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A systematic review and meta-analysis of effect of vitamin D levels on the incidence of COVID-19

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Abstract

Background: *Coronavirus disease 2019 (COVID-19) is a disease primarily affecting the respiratory tract, however due to the nature of the pathogenesis it is able to affect the whole body. So far, no causative treatment has been found and the main strategy when dealing with COVID-19 relies on widespread vaccination programs and symptomatic treatment. Vitamin D due to its ability to modulate the immunological system has been proposed as a factor playing role in the organism response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Therefore, we decided to perform this meta-analysis which aimed to establish a connection between vitamin D status and COVID-19 infection.*

Methods: *Study was designed as a systematic review and meta-analysis. PubMed, EMBASE, Web of Science, Cochrane Collaboration Databases and Scopus electronic databases were searched for relevant studies from database inception to May 10th, 2021. Mean differences (MDs) with their 95% confidence intervals (CI) were calculated.*

Results: *Thirteen studies providing data for 14,485 participants met the inclusion criteria. Mean vitamin D levels in SARS-CoV-2 negative patients was 17.7 ± 6.9 ng/mL compared to SARS-CoV-2 positive patients 14.1 ± 8.2 ng/mL (MD = 3.93; 95% CI 2.84–5.02; I^2 = 99%; p < 0.001).*

Conclusions: *Low serum vitamin D levels are statistically significantly associated with the risk of COVID-19 infection. Supplementation of vitamin D especially in the deficiency risk groups is indicated.*
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Key words: vitamin D, COVID-19, coronavirus disease 2019, SARS-CoV-2, systematic review, meta-analysis

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Introduction

Since the outbreak of the new type of coronavirus disease called novel coronavirus disease 2019 (COVID-19) in Wuhan China in 2019 [1, 2] medical systems all over the world have been under immense pressure, resulting in a rapid increase in the cost of care [3]. The virus infects the host via angiotensin converting enzyme 2 (ACE2) [4]. Due to the fact that ACE2 expression is the highest in the respiratory tract [5] it is the respiratory symptoms that are most prominent in COVID-19, however the ACE2 is expressed in the whole body which explains the multisymptomatic nature of the disease [6]. Due to rapidly spreading nature of the disease and its ability to disorganize the healthcare systems by the increased number of patients requiring intensive care the research was focused on finding a causative treatment. Several drugs have been proposed which include, but are not limited to: hydroxychloroquine [7, 8], janus kinase 2 inhibitor Fedratinib [9] or Remdesmivir [10]. None of which had been able to demonstrate utility in the treatment of COVID-19. Therefore, the efforts were focused on the development of the vaccines and so far, there are several drugs on the market that are able to relieve some of the tension placed on the healthcare system by COVID-19 [11, 12]. However, while vaccination programs are widespread and the number of vaccinated patients grows, the underlying risk factors for the severe course of COVID-19 are still being investigated. So far, several factors were established i.e.: obesity [13], diabetes [14] and smoking [15]. The common denominator for all of these risk factors is the disturbed immunological response which may in fact be the underlying mechanism for the severe course of COVID-19. One of the most common and thoroughly examined causes of immunosuppression is vitamin D deficiency [16]. Vitamin D plays a key role the modulation of the immunological response in both autoimmune and infectious diseases [17], via multiple patterns. Among many others it modulates the maturation of macrophages [18], regulates the T-lymphocyte stimulatory function of antigen-presenting cells [19] and regulates B-lymphocyte proliferation [18]. Therefore, it comes as no surprise that in the era of COVID-19, vitamin D became an object of interest for much research worldwide in terms of preventing the severe course of the disease. We decided to perform this meta-analysis in order to establish a possible link between the levels of vitamin D and COVID-19 infections.

Methods

This trial was prepared following the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [19]. Before commencing the study, analyses methods as well as inclusion and exclusion criteria to be used were agreed upon. Because of the nature of this systematic review and meta-analysis, this study was exempt review by the institutional review board.

Literature search

A systematic review was carried out using PubMed, EMBASE, Web of Science, Cochrane Collaboration Databases and Scopus electronic databases. The most recent search was performed on May 10th, 2021. Titles and abstracts were screened by two authors independently (A.G. and W.G.). All retrieved articles were reviewed by two authors (J.S. and A.G.). Any disagreement was resolved through consensus or, if necessary, by discussion with a third author (L.S.).

The search was performed using the following terms: "25-hydroxyvitamin D" OR "25(OH)D" OR "vitamin D" AND "coronavirus" OR "SARS--CoV-2" OR "COVID-19". A manual search of references listed in reviews and reports was also performed. Only full articles in the English language were considered. All references were saved in an EndNote (End Note, Inc, Philadelphia, PA) library used to identify duplicates.

Inclusion and exclusion criteria

Studies included in this meta-analysis met the following PICOS criteria: (1) PARTICIPANTS; patients > 18 years of age, (2) INTERVENTION; SARS-CoV-2 positive patients, (3) COMPARISON; SARS-CoV-2 negative patients, (4) OUTCOMES; detailed information for vitamin D-3 levels, (5) STUDY DESIGN; randomized controlled trials, quasi-randomized or observational studies comparing cardiac arrest during and before the COVID-19 period for their effects in patients with cardiac arrest. Reviews, simulation trials, animal studies, letters, conference papers and case studies were excluded.

Data extraction

Two reviewers (L.S. and W.G.) independently assessed each article to determine which article met the inclusion criteria. Any disagreements were resolved by consensus with a third reviewer (A.G.). The following information was extracted from each included study: the first author's name,

year of publication, study design, country, sample size, age, gender, vitamin D level in SARS-CoV-2 positive and negative patients.

Quality assessment

Two reviewers (A.G. and H.K.) independently extracted individual study data and evaluated studies for risk of bias. Any disagreements were discussed and resolved in a consensus meeting with the third reviewer (M.M.). The revised tool for risk of bias in randomized trials — RoB 2 tool was used to assess the quality of randomized studies [20]. Moreover, the Robvis application was used to visualize risk of bias assessments [21].

The evaluation consisted of the following domains: confounding, participant selection, classification of interventions, deviation from interventions, missing data, outcome measurement and selection of reported results. Each domain was assessed according to the following scale: serious, moderate and low.

Statistical analysis

All statistical analysis were performed using RevMan v.5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark) and STATA v.16.1. (StataCorp LLC, Texas, USA). All tests were 2-sided and a p value of less than 0.05 was considered as statistically significant. To analyze dichotomous outcomes the Mantel-Haenszel method was used, and results are reported as odds ratios with a 95% confidence interval (CI) and two tailed p values. The inverse variance model with a 95% CI was used to analyze continuous outcome differences and data are reported as the mean difference (MD). Results are presented as risk ratios with 95% CI for dichotomous measures. When the continuous data were reported in the articles as the median and interquartile range, estimated means and standard deviations were calculated using the formula described by Hozo et al. [22].

Data heterogeneity was assessed using the tau-squared and I-squared statistics. Heterogeneity

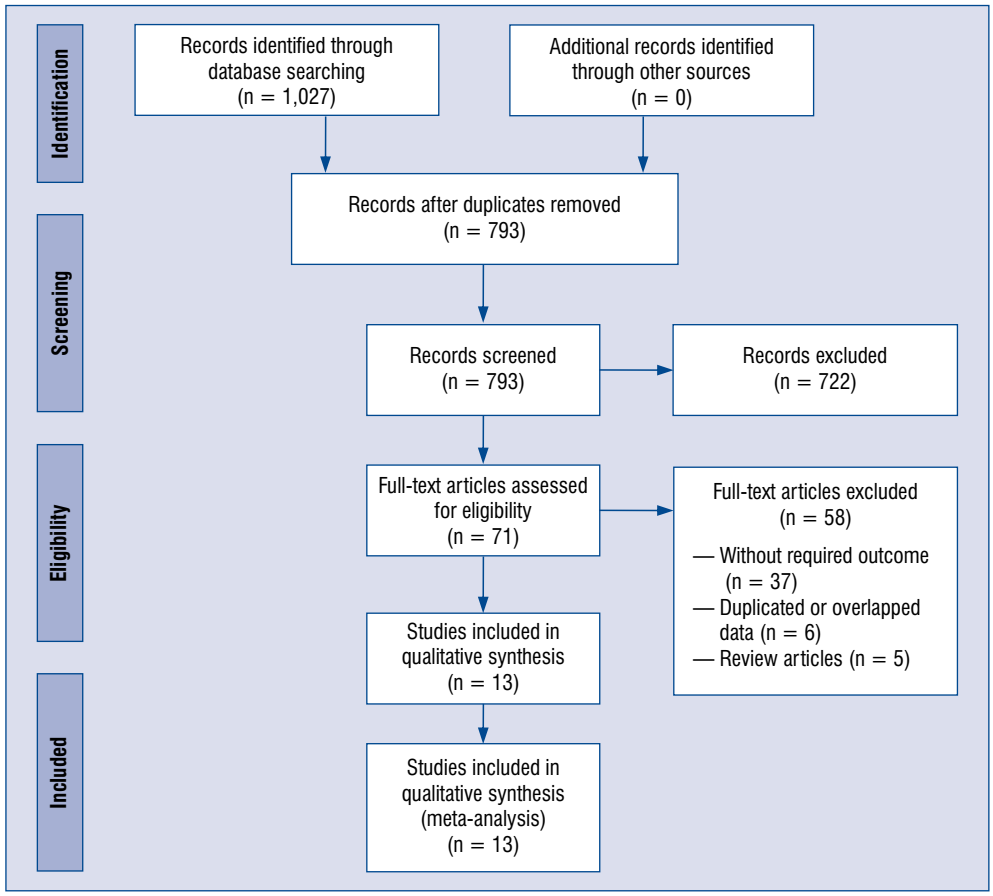

Figure 1. Flow diagram showing stages of the database search and study selection as per Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guideline.

was detected with the chi-squared test with n – 1 degrees of freedom, which was expressed as I^2 [23]. For all analysis a random model was used.

Results

Characteristics of studies included in the meta-analysis

A detailed description of the process of study selection was presented in Figure 1. We found 1,027 potential citations during the search of databases. 234 articles were excluded because they were duplicates, and 722 articles were also excluded because they were unrelated studies. The remaining 71 articles were fully reviewed, and 13 studies providing data for 14,485 participants met the inclusion criteria and were included in the current meta-analysis [24–36]. The details of selected trials are summarized in Table 1. Of those trials, 3 studies were performed in United Kingdom, 2 studies in Iran, 2 in Saudi Arabia, 2 in Italy, and 1 in each of the following countries: Spain, Republic of Korea, Israel and China.

Result of the meta-analysis

Polled analysis of all 13 studies reported vitamin D levels in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) negative versus positive patients is shown in Figure 2. Mean vitamin D levels in SARS-CoV-2 negative patients was 17.7 ± 6.9 ng/mL compared to SARS-CoV-2 positive patients 14.1 ± 8.2 ng/mL (MD = 3.93; 95% CI 2.84–5.02; I^2 = 99%; $p < 0.001$).

The detailed risk of bias abuts the methodological quality of the included studies that are elaborated and summarized in Figures 3 and 4.

Discussion

The number of reports indicating the potential role of vitamin D deficiency in the COVID-19 increases [37]. The potential role in the prevention of a severe course of COVID-19 was further strengthened by the identification of calcitriol (active form of vitamin D) as the regulator of renin-angiotensin system (RAS), of which an overactivation is associated with poor prognosis [38, 39]. Abdollahi et al. [24] found that patients who suffer from vitamin D deficiency are more vulnerable to COVID-19 infection. However, he underlines that the patients suffering from COVID-19 were more likely to be overweight or obese, while obesity is an independent risk factor for a more severe course of the disease [40] it must be noted that patients who are

Table 1. Patient characteristics in included studies.

Study	Country	Study design	SARS-CoV-2 negative group			SARS-CoV-2 positive group		
			Number	Age	Sex, male	Number	Age	Sex, male
Abdollahi et al. 2020	Iran	Case-control study	201	48 ± 16.95	Not specified	201	46.34 ± 13.5	Not specified
Alguwalhes et al. 2021	Saudi Arabia	Retrospective study	72	59.1 ± 16.8	38 (52.8%)	150	55.5 ± 15.8	97 (64.7%)
Al-Daghri et al. 2021	Saudi Arabia	Multi-center case-control study	82	32 ± 13	41 (50.0%)	138	50 ± 13	79 (57.2%)
Baktash et al. 2020	United Kingdom	Prospective cohort study	35	83.4 ± 8.1	15 (42.9%)	70	80.2 ± 8.6	42 (60.0%)
D'Avolio et al. 2020	Italy	Retrospective study	80	72.3 ± 6.1	39 (48.8%)	27	73.5 ± 4.6	19 (70.4%)
Hernández et al. 2020	Spain	Retrospective case-control study	197	61 ± 1.7	123 (62.4%)	216	60.2 ± 4	130 (60.2%)
Im et al. 2020	Republic of Korea	Prospective cohort study	50	52.4 ± 20.2	Not specified	150	52.2 ± 20.7	Not specified
Livingston et al. 2021	United Kingdom	Prospective cohort study	57	68.5 ± 18.1	19 (33.3%)	47	68.6 ± 18.7	20 (42.6%)
Mardani et al. 2020	Iran	Case-control study	60	40.8 ± 15.5	30 (50.0%)	63	43.3 ± 14.5	35 (55.6%)
Merzon et al. 2020	Israel	Population-based study	7,025	47.4 ± 0.2	2,849 (40.6%)	782	35.6 ± 0.4	385 (49.2%)
Raisi-Estabragh et al. 2020	United Kingdom	Prospective cohort study	3,184	68.9 ± 8.7	1,505 (47.3%)	1,326	68.1 ± 9.2	696 (52.5%)
Sulli et al. 2021	Italy	Case-control study	65	76 ± 13	30 (46.2%)	65	76 ± 13	30 (46.2%)
Ye et al. 2020	China	Case-control study	80	41.8 ± 3.5	32 (40.0%)	62	44.3 ± 7.8	23 (37.1%)

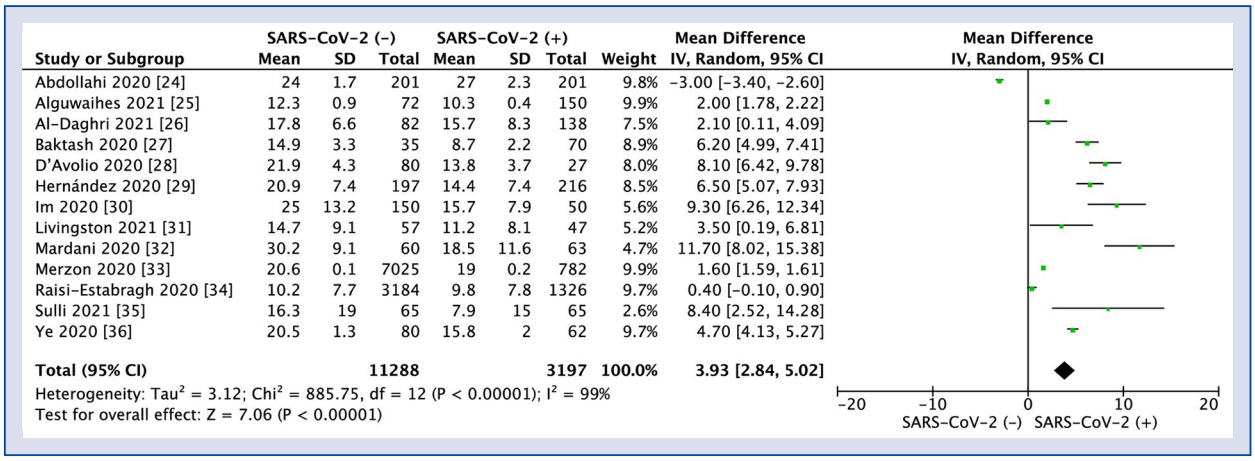

Figure 2. Forest plot of vitamin D levels between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) negative versus positive patients. The center of each square represents the weighted odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

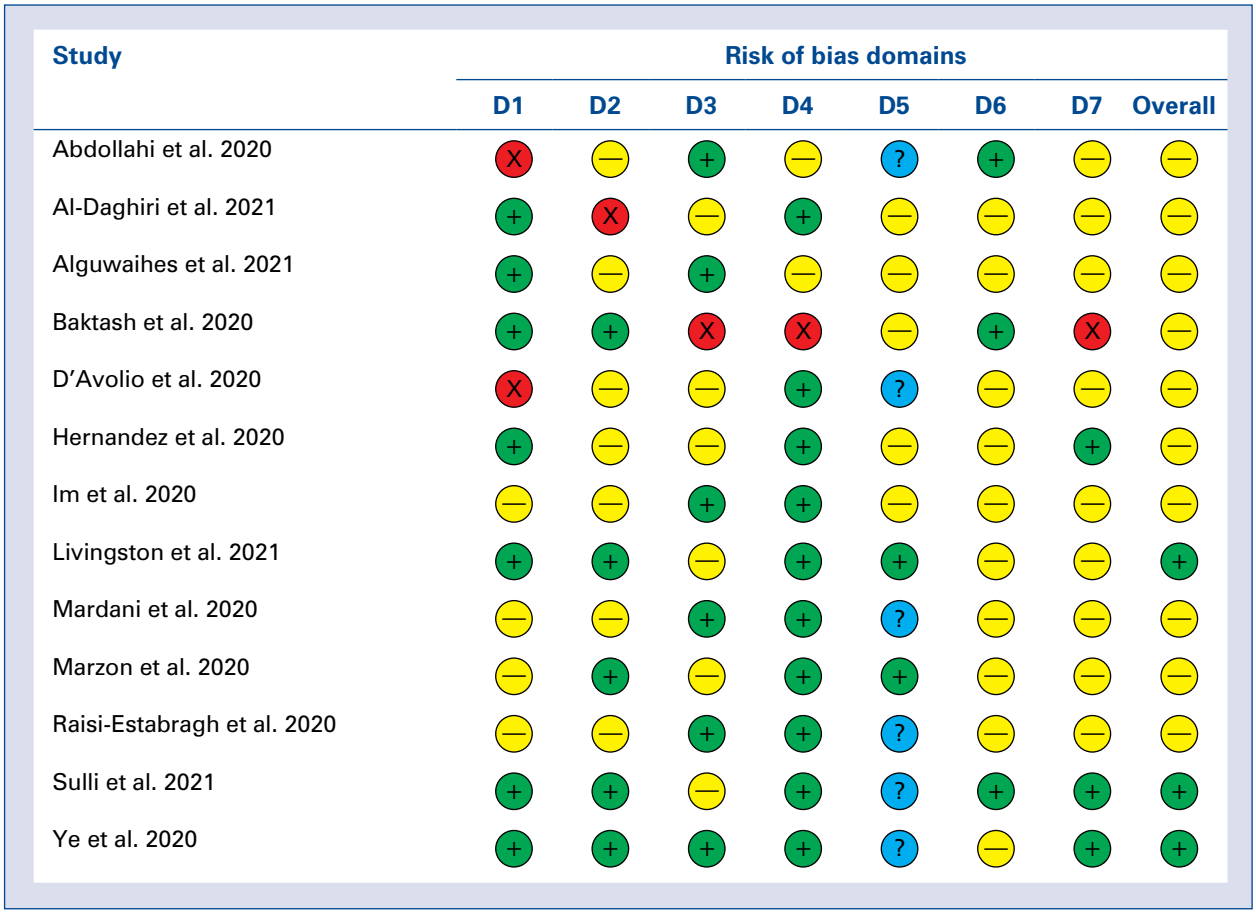

Figure 3. A summary table of review authors' judgements for each risk of bias item for each study. Domains: D1 — bias due to confouding; D2 — bias due to selection of participats; D3 — bias in classification of interventions; D4 — bias due to deviations from intended interventions; D5 — bias due to missing data; D6 — bias in measurement of outcomes; D7 — bias in selection of the reported result. Judgement: X Serious; — Moderate; + Low; ? No information.

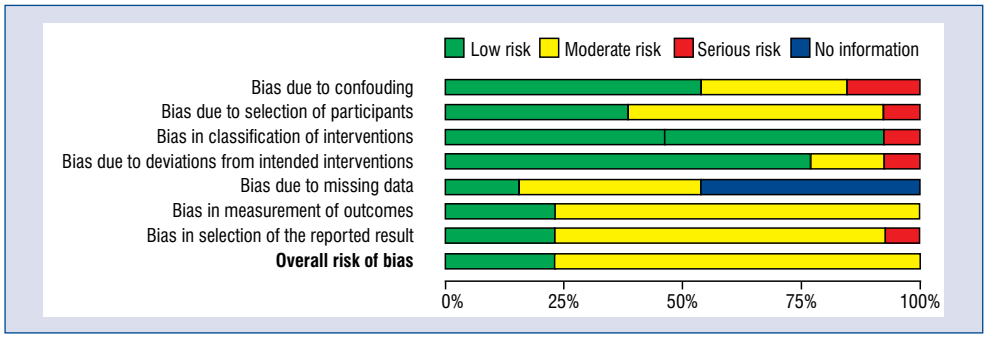

Figure 4. A plot of the distribution of review authors' judgements across studies for each risk of bias item.

obese are also more likely to suffer from vitamin D deficiency [41]. Another group that suffers from the vitamin D deficiency are older patients [42] both due to the worse overall state of health and due to drugs, they take. The study by Baktash et al. [27] found that the patients who are older than 65 years and present with the COVID-19 symptoms are more likely to be vitamin D deficient, have elevated markers of cytokine release syndrome and have an increased risk of respiratory failure. However, no difference was found in terms of mortality between the patients who were deficient and those who had their vitamin D within normal ranges, indicating that in the older group the overall poor prognosis is associated with the general health status and presence of comorbidities. These findings are consistent with those achieved by D'Avolio et al. [28], who also found that vitamin D was lower in the patients positive for COVID-19, while indicating that the supplementation of vitamin D might be useful for prevention of infection.

The strategy of vitamin D supplementation as indicated by Grant et al. [43] suggests the rapid increase of vitamin D serum levels through the high supplementation for a few weeks going as high as 10,000 IU/day in order to achieve the normal range. This strategy has been used for considerable time and has proven to be safe in delaying frailty [44]. In the study by Al-Daghri et al. [26] vitamin D deficiency was only observed in the group of older patients, those with type 2 diabetes and lower density lipoprotein levels. Interestingly the author, contrary to Grant et al. [43] supports the idea of rather moderate vitamin D loading in deficient patients, not exceeding 2000 iu/day, which is supported by Bergman [45]. Alguwaihes et al. [25] provides interesting data regarding vitamin D deficiency and the risk of COVID-19 in a hospital setting. While he did not find any evidence suggesting that the risk of infection increases in deficient patients, they are, in fact, at higher risk of mortality, possibly through an unregulated inflammatory response and cytokine storm [46]. Contrary to these findings Hernandez et al. [29] found no difference in the severity of the disease when accounting for vitamin D deficiency, however he did find a higher prevalence of deficiency among hospitalized COVID-19 patients. When analyzing the nutritional status of patients suffering from COVID-19, Im et al. [30] they found that patients suffering from COVID-19 presented a higher percentage of vitamin D deficiency when compared with a control group, additionally while not statistically significant 30 out of 38 patients who suffered from respiratory distress were deficient in vitamin D. What is worth noting is that the patients who required mechanical ventilation were deficient in at least one nutrient. Therefore, it is advised to monitor and react to the nutritional status of the COVID-19 patients [47]. Mardani et al. [32], in his study, analyzed an association in the level of vitamin D and the severity of COVID-19, along with levels of ACE2 and neutrophil to lymphocyte ratio (NLR). The NLR is a useful tool to assess systemic inflammation [48] also in acute lung injury and acute respiratory distress syndrome [49] which are common findings in the severe course of COVID-19. Having found lower levels of vitamin D in COVID-19 patients, the authors concluded that the deficiency may cause an immunological imbalance, overactivation of the RAS pathway and therefore a hyperinflammation state. Raisi-Estabragh et al. [34] in her study found that vitamin D deficiency was not an independent risk factor for black, Asian and minority ethnicities and that a cascade of factors play a role rather than a single one that can be pinpointed. In a study by Ye et al. [36], he found that vitamin D deficiency increases risk of COVID-19 infection, while the supplementation of it provides protective effects against

a severe course of the disease. These findings are further reinforced by Sulli et al. [35] who found that vitamin D deficiency is associated with more severe lung involvement, longer disease duration, and risk of death in elderly COVID-19 patients. A study by Livingstone et al. [31] among vitamin D deficiency indicates that social deprivation plays role in COVID-19 infection. While studies for the general population showed that social distancing is beneficial for the reduction in COVID-19 incidence rate [50], we must differentiate between social distancing and deprivation since the latter is a well-established risk factor for worsening of health outcomes [51]. Merzon et al. [33] identified vitamin D deficiency as an independent risk factor not only for COVID-19 infection, but also hospitalization, other risk factors included were being male and over the age of 50.

All of the studies measured levels of vitamin D at the moment of acute COVID-19 infection, however as previous studies showed [52], acute respiratory infection does not alter the vitamin D levels, therefore a sample on admission is representative.

Conclusions

Low serum vitamin D levels are statistically and significantly associated with the risk of COVID-19 infection. Supplementation of vitamin D especially in deficiency, risk groups are indicated.

Acknowledgments

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Conflict of interest: None declared

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