Clinical Cancer Investigation Journal-ISSN: 2278-0513

Role of vitamin D in severe outcomes of COVID-19: A systematic review and meta-analysis

Running title: Vitamin D and severe outcomes of COVID-19

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Abstract

There are contradictory information regarding the Vitamin D impact on the COVID-19 pandemic. The current meta-analysis was conducted aiming to clarifying the relation between severe outcomes of Covid-19 and vitamin D. We searched electronic databases, such as Web of Science, Scopus, and PubMed until October 16, 2020, and "Vitamin D" AND "COVID-19" we're used as keywords without any time limitation. The relationship between severe outcomes of covid-19 and vitamin d levels was calculated as hazard ratio (HR) and odds ratio (OR). Results were combined using a random-effect meta-analysis. Ten observational surveys were implemented including 359,819 participants. As shown by Meta-analysis, subjects with vitamin D deficiency (serum 25-(OH)-D levels <20ng/mL) encountered a considerably higher risk of death (HR) = 1.93, (95% CI; 1.29 to 2.88). Moreover, the risk of severe outcomes of disease significantly increased with vitamin D insufficiency (VID) (OR) = 2.33, (95% CI; 1.52 to 3.59) in COVID-19 patients. This meta-analysis showed a negative relationship between vitamin D and the higher risk severity of disease and death from COVID-19 patients. However, despite interventional studies being required to confirm this effect, taking vitamin D may be recommended to prevent COVID-19.

Keywords: *Vitamin D, COVID-19, critical outcomes, death*

Introduction

COVID-19 as a respiratory disorder is developed by severe acute respiratory syndrome (SARS-CoV-2). The disease started in late 2019 in China and then spread rapidly around the world [1].

The studies reported many factors are associated with morbidity and mortality of COVID-19. Factors such as age over 50, hypertension, coronary artery disease, and diabetes are associated with the increased severity of symptoms and death [2]. According to the findings of three meta-analysis examinations, smokers show a higher risk of severe outcomes of the COVID-19 by 1.5 times, and it is3 higher times in diabetic individuals and 3.5 times higher in those with high blood pressure [3]. Furthermore, another meta-analysis reported that patients with chronic obstructive lung disease have a higher risk of developing severe symptoms or death from COVID-19 disease [3-5]. At all times, the role of vitamin D in morbidity and mortality of diseases, especially respiratory diseases such as influenza have been paid attention to by researchers. However, Vitamin D is One of the modulators of the immune system that has a protective effect against respiratory infections [6]. In a meta-analysis, vitamin D supplementation was shown to reduce acute respiratory infections remarkably [6]. Nonetheless, well-established evidence is available on the vitamin D role in mortality and morbidity of COVID-19, and there are contradictory

research findings. While some studies indicate the protective role of vitamin D against COVID-19 disease [7]. When there is an inconsistency between studies, a meta-analysis study is recommended to extract a reliable and valid conclusion. Therefore, the present study aimed at providing a valid and strong outcome of the quantitative association between vitamin D and its severe influences and death in patients with COVID-19 through meta-analysis and systematic review.

Methods

This meta-analysis has been prepared and reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [8].

Protocol and Registration

This review was not registered in any database.

Eligibility criteria

Based on the PICOS principle (**P**opulation, **I**ntervention, **C**omparison, **O**utcome, and **S**tudy) in systematic review studies, our criteria were as follows:

Population: Individuals with Coronavirus disease (COVID-19)

Intervention (in an observational study is called "predictor"): Vitamin D status

Individuals with deficiency and insufficiency as a circulating level of 25-(OH)-D of <20 ng/mL and 20–29 ng/mL.

Serum 25-(OH) vitamin D levels were studied by electrochemiluminescence method. Patients were stratified into different groups according to their serum 25-(OH) vitamin D levels. Serum 25-(OH) vitamin D level > 30 ng/ml was accepted as normal. Vitamin D insufficiency and deficiency were defined as serum 25-(OH) vitamin D levels of 21-29 ng/ml and < 20 ng/ml, respectively [9].

Comparison: Individuals with vitamin D sufficiency (25-(OH)-D > 30 ng/ml)

Outcome: Severe outcomes of COVID-19.

Study: Cross-sectional, case-control, and cohort

Information Sources

We selected relevant studies published up to October 16, 2020, by searching Web of Science, PubMed, and Scopus to retrieve the studies to investigate the association between vitamin D with severe outcomes of covid-19. They were included in the study without any time limitation.

Searches

We developed a separate search strategy for each database. The search terms (include vitamin D AND COVID-19 AND Critical Care Outcomes) were used individually and in combination with each other:("Vitamin D" OR "25-Hydroxyvitamin D" OR "cholecalciferol" OR "25-(OH)-D") AND ("COVID 19 OR COVID-19 Virus Disease OR COVID 19 Virus Disease OR COVID-19 Virus Diseases OR Disease, COVID-19 Virus OR Virus Disease, COVID-19 OR COVID-19 Virus Infection OR COVID 19 Virus Infection OR COVID-19 Virus Infections OR Infection, COVID-19 Virus OR Virus Infection, COVID-19 OR 2019-nCoV Infection OR 2019 nCoV Infection OR 2019-nCoV Infections OR Infection, 2019-nCoV OR Coronavirus Disease-19 OR Coronavirus Disease 19 OR 2019 Novel Coronavirus Disease OR 2019 Novel Coronavirus Infection OR 2019-nCoV Disease OR 2019 nCoV Disease OR 2019-nCoV Diseases OR Disease, 2019-nCoV OR COVID19 OR Coronavirus Disease 2019 OR Disease 2019, Coronavirus OR SARS Coronavirus 2 Infection OR SARS-CoV-2 Infection OR Infection, SARS-CoV-2 OR SARS CoV 2 Infection OR SARS-CoV-2 Infections OR COVID-19 Pandemic OR COVID 19 Pandemic OR COVID-19 Pandemics OR Pandemic, COVID-19") AND (Patient Outcome Assessment OR Critical Care Outcomes OR Fatal Outcome).

No time restrictions were adopted, and queries were limited to human studies. Moreover, we screened reference lists of all relevant articles to ensure we would not miss pertinent studies. As an alternative for grey literature, we searched Google and Google scholar to find conference proceedings, thesis, and dissertation, unpublished reports as papers. Moreover, we activated a search alarm to notify the latest papers related to our search queries.

Study Selection

The search results were entered in all retrieved studies into EndNote software, and duplicate cases were removed. Subsequently, we screened the studies based on the title and abstract of the studies. For the next step, we read the full text of the remained papers to determine the relevant studies. Two independent reviewers (T.O and M.D.M) assessed the eligibility of the studies based on the criteria mentioned above.

Data collection process

After the selection of the eligible studies, we used a datasheet to extract information of interest. This datasheet includes the name of the first author, country, sex, age, study design (case-control, cohort, and cross-sectional), sample size and effect size for each study, and type of effect size (adjusted, unadjusted) with associated 95% confidence interval (95% CI) were extracted.

Data Items

Our main variables for this study were deficiency and insufficiency of 25-(OH)-D and severe infection and death of COVID-19 disease.

Risk of bias in individual studies

We assessed the risk of bias and quality in each study by the Newcastle Ottawa statement (NOS) checklist.

Summary Measures

In this study, we used two different effect sizes for each association, because we couldn't convert them into each other. Odds Ratio (OR) and Hazard ratio (HR) with a 95% confidence

Interval as our summary measure of interest were reported.

Synthesis of results

In this study, we used a random effect method for combining the results of studies. Moreover, we performed statistical analyses at a significance level of less than 0.05. Moreover, heterogeneity and publication bias was assessed by I^2 statistics and Egger and Begg's test, respectively [10, 11]. The data were analyzed by 'ipdmetan' packages of R software.

Results

The steps for implementation of the meta-analysis are shown in Fig.1. 721 articles were obtained from the systematic literature review in databases (Web of Science 166, Scopus 284, PubMed 271) until October 16, 2020, and screening the reference lists. The EndNote online library was used to manually remove duplicates, which were 245. After examining the titles and abstracts of 489 articles, the authors excluded 464 irrelevant articles. Therefore, the eligibility of 25 full articles was evaluated. 15 articles were removed since they did not meet the inclusion criteria. Lastly, 10 works were examined in the meta-analysis. These 10 studies included 359,819 participants.

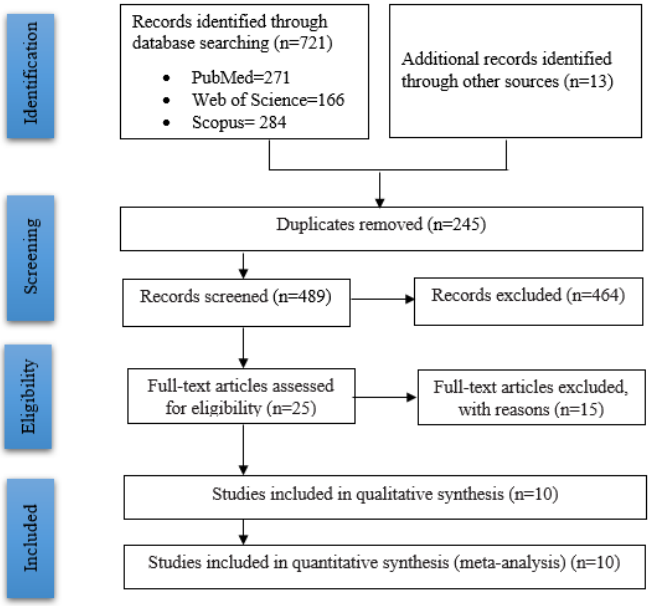

Fig 1. The flow diagram of information in the various phases of the systematic review and meta-analysis

Table 1 reports the characteristics of the articles. We present the result of the meta-analysis for the association of deficiency and insufficiency of 25-(OH)-D with Severe outcomes and death of COVID-19 disease separately. The quality of the studies was assessed using the NOS manual. Based on this scale, all studies [12-21] had the highest quality score and good quality.

Table1: Summary of articles contained in the final step of meta-analysis

	Age (yr)					
Author	Mean	Range	Study	Estimate	Sample size	NOS
Maghbooli [18]	58.7	20-29	Cross-sectional	Crude	235	8
Macaya [17]	-	50-84	Cohort	Adjusted	80	7
Radujkovic [20]	-	49-74	Cohort	Adjusted	185	8
Brenner [14]	62.1	50-75	Cohort	Adjusted	9548	8
Merzon [19]	-	0-80+	Cohort	Adjusted	7807	8
Abrishami [12]	55.18	-	Cohort	Adjusted	73	6
Baktash [13]	81	65-102	Cohort	Crude	105	6
Ye [21]	-	31-69	Case-control	adjusted	142	7
Hars [15]	85.9	-	Cohort	Adjusted	160	7
Hasti [16]	-	37-73	Cohort	Adjusted	341484	8

Association of vitamin D with the death of COVID-19

Nine studies examined the association of vitamin D status with death from COVID-19. The relationship between the COVID-19 mortality and vitamin D deficiency (VDD) was assessed by seven studies, and two articles examined the relation between vitamin D insufficiency (VID) and death.

Five studies used HR to assess the association between VDD and death from COVID. Meta-analysis of these studies showed that the association between VDD and death from COVID-19 was significant. A pooled hazard ratio (HR) of association of VDD with death was 1.93 (95% CI; 1.29 to 2.88, I^2= 60%) (Fig.2).

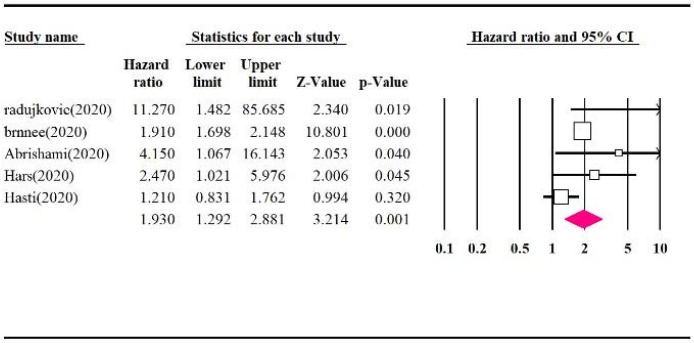

Fig.2: Forest plot of the association between VDD and mortality from COVID-19 (Effect size=Hazard Ratio)

Two studies assessed the association between VDD and death from COVID-19 using OR as effect size. Accordingly, despite the meta-analysis showing that VDD increases the risk of death from COVID-19 by three times, it statistically was not significant. (OR=3.01, 95% CI; 0.64 to 14.21, I^2= 58.02) (Fig.3).

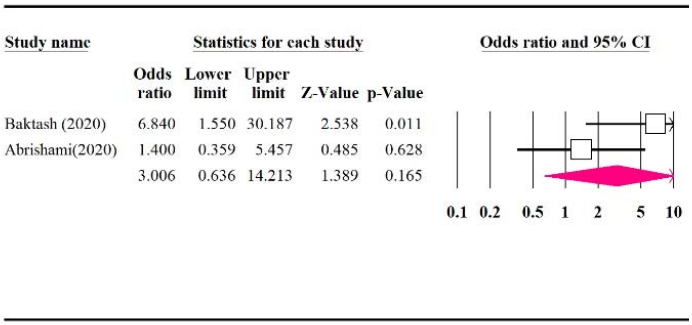

Fig.3: Forest plot of the association between VDD and mortality from COVID-19. (Effect size=odds ratio)

Two studies reported OR as a summary measure to assess the association between VID and death from COVID-19. However, the meta-analysis didn't show a significant result. A pooled odds ratio of association of VID with the death of COVID-19 was 1.19 (95% CI; 0.99 to 1.47, I^2= 48.3) (Fig.4). Egger and Begg's test did not have a significant result, which indicates the absence of bias in reporting of the studies (P=0.14).

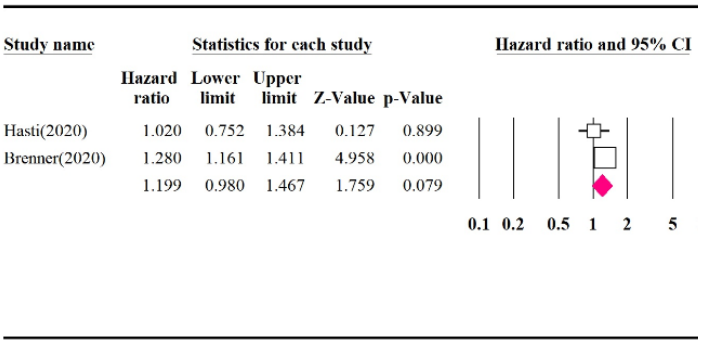

Fig.4: Forest plot of the association between VDI and death of COVID-19. (Effect size=Hazard Ratio)

Association of vitamin D with Severe outcome of COVID-19

In this sub-section, we assessed the association of vitamin D with all forms of severe outcomes of COVID-19 including death.

Seven studies examined the association of vitamin D status with severe outcomes of COVID-19. Out of the seven studies, five ones studied the relationship between VDD and severe outcome of COVID-19 and two articles studied the relationship between VID and severe outcome.

Discussion

The purpose of the present meta-analysis was examining the effect of vitamin D on the Covid-19 severe consequences.

In this meta-analysis, we found that individuals with vitamin D deficiency or vitamin D insufficiency are at more risk of severe outcomes of COVID-19. Therefore, death risk in patients with COVID-19 who suffered from VDD was 1.93 times more than those with sufficient levels of vitamin D, and it was a statistically significant association.

Furthermore, we found that odds of the severe disease outcomes in patients with a serum vitamin D level of less than 20 ng/ml (25 (OH) D < 20 ng/ml) or VDD was 2.03 times higher than in patients with adequate serum vitamin D level (25-(OH)-D > 30 ng/ml). However, The pooled odds ratio of the two studies showed that the risk of death from COVID-19

A meta-analysis of five studies for an association between VDD and severe outcomes of COVID-19 showed a significant result. A pooled odds ratio of association of VDD with the severe outcomes of COVID-19 was 2.33 (95% CI; 1.52 to 3.59, I^2= 0.0) (Fig.5).

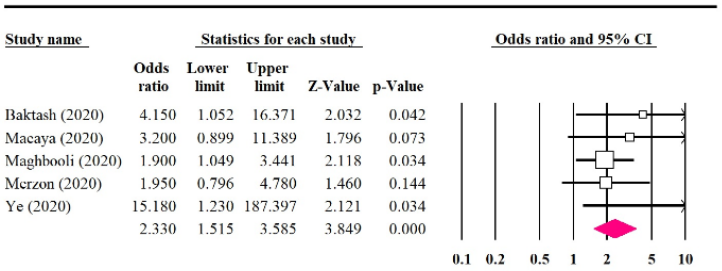

Fig.5: Forest plot of the association between VDD and severe outcome of COVID-19. (Effect size=Odds Ratio)

Meta-analysis of two studies showed that the association between VID and severe outcomes of COVID-19 was not significant. A pooled hazard ratio of association of VID with the severe outcomes of COVID-19 was 2.25 (95% CI; 0.45 to 11.24, I^2= 85.3) (Fig.6).

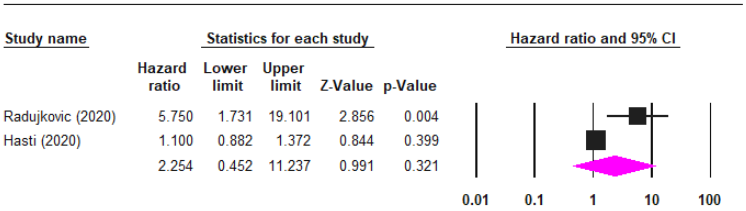

Fig.6: Forest plot of the association between VDI and severe outcome of COVID-19. (Effect size=Hazard Ratio)

Quality assessment

Assessing the quality of the studies using NOS showed that two studies (Baktash and Abrishamchi) had the lowest score (6 out of 8) and other studies had the higher score.

Publication bias

None of the analyses showed a statistically significant result for Begg's and Egger's tests for evaluating the potential presence of bias reporting (P>0.05).

in patients with VDD is 3.02 times higher than those with adequate serum vitamin D levels (25-(OH)-D > 30 ng/ml), this association was not statistically significant. Moreover, the pooled odd ratios of the two studies showed that the risk of death from COVID-19 in patients with vitamin D insufficiency is 1.19 times higher than in patients with adequate serum vitamin D level (25-(OH)-D > 30 ng/ml); but this relationship was not statistically significant as well. The mixed risk ratios of the two studies showed that the risk of severe disease outcome was 2.21 times higher in patients with inadequate vitamin D levels (VID) than in those with adequate serum vitamin D levels (25-(OH)-D > 30 ng/ml), but this relationship was not statistically significant (P = 0.323). It seems that two major factors make non-significant results. First, the meta-analysis included a small number of studies. Second, the original studies presented a low precision. Thus, an insignificant outcome was obtained in the meta-analysis of two articles. It is well-known that vitamin D has a critical role modulating immune responses and functions [22]. Hence, the appearance and adverse consequences of respiratory infectious diseases, e.g., COVID-19, can be affected by serum vitamin D levels. Many studies have so far investigated the relationship between serum vitamin D levels and their outcomes on COVID-19. Innate immunity (the immediate response of macrophages to invading bacteria and viruses in the mucous membranes) is affected by vitamin D, which decreases the severity and incidence of acute respiratory infections and adaptive immunity. As a result, the cellular immune response is modulated and cytokine storms are attenuated, which is a fatal event in SARS-CoV2-induced pneumonia [23].

However, there is widespread evidence that vitamin D strengthens the immune system and reduces inflammation [24]. The body's physical barriers are improved by immunomodulatory characteristics of vitamin D through regulation of the protein production for adheren junctions, gap junctions, and tight junctions, which microorganisms can disturb them. These microorganisms include viruses. Also, the production of antimicrobial peptides, like defensins and cathelicidin can be stimulated, T helper (Th) cell responses can be modulated for inducing a shift from Th1 to Th2 responses, and cytokine storms can be prevented by reducing inflammatory cytokines and activating nuclear factor κB (NF-κB) [25]. Also, the expression of the angiotensin-converting enzyme 2 (ACE2: the important receptor for CoV-2 entry into host cells) and some important genes of the virulence mechanisms of COVID-19 are modulated by vitamin D [26, 27]. Consequently, the coronavirus invasion can be prevented by sufficient levels of vitamin D through strengthening physical barriers and elevating the antimicrobial peptide production in the lung epithelium [25].

Many mechanisms are involved in vitamin D that are able to decrease the death and microbial infection risks [28, 29]. The results of several studies have shown that vitamin D reduces the risk of respiratory infections [30-32]. Vitamin D increases antimicrobial peptides including human cathelicidin LL-37 in the innate immunity of the cell [33]. Cathelicidins present antimicrobial action, which include anti-gram-negative and gram-positive bacteria, fungi, and nonenveloped and enveloped viruses [34]. The results of a laboratory study showed that 1,25-(OH)2-D reduces rotavirus replication in vitro and in vivo [35]. The result of a clinical trial study showed that vitamin D supplementation of 4000 IU/d reduces dengue virus infection [36]. Besides, the cellular immune system is boosted by vitamin D through the reduction of the cytokine storms, resulting from innate immunity. It is observed in COVID-19 patients that the innate immune system generates anti- and pro-inflammatory cytokines in reaction to bacterial and viral infections [37]. The results of the Gruber-Bzura study showed that vitamin D reduced the risk of influenza [37]. Pro-inflammatory cytokine storms from CoV infections exacerbate cases in SARS-CoV [38] and MERS-CoV (20). As shown by recent surveys on COVID-19 infection, there is an association between this disease and a higher generation of pro-inflammatory cytokines, like interleukin-6 and C-reactive protein [39], increased risk of pneumonia [40], heart failure, and acute respiratory distress syndrome [41]. Patients with severe COVID-19 infection have severe inflammatory responses that ultimately endanger their health and survival [42]. In general, vitamin D has receptor (VDR) on almost all cells of the immune system [43] plus affects macrophages and monocytes (↑ antimicrobial peptides including cathelicidins and β-defensin and phagocytosis and ↓ IL-6 and IL12), T helper cells (↓ differentiation in Th17 and Th1, IL17A, IL17F, TNFγ, IL21, TNFα, IL2, IL9, and IL22 and ↑ apoptosis of Th17 and Th1 cells, differentiation in Th2, IL3, IL4, IL5, and IL10), dendritic cells (↓ expression MHCII, presenting antigen cells, IL12, and IL23 and ↑ TGFβ and IL10), B cells (↓ proliferation, differentiation in plasma cells, and secretion Ig), and T regulatory cells (↑ differentiation, IL10, and TGFβ)[44, 45]. Vitamin D can be considered an important factor in the pathophysiology of SARS in COVID-19. In a study by Davolio et al., it was indicated that positive COVID-19 patients had lower 25-OH-D levels compared to those with a negative test [46]. Macayz et al. [47] indicated the relation between VDD and severe outcomes of COVID-19 disease. Besides, an ecological survey indicated that vitamin D level is inversely related to death from COVID-19 in each country [7]. Zhou et al. [48] performed a meta-analysis to determine the association between vitamin D deficiency and community-acquired pneumonia (CAP). The present meta-analysis demonstrated that vitamin D deficiency is related to a higher risk of CAP.

Nevertheless, a meta-analysis was conducted by Munshi et al. [49] using Web of Science, PubMed, Google Scholar, Science Direct, MedRxiV, and Scopus databases until June 8, 2020. Finally, they retrieved 6 retrospective studies. They reported that serum vitamin D levels may play a role in the prognosis of COVID-19 disease. A study by Grant et al. [50] showed that prescribing vitamin D for people with vitamin D deficiency can prevent viral infections of the respiratory tract, especially influenza and coronaviruses.

The results of this study provide reliable and valid information about the role of vitamin D in the severe consequences of COVID-19 disease by combining many different studies. This work presented valid and reliable data on the role of vitamin D in the severe outcomes of COVID-19 by integrating a large number of studies. Consequently, it can be stated that serum vitamin D levels has a role in the severe consequences and mortality of COVID-19 patients. It can be recommended to take foods containing vitamin D and its supplements for boosting the immunity system and decreasing the risk of severe consequences of COVID-19, particulate mortality.

However, despite the advantages of this meta-analysis, several limitations should be paid attention to. First, all studies included in this meta-analysis were observational, and no interventional study exists to include them in the study. The major defect of observational studies is the confounding effect of other factors such as age, sex, gene, etc. interventional studies through randomization remove the confounding effects of other factors. Therefore, designing interventional studies on large scale is recommended. Second, we search international and English language databases and not local and non-English databases, therefore, we may miss relevant studies. Third, because the studies have used different definitions and effect sizes, therefore we can't report one single effect size and we are forced to report several reports of an association between vitamin D and COVID-19.

Conclusion

This meta-analysis endorses the protective effect of vitamin D on severe outcomes of COVID-19, especially death. Taking foods that contain vitamin D to obtain sufficient vitamin D is necessary. Nevertheless, further research is needed for a comprehensive demonstration of the role of vitamin D levels or its supplement and its impact on the severe outcomes and mortality from COVID-19.

Abbreviations

Vitamin D deficiency (VDD)

Vitamin D insufficiency (VID)

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

Newcastle Ottawa Statement (NOS)

Chronic obstructive L disease (COLD)

Consent for publication

Not applicable.

Standards of reporting

PRISMA guidelines were used in this study

Availability of data and materials

The corresponding author is responsible for the data. Access to all relevant raw data will be free to any scientist.

Conflicts of interest

The authors have no conflict of interest.

Financial support

The study was funded by the Hamadan University of Medical Sciences (No. 9910256386).

Acknowledgments

The authors of this article express their gratitude to the Research and Technology Vice-Chancellor of Hamedan University of Medical Sciences and all those involved in this project.

Authors' contribution

All authors participated in all stages of the article and approved the final version of the article.

Ethical statement

All cases including data fabrication, plagiarism and double publication have been completely observed by the authors.

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