Effects of Vitamin D Serum Level on Morbidity and Mortality in Patients with COVID-19: A Systematic Review and Meta-Analysis

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ABSTRACT -- Purpose: It has been shown that low Vitamin D serum concentration is associated with increased pneumonia and viral respiratory infections. Vitamin D is readily available, inexpensive, and easy to administer to subjects infected with COVID-19. If effective in reducing the severity of COVID-19, it could be an important and feasible therapeutic intervention. **Methods:** We performed a systematic review and meta-analysis of the literature to determine the effects of Vitamin D serum concentration on mortality and morbidity in COVID-19 patients. The primary objectives were to determine if Vitamin D serum concentration decrease mortality, ICU admissions, ventilator support, and length of hospital stay in COVID-19 patients. **Results:** A total of 3572 publications were identified. Ultimately, 20 studies are included. A total of 12,806 patients aged between 42 to 81 years old were analyzed. The pooled estimated RR for mortality, ICU admission, ventilator support and length of hospital stay were 1.49 (95% CI: 1.34, 1.65), 0.87 (95% CI: 0.67, 1.14), 1.29 (95% CI: 0.79, 1.84), and 0.84 (95% CI -0.45, 2.13). **Conclusion:** There is no statistical difference in mortality, ICU admission rate, ventilator support requirement, and length of hospital stay in COVID-19 patients with low and high Vitamin D serum concentration.

INTRODUCTION

In March 2020, the WHO declared a world pandemic of COVID-19 caused by SARS-CoV-2 infection (1). The infection is associated with severe acute respiratory syndrome resulting from the excessive inflammatory response at 5-7 days. This has a high mortality and patients often require Intensive Care Unit (ICU) care and intubation to cope with the pulmonary response. Another serious complication from COVID-19 is the occurrence of severe thrombotic events affecting limbs, kidneys, or heart (2). In the initial months of the pandemic, there were limited therapeutic treatment options apart from dexamethasone to reduce the body's excessive immune response and no preventive vaccine was yet available.

It has been shown that low Vitamin D serum concentration is associated with increased pneumonia (3) and viral respiratory infections (4). It is postulated that Vitamin D decreases inflammatory mediators such as cytokines (5), platelets (6), and TNF-alpha (7). Vitamin D also regulates the thrombotic pathways.

Vitamin D is readily available, inexpensive, and easy to administer to patients at risk or recently infected. If effective in reducing the severity of the disease response, this would be an important and feasible therapeutic intervention to reduce the inflammatory response of infectious diseases such as COVID-19. The results from the published studies are conflicting. We therefore performed a systematic review and meta-analysis of the literature to determine the clinical effects of Vitamin D serum concentration in COVID-19 patients. The primary objectives are to determine if Vitamin D serum concentration affects the mortality in patients with COVID-19. The secondary objectives are to determine if Vitamin D serum concentration affects: 1) ICU admissions, 2) length of hospital stay, and 3) ventilator support requirement. The systematic review and meta-analysis are registered on PROSPERO (CRD42021243290).

METHOD

The reporting of this systematic review was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement (8)

Search Strategy

The medical librarian (JYK) conducted comprehensive searches in Ovid MEDLINE, Ovid Embase, CINAHL, Scopus, Web of Science Core Collection, and Cochrane Library (via Wiley) on May 1, 2021. To capture all relevant literature pertaining to Vitamin D and COVID-19, search filters were used to optimise the comprehensiveness of the search such as adapting the search from a Cochrane review related to Vitamin D (9). The confirmation of the first COVID-19 case in November 2019, (10) search strategies were limited by publication date from 2019 to current. Refer to the appendices for full-text search strategies. A total of 3572 results were retrieved and when all duplicates were removed, 1570 unique results remained for the initial title and abstract screening in a web-based tool called Covidence (11) In addition to subscription databases, the team searched trial registries (e.g., ClinicalTrials.gov) and Google Scholar. The first 200 results from Google Scholar were evaluated for inclusion, which has been demonstrated to be a reasonable number of results to screen since there is high overlap between Web of Science and Google Scholar (12). Bibliographies from included studies were also reviewed (Supplements).

Data extraction and quality assessment

The references were independently reviewed by two authors (YYH, HLB). Disagreements were resolved by a third author (AC). The data were independently extracted by two authors (YYH, HLB). This included: subject demographic characteristics, first author and year of publication, design of the study, population, intervention, comparator, sample size, and all outcome measures. The meta-analysis consisted of randomized controlled, and observational studies with the following inclusion criteria: 1) COVID-19 positive patients, 2) low Vitamin D serum concentration group, 3) normal Vitamin D serum concentration group, 4) mortality, 5) intensive care unit (ICU) admission, 6) ventilator support, and 7) length of hospital stay. Exclusion criteria were: 1) non-COVID-19 patients, and 2) no serum concentration reported.

STATISTICAL ANALYSIS

The pooled estimates of odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to compare the OR of clinical outcomes between the Vitamin D group and a placebo or standard of care group based on the events of reported mortality, ICU admission, ventilator support, and length of hospital stay. I^2 statistic was applied to inspect heterogeneity. For $I^2 < 50\%$ and p value > 0.1, heterogeneity was acceptable. For $I^2 > 50\%$ and p value < 0.1, the random effect or a meta-regression method to find sources for the obvious heterogeneity was performed. Because the meta-analysis had less than 10 studies, the funnel plot and Egger test were not used to assess the presence of small study effects. All the statistical analyses were performed in Stata 14.1 (Stata Corp, College Station, TX).

RESULT

A total of 3572 publications were identified. After 2002 duplications were removed, the abstracts of 1570 papers were screened. 1521 irrelevant publications were removed and full text for the 49 remaining studies were reviewed. Ultimately, 20 studies are included (Figure 1).

Effect of Vitamin D serum concentration on mortality

The number of deaths reported for low concentration group vs normal concentration group were 819/3125 (26%) and 2162/9681 (22%) patients respectively. The overall pooled estimate of risk ratio (RR) for all studies was 1.49 (95% CI: 1.34, 1.65) using the random effect model with high observed heterogeneity ($I^2 = 83\%$, $P < 0.00001$) (Figure 2).

There are 279/1531 (18%) deaths in the low serum concentration (measured as 25-hydroxyvitamin) group defined as < 20 ng/mL and 252/1369 (18%) deaths in the normal serum concentration group defined as ≥ 20 ng/mL. The overall pooled estimate of RR for these studies is 1.02 (95% CI: 0.64, 1.62) using the random effect model with high observed heterogeneity ($I^2 = 80\%$, $P < 0.0001$) (Figure 3).

Effect of Vitamin D serum concentration on ICU admission

Only three studies reported ICU admission. There were 67/332 (20%) and 114/457 (25%) patients admitted to the ICU in the low serum concentration

group and normal serum concentration group respectively. The pooled estimated RR was 0.87 (95% CI: 0.67, 1.14) with low heterogeneity (I^2 = 0%, p = 0.49) Figure 4.

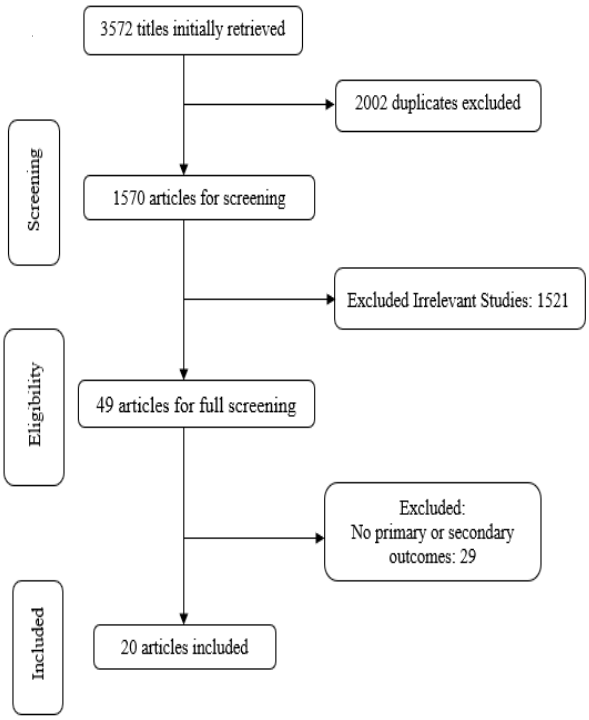

Figure 1. Search Strategy. The characteristics of the studies are summarized in Table 1. A total of 12,806 patients aged between 42 to 81 years old were analyzed. The studies were conducted in United Kingdom (3), Italy (3), United States (2), Iran (2), Germany (2), India (2), Pakistan (1), Thailand (1), Spain (1), Turkey (1), China (1), and Greece (1). The pre-defined Vitamin D serum concentrations varied significantly in the studies. Because the studies are observational studies, the quality of the studies were not assessed as they all have high risk of bias.

The effect of Vitamin D serum concentration on ventilator support requirement.

The reported number of patients requiring ventilator support for the low serum concentration and normal concentration were 267/708 (38%) and 233/920 (25%) respectively. The pooled estimate RR was 1.29 (95% CI: 0.79, 1.84) with high heterogeneity observed between studies (I^2 = 86%, P < 0.00001) (Figure 5). The study from Radujkovic was removed from the analysis and the results showed no difference.

Length of hospital stay

A total of six studies reported the length of hospital stay. The pooled estimate mean difference was 0.84 (95% CI -0.45, 2.13) with low heterogenicity observed between studies (I^2 = 0%, P=0.90) (Figure 6).

DISCUSSION

In this meta-analysis, the results show that Vitamin D serum concentration was not statistically associated with mortality and ICU admission, ventilator support requirement, and length of hospital stay. The studies included in the meta-analysis had various pre-define concentration as low. We conducted a subgroup analysis of the studies with a defined low concentration as < 20 ng/mL since the normal Vitamin D serum concentration is > 20 ng/mL (33). The results did not show a difference. In addition, removing the studies with wide CI did not make a difference.

Vitamin D is a hormone that regulates both innate and adaptive immune responses. Some observational studies showed that patients with respiratory diseases who have higher 25-hydroxyvitamin D levels have better clinical outcomes (34). Vitamin D regulates the inflammatory and oxidative pathways which are triggered in COVID-19 patients (35). In addition, Vitamin D maintains cellular homeostasis (34) by modulating the renin-angiotensin-aldosterone system (RAAS) pathways (36). The RAAS regulates body electrolytes and hemodynamics. It has been observed that serum angiotensin II levels are significantly elevated in COVID-19 infection which is correlated with COVID-19 viral load and lung damage (37). The COVID-19 virus binds to angiotensin-converting enzyme 2 (ACE2) receptors to attack human lung epithelial cells and trigger an infection (38-40). The binding of the ACE2 receptors results in ACE2 inhibiting inflammatory, oxidant, fibrotic, and hyperplasia effects. Moreover, with COVID-19 blocking the ACE2 receptors, the angiotensin II will metabolize ACE2. This results in an accumulation of toxicity, which causes acute respiratory syndrome in patients with COVID-19 (41-43). Vitamin D is a potent suppressor in producing renin (44). When Vitamin D is low, the renin level is high which will put the RAAS in overdrive and resulting in an overproduction of angiotensin II (34,45). It is shown that Vitamin D deficiency can cause an over production of the angiotensin converting enzymes (ACE and ACE2) (46). The active form of Vitamin D (1,25-dihydroxyvitamin D) is also called calcitriol which

inhibits the production and secretion of many cytokines from the smooth bronchial smooth muscle

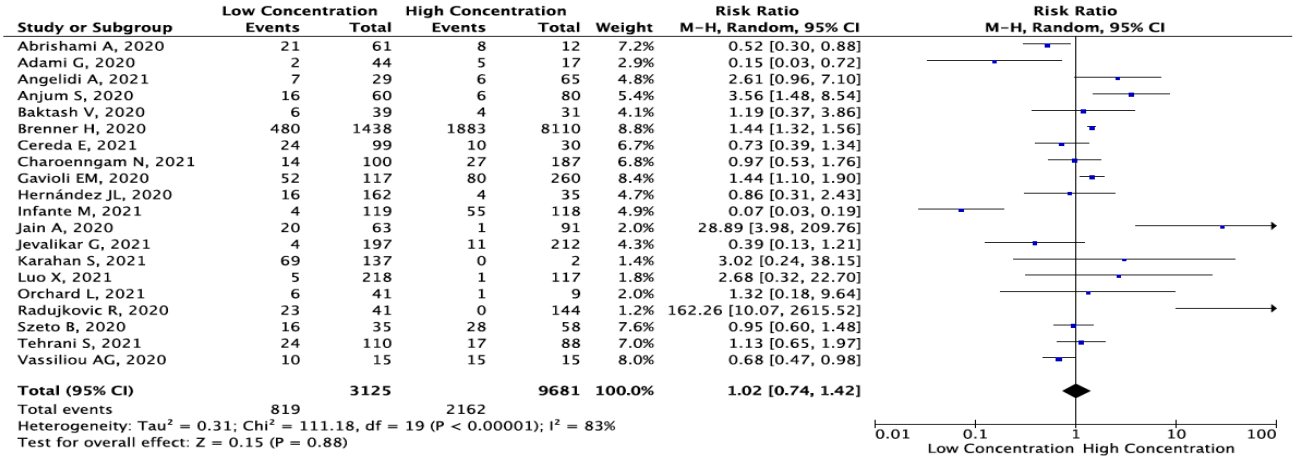

Figure 2. Vitamin D serum concentration and mortality.

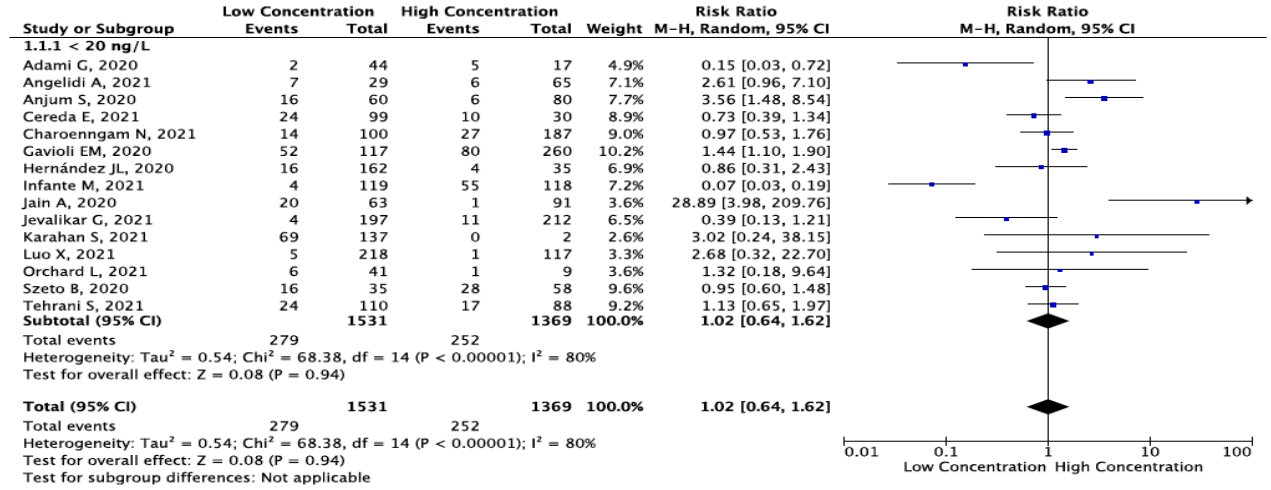

Figure 3. Vitamin D serum concentration of < 20 ng/mL and mortality.

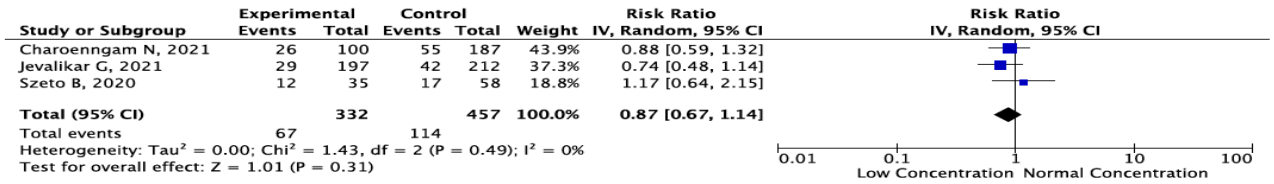

Figure 4. ICU admission between low Vitamin D concentration and normal Vitamin D concentration.

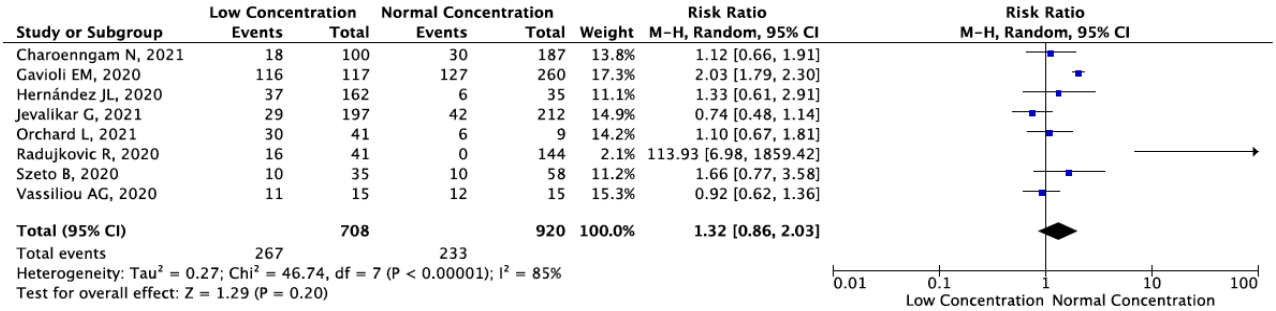

Figure 5. Ventilator support requirement.

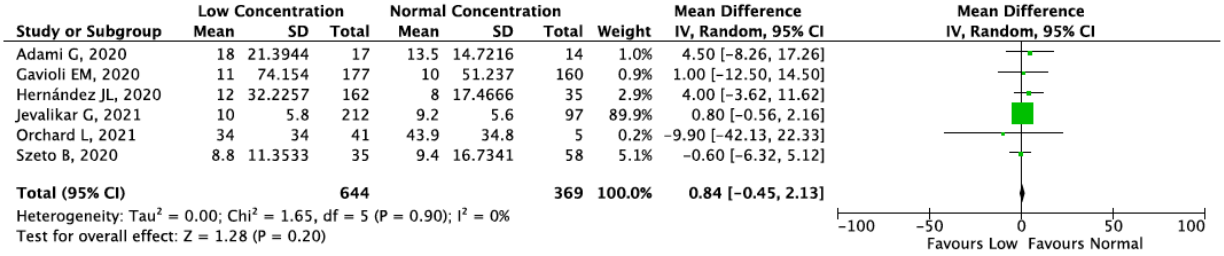

Figure 6. Length of hospital stay.

Table 1. Basic characteristics of studies

Author, year	**Design/Country**	**Patients characteristics, sample size**	**Outcomes**	**Low Concentration (G1)**	**Normal Concentration (G2)**
Abrishami A, 2020	Retrospective Iran	Patients: 73 (G1=61, G2=12)	Mortality	38.41 ± 18.51 (21)	13.83 ± 12.53 (8)
Adami G, 2021	Retrospective Italy	Patients: 61 (G1=44, G2=17)	Mortality	< 20 ng/mL	≥ 20 ng/mL
Angelidi A, 2021	Retrospective, Observational United States	Patients: 144 (G1=29, G2=65)	Mortality	< 30 ng/mL	≥ 30 ng/mL
Anjum S, 2020	Prospective, Observational Pakistan	Patients: 140 (G1=60, G2=80)	Mortality	< 25 nmol/L	≥ 25 nmol/L
Baktash V, 2020	Prospective, Cohort United Kingdom	Patients: 70 (G1=39, G2=31)	Mortality	≤30 nmol/L	>30 nmol/L
Brenner H, 2020	Retrospective Germany	Patients: 9548 (G1= 1438, G2=8110)	Mortality	<30 nmol/L	≥ 30 nmol/L
Cereda E, 2021	Prospective Italy	Patients: 129 (G1= 99, G2= 30)	Mortality	< 30 ng/mL	≥ 30 ng/mL
Charoenngam N, 2021	Retrospective Thailand	Patients: 287 (G1= 100, G2=187)	Mortality Intubation	< 30 ng/mL	≥ 30 ng/mL
Gavioli EM, 2020	Retrospective, Observational United Kingdom	Patients: 437 (G1= 117, G2= 260)	Mortality Intubation	< 20 ng/mL	≥ 20 ng/mL
Hernández JL, 2020	Retrospective, Observational Spain	Patients: 216 (G1= 162, G2= 35)	Mortality Intubation	< 20 ng/mL	≥ 20 ng/mL
Infante M, 2021	Retrospective Italy	Patients: (G1= 19, G2= 118)	Mortality	< 20 ng/mL	≥ 20 ng/mL
Jain A, 2020	Prospective, Observational India	Patients: 154 (G1= 63, G2= 91)	Mortality	14.35 ± 5.79 ng/mL	27.89 ± 6.21 ng/mL
Jevalikar G, 2021	Prospective, Cross sectional India	Patients: 410 (G1= 197, G2= 212)	Mortality ICU Intubation	< 20 ng/mL	≥ 20 ng/mL
Karahan S, 2021	Retrospective, Observational Turkey	Patients: 149 (G1= 137, G2= 2)	Mortality	≤ 30 ng/mL	> 30 ng/mL
Luo X, 2021	Retrospective, Cross sectional China	Patients: 335 (G1= 218, G2= 117)	Mortality	< 30 nmol/L	≥30 nmol/L
Orchard L, 2021	Retrospective Cohort study United Kingdom	Patients: 50 (G1=41, G2=9)	Mortality Intubation	50 nmol/L	> 50 nmol/L
Radujkovic R, 2020	Prospective, Observational Germany	Patients: 185 (G1= 41, G2= 144)	Mortality Intubation	<12 ng/mL	≥ 12 ng/mL
Szeto B, 2020	Retrospective, Cohort United States	Patients: 93 (G1= 35, G2= 58)	Mortality ICU Intubation	< 20 ng/mL	≥ 20 ng/mL
Tehrani S, 2021	Retrospective Iran	Patients: 205 (G1=110, G2= 88, G3 = 7)	Mortality	< 30 ng/ml	≥ 30 ng/ml >100 ng/ml
Vassiliou AG, 2020	Prospective, Observational Greece	Patients: 30 (G1= 15, G2= 15)	Mortality Intubation	< 15.2 ng/mL	≥15.2 ng/mL

*One nmol/L is equal to 0.4 ng/mL, and 1 ng/mL is equal to 2.5 nmol/L.

cells (47-48). It has been proposed that Vitamin D provides a natural anti-inflammatory and antioxidant effect resulting in improved clinical outcomes in patients with COPD (chronic obstructive pulmonary disease) (49). A possible focus in the management of COVID-19 is supplementing Vitamin D in order to prevent or reverse the inflammatory process from the RAAS (50).

Several recent studies suggest patients receiving Vitamin D supplements targeting a serum concentration could reduce the risk of influenza and COVID-19 infections (51-53). This meta-analysis suggests no statistical difference in mortality, ICU admission, and ventilator support requirement between low and normal serum concentration of vitamin D in patients with COVID-19. This renders the determination of the optimal 25-dihydroxyvitamin D serum concentration required for COVID-19 infection challenge.

The most effective and safe dose to administer to achieve a targeted Vitamin D serum concentration is also unknown. A proposed dosing for patients with COVID-19 is between 5,000 IU or 10,000 IU daily, or 50,000 IU to 100,000 IU weekly (52). Additional randomized controlled trials are needed to determine the ideal dose and Vitamin D serum concentration required for attenuation of COVID-19 infection.

Vitamin D has proven to play an important role in calcium absorption and prevention of osteoporosis (54). In addition, observational studies showed a strong correlation between Vitamin D and cancer, type 1 diabetes, and heart diseases (55). It is essential that adequate Vitamin D supplement is consumed to maintain healthy bone and normal calcium metabolism in healthy individuals. Currently, Health Canada recommends daily intake of Vitamin D between 400 IU and 800 IU (56).

Limitations

The meta-analysis consists of 20 observational studies, and they all have high risk of publication bias. Most of the studies are retrospective studies which present a potential risk of bias. The sample size is very small in all but one study (Brenner) which leads to inadequate statistical power. The defined low concentration varied significantly among the pooled analysis. Most of these studies did not disclose if the patients were receiving supplemental Vitamin D and Vitamin D serum concentrations used in the studies are not consistent. In addition, not all of the studies reported the co-morbidities existing in the patients with COVID-19 infection. Lastly, potential confounders such as administration of antiretroviral medications, convalescent plasma or SARS-CoV-2 antibody-based intravenous immunoglobulin therapy which could affect clinical outcomes were given to patients in many of the studies and may cause bias.

CONCLUSION

There is no statistical difference in mortality, {RR 1.02 (95% CI: 0.74, 1.42)}, ICU admission rate, {RR 0.87(95% CI: 0.67, 1.14)} and ventilator support requirement, {RR was 1.29 (95% CI: 0.79, 1.84)}, and length of hospital stay {0.84 (95% CI -0.45, 2.13)} in COVID-19 patients with low and high Vitamin D serum concentration. Additional randomized controlled trials are needed to provide a specific supplemental vitamin dose and Vitamin D serum concentration to target.

CONFLICT OF INTEREST. None.

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