The Role of Vitamin D in The Age of COVID-19:
A Systematic Review and Meta-Analysis Along with an Ecological Approach

Roya Ghasemian[1], Amir Shamshirian[2,3]*, Keyvan Heydari[3,4], Mohammad Malekan[4], Reza Alizadeh-Navaei[3], Mohammad Ali Ebrahimzadeh[5], Hamed Jafarpour[4], Arash Rezaei Shahmirzadi[8], Mehrdad Khodabandeh[9], Benyamin Seyfari[10], Alireza Motamedzadeh[11], Ehsan Dadgostar[12], Marzieh Aalinezhad[13], Meghdad Sedaghat[14], Morteza Behnamfar[15], Anahita Asadi[5], Bahman Zarandi[16], Nazanin Razzaghi[8], Vahid Yaghoubi Naei[17], Amirhossein Hessami[2], Soheil Azizi[18], Ali Reza Mohseni[18,19], Danial Shamshirian[20]*

1. Antimicrobial Resistance Research Center, Department of Infectious Diseases, Mazandaran University of Medical Sciences, Sari, Iran.

2. Department of Medical Laboratory Sciences, Student Research Committee, School of Allied Medical Science, Mazandaran University of Medical Sciences, Sari, Iran.

3. Gastrointestinal Cancer Research Center, Mazandaran University of Medical Sciences, Sari, Iran.

4. Student Research Committee, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.

5. Pharmaceutical Sciences Research Center, Department of Medicinal Chemistry, School of Pharmacy, Mazandaran University of Medical Science, Sari, Iran.

6. School of Biomedical Engineering, University of Technology Sydney, Sydney, Ultimo, NSW, 2007, Australia.

7. Institute of Molecular Medicine, Sechenov First Moscow State University, Moscow, 119991, Russia.

8. Student Research Committee, Golestan University of Medical Sciences, Gorgan, Iran.

9. Neuromusculoskeletal Research Center, Department of Physical Medicine and Rehabilitation, Iran University of Medical Sciences, Tehran, Iran.

10. Department of Surgery, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran.

11. Department of Internal Medicine, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran.

12. Halal Research Center of IRI, FDA, Tehran, Iran.

13. Department of Radiology, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.

14. Department of Internal Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

15. Student Research Committee, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran.

16. Student Research Committee, Iran University of Medical Sciences, Tehran, Iran.

17. Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

18. Department of Medical Laboratory Sciences, School of Allied Medical Science, Mazandaran University of Medical Sciences, Sari, Iran.

19. Thalassemia Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran.

20. Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Corresponding authors:
1. Danial Shamshirian, Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-Mail: shamshirian@sbmu.ac.ir
Tel: +98 912 640 6146
2. Amir Shamshirian; Gastrointestinal Cancer Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
E-Mail: shamshirian.amir@gmail.com
Tel: +98 915 187 2961

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Abstract

Background: Following emerge of a novel coronavirus from Wuhan, China, in December 2019, it has affected the whole world and after months of efforts by the medical communities, there is still no specific approach for prevention and treatment against the Coronavirus Disease 2019 (COVID-19). Evidence recommends that vitamin D might be an important supportive agent for the immune system, mainly in cytokine response regulation against COVID-19. Hence, we carried out a rapid systematic review and meta-analysis along with an ecological investigation in order to maximize the use of everything that exists about the role of vitamin D in the COVID-19.

Methods: A systematic search was performed in PubMed, Scopus, Embase, Cochrane Library, Web of Science and Google Scholar (intitle) as well as preprint database of medRxiv, bioRxiv, Research Square, preprints.org, search engine of ScienceDirect and a rapid search through famous journals up to August 4, 2020. Studies focused on the role of vitamin D in confirmed COVID-19 patients were entered into the systematic review. Along with our main aim, to find the second objective "*correlation of global vitamin D status and COVID-19 recovery and mortality*" we carried out a literature search in PubMed database to identify the national or regional studies reported the vitamin D status globally. CMA *v*. 2.2.064 and SPSS *v*.16 were used for data analysis.

Results: Eleven studies containing 360,972 participants entered into the meta-analysis. The meta-analysis indicated that 37.7% of COVID-19 patients were suffering from vitamin D deficiency (95% CI, 26.7%-50.1%) and in 32.2% of patients, levels of vitamin D were insufficient (95% CI, 13.8%-58.4%). Also, a significant increased risk of COVID-19 was found in individuals with low levels of vitamin D (OR: 1.33; 95% CI, 1.01-1.75). In regard to our ecological investigation on 51 countries including 408,748 participants, analyses indicated no correlation between vitamin D levels and recovery rate (r= 0.041) as well as mortality rate (r=-0.073) globally. However, given latitude, a small reverse correlation between mortality rate and vitamin D status was observed throughout the globe (r= -0.177). In Asia, a medium direct correlation was observed for recovery rate (r= 0.317) and a significant reveres correlation for mortality rate (r= -0.700) with vitamin D status in such patients. In Europe, there were no correlations for both recovery (r= 0.040) and mortality rate (r= -0.035). In Middle East, the recovery rate (r= 0.267) and mortality rate (r= -0.217) showed a medium correlation. In North and Sought America, surprisingly, both recovery and mortality rate demonstrated a direct correlation respectively (r= 1.000, r=0.500). In Oceania, unexpectedly, recovery (r= -1.000) and mortality (r= -1.000) rates were in considerable reverse correlation with vitamin D levels.

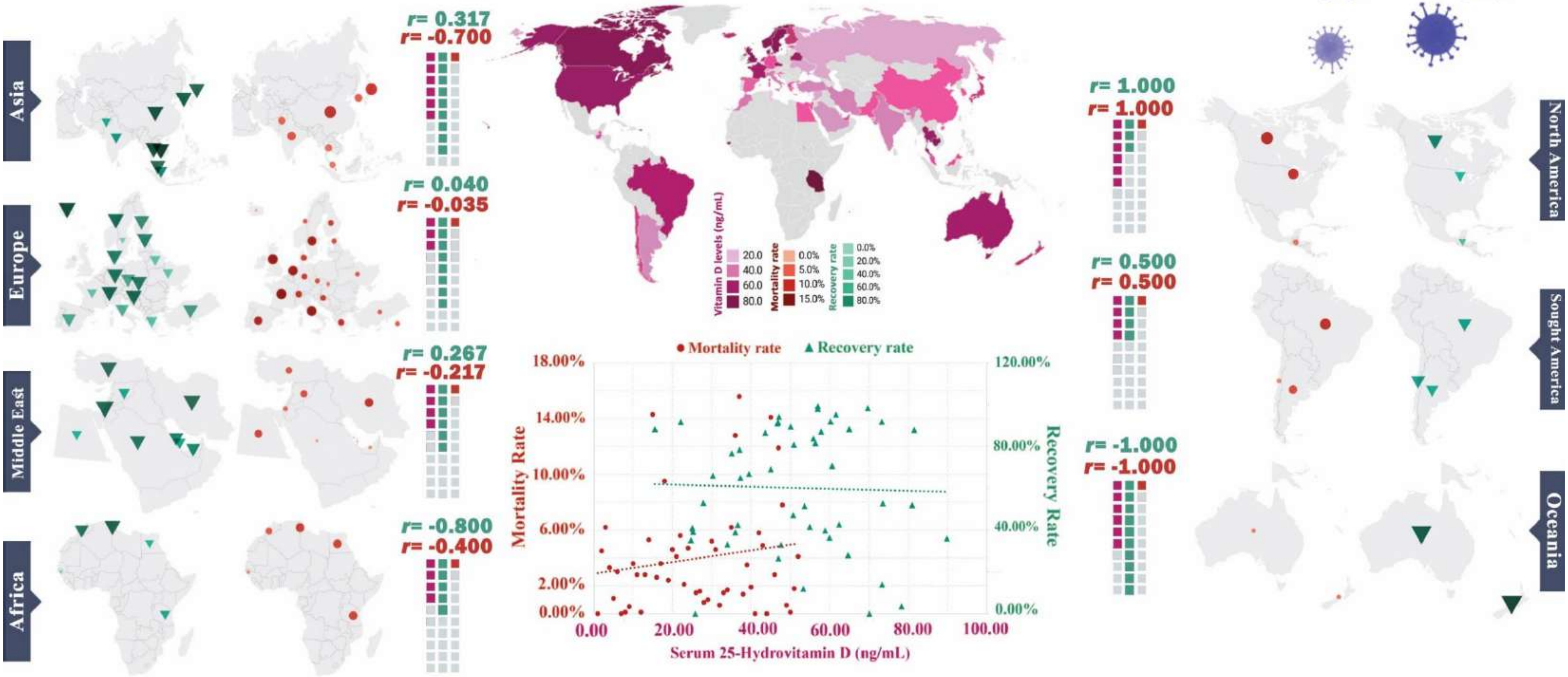
Conclusion:

In this systematic review and meta-analysis with an ecological approach, we found a high percentage of COVID-19 patients who suffer from vitamin D deficiency or insufficiency as well as **a significant increased risk of COVID-19 infection in patients with low levels of vitamin D**. Our ecological investigation resulted in substantial direct and reverse correlations between recovery and mortality rates of COVID-19 patients with vitamin D status in different countries. Considering latitudes, a small reverse correlation between vitamin D status and mortality rate was found globally. It seems that populations with lower levels of vitamin D might be more susceptible to the novel coronavirus infection. Nevertheless, due to multiple limitations, if this study does not allow to quantify a "value" of the Vitamin D with full confidence, it allows at least to know what the Vitamin D might be and that it would be prudent to invest in this direction through comprehensive large randomized clinical trials.

Keywords: Pandemic, 2019-nCoV, Coronavirus Outbreaks, SARS-CoV-2, Vitamin D, 25-hydroxyvitamin D, 25(OH)D.

SnapShot:

Global VITAMIN D Status Vs. COVID-19 Recovery & Mortality Rate



Introduction:

Following emerge of a novel coronavirus from Wuhan, China, in December 2019, the respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected the whole world and declared as a pandemic by World Health Organization (WHO) on March 26, 2020[1]. According to Worldometer metrics, this novel virus has been responsible for approximately 18,447,759 infections, of which 11,680,369 cases are recovered and 697,245 cases were died worldwide up to August 4, 2020.

After months of efforts by the medical communities, there is still no specific approach for prevention and treatment against the Coronavirus Disease 2019 (COVID-19). Also, competition of pandemic with infodemic has led to many controversies and challenges globally.

In this regard, one of the hottest topics these days is the role of *Vitamin D* in prevention or treatment of COVID-19. Several functions such as modulating adaptive immune system and cell-mediated immunity, as well as increase of antioxidative-related genes expression have been proven for Vitamin D as an adjuvant in the prevention and treatment of acute respiratory infections [2, 3]. According to available investigations, it seems that such functions lead to cytokine storm suppression and avoid Acute Respiratory Distress Syndrome (ARDS), which has been studied on other pandemics and infectious diseases in recent years [4-6].

To best of our knowledge, unfortunately, after several months there is no adequate high-quality data on different treatments regimen, which raises questions about gaps in scientific works. In this occasion, when there is an essential need for controlled randomized trials, it is surprising to see only observational studies without a control group or non-randomized controlled studies with retrospective nature covering a small number of patients.

The same issue is debatable for 25-hydroxyvitamin D (25(OH)D); hence, concerning all of the limitations and analyze difficulties, we carried out a rapid systematic review and meta-analysis with great caution and sensitivity in order to try for maximizing the use of everything that exists about the role of this vitamin in the COVID-19. Additionally, along with this systematic review, we also performed an ecological evaluation to find any relations between global status of vitamin D and COVID-19 recovery/mortality rates. To be honest, we know that working on observational studies give an overestimation of the required value. Therefore, whatever the result with the vitamin D we can present that the result, by our approaches, is also an overestimation of reality; which is very fascinating in itself to get in the current situation, especially through what we found in our ecological approach.

Methods:

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was considered for study plan. A systematic search through databases of PubMed, Scopus, Embase, Cochrane Library, Web of Science and Google Scholar (intitle) as well as preprint database of medRxiv, bioRxiv, Research Square, preprints.org, search engine of ScienceDirect and a rapid search through famous journals was done up to August 4, 2020. Moreover, to obtain more data we considered gray literatures and references of eligible papers. The search strategy included all MeSH terms and free keywords found for COVID-19, SARS-CoV-2, and Vitamin D. There was no time/location/ language limitation in this search.

Criteria study selection

Four researchers have screened and selected the papers independently and the supervisor solved the disagreements. Studies met the following criteria included into meta-analysis: 1) comparative or non-comparative studies with retrospective or prospective nature; and 2) studies reported the role of vitamin D in confirmed COVID-19 patients. Studies were excluded if they were: 1) *in vitro* studies, experimental studies, reviews; 2) duplicate publications.

Data extraction & quality assessment

Two researchers (H.J and M.M) have evaluated quality assessment of the papers and extracted data from selected papers. The supervisor (D.Sh) resolved any disagreements in this step. Data extraction checklist included the name of the first author, publication year, region of study, number of patients, comorbidity, vitamin D Status, serum 25-hydrovitamin D levels, ethnicity, mean age, medication dosage, treatment duration, adverse effects, radiological results, and mortality. The modified Newcastle-Ottawa Scale (NOS) checklist for cross-sectional studies was used to value the studies, concerning various aspects of the methodology and study process.

Hypothetical strategy

According to risk factors such as older age, male, obesity, underlying chronic disorders, higher latitudes, darker skin pigmentation etc., which are common between Vitamin D deficiency and COVID-19 toward the severity of the condition, despite the various possible explanations, we hypothesize that vitamin D plays a role in severity of responses to COVID-19 and vitamin D deficiency can be in correlation with COVID-19 mortality rate and recovery rate.

In this regard, alongside with our main objective, to find the second aim as an ecological investigation we carried out a literature search in PubMed database for identifying the national or regional studies reported the vitamin D status throughout the world. Data of infection, mortality and recovery of COVID-19 cases were gathered from the *Worldometer* metrics. The meta-analysis was done between all of the published studies in each region for pooling vitamin D mean levels.

In this case, according to an international conference on "***Controversies in Vitamin D***" [7], vitamin D cut-off points were considered as follows:

- *Vitamin D sufficiency: 25(OH)D concentration greater than 20 ng/mL (50 nmol/L)*
- *Vitamin D insufficiency: 25(OH)D concentration of 12 to 20 ng/mL (30 to 50 nmol/L)*
- *Vitamin D deficiency: 25(OH)D level less than 12 ng/mL (30 nmol/L)*
- *A "risk" of vitamin D toxicity: 25(OH)D level >100 ng/mL (>250 nmol/mL)*

Targeted outcomes

1) Frequency of Vitamin D deficiency and insufficiency in COVID-19 patients; 2) Mortality rates; 3) Recovery rates; 4) Correlation of mortality and recovery rate in COVID-19 patients with vitamin D status; 5) Latitude dependence of the mortality and recovery rate.

Heterogeneity assessment

I-square (I^2) statistic was used for heterogeneity evaluation. Following Cochrane Handbook for Systematic Reviews of Interventions [8], the I^2 was interpreted as follows: "*0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity. The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P-value from the chi-squared test, or a confidence interval for I^2).*" Thus, random-effects model was used for pooling the outcomes in case of heterogeneity; otherwise, the inverse variance fixed-effect model was used. Forest plots were presented to visualize the degree of variation between studies.

Data analysis

Meta-analysis was performed using Comprehensive Meta-Analysis (CMA) *v.* 2.2.064 software. Pooling of effect sizes was done with 95% Confident Interval (CI). Fixed/random-effects model was used according to heterogeneities. In case of zero frequency, the correction value of 0.1 was used.

Correlation of mortality and recovery rates in COVID-19 patients with vitamin D status was evaluated using Spearman's rank correlation coefficient (*r*). According to Cohen's classification of effect width [(9)], value of *r*=0.1 was considered as small effect, *r*=0.25 as medium effect and *r*=0.4 as large effect. The *P*-value less than 0.05 was considered statistically significant. Data were analyzed using SPSS software *v.* 16 (SPSS Inc., Chicago, IL, U.S.A.).

Publication bias & sensitivity analysis

Begg's and Egger's tests as well as funnel plot was used for publication bias evaluation. *P*-value less than 0.05 was considered as statistically significant.

Results

Study selection process

The first search through databases resulted in 717 papers. After removing duplicated papers and first step screening based on title and abstract, 62 papers were assessed for eligibility. Finally, 11 papers entered into the meta-analysis. PRISMA flow diagram for the study selection process presented in Figure 1.

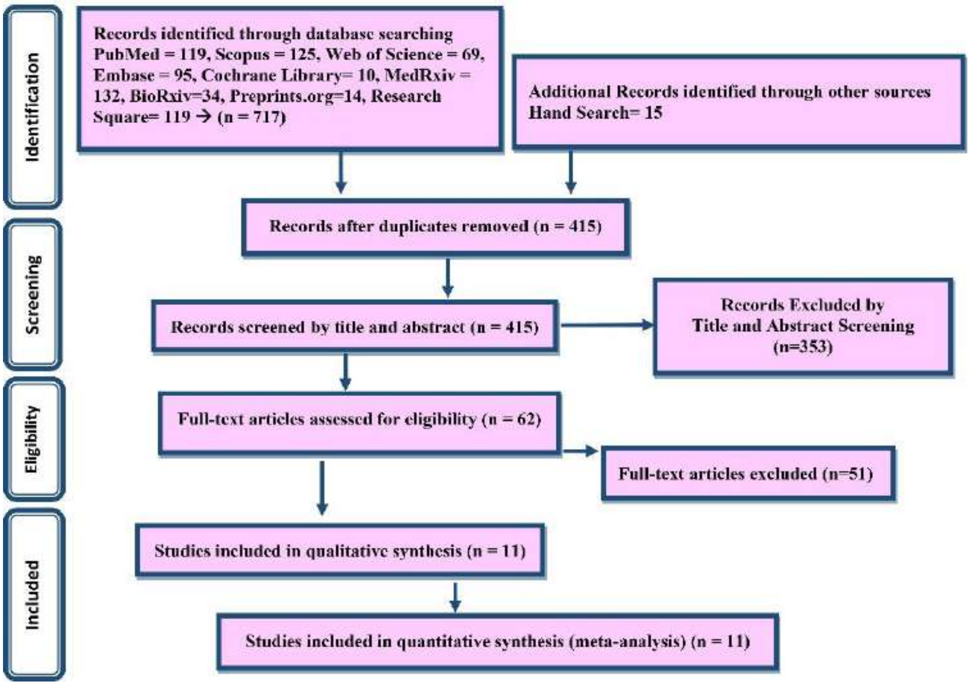


Figure 1.PRISMA flow diagram for the study selection process

Study characteristics

Among the six studies included in meta-analysis, all of them were designed in retrospective nature. The studies' sample size ranged from 10 to 348,648 including 360,972 participants. Characteristics of studies entered into the systematic review presented in Table 1.

Table 1. Characteristics of studies entered into the systematic review

Study	Country	Study design	No. of Patients (male/female)	Controls (male/female)	Median age (IQR)	Comorbidity	Vitamin D Status			Ethnicity		
							N	**I**	**D**	W	B	O
Raharusuna *et al.* 2020 (10)	Indonesia	Retrospective cohort study	780 (380/400)	-	54.5	Yes: 383 No: 397	388	213	179	-	-	-
De Smet *et al.* 2020 (11)	Belgium	Single-center observational study	186 (109/77)	2717 (999/1718)	69 (52-80)	-	77	-	109	-	-	-
Lau *et al.* 2020 (12)	U.S.	Retrospective cross sectional	20 (9/11)	-	65.2	Hypertension: 15 Diabetes: 7	2	8	10	5	15	-
Cuñat *et al.* 2020 (13)	Spain	Retrospective analysis	17 (10/7)	-	64.94	CKD: 2	-	-	17	-	-	-
Pinzon *et al.* 2020 (14)	Indonesia	Case Series and Recent Literature Review	10 (5/5)	-	49.6	Hypertension: 4 Diabetes: 1 COPD: 1 Stroke: 1	0	1	9	-	-	-
Meltzer *et al.* 2020 (15)	U.S.	Retrospective cohort study	499 (126/373)	-	-	Hypertension:261 Diabetes:137 COPD:117 Pulmonary circulation disorders: 20 Depression :119 CKD:116 Liver disease :56 Comorbidities with immunosuppression: 105	321	-	178	41	448	-
Hastie *et al.* 2020 (16)	UK	Retrospective cross sectional	449 (265/184)	348,149 (168,391/ 179,758)	-	Diabetes: 400	-	-	-	385	32	32
Alipio *et al.* 2020 (17)	Philippines	A retrospective multicenter study	112	-	-	-	55	80	77	-	-	-
Merzon *et al.* 2020 (18)	Israel	Retrospective cohort study	782 (385/397)	7,025 (2,849, 4,176)	35.58	Depression/Anxiety: 73 Schizophrenia: 15 Dementia: 27 Diabetes mellitus: 154 Hypertension: 174 Cardiovascular disease: 78 Chronic lung disorders: 66 Obesity: 235	79	598	105	-	-	-
Panagiotou *et al.* 2020 (19)	UK	Retrospective cross sectional	134 (73/61)	-	-	Hypertension: 56 Diabetes: 38 Obesity: 14 Malignancy: 15 Respiratory: 42 Cardiovascular disease: 20 Kidney and Liver diseases: 19	-	-	44	132	1	1
Carpagnano *et al.* 2020 (20)	Italy	Retrospective cohort study	42 (30/12)	-	65 (±13) *mean	Hypertension: 26 Cardiovascular disease: 16 CKD: 16 Diabetes type II: 11 Cerebrovascular disease: 5 Psychosis, depression, anxiety: 10 Malignancy: 5 COPD: 5 Asthma: 2	8	11	23	-	-	-

IQR: Interquartile range, U.S.: United States, UK: United Kingdom, N: Normal, I: Insufficient, D: Deficient, W: White, B: Black, O: Other, COPD: Chronic obstructive pulmonary disease, CKD: Chronic Kidney Disease

Quality assessment

Results of quality assessment for studies entered into meta-analysis based on modified version of NOS tool for cross-sectional studies were fair.

Publication bias

Results of Begg's and Egger's tests in effect size meta-analysis showed no significant publication bias (P_B=0.92; P_E=0.23). The funnel plot for publication bias of studies presented in Fig. 2.

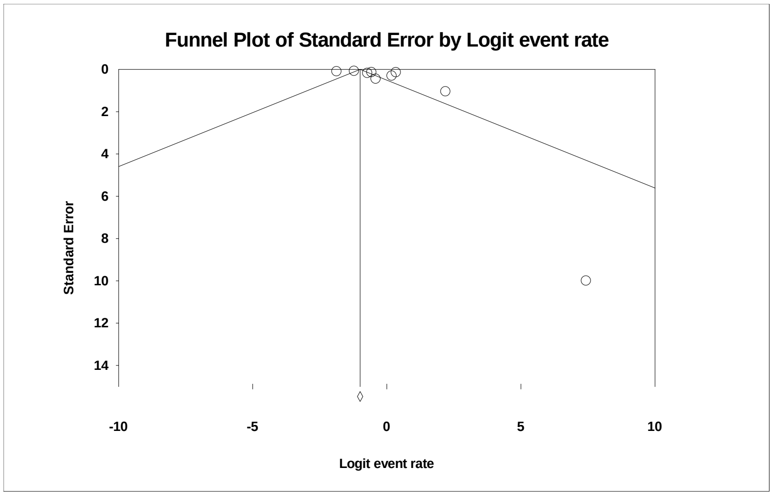


Figure 2. Funnel plot for publication bias of studies

Meta-analysis findings

The meta-analysis of event rates showed that 37.7% of COVID-19 patients were suffering from vitamin D deficiency (95% CI, 26.7%-50.1%) and in 32.2% of patients, levels of vitamin D were lower than the normal range (95% CI, 13.8%-58.4%) (Fig. 3).

Group by Subgroup within study	Study name	Subgroup within study	Statistics for each study					
			Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total
Deficiency	D. O. Meltzer	Deficiency	0.357	0.316	0.400	-6.310	0.000	178 / 499
Deficiency	D. Smet	Deficiency	0.586	0.514	0.655	2.335	0.020	109 / 186
Deficiency	E. Merzon	Deficiency	0.134	0.112	0.160	-17.769	0.000	105 / 782
Deficiency	F. H. Lau	Deficiency	0.400	0.214	0.620	-0.888	0.374	8 / 20
Deficiency	G. E. Carpagnano	Deficiency	0.548	0.397	0.690	0.616	0.538	23 / 42
Deficiency	G. Panagiotou	Deficiency	0.328	0.254	0.412	-3.890	0.000	44 / 134
Deficiency	M. M. Alipio	Deficiency	0.363	0.301	0.430	-3.932	0.000	77 / 212
Deficiency	P. Raharusuna	Deficiency	0.229	0.201	0.260	-14.224	0.000	179 / 780
Deficiency	R. T. Pinzon	Deficiency	0.900	0.533	0.986	2.084	0.037	9 / 10
Deficiency	T. Cunat	Deficiency	0.999	0.000	1.000	0.744	0.457	17 / 17
Deficiency			0.377	0.267	0.501	-1.948	0.051	
Insufficiency	E. Merzon	Insufficiency	0.765	0.734	0.793	13.981	0.000	598 / 782
Insufficiency	F. H. Lau	Insufficiency	0.150	0.049	0.376	-2.770	0.006	3 / 20
Insufficiency	G. E. Carpagnano	Insufficiency	0.262	0.151	0.414	-2.952	0.003	11 / 42
Insufficiency	M. M. Alipio	Insufficiency	0.377	0.315	0.444	-3.534	0.000	80 / 212
Insufficiency	P. Raharusuna	Insufficiency	0.273	0.243	0.305	-12.183	0.000	213 / 780
Insufficiency	R. T. Pinzon	Insufficiency	0.100	0.014	0.467	-2.084	0.037	1 / 10
Insufficiency			0.322	0.138	0.584	-1.347	0.178	
Normal	E. Merzon	Normal	0.101	0.082	0.124	-18.421	0.000	79 / 782
Normal	G. E. Carpagnano	Normal	0.190	0.098	0.337	-3.682	0.000	8 / 42
Normal	M. M. Alipio	Normal	0.259	0.205	0.323	-6.694	0.000	55 / 212
Normal	P. Raharusuna	Normal	0.497	0.462	0.532	-0.143	0.886	388 / 780
Normal			0.238	0.084	0.513	-1.876	0.061	

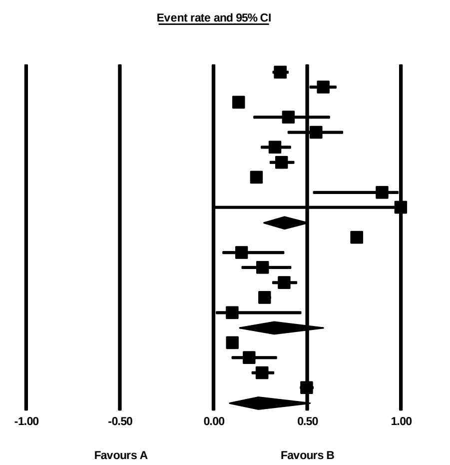


Figure 3. Forest plot for pooling events of vitamin D deficiency and vitamin D insufficiency

Association between Vitamin D insufficiency and COVID-19

The meta-analysis indicated a substantial higher risk of COVID-19 infection in individuals with vitamin D deficiency between two studies with 1231 cases (OR: 1.33; 95% CI, 1.01-1.75) (Fig. 4).

Study name	Statistics for each study					Point (raw) and 95% CI
	Point (raw)	Lower limit	Upper limit	Z-Value	p-Value	
E. Merzon	1.580	1.162	2.149	2.916	0.004	
C. E. Hastie	1.190	0.987	1.435	1.820	0.069	
	1.334	1.016	1.752	2.074	0.038	

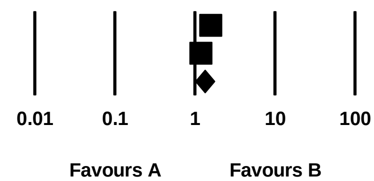


Figure 4. Association between Vitamin D insufficiency and COVID-19

Ecological hypothetical strategy

In this part of study, available data from 51 countries on vitamin D status including 408,748 participants were collected from 75 papers [21-95]. Meta-analysis findings indicated 50.544 ng/mL mean levels of vitamin D globally (95% CI: 47.068-54.021). Details on continents and countries are presented in Table 2. Also, forest plots of pooling Serum 25-Hydrovitamin D concentration as well as recovery/mortality rates are presented in Supplementary File 1.

Vitamin D status Vs. Mortality and Recovery rate (Table 2)

The world vitamin D distribution map and its relations with recovery rate as well as mortality are presented in Figure 4. Considering mean levels of vitamin D, SARS-CoV-2 infection as well as COVID-19 mortality and recovery data throughout the world, Spearman's rank correlation coefficient analyses indicated no correlation between vitamin D levels and recovery rate (*r*= 0.041) as well as mortality rate (*r*=-0.073) globally.

In detail, in Asia with overall mean levels of 57.326 25(OH)D (95% CI, 56.959-57.693) a substantial direct correlation was observed between vitamin D status and recovery rate (*r*= 0.317) as well as a significant reverse correlation for the mortality rate (*r*= -0.700). In Europe, there were no correlations for both recovery (*r*= 0.040) and mortality rate (*r*= -0.035). In Middle East, although there was a direct correlation between recovery rate and vitamin D status (*r*= 0.267); also, mortality rate was mediumly in reverse correlation with vitamin D status (*r*= -0.217). In North America, surprisingly, both recovery (*r*= 1.000) and mortality rates (*r*= 1.000) were highly correlated to the vitamin D levels. In Sought America, both recovery rate (*r*=0.500) and mortality rate (*r*=0.500) were in a significant direct correlation with 25(OH)D levels. In Oceania, unexpectedly, recovery (*r*= -1.000) and mortality (*r*= -1.000) rates were in substantial reverse correlation with 25(OH)D levels.

Considering latitude factor as an adjustment for countries in latitudes higher than ±50°, partial correlation analysis showed a small reverse correlation between mortality rate and vitamin D status throughout the globe (*r*= -0.177), but no correlation was observed for recovery rate (*r*= -0.072). This analysis showed a direct correlation in case of mortality rate in Europe *r*= 0.164.

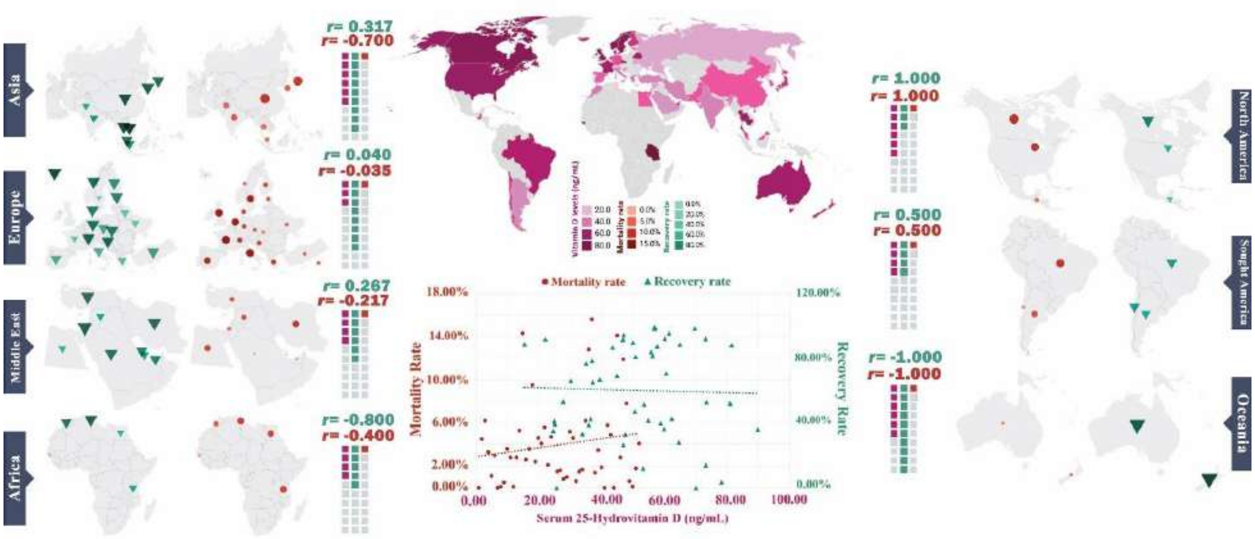


Figure 5. Global distribution of vitamin D levels and its association with mortality rate and recovery rate related to COVID-19 patients

Table 2. Worldwide vitamin D status, COVID-19 infection, mortality and recovery rates

Region	Latitude	No. of Patients	Serum 25-Hydrovitamin D ng/mL (Mean & 95% CI)	Infection	Recovered	Deaths	Recovery rate	*r/p*	Mortality rate	*r/p*
Asia	**34.0479° N**	**41205**	**57.326 (56.959-57.693)**	**381220**	**219446**	**11899**	**0.824 (0.684 – 0.911)**		**0.019 (0.013 – 0.027)**	
Cambodia	12.5657° N	725	69.700 (67.429-71.971)	124	122	0	0.984 (0.938 – 0.996)		0.000 (0.000 – 0.285)	
China	35.8617° N	16143	47.143 (42.297-51.989)	82995	78288	4634	0.943 (0.942 – 0.945)		0.056 (0.054 – 0.057)	
India	20.5937° N	1678	36.61 (21.167-52.070)	164936	70102	4673	0.425 (0.423 – 0.427)		0.028 (0.028 – 0.029)	
Japan	36.2048° N	9084	55.900 (55.513-56.287)	16651	13973	858	0.839 (0.834 – 0.845)	*r*= 0.317 *P*= 0.406	0.052 (0.048 – 0.055)	*r*= -0.700 *P*= 0.036
Korea	35.9078° N	8987	46.706 (42.227-51.185)	11344	10340	269	0.911 (0.906 – 0.917)		0.024 (0.021 – 0.027)	
Malaysia	4.2105° N	558	50.913 (34.415-67.411)	7629	6169	115	0.809 (0.800 – 0.817)		0.015 (0.013 – 0.018)	
Pakistan	30.3753° N	1073	47.669 (34.325-61.014)	61227	20231	1260	0.330 (0.327 – 0.334)		0.021 (0.019 – 0.022)	
Singapore	1.3521° N	940	81.000 (79.261-82.739)	33249	17276	33	0.520 (0.514 – 0.525)		0.001 (0.001 – 0.001)	
Thailand	15.8700° N	147	61.600 (58.480-64.720)	3065	2945	57	0.953 (0.953 – 0.967)		0.019 (0.014 – 0.024)	
Europe	**54.5260° N**	**52791**	**25.975 (25.954 – 25.995)**	**1760893**	**834302**	**154430**	**0.753 (0.667 – 0.823)**		**0.045 (0.034 – 0.060)**	
Belarus	53.7098° N	623	62.422 (50.385-74.458)	40764	17390	224	0.427 (0.422 – 0.431)		0.000 (0.005 – 0.006)	
Croatia	45.1000° N	120	46.900 (43.894-49.906)	2245	2059	103	0.917 (0.905 – 0.928)		0.046 (0.038 – 0.055)	
Czech Republic	49.8175° N	688	60.641 (57.996-63.285)	9143	6464	319	0.707 (0.698 – 0.716)		0.035 (0.031 – 0.039)	
Denmark	56.2639° N	3409	65.000 (64.355-65.645)	11593	10240	568	0.883 (0.877 – 0.889)		0.049 (0.045 – 0.053)	
Estonia	58.5953° N	367	43.630 (41.769-45.492)	1859	1610	67	0.866 (0.850 – 0.881)		0.036 (0.028 – 0.046)	
Finland	61.9241° N	4200	56.381 (34.136-78.627)	6743	5500	313	0.816 (0.806 – 0.825)		0.046 (0.042 – 0.052)	
France	46.2276° N	829	60.000 (58.688-61.312)	182913	66584	28596	0.364 (0.362 – 0.366)		0.156 (0.155 – 0.158)	
Germany	51.1657° N	6995	50.100 (49.676-50.524)	182209	163200	8552	0.896 (0.894 – 0.897)		0.047 (0.046 – 0.048)	
Greece	39.0742° N	1028	50.735 (43.876-57.593)	2909	1374	175	0.472 (0.454 – 0.490)		0.060 (0.052 – 0.069)	
Iceland	64.9631° N	5519	57.000 (56.530-57.470)	1805	1792	10	0.993 (0.988 – 0.996)	*r*= 0.040 *P*= 0.874	0.006 (0.003 – 0.010)	*r*= -0.035 *P*= 0.882
Italy	41.8719° N	533	37.304 (22.408-52.199)	231732	150604	33142	0.650 (0.648 – 0.652)		0.143 (0.142 – 0.144)	
Netherlands	52.1326° N	4851	59.226 (53.785-64.666)	45950	N/A	5903	-		0.128 (0.125 – 0.132)	
Norway	60.4720° N	13887	73.262 (66.267-80.257)	8406	7727	236	0.919 (0.913 – 0.925)		0.028 (0.025 – 0.032)	
Russia	61.5240° N	160	25.074 (19.196-30.952)	387623	159257	4374	0.411 (0409 – 0.412)		0.011 (0.011 – 0.012)	
Slovakia	48.6690° N	162	81.500 (76.649-86.351)	1520	1338	28	0.880 (0.863 – 0.896)		0.018 (0.013 – 0.027)	
Spain	40.4637° N	570	45.000 (43.358-46.642)	284986	196958	27119	0.691 (0.689 – 0.693)		0.095 (0.094 – 0.096)	
Sweden	60.1282° N	2189	73.318 (64.204-82.431)	35727	4971	4266	0.139 (0.136 – 0.143)		0.119 (0.116 – 0.123)	
Switzerland	46.8182° N	542	22.137 (17.838-26.435)	30828	28300	1919	0.918 (0.915 – 0.921)		0.062 (0.060 – 0.065)	
UK	55.3781° N	3663	70.114 (44.024-96.204)	269127	N/A	37837	-		0.141 (0.139 – 0.142)	
Ukraine	48.3794° N	1575	25.281 (21.537-29.026)	22811	8934	679	0.392 (0.385 – 0.398)		0.030 (0.028 – 0.032)	
Siberia	61.0137° N	818	25.800 (25.779-25.821)	-	-	-	-		-	
Middle East	**29.2985° N**	**243909**	**32.705 (31.804-33.605)**	**516935**	**353501**	**13914**	**0.591 (0.462 – 0.709)**		**0.010 (0.006 – 0.017)**	
Bahrein	26.0667° N	500	27.900 (26.208-29.592)	10352	5491	15	0.530 (0.521 – 0.540)		0.001 (0.001 – 0.002)	
Egypt	26.8206° N	50	47.000 (43.258-50.742)	19666	5205	816	0.265 (0.259 – 0.271)		0.041 (0.039 – 0.044)	
Iran	32.4279° N	2624	37.067 (32.463-41.671)	143849	112988	7627	0.785 (0.783 – 0.788)		0.053 (0.052 – 0.054)	
Israel	31.0461° N	234150	57.818 (54.187-61.449)	16887	14727	284	0.872 (0.867 – 0.877)	*r*= 0.267 *P*= 0.488	0.017 (0.015 – 0.019)	*r*= -0.217 *P*= 0.576
Qatar	25.3548° N	547	36.000 (33.695-38.305)	52907	20604	36	0.389 (0.385 – 0.394)		0.001 (0.00 – 0.001)	
Saudi Arabia	23.8859° N	3700	30.299 (27.311-33.288)	80185	54553	441	0.660 (0.677 – 0.684)		0.005 (0.005 – 0.006)	
Syria	34.8021° N	372	24.700 (22.983-26.417)	122	43	4	0.352 (0.27 – 0.441)		0.033 (0.012 – 0.084)	
Turkey	38.9637° N	1431	35.126 (23.488-46.763)	159797	122793	4431	0.768 (0.766 – 0.770)		0.028 (0.027 – 0.029)	
UAE	23.4241° N	183	53.600 (48.761-58.439)	33170	17097	260	0.515 (0.510 – 0.521)		0.008 (0.007 – 0.009)	
Africa	**8.7832° S**	**2044**	**38.503 (37.169–39.837)**	**10411**	**6280**	**278**	**0.429 (0.153 – 0.758)**		**0.097 (0.004 – 0.739)**	
Guinea-Bissau	11.8037° N	365	78.300 (75.961-80.639)	1195	42	7	0.006 (0.003 – 0.012)	*r*= -0.800 *P*= 0.200	0.035 (0.025 – 0.047)	*r*= -0.400 *P*= 0.600
Tanzania	6.3690° S	1327	89.825 (63.601-116-050)	509	183	21	0.041 (0.027 – 0.062)		0.360 (0.319 – 0.402)	
Tunisia	33.8869° N	174	15.560 (13.800-17.321)	1071	946	48	0.045 (0.034 – 0.059)		0.883 (0.863 – 0.901)	
Morocco	31.7917° N	178	39.500 (35.240-43.760)	7636	5109	202	0.026 (0.023 – 0.030)		0.669 (0.658 – 0.660)	
North America	**54.5260° N**	**15024**	**54.879 (52.233-57.524)**	**1842338**	**537521**	**109190**	**0.280 (0.143 – 0.477)**		**0.046 (0.035 – 0.059)**	
Canada	56.1304° N	6756	73.506 (52.926-94.086)	88467	46766	6873	0.529 (0.525 – 0.532)	*r*= 1.000 *P*=.	0.078 (0.076 – 0.079)	*r*= 1.000 *P*=.
Guatemala	15.7835° N	108	53.300 (50.471-56.129)	4145	493	68	0.119 (0.109 – 0.129)		0.016 (0.013 – 0.021)	
USA	37.0902° N	8160	64.702 (56.696-72.708)	1749726	490262	102249	0.280 (0.280 – 0.281)		0.058 (0.058 – 0.059)	
Sought America	**8.7832° S**	**40192**	**40.710 (37.048-44.373)**	**519484**	**207414**	**27326**	**0.382 (0.356 – 0.408)**		**0.025 (0.009 – 0.068)**	
Argentina	38.4161° S	48	34.000 (29.672-38.328)	13933	4617	501	0.331 (0.324 – 0.339)	*r*= 0.500 *P*=0.667	0.036 (0.033 – 0.039)	*r*= 0.500 *P*=0.667
Brazil	14.2350° S	40054	58.856 (50.553-67.158)	418608	166647	25935	0.398 (0.397 – 0.400)		0.062 (0.061 – 0.063)	
Chile	35.6751° S	90	54.953 (42.705-67.201)	86943	36150	890	0.416 (0.413 – 0.419)		0.010 (0.010 – 0.011)	
Oceania	**22.7359° S**	**15868**	**57.153 (56.071-58.236)**	**8654**	**8054**	**125**	**0.959 (0.851 – 0.990)**	*r*= -1.000 *P*=.	**0.014 (0.012 – 0.017)**	*r*= -1.000 *P*=.
Australia	25.2744° S	15490	60.249 (55.264-65.234)	7150	6580	103	0.920 (0.914 – 0.926)		0.014 (0.012 – 0.017)	
New Zealand	40.9006° S	378	57.000 (55.891-58.109)	1504	1474	22	0.980 (0.972 – 0.966)		0.015 (0.010 – 0.022)	
Overall	-	**408748**	**50.544 (47.068-54.021)**	**5039935**	**2166518**	**317162**	**0.686 (0.628 – 0.739)**	***r*= 0.041 *P*= 0.780**	**0.030 (0.025 – 0.036)**	***r*= -0.073 *P*= 0.616**
Partial Correlation through adjusting by latitude higher than 50° N/S										
Europe	54.5260° N	-	25.975 (25.954 – 25.995)	-	-	-	0.753 (0.667 – 0.823)	*r*= 0.043 *P*= 0.869	0.045 (0.034 – 0.060)	*r*= 0.164 *P*= 0.501
Overall	-	-	50.544 (47.068-54.021)	-	-	-	0.686 (0.628 – 0.739)	*r*= -0.072 *P*= 0.629	0.030 (0.025 – 0.036)	*r*= -0.177 *P*= 0.223

UK: United Kingdom, UAE: United Arab Emirates, USA: United States of America, N: North, S: Sought

Discussion

Although comparing global statistics of COVID-19 outcomes is difficult, it is clear that the mortality rate is higher in several countries. It seems that various factors such as age, healthcare system quality, general health status, socioeconomic status, etc. Nonetheless, one of the underestimated factors, which might be associated with COVID-19 outcome is the vitamin D status in every populations. Investigations on respiratory infections indicated that 25-hydroxyvitamin D can effectively induce the host defense peptides against bacterial or viral agents and vitamin D insufficiency/deficiency can lead to non-communicable as well as infectious diseases [2, 96, 97]. The other potential role of vitamin D is reduction of inflammatory induced following SARS-CoV-2 infection. In fact, vitamin D affects the renin–angiotensin system pathway and promotes the expression of angiotensin-converting enzyme 2 (ACE2), which downregulates by SARS-CoV-2 [98].

Concerning all of the limitations and no adequate high-quality data about relation of vitamin D status and COVID-19 after several months, we have conducted this systematic review and meta-analysis in order to maximize the use of every available data, which would give us an overview toward further studies like what we have done recently on the effectiveness of hydroxychloroquine in COVID-19 patients [99], which have underestimated first, but the value was revealed after a while. We also hypothesize that vitamin D deficiency can be in correlation with COVID-19 mortality rates and recovery rate, which has studied through an ecological strategy.

Unfortunately, there were no clinical trials and high-quality data regarding the role of vitamin D in COVID-19. According to available data entered into our meta-analysis, we could find that approximately more than one-third of the patients infected with SARS-CoV-2 were suffering from vitamin D deficiency and this vitamin was insufficient in about 32% of them. In addition, meta-analysis of odds ratios showed a significant increased risk of COVID-19 infection in patients with low levels of plasma vitamin D. These findings are in the same line with other studies, which have debated the association of vitamin D and COVID-19 [100-104].

In case of vitamin D supplement's benefits against acute respiratory tract infections, Martineau *et al.* conducted a met-analysis of randomized controlled on 10.933 participants and resulted in inverse association between vitamin D levels and risk of acute respiratory tract infections. Thus, it can be concluded that patients with lower levels of vitamin D or patients with vitamin D deficiency are at higher risk of developing the disease to the severe form [105].

Despite the great importance of the issue there is still no results from underway randomized clinical trials (RCTs). To identify the ongoing RCTs, searching clinical trials registry databases resulted in 22 registered trials on the subject of prevention and treatment role of vitamin D in COVID-19 patients. Hence, following the results of these trials will help the medical associations to reach a general agreement regarding the utilization of vitamin D as a preventive and/or treatment option for COVID-19 patients. Ongoing RCTs can be tracked through following registry codes:

Iranian Registry of Clinical Trials (IRCT20200401046909N2, IRCT20200401046909N1, IRCT20200411047024N1, IRCT20200319046819N1, IRCT20140305016852N4); Chinese Clinical Trial Registry (ChiCTR2000029732, ChiCTR2000031163), EU Clinical Trials Register EudraCT Number (2020-002274-28, 2020-001363-85, 2020-001602-34, 2020-001717-20);

ClinicalTrials.gov (NCT04386044, NCT04370808, NCT04385940, NCT04334005, NCT04363840, NCT04351490, NCT04344041, NCT04335084, NCT04394390, NCT04395768, NCT04386850).

In case of relation between vitamin D levels and mortality/recovery rate of COVID-19 patients, some researchers were reported the dependence of COVID-19 morbidity and mortality to the latitude [106, 107]; similarly, our hypothetical strategy and big data analysis resulted several direct and reverse correlations in this regard. A quick look at the Fig. 5 shows that there is no regular relation for mortality or recovery rate by increasing vitamin D levels, but significant fluctuations observe regarding each country.

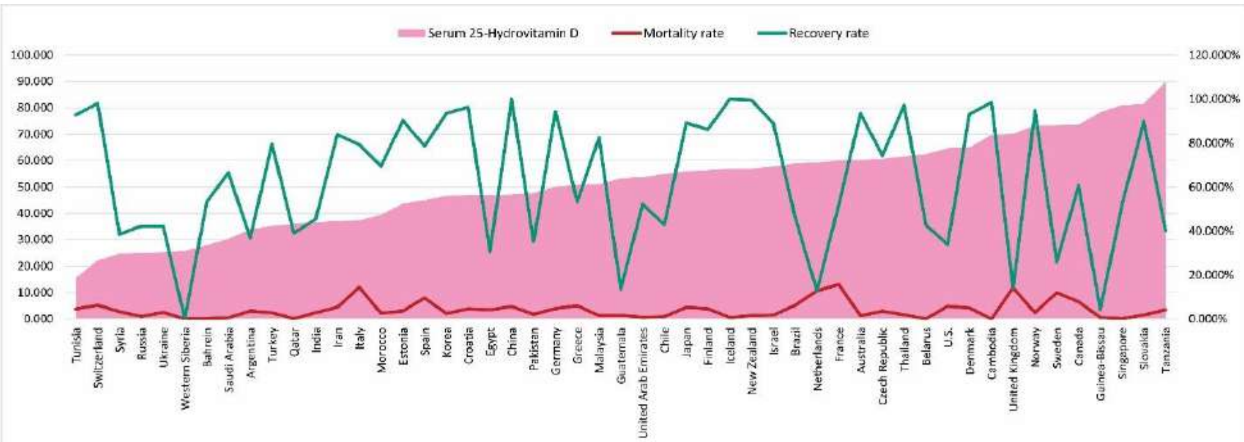


Figure 6. Comparison of national mortality and recovery changes by increasing of vitamin D levels in different populations

Despite the fluctuation, considering latitudes, showed a small reverse correlation between vitamin D status and mortality rate worldwide, which indicates that populations with lower levels of vitamin D might be in higher risk of SARS-CoV-2 infection. However, focusing on continents and countries one by one, indicates interesting findings in this case. For example, vitamin D status in Asia, Middle East, Africa and Oceania is correlated to the mortality reversely, whereas, it is in direct correlation with mortality in both North and Sought America. This might attract the considerations to the racial and ethnic aspects of the subject in different regions and populations [108, 109]. In case of recovery rate, while most of the continents indicated a direct correlation with vitamin D status, Africa and Oceania are significantly showed a reverse correlation in this regard. Considering Table 2, in Africa, the highest mean levels of vitamin D is related to Guinea-Bissau and Tanzania. This finding might be due to the numerous challenges such as human resource, health care systems budgetary, poor management, etc. in such regions [110-112], which unavoidably affects the subject significantly. About Oceania, it seems that extremely high rate of recovery in both Australia and New Zealand led to this statistical outcome.

Ultimately, to best of our knowledge, this is the most comprehensive systematic review that carried out a meta-analysis for investigating the role of vitamin D in COVID-19 patients along with a wide ecological consideration. However, after releasing outcomes of underway mentioned RCTs, an updated systematic review and meta-analysis on this subject could be more conclusive and reliable.

It is worth noticing that the current meta-analysis includes the following limitations:1) studies entered into the meta-analysis were observational and cross-sectional; thus, comparative analyses were not applicable in first part of study; 2) There are inevitable challenges with reliability of data due to different strategies in testing (e.g. vitamin D measurement, COVID-19 test, etc.), various subpopulations, etc. in both first part and ecological part of study; 3) other immunomodulator factors (e.g. vitamin C, zinc, selenium, etc.), which might be effective in the outcome of COVID-19 patients, have not considered in included studies; and 4) type *II* statistical errors following studies with small sample size. Eventually, to overcome the limitations and bias, results of the study should be confirmed by robustly large multicentral randomized clinical trials.

Conclusion

The conditional evidence recommends that vitamin D might be an important supportive agent for the immune system, mainly in cytokine response regulation against pathogens. In this systematic review and meta-analysis along with an ecological approach, we found a high percentage of COVID-19 patients who suffer from vitamin D deficiency or insufficiency as well as a significant increased risk of COVID-19 infection in patients with low levels of vitamin D. More importantly, our ecological investigation resulted in substantial direct and reverse correlations between recovery and mortality rate of COVID-19 patients with vitamin D status respectively in different countries. Considering latitudes, a small reverse correlation between vitamin D status and mortality rate was found throughout the world. Altogether, it seems that populations with lower levels of vitamin D might be in higher risk of SARS-CoV-2 infection. However, further large clinical trials following comprehensive meta-analysis should be taken into account in order to achieve more reliable findings. Additionally, due to multiple limitations, if this study does not allow to quantify a "value" of the Vitamin D with full confidence, it allows at least to know what the Vitamin D might be and that it would be prudent to invest in this direction through comprehensive RCTs.

Conflict of interests

The authors declare that they have no conflict of interests.

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