Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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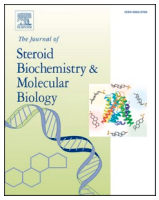

Short communication

Therapeutic and prognostic role of vitamin D for COVID-19 infection: A systematic review and meta-analysis of 43 observational studies

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ABSTRACT

Vitamin D modulates the systemic inflammatory response through interaction with immune system. As such, it has a possible protective role against the risk of respiratory tract infections and other diseases. It may be useful in particular, during COVID-19 pandemic. PubMed, the Cochrane Library, and EMBASE were searched from inception until January 31, 2021, for observational or clinical studies reporting the prognosis (and therapeutic effect) of COVID-19 infection in patients with deficient vitamin D levels. The infection rate, severity, and death from COVID-19 infection were pooled to provide an odds ratio with a 95 % confidence interval (OR 95 % CI). An OR > 1 was associated with the worst outcome in deficient compared with nondeficient patients.

We assessed the association between vitamin D and risk, severity, and mortality for COVID-19 infection, through a review of 43 observational studies. Among subjects with deficient vitamin D values, risk of COVID-19 infection was higher compared to those with replete values (OR = 1.26; 95 % CI, 1.19–1.34; $P < .01$). Vitamin D deficiency was also associated with worse severity and higher mortality than in nondeficient patients (OR = 2.6; 95 % CI, 1.84–3.67; $P < .01$ and OR = 1.22; 95 % CI, 1.04–1.43; $P < .01$, respectively).

Reduced vitamin D values resulted in a higher infection risk, mortality and severity COVID-19 infection. Supplementation may be considered as preventive and therapeutic measure.

Vitamin D modulates the systemic inflammatory response through interaction with most cells of the immune system. As such, it has a possible protective role against the risk of respiratory tract infections and other diseases [1]. Vitamin D supplementation resulted in reduced all-cause mortality, according to a recently published meta-analysis [2].

We aimed to assess the association between vitamin D and risk, severity, and mortality for COVID-19 infection. PubMed, the Cochrane Library, and EMBASE were searched from inception until January 31, 2021, for observational or clinical studies reporting the prognosis (and therapeutic effect) of COVID-19 infection in patients with deficient vitamin D levels. The search terms were as follows: *((vitamin D [MeSH Terms]) or (vitamin D) or (25OH vitamin D) OR cholecalciferol OR ergocalciferol OR calcitriol)) and ("covid-19")*.

The infection rate, severity, and death from COVID-19 infection were pooled to provide an odds ratio with a 95 % confidence interval (OR 95 % CI). An OR > 1 was associated with the worst outcome in deficient compared with nondeficient patients.

The study adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. The study's primary outcome was COVID-19 infection risk in vitamin D-deficient vs non-deficient patients. Secondary endpoints were severity (intensive care unit and/or mechanical ventilation), death, and therapeutic effect of vitamin D supplementation in COVID-19-affected patients.

The systematic search led to 43 eligible studies (Table 1) from 737 retrieved, mainly retrospective or observational studies (n = 612,601 patients), analyzing the effect of vitamin D deficiency or insufficiency and COVID-19 disease (infection, severity, or mortality). Among them, 8 reported on the therapeutic effect of supplementation on severity and mortality rate.

Among subjects with deficient vitamin D values, risk of COVID-19 infection was higher compared to those with replete values (OR = 1.26; 95 % CI, 1.19–1.34; $P < .01$). The funnel plot shows a minimal risk

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Table 1
Characteristics of included studies.

Author/year	Type of study	N° of pts	Vit. D3 cutoff (ng/mL) %*	Median age (years)	Country	Infection risk in low vitamin D	Severity scale	Supplem.dose	Type of analysis	NOS score
Abdollahi/ 2020	Retrospective case-control	402	30 (80.5)	47.1	Iran	↑	–	–	–	6
Abrishami/ 2020	Retrospective	73	25 (-)	55.1	Iran	–	–	–	MVA	5
Alguwaihes/ 2020	Retrospective	439	20 (-)	55	Saudi Arabia	–	ICU	–	MVA	6
Annweiler/ 2020	Retrospective	77	–	88	France	–	–	50,000 IU per month or 80,000/100,000 IU every 2–3 months 80,000 IU within a few hours of the diagnosis of COVID-19	MVA	5
Annweiler/ 2020	Retrospective	66	–	87.7	France	–	–	80,000 IU either in the week following the diagnosis of COVID-19, or during the previous month	MVA	5
Baktash/2020	Prospective cohort	105	30 (55.7)	81.3	Cyprus	–	NIV	–	–	6
Barassi/2021	Retrospective	118	20 (44.9)	61	Italy	–	CPAP/ NIMV	–	UVA	6
Bennouar/ 2021	Prospective	120	20 (55.9)	62.3	Algeria	–	–	–	MVA	6
Blanch-Rubió/ 2020	Cross-sectional	2102	–	66.4	Spain	–	–	–	–	7
Cangiano/ 2020	Observational	157	–	89.8	Italy	–	–	–	MVA	6
Carpagnano/ 2020	Retrospective	42	30 (81)	65	Italy	–	ICU	–	–	5
Cereda/2020	Prospective cohort	129	20 (76.7)	77	Italy	–	–	–	MVA	6
Chang/2020	Retrospective case-control	992	–	–	US	↑	–	–	–	8
De Smet/2020	Retrospective observational	186	20 (59)	69	Belgium	–	–	–	MVA	6
Demir/2021	Retrospective	487	30 (93)	44.6	Turkey	↑	–	–	UVA	6
Entrenas Castillo/ 2020	Randomized	76	–	52.9	Spain	–	–	0.532 mg d1, 0.266 mg d3,7 then weekly	MVA	5
Ferrari/2020	Retrospective	347	30 (78.9)	65	Italy	↑	–	–	UVA	6
Giannini/2021	Retrospective	91	20 (-)	74	Italy	–	–	200,000 IU in two consecutive days	MVA	6
Hastie/2020	Retrospective	656	20 (-)	–	UK	↑	–	–	MVA	7
Hernandez/ 2020	Case-control	403	20 (-)	61	Spain	–	ICU	25,000 IU monthly or 5600 IU weekly	UVA	6
Jain/2020	Prospective observational	154	20 (58.4)	46.8	India	–	ICU	–	–	6
Karahan/2020	Retrospective observational	149	30 (91.9)	65	Turkey	–	–	–	MVA	6
Katz/2021	Retrospective cross-sectional	884	–	–	US	↑	–	–	MVA	7
Kaufman/ 2020	Retrospective observational	191,779	20 (12.5)	54	US	↑	–	–	MVA	8
Li/2021	Prospective	353,299	25 (12.1)	67.7	UK	↑	Not defined	–	MVA	6
Ling/2020	Retrospective	444	25 (37.8)	74	UK	–	–	Various doses	MVA	6
Lohia/2021	Retrospective	270	20 (35.2)	63.81	US	–	ICU	–	MVA	6
Luo/2020	Retrospective	335	30 (65.1)	56	China	↑	Various criteria	–	MVA	7
Ma/2021	Prospective observational	8297	20 (-)	58.2	UK	↓	–	–	MVA	
Macaya/2020	Retrospective	80	20 (56)	–	Spain	–	Various criteria	–	UVA	6
Maghbooli/ 2020	Retrospective	325	30 (67.2)	58.7	Iran	–	Not defined	–	UVA	6
Mariani/2020	Registry data	37,900	20 (49)	–	International	↑	–	–	MVA	6
Meltzer/2020	Retrospective	489	20 (25)	49.2	US	↑	–	–	MVA	6
Mendy/2020	Retrospective	689	20 (12.9)	49.5	US	–	ICU or death	–	MVA	6
Merzon/2020	Population-based study	7807	30 (13.4)	35.5	Israel	↑	–	–	MVA	6
Pal/2020	Retrospective	72	20 (97)	36	India	↑	–	–	UVA	6

(*continued on next page*)

Table 1 (*continued*)

Author/year	Type of study	N° of pts	Vit. D3 cutoff (ng/mL) %*	Median age (years)	Country	Infection risk in low vitamin D	Severity scale	Supplem.dose	Type of analysis	NOS score
Panagiotou/ 2020	Retrospective	134	20 (37.3)	68.7	UK	–	ICU	–	UVA	6
Radujkovic/ 2020	Retrospective	185	30 (22)	60	Germany	–	MV or death	–	MVA	7
Raisi-Estabragh/ 2020	Prospective	1326	–	68.1	UK	=	–	–	MVA	6
Szeto/2020	Retrospective	700	20 (37.6)	63	US	–	ICU or death	–	MVA	6
Tan/2020	Prospective	43	–	61.2	Asia	–	–	1000 IU die	MVA	6
Vessiliou/ 2020	Prospective	30	15 (80)	65	Greece	–	–	–	UVA	7
Ye/2020	Case-control	142	20 (29)	42.5	China	↑	Not defined	–	MVA	6

* refers to COVID-19 infected patients.

^ oral calcifediol; ICU, intensive care unit; NIV, non-invasive ventilation; NIMV, non-invasive mechanical ventilation; MV, mechanical ventilation; CPAP, continuous positive airway pressure; UVA, univariate analysis; MVA, multivariate analysis.

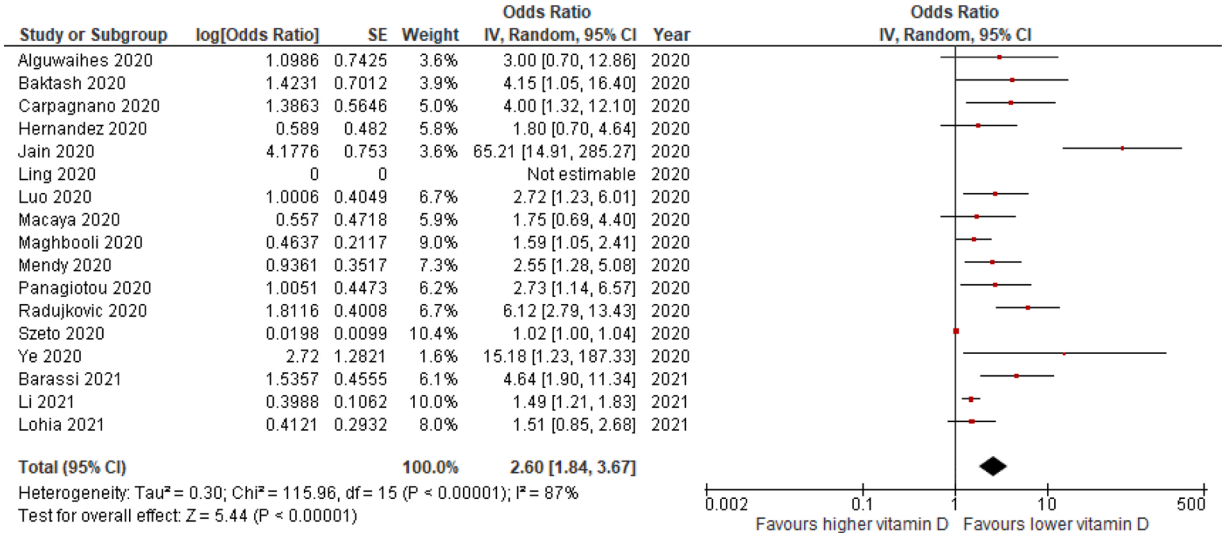

Fig. 1. risk of covid-19 severity in patients with low vitamin D levels.

of publication bias for the primary endpoint analysis (Egger test $P = .04$). Where deficient (<20 ng/mL) vitamin D cutoff was used, the risk of infection was 50 % higher compared to subjects with nondeficient values (OR 1.5, 95 %CI 1.08–2.08; P=.02). Vitamin D deficiency was also associated with worse severity and higher mortality than in non-deficient patients (OR = 2.6; 95 % CI, 1.84–3.67; $P < .01$, Fig. 1, and OR = 1.22; 95 % CI, 1.04–1.43; $P < .01$, respectively).

In n = 6 and n = 7 studies respectively, supplementation with various vitamin D doses reduced the risk of severe forms and death events in COVID-19-infected patients (OR = 0.27; 95 % CI, 0.11−0.66; $P < .01$ and OR = 0.41; 95 % CI, 0.21−0.81; $P = .01$).

Vitamin D influences the expression of various genes involved in the immune system (innate immunity, adaptive immunity) and the downstream inflammatory cascade, thus affecting the susceptibility to and severity of bacterial and viral infections [3,4]. Supplementation with vitamin D may be useful in COVID-19 infection, as both a preventive and therapeutic agent [5]. Vitamin D deficiency correlates strongly with infection risk in observational studies, which is likely linked to the impaired immune response to viral infection. Older persons with a weaker immune system and associated comorbidities are more vulnerable to dysfunctional immune responses, as most of them concomitantly have severe hypovitaminosis D. Gene response analysis revealed that vitamin D binds with its receptor and may affect 2 different pathways: (i) It inhibits the expression of pro-inflammatory cytokines interfering with the TNF-induced NFkB1 signaling pathway, and (ii) it initiates the expression of interferon-stimulating genes deputed to antiviral response activating the IFN-α-induced Jak-STAT signaling pathway [6]. This action mode explains why vitamin D deficiency is associated with mortality and severity of COVID-19 infection in our meta-analysis. In light of the present data and recent published health authorities' recommendations, 7 check and supplementation with vitamin D of subjects with deficient levels should be a priority during the COVID-19 pandemic.

Authors statement

Fausto Petrelli: Conceptualization, Methodology, Software Writing-Original draft preparation.

Antonio Ghidini, Gianluca Perego: Data curation.

Andrea Luciani: Supervision, Visualization, Investigation.

Paolo Colombelli: Supervision.

Giuseppina Dognini: Writing- Reviewing and Editing.

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