatory disease group (74). Lopez-Munoz et al. (2019) conducted a retrospective longitudinal study to examine the association with vitamin D levels and inflammatory markers in Inflammatory Bowel Disease patients. They also found an inverse correlation between serum vitamin D levels and CRP and intestinal inflammatory markers (75). These relationships between inflammatory markers and serum vitamin D are very important in COVID-19 patients because excessive and dysregulated cytokines is a predictor of COVID-19 severity and a common cause of death in COVID-19 patients (6, 7). It can be postulated that interventional high dose vitamin D supplementation may be able to decrease COVID-19 mortality and improve outcomes through reduction of inflammatory complications. Based on the results from Hashemi et al. (2018) a weekly dose of 50,000 IU for 8 weeks may be sufficient for this purpose (76). The connection between vitamin D, fibrinogen and D-dimer is complex but can be explained by crosstalk between inflammatory and coagulation pathways. Inflammation induces coagulation through 3 main mechanisms; tissue factor mediated thrombin generation, downregulation of anticoagulant pathways, and impairment of fibrinolytic activity (77). Through the inflammation-induced coagulation pathway, pro-coagulation factors such as D-dimer and fibrinogen will increase and therefore raise the risk of thrombosis (77). Thus, reducing inflammation through vitamin D supplementation in patients who are deficient should result in reductions in D-dimer and fibrinogen levels. A clinical trial by Rastogi et al. (2020) found significant reductions in fibrinogen (P <0.01), but not D-dimer, when treating COVID-19 patients (pre-treatment vitamin D levels <20ng/mL) with 60,000 IU of cholecalciferol for 7 days (78). The mechanism of vitamin D and its role in regulation of ferritin and ESR are not well documented. Much of the current literature finds that vitamin D supplementation or serum levels do not have a significant effect on serum ferritin (79, 80). In a systematic review and meta-analysis, vitamin D supplementation at a variety of different doses has been found to be beneficial on ESR in patients with rheumatoid arthritis, but the mechanism has not yet been identified (81). Al-Samkari et al. (2020) retrospectively studied thrombotic complications in 400 hospital admitted COVID-19 patients. They found that elevations in ferritin at initial presentation was predictive of critical illness and initial elevations in ESR was predictive of thrombotic complications in COVID-19 patients (82). Thrombosis is a major complication in COVID-19 patients due to the severe elevation in inflammatory markers (7). The potential of vitamin D supplementation in reducing risk of thrombosis through reductions in fibrinogen levels and ESR could provide another path to reduce COVID-19 complications. Based on the clinical trial by Rastogi et al. (2020), a dose of 60,000 IUs of vitamin D_3 for 7 days may be beneficial in COVID-19 patients (78).

This heterogeneity in retrospective study results highlights the need for randomized clinical trials to determine the efficacy of vitamin D as a treatment for COVID-19 and the effects of sufficient

vitamin D levels on COVID-19 outcomes. Entrenas Castillo et al. (2020) conducted a parallel pilot randomized open label, double-masked clinical trial consisting of 76 patients and found a reduced odds of ICU admission with calcifediol treatment (multivariate risk estimate odds ratio for ICU in patients with calcifediol treatment vs without calcifediol treatment ICU: 0.03; 95%CI: 0.003−0.25) (83). It is plausible that vitamin D will have the same immunomodulatory effects in COVID-19 patients as in other disease states. Calcitriol (active vitamin D) can inhibit production of IL-2, IL-17 and IL-6 translating into the induction of regulatory T-cells (84). A randomized controlled trial by Lakkireddy et al. (2021) studied 87 patients to investigate how N/L ratio, CRP, LDH, IL-6 and Ferritin levels are impacted by 8-10 days (60,000 IUs daily) of vitamin D supplementation in combination with standard treatment. They found highly significant reductions ($P < 0.01$) of all markers (N/L ratio, CRP, LDH, IL-6 and Ferritin) when comparing the vitamin D supplemented group with the standard treatment alone group (85). Vitamin D has a significant effect on regulating pro-inflammatory responses through inhibiting the production of IL-6, IFN-γ, IL-2, and TNF-α; thus, downregulating Th1 mediated immune responses (86). This role in the IL-6 pathway is further validated by another clinical trial where they treated patients with 50,000 IU of vitamin D_3 once a week for 8 weeks and found significant decreases in IL-6 ranging from 5.1-fold to 5.6-fold in multiple sclerosis patients, first degree relatives, and healthy patients (76).

There are several limitations to this meta-analysis stemming from the quality of the available studies and their scarcity leading to a small overall sample size of patients. All included studies were observational studies, primarily non-randomized. Due to the rapid nature of the pandemic, this may have led to potential confounding variables, such as patients being on other treatments, as well as high heterogeneity of the data. Many of the studies included did not assess baseline characteristics between the two groups. 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. In the analysis of fibrinogen and ESR there were only 3 available studies with the necessary information. We attempted to analyze TNF-α levels as well, but there were only two available studies with the information of interest, so it was excluded due to lack of sufficient data. Additionally, many of the studies defined vitamin D deficiency differently which makes it difficult to compile and analyze all the data into one meta-analysis due to the inconsistency of the data. At this point, the results of this meta-analysis show an association and true randomized clinical trials are needed to prove causality and validate the recommendation of Vitamin D supplementation for COVID-19 patients.

CONCLUSIONS

High levels of inflammatory markers in COVID-19 patients have been extensively researched and are well known to increase COVID-19 mortality and severity. Our results showed that low vitamin D levels were associated with increased levels of inflammatory markers in COVID-19 patients. These findings point towards a possible role of vitamin D in reducing cytokine storm. Randomized controlled trials should be conducted to further validate the results of this meta-analysis and establish a causal relationship between vitamin D sufficiency and reduction of inflammatory complications in COVID-19 patients.

CONFLICTS OF INTEREST. None.

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