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.

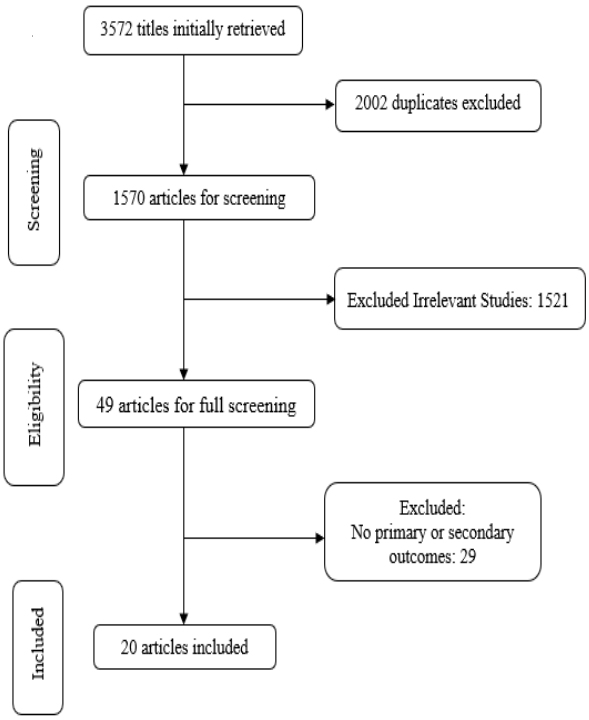

Figure 1. Search Strategy. The characteristics of the studies are summarized in Table 1. A total of 12,806 patients aged between 42 to 81 years old were analyzed. The studies were conducted in United Kingdom (3), Italy (3), United States (2), Iran (2), Germany (2), India (2), Pakistan (1), Thailand (1), 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

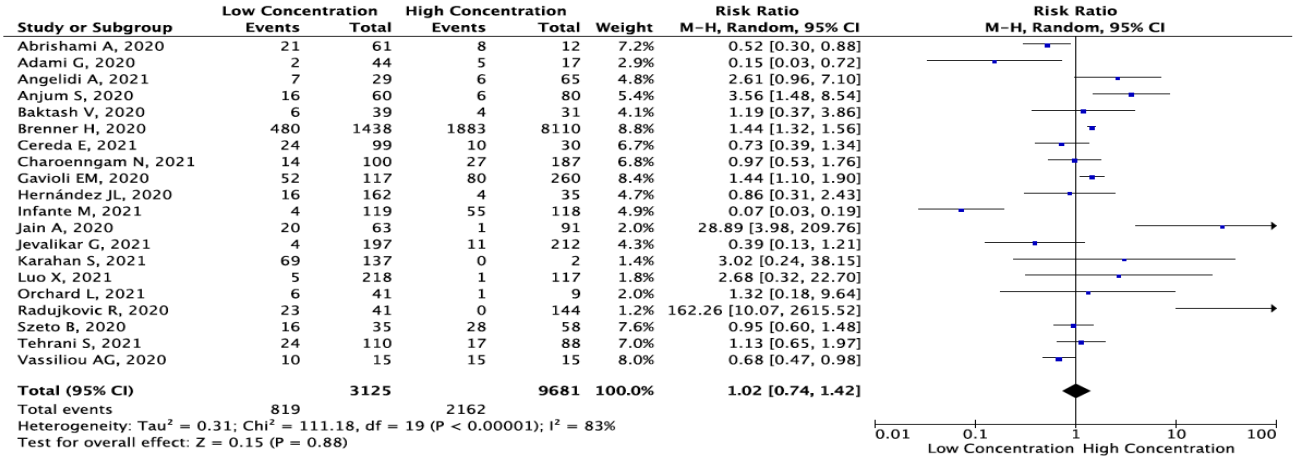

Figure 2. Vitamin D serum concentration and mortality.

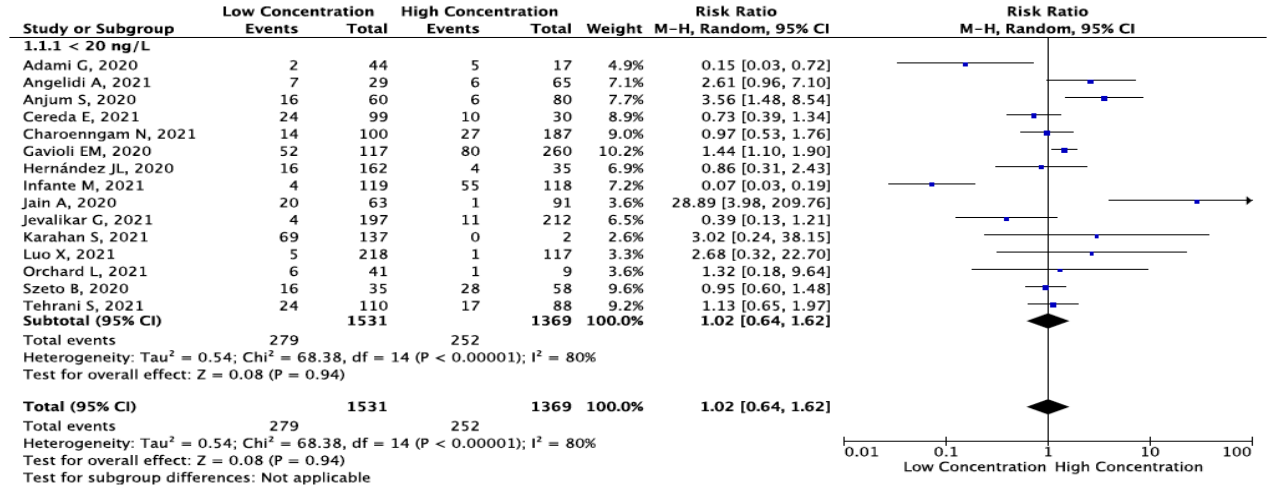

Figure 3. Vitamin D serum concentration of < 20 ng/mL and mortality.

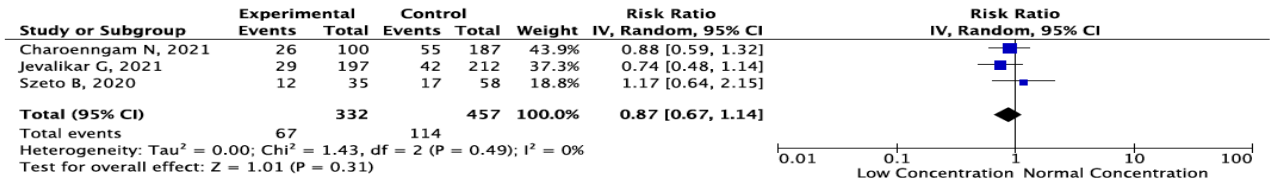

Figure 4. ICU admission between low Vitamin D concentration and normal Vitamin D concentration.

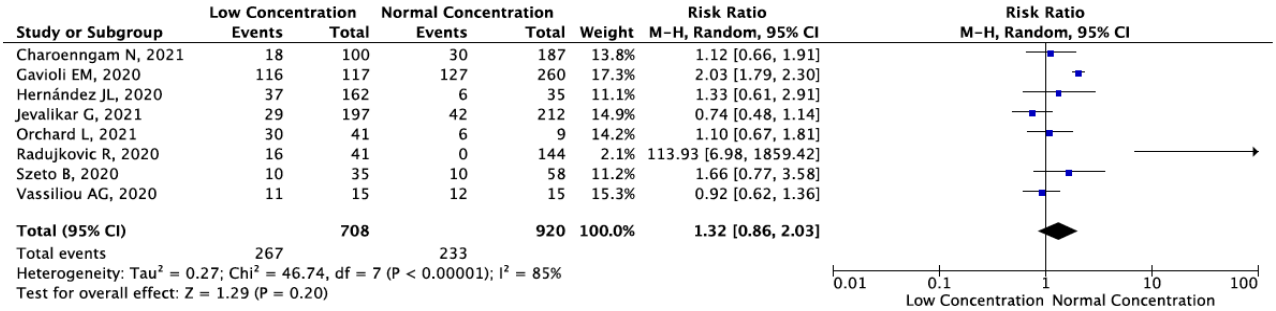

Figure 5. Ventilator support requirement.

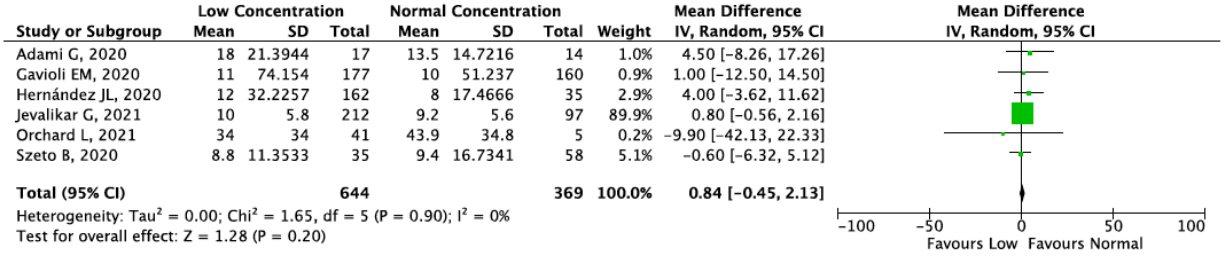

Figure 6. Length of hospital stay.

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

Yiyun Hu[1], Janice Y. Kung[2], Andrew Cave[3], Hoan Linh Banh[3]

SUPPLEMENTS

Database	Search Strategy
MEDLINE **Ovid MEDLINE(R) ALL** 1946 to March 09, 2021	1. vitamin D.mp. 2. vitamin D2.mp. 3. vitamin D3.mp. 4. 1-alpha hydroxyvitamin D3.mp. 5. 1-alpha-hydroxy-vitamin D3.mp. 6. 1-alpha hydroxy calciferol.mp. 7. 1-alpha-hydroxy-calciferol.mp. 8. 1,25 dihydroxyvitamin D3.mp. 9. 1,25-dihydroxy-vitamin D3.mp. 10. 1,25 dihydroxycholecalciferol.mp. 11. 1,25-dihydroxycholecalciferol.mp. 12. 25-hydroxy-vitamin D.mp. 13. 25 hydroxy vitamin D.mp. 14. alfacalcidol.mp. 15. calcidiol.mp. 16. calcitriol.mp. 17. calciferol.mp. 18. ergocalciferol*.mp. 19. cholecalciferol.mp. 20. or/1-19 21. limit 20 to covid-19 22. randomized controlled trial.pt. 23. clinical trial.pt. 24. randomi?ed.ti,ab. 25. placebo.ti,ab. 26. dt.fs. 27. randomly.ti,ab. 28. trial.ti,ab. 29. groups.ti,ab. 30. or/22-29 31. animals/ 32. humans/ 33. 31 not (31 and 32) 34. 30 not 33 35. 21 and 34
Embase **Ovid Embase** 1974 to 2021 March 09	1. vitamin D.mp. 2. vitamin D2.mp. 3. vitamin D3.mp. 4. 1-alpha hydroxyvitamin D3.mp. 5. 1-alpha-hydroxy-vitamin D3.mp. 6. 1-alpha hydroxy calciferol.mp. 7. 1-alpha-hydroxy-calciferol.mp. 8. 1,25 dihydroxyvitamin D3.mp. 9. 1,25-dihydroxy-vitamin D3.mp. 10. 1,25 dihydroxycholecalciferol.mp. 11. 1,25-dihydroxycholecalciferol.mp.

12. 25-hydroxy-vitamin D.mp.
13. 25 hydroxy vitamin D.mp.
14. alfacalcidol.mp.
15. calcidiol.mp.
16. calcitriol.mp.
17. calciferol.mp.
18. ergocalciferol*.mp.
19. cholecalciferol.mp.
20. or/1-19
21. limit 20 to covid-19
22. Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/
23. (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or cross over or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers).ti,ab.
24. (compare or compared or comparison or trial).ti.
25. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
26. or/22-25
27. (random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
28. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

29. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
30. (Systematic review not (trial or study)).ti.
31. (nonrandom$ not random$).ti,ab.
32. Random field$.ti,ab.
33. (random cluster adj3 sampl$).ti,ab.
34. (review.ab. and review.pt.) not trial.ti.
35. "we searched".ab. and (review.ti. or review.pt.)
36. update review.ab.
37. (databases adj4 searched).ab.
38. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
39. Animal experiment/ not (human experiment/ or human/)
40. or/27-39
41. 26 not 40
42. 21 and 41

CINAHL

1 "vitamin D"
2 "vitamin D2"
3 "vitamin D3"
4 alfacalcidol
5 calcidiol
6 calcitriol
7 calciferol
8 ergocalciferol*
9 cholecalciferol
10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
11 ((MH "Coronavirus+") or coronavirus* or covid) AND (wuhan or beijing or shanghai)) OR (("novel coronavirus*" AND ((MH "China") or China)) OR TI coronavirus* OR (((MH pneumonia) or pneumonia) AND Wuhan) OR ((D614G

		or "Covid-19" or Covid19 or "2019-nCoV" or "SARS-CoV-2" or (MH Coronavirus Infections))))) AND ((MH "Coronavirus+") or coronavirus* or covid) AND (wuhan or beijing or shanghai)) OR (("novel coronavirus*" AND ((MH "China") or China)) OR TI coronavirus* OR (((MH pneumonia) or pneumonia) AND Wuhan) OR ((D614G or "Covid-19" or Covid19 or "2019-nCoV" or "SARS-CoV-2" or (MH Coronavirus Infections))))) AND DT 20191201-20300101)
	12	S10 AND S11
	13	(MH (randomized controlled trials OR double-blind studies OR single-blind studies OR random assignment OR pretest-posttest design OR cluster sample) OR TI (randomised OR randomized) OR AB random* OR TI trial OR ((MH (sample size) AND AB (assigned OR allocated OR control))) OR MH (placebos OR crossover design OR comparative studies) OR AB ((control W5 group) OR (cluster W3 RCT) OR PT (randomized controlled trial))) NOT ((MH animals+ OR MH (animal studies) OR TI (animal model*)) NOT MH (human))
	14	S12 AND S13
Scopus		TITLE-ABS-KEY ({vitamin D} OR {vitamin D2} OR {vitamin D3} OR "1-alpha hydroxyvitamin D3" OR "1,25 dihydroxyvitamin D3" OR "1,25-dihydroxy-vitamin D3" OR "1,25 dihydroxycholecalciferol" OR "1,25-dihydroxycholecalciferol" OR "25-hydroxy-vitamin D" OR alfacalcidol OR calcidiol OR calcitriol OR calciferol OR ergocalciferol* OR cholecalciferol) AND ((TITLE-ABS-KEY ((coronavirus* OR "corona virus*" OR oc43 OR nl63 OR 229e OR hku1 OR hcov* OR ncov* OR covid* OR "sars-cov*" OR sarscov* OR "Sars-coronavirus*" OR "Severe Acute Respiratory Syndrome Coronavirus*" OR d614g))) AND NOT ((TITLE-ABS-KEY ((sars OR sars-cov OR mers OR mers-cov OR "Middle East respiratory syndrome or camel*" OR dromedar* OR equine OR coronary OR coronal OR covidence* OR covidien OR "influenza virus" OR hiv OR bovine OR calves OR tgev OR feline OR porcine OR bcov))) OR (TITLE-ABS-KEY ((ped OR pedv OR pdcov OR fipv OR fcov OR sads-cov OR canine OR ccov OR zoonotic OR "avian influenza" OR h1n1 OR h5n1 OR h5n6 OR ibv OR "murine corona*"))))) OR (TITLE-ABS-KEY ((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND wuhan) OR ((2019-ncov OR ncov19 OR ncov-19 OR "2019-novel cov" OR sars-cov2 OR sars-cov-2 OR sarscov2 OR sarscov-2 OR sars-coronavirus2 OR sars-coronavirus-2 OR "SARS-like coronavirus*" OR coronavirus-19 OR covid19 OR covid-19 OR "covid 2019" OR ((covid OR covid19 OR covid-19) AND pandemi*) OR (coronavirus* AND pneumonia)))) OR (TITLE ((novel OR new OR nouveau) AND (cov OR ncov OR covid OR coronavirus* OR "corona virus" OR pandemi*))) OR (ABS ((novel OR new OR nouveau) AND (cov OR ncov OR covid OR coronavirus* OR "corona virus" OR pandemi*))) OR (KEY ((novel OR new OR nouveau) AND (cov OR ncov OR covid OR coronavirus* OR "corona virus" OR pandemi*))) AND (TITLE-ABS-KEY ({Clinical-trial} OR {controlled-trial} OR randomi* OR randomly OR (random W/4 (allocat* OR distribut* OR assign*)) OR {placebo} OR {trial} OR {groups} OR {subgroups}) OR TITLE (rct)) AND (LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019))
Cochrane Library	1	MeSH descriptor: [Vitamin D] explode all trees
	2	vitamin D

via Wiley	3	vitamin D2
	4	vitamin D3
	5	1-alpha hydroxyvitamin D3
	6	1-alpha-hydroxy-vitamin D3
	7	1-alpha hydroxy calciferol
	8	1-alpha-hydroxy-calciferol
	9	1,25 dihydroxyvitamin D3
	10	1,25-dihydroxy-vitamin D3
	11	1,25 dihydroxycholecalciferol
	12	25-hydroxy-vitamin D
	13	alfacalcidol
	14	calcidiol
	15	calcitriol
	16	calciferol
	17	ergocalciferol*
	18	cholecalciferol
	19	{OR #1-#18}
	20	[mh Coronavirus]
	21	[mh "Coronavirus Infections"]
	22	D614G or coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars cov* or sarscov* or Sars coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*
	23	pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019 ncov or sars*
	24	[mh pneumonia] and Wuhan
	25	2019 ncov or ncov19 or ncov 19 or 2019 novel CoV or sars cov2 or sars cov 2 or sarscov2 or sarscov 2 or Sars coronavirus2 or Sars coronavirus 2 or SARS like coronavirus* or coronavirus 19 or covid19 or covid 19 or covid 2019
	26	(novel or new or nouveau) NEAR/2 (CoV on nCoV or covid or coronavirus* or corona virus or pandemi*)
	27	(covid or covid19 or covid 19) and pandemi*
	28	coronavirus* and pneumonia
	29	{OR #20-#28}
	30	#19 AND #29
	31	(randomi* or placebo or randomly or trial* or groups or "drug therapy"):ti,ab
	32	#30 AND #31
		ustom date range: 2019 - 2021
Web of Science Core Collection	1	TS=("vitamin D" OR "vitamin D2" OR "vitamin D3" OR "1alpha hydroxyvitamin D3" OR "1,25 dihydroxyvitamin D3" OR "1,25dihydroxyvitamin D3" OR "1,25 dihydroxycholecalciferol" OR "1,25dihydroxycholecalciferol" OR "25hydroxyvitamin D" OR alfacalcidol OR calcidiol OR calcitriol OR calciferol OR ergocalciferol* OR cholecalciferol)
	2	TS= ((coronavirus* OR "corona virus*" OR oc43 OR nl63 OR 229e OR hku1 OR hcov* OR ncov* OR covid* OR "sars-cov*" OR sarscov* OR "Sars-coronavirus*" OR "Severe Acute Respiratory Syndrome Coronavirus*" OR d614g) NOT (sars OR sars-cov OR mers OR mers-cov OR "Middle East respiratory syndrome" OR camel* OR dromedar* OR equine OR coronary OR coronal OR covidence* OR covidien OR "influenza virus" OR hiv OR bovine OR calves OR tgev OR feline OR porcine OR bcov OR ped OR pedv OR pdcov OR fipv OR fcov OR sads-cov OR canine OR ccov OR zoonotic OR "avian influenza" OR h1n1 OR h5n1 OR h5n6 OR ibv OR "murine corona*"))
	3	TS=(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND wuhan) OR (2019-ncov OR ncov19 OR ncov-19 OR 2019-novel AND cov OR sars-cov2 OR sars-cov-2 OR sarscov2 OR sarscov-2 OR sars-coronavirus2 OR sars-coronavirus-2 OR "SARS-like coronavirus*" OR

coronavirus-19 OR covid19 OR covid-19 OR "covid 2019") OR ((covid OR covid19 OR covid-19) AND pandemic*) OR (coronavirus* AND pneumonia))

4 TI= ((novel OR new OR nouveau) AND (cov OR ncov OR covid OR coronavirus* OR "corona virus" OR pandemi*))

5 AB= ((novel OR new OR nouveau) AND (cov OR ncov OR covid OR coronavirus* OR "corona virus" OR pandemi*))

6 TS= ((novel OR new OR nouveau) AND (cov OR ncov OR covid OR coronavirus* OR "corona virus" OR pandemi*))

7 #6 OR #5 OR #4 OR #3 OR #2

8 #7 AND #1

9 TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple))) NOT TS=(animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or

lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes)

10 #9 AND #8

Web of Science Core Collection: Citation Indexes

- Science Citation Index Expanded (SCI-EXPANDED) --1900-present
- Social Sciences Citation Index (SSCI) --1900-present
- Arts & Humanities Citation Index (A&HCI) --1975-present
- Conference Proceedings Citation Index- Science (CPCI-S) --1990-present
- Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present
- Book Citation Index– Social Sciences & Humanities (BKCI-SSH) --2005-present
- Emerging Sources Citation Index (ESCI) --2015-present

Web of Science Core Collection: Chemical Indexes

- Current Chemical Reactions (CCR-EXPANDED) --1985-present (Includes Institut National de la Propriete Industrielle structure data back to 1840)
- Index Chemicus (IC) --1993-present

Google Scholar vitamin D" AND (covid-19 OR coronavirus)