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Corrigendum

Corrigendum to: Influence of 25-hydroxy-cholecalciferol levels on SARS-CoV-2 infection and COVID-19 severity: A systematic review and meta-analysis [EClinicalMedicine 37 (2021) 100,967]

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We published a comprehensive systematic review and meta-analysis evaluating the current evidence on the impact of 25-hydroxy-cholecalciferol [25(OH)D] and its deficiency, on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and the severity and mortality of the coronavirus 19 disease (COVID-19).

Recently, we were informed that two studies included in our meta-analysis and published on pre-print platforms were withdrawn (original article references 39, 55). For this reason, in the attempt to understand whether the inclusion of these pre-prints could have affected the results of our meta-analysis, we decided to make an

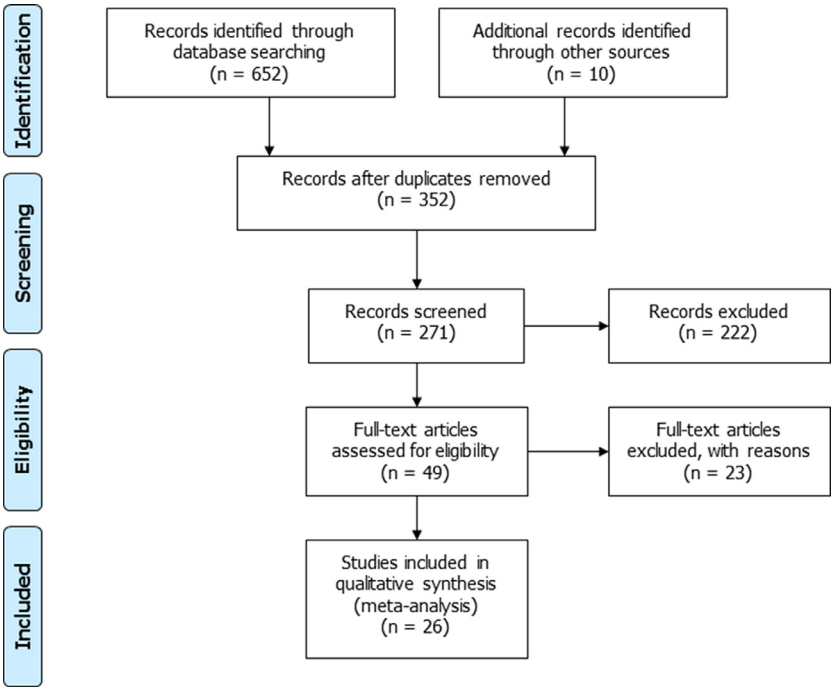

Fig. 1. Flowchart of the studies included in the meta-analysis.

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Table 1
Main characteristics of the studies included in this meta-analysis.

First Author	Year	Country	Study design	Sample size		Mean Age		Gender Male/Female		Ethnicity	Outcome evaluated	Time at 25(OH)D levels assessment
Abdollahi	2020 [27]	Iran	Case-control study	402	SARS-CoV-2 +	48.0 ± 16.5	SARS-CoV-2 +	66/135	NR	Difference in mean 25 (OH)D levels between COVID-19 positive and controls	NR	
					SARS-CoV-2 -	46.34 ± 13.5	SARS-CoV-2 -	66/135				
Abrishami	2020	Iran	Retrospective study	73	SARS-CoV-2 +	55.2 ± 15.0	SARS-CoV-2 +	47/26	NR	Difference in 25(OH)D levels between dead and discharged	Generally performed within 3 days of hospital admission	
					SARS-CoV-2 -	/	SARS-CoV-2 -	/				
Arvinte	2020	USA	Pilot study	21	SARS-CoV-2 +	60.2 ± 17.4	SARS-CoV-2 +	15/6	SARS-CoV-2 +	Caucasian: 4 Hispanic: 17	Difference in 25(OH)D levels between patients who died or were discharged from the hospital	Admission to hospital
					SARS-CoV-2 -	/	SARS-CoV-2 -	/	SARS-CoV-2 -	/		
Baktash	2020	UK	Prospective Cohort Study	105	SARS-CoV-2 +	81 (SD NR)	SARS-CoV-2 +	42/28	SARS-CoV-2 +	Caucasian: 50 South Asian: 18 East Asian: 2 Afro-Caribbean: 1	Difference in mean 25 (OH)D levels between COVID-19 patients and controls. Assessment of the risk for COVID-19 related mortality in patients with VDD	Admission to hospital
					SARS-CoV-2 -	83.4 ± 8.1	SARS-CoV-2 -	15/20	SARS-CoV-2 -	Caucasian: 30 South Asian: 3 East Asian: 0 Afro-Caribbean: 3		
Carpagnano	2020	Italy	Retrospective, observational single-center study	42	SARS-CoV-2 +	65.0 ± 13.0	SARS-CoV-2 +	30/12	NR	Assessment of the risk for mortality by COVID-19 in patients with VDD	Performed within 12 h of admission to RICU	
					SARS-CoV-2 -	/	SARS-CoV-2 -	/				
Cereda	2020	Italy	Single-center cohort study	129	SARS-CoV-2 +	73.6 ± 13.9	SARS-CoV-2 +	70/59	SARS-CoV-2 +	/	Assessment of the risk for COVID-19 severity and related mortality in patients with VDD	Performed within 48 h of admission to hospital
					SARS-CoV-2 -	/	SARS-CoV-2 -	/	SARS-CoV-2 -	/		
Chodick	2020	Israel	Cross-sectional study	14,520	SARS-CoV-2 +	40.6 (19.1)	SARS-CoV-2 +	788/529	NR	Difference in mean 25 (OH)D levels between COVID-19 patients and controls	NR	
					SARS-CoV-2 -	37.0 (19.1)	SARS-CoV-2 -	6092/7111				
D'Avolio	2020	Swiss	Retrospective Cohort Study	107	SARS-CoV-2 +	73.3 ± 12.5	SARS-CoV-2 +	19/8	NR	Difference in mean 25 (OH)D levels between COVID-19 patients and controls	Generally performed within 3 days of molecular testing for diagnosis of SARS-CoV-2 infection	
					SARS-CoV-2 -	72.0 ± 15.9	SARS-CoV-2 -	39/41				

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Table 1 (*Continued*)

First Author	Year	Country	Study design	Sample size	Mean Age	Gender Male/Female	Ethnicity	Outcome evaluated	Time at 25(OH)D levels assessment
De Smet	2020	Belgium	Retrospective observational study	186	SARS-CoV-2 + 67.0 ± 20.9	SARS-CoV-2 + 109/77	NR	Difference in 25(OH)D levels between mild and severe cases and between dead or discharged patients. Assessment of the risk for COVID-19 severe forms in patients with VDD	Admission to hospital	
Faul	2020 [41]	Ireland	Observational study	33	SARS-CoV-2 - / SARS-CoV-2 + NR	SARS-CoV-2 - / SARS-CoV-2 + 33/0	SARS-CoV-2 +	Caucasian: 33	Difference in 25(OH)D levels between mild and severe COVID-19 patients	Admission to hospital
Hastie-Mackay	2020	UK	Retrospective cohort study	348,598	SARS-CoV-2 - / SARS-CoV-2 + NR	SARS-CoV-2 - / SARS-CoV-2 + 265/184	SARS-CoV-2 - / SARS-CoV-2 +	White: 385 Black: 32 South Asian:19 Other: 13	Difference in mean 25 (OH)D levels between COVID-19 patients and controls	Pre-hospedalization (at least 10 years old dosages)
					SARS-CoV-2 - NR	SARS-CoV-2 - 168,391/179,758	SARS-CoV-2 -	White: 331,464 Black: 5022 South Asian:5917 Other: 5746		
Hernandez	2020	Spain	Case-control Study	394	SARS-CoV-2 + 59.5 ± 16.8	SARS-CoV-2 + 123/74	NR	Difference in mean 25 (OH)D levels between COVID-19 patients and controls. Assessment of the risk for COVID-19 severity and related mortality in patients with VDD	Admission to hospital	
Im	2020 [33]	South Korea	Case-control study	200	SARS-CoV-2 - 61.0 ± 7.47 SARS-CoV-2 + 52.2 ± 20.7	SARS-CoV-2 - 123/74 SARS-CoV-2 + 21/29	NR	Difference in mean 25 (OH)D levels between COVID-19 patients and controls	Dosing performed on average within 2 days of hospital admission and no later than 7 days	
Jain	2020	India	Prospective observational study	154	SARS-CoV-2 - 52.4 ± 20.2 SARS-CoV-2 + NR	SARS-CoV-2 - NR SARS-CoV-2 + 95/69	NR	Difference in 25(OH)D levels between mild and severe cases. Assessment of the risk for COVID-19 severe forms or mortality in patients with VDD	Admission to hospital	
Karonova	2020	Russia	Observational cohort study	80	SARS-CoV-2 - / SARS-CoV-2 + 53.2 ± 15.7	SARS-CoV-2 - / SARS-CoV-2 + 43/37	NR	Difference in 25(OH)D levels between mild and severe COVID-19 forms and between dead or discharged patients	NE	
					SARS-CoV-2 - /	SARS-CoV-2 - /				

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Table 1 (*Continued*)

First Author	Year	Country	Study design	Sample size	Mean Age	Gender Male/Female	Ethnicity	Outcome evaluated	Time at 25(OH)D levels assessment
Kerget	2020 [44]	Turkey	Case-control Study	88	SARS-CoV-2 + 49±21.1	SARS-CoV-2 + 41/47	NR	Difference in 25(OH)D levels between mild and severe COVID-19 forms and between dead or discharged patients	Admission to hospital	
Luo	2020	China	Retrospective cross-sectional study	895	SARS-CoV-2 - 35.2 ± 6.9 SARS-CoV-2 + 54.3 ± 15.6	SARS-CoV-2 - 8/12 SARS-CoV-2 + 148/187	NR	Difference in 25(OH)D levels between COVID-19 patients and controls. Difference in 25 (OH)D levels between mild and severe COVID-19 forms and between dead or discharged patients. Assessment of the risk for COVID-19 severity and related mortality in patients with VDD	Admission to hospital	
Mardani	2020 [35]	Iran	Case-control study	123	SARS-CoV-2 - 54.7 ± 8.2 SARS-CoV-2 - / SARS-CoV-2 + 43.3 ± 14.5	SARS-CoV-2 - 257/303 SARS-CoV-2 - / SARS-CoV-2 + 35/28	NR	Difference in mean 25 (OH)D levels between COVID-19 patients and controls and between dead or discharged patients	Admission to hospital	
Merzon	2020	Israel	Population based study	7807	SARS-CoV-2 - 40.8 ± 15.8 SARS-CoV-2 + 35.6 ± 15.6	SARS-CoV-2 - 30/30 SARS-CoV-2 + 385/397	NR	Difference in mean 25 (OH)D levels between COVID-19 patients and controls	Pre-hospedalization (not specified when)	
Panagiotou	2020	UK	Retrospective study	134	SARS-CoV-2 - 47.4 ± 21.0 SARS-CoV-2 + NR	SARS-CoV-2 - 2849/4176 SARS-CoV-2 + 73/61	SARS-CoV-2 +	Caucasian: 128 Asian: 4 Afro-Caribbean: 1 Other: 1	Difference in 25(OH)D levels between mild and severe COVID-19 forms. Assessment of the risk for severe COVID-19 forms in patients with VDD	Admission to hospital
Pizzini	2020	Austria	Prospective Multicenter Observational Study	109	SARS-CoV-2 - / SARS-CoV-2 + 58.0 ± 14.0	SARS-CoV-2 - / SARS-CoV-2 + 65/44	SARS-CoV-2 - NR	/ Difference in 25(OH)D levels between mild and severe COVID-19 forms	25(OH)D assays performed 8 weeks after disease onset	
Radujkovic	2020	Germany	Prospective Observational Study	185	SARS-CoV-2 - / SARS-CoV-2 + 50.7 ± 15.7	SARS-CoV-2 - / SARS-CoV-2 + 95/90	NR	Difference in 25(OH)D levels between mild and severe COVID-19 forms	Admission to hospital	
					SARS-CoV-2 - / SARS-CoV-2 - /	SARS-CoV-2 - / SARS-CoV-2 - /				

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Table 1 (*Continued*)

First Author	Year	Country	Study design	Sample size	Mean Age	Gender Male/Female	Ethnicity	Outcome evaluated	Time at 25(OH)D levels assessment
Raisi-Estabragh	2020	UK	Prospective cohort study	4510	SARS-CoV-2 + 68.1 ± 9.2 SARS-CoV-2 - 68.91 ± 8.72	SARS-CoV-2 + 696/630 SARS-CoV-2 - 1505/1679	SARS-CoV-2 + White: 1.141 Black: 76 Asian: 60 Chinese: 6 Mixed: 9 Other: 34 SARS-CoV-2 - White: 2927 Black: 91 Asian: 78 Chinese: 3 Mixed: 24 Other: 61	Difference in mean 25 (OH)D levels between COVID-19 patients and controls	Pre-hospedalization (at least 10 years old dosages)
Szeto	2020	USA	Retrospective cohort study	93	SARS-CoV-2 + NR SARS-CoV-2 - /	SARS-CoV-2 + 44/49 SARS-CoV-2 - /	SARS-CoV-2 + Black: 27 SARS-CoV-2 - /	Assessment of the risk for COVID-19 severity and related mortality in patients with VDD	Prehospitalization (25 (OH)D levels measured within the previous year and on average 136 days prior to hospital admission)
Vassiliou	2020	Greek	Prospective observational cohort study	30	SARS-CoV-2 + 65.0 ± 11.0	SARS-CoV-2 + 24/6	NR	Difference in 25(OH)D levels between dead and discharged COVID-19 patients and assessment of the risk for COVID-19 mortality in patients with VDD	Admission to ICU
Ye	2020 [38]	China	Case-control study	142	SARS-CoV-2 + 41.7 ± 15.9 SARS-CoV-2 - 44.7 ± 20.5	SARS-CoV-2 + 32/48 SARS-CoV-2 - 23/39	NR	Difference in mean 25 (OH)D levels between COVID-19 patients and controls, and between patients with severe or non-severe forms of COVID-19. Assessment of the risk for severe COVID-19 forms in patients with VDD	Admission to hospital

Abbreviation: 25(OH)D, 25-hydroxy-cholecalciferol; VDD, vitamin D deficiency; COVID-19, coronavirus disease 19; NR, Not Reported; SARS-CoV-2 +, patients positive for severe acute respiratory syndrome coronavirus 2 infection; SARS-CoV-2 -, patients negative for severe acute respiratory syndrome coronavirus 2 infection; SD, standard deviation; NE, Not evaluated; ICU, Intensive Care Unit; RICU, Respiratory Intermediate Care Unit.

Table 2
Quality assessment tool for observational cohort and cross-sectional studies.

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Abrishami et al. (2020) [49]	+	+	+	+	–	NR	+	–	+	–	+	NA	+	+
Arvinte et al. (2020) [50]	+	+	+	–	–	NR	–	–	+	–	+	NA	+	–
Baktash et al. (2020) [28]	+	+	+	–	–	–	–	+	+	–	+	NA	+	–
Carpagnano et al. (2020) [54]	+	+	+	–	–	NR	–	+	+	–	+	NA	+	+
Cereda et al. (2020)	+	+	+	–	–	+	–	+	+	–	+	NA	+	+
Chodick et al. (2020) [29]	+	+	+	–	–	NR	–	–	+	–	+	NA	+	+
D'Avolio et al. (2020) [30]	+	+	+	+	–	–	–	–	+	–	+	NA	+	–
De Smet et al. (2020) [40]	+	+	+	–	–	–	–	+	+	–	+	NA	+	–
Faul et al. (2020) [41]	+	+	+	–	–	NR	NR	–	NR	NR	+	NA	+	–
Hastie-Mackay et al. (2020) [31]	+	+	+	+	–	+	+	+	+	NR	+	NA	+	+
Jain et al. (2020)	+	+	+	+	+	NR	–	+	+	–	+	NA	+	+
Karonova et al. (2020) [43]	not assessable because in Russian language													
Luo et al. (2020)	+	+	+	–	–	+	–	+	+	–	+	NA	+	+
Merzon et al. (2020) [36]	+	+	+	+	–	+	NA	+	+	NR	+	NA	+	+
Panagiotou et al. (2020) [46]	+	+	+	–	–	NR	–	+	+	–	+	NA	+	–
Pizzini et al. (2020) [47]	+	+	+	+	–	+	–	+	+	–	+	NA	+	–
Radujkovic et al. (2020) [48]	+	+	+	–	–	+	–	+	+	–	+	NA	+	+
Raisi-Estabragh et al. (2020) [37]	+	+	+	+	–	+	+	–	+	–	+	NA	+	+
Szeto et al. (2020) [53]	+	+	+	–	–	+	NR	+	+	+	+	NA	+	+
Vassiliou et al. (2020) [51]	+	+	+	+	–	+	–	+	+	–	+	NA	+	–

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

additional analysis after excluding not only the two withdrawn pre-prints but also a third one originally included in the analysis (45).

Because of the exclusion of the 3 pre-prints (original article references 39, 45, 55), the flowchart of the included studies was modified (Fig. 1). Table 1, showing the characteristics of the included studies, and Table 2, concerning the quality analysis of the studies, were also updated after exclusion of the 3 pre-prints (original article references 39, 45, 55).

Analysis of serum 25(OH)D levels in SARS-CoV2-positive versus negative patients, and also analysis of patients with infection discharged versus those who died from the disease, were not performed, since pre-prints (original article references 39, 45, 55) were not included for these outcomes in the original meta-analysis.

Regarding analysis related to 25(OH)D levels in patients with severe or non-severe COVID-19 (original article Fig. 3), after exclusion of the pre-prints referenced originally as 39 and 45, 10 studies assessing this outcome remained. Specifically, the new analysis confirmed that 25(OH)D levels were clearly lower in the 492 patients with severe disease compared to the 817 patients with a non-severe course of the disease [MD −5.50 (−8.86, −2.14); $p = 0.001$] (Fig. 3A). After exclusion of the two pre-prints mentioned above, high inter-study heterogeneity was still found (Chi2 $P < 0.00001$, I2=93%) (Fig. 3B). After the removal of the studies by Luo and colleagues (original article reference 34), and Jain and colleagues (original article reference 42), identified as a source of heterogeneity at the Funnel Plot, the analysis showed homogeneity of the remaining studies (Chi2 $P = 0.86$, I2=0%) maintaining the statistical significance [MD −4.80 (−6.27, −3.32); $p < 0.00001$].

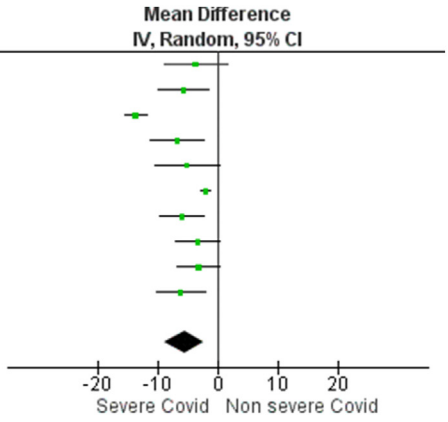
Also, the analysis of the risk of severe COVID-19 in patients with VDD (original article Fig. 5) did not change after the exclusion of pre-print reference 39. This outcome was assessed on data extracted from 10 studies. The study by Cereda and colleagues (original article reference 52) was considered twice since it evaluated both the percentage of patients with severe pneumonia and patients admitted to the intensive care units as an outcome of severity. The study by Jain and colleagues (original article reference 42) was also considered twice since they assessed the risk of infection severity both in patients with 25(OH)D<20 ng/ml and then in patients with levels below 10 ng/ml. The new statistical analysis confirmed that patients with VDD had a higher risk of a severe disease course than patients without deficiency [OR 3.78 (1.77, 8.06); $p = 0.0006$], regardless of the cut-off values considered to establish the efficiency (Fig. 5A). The Funnel plot showed that the heterogeneity found (Chi2 $P < 0.00001$, I2=85%) was attributable to the studies Jain and colleagues' (original article reference 42) and Hernandez and coworkers' (original article reference 32) (Fig. 5B). Once the data from these studies were excluded, heterogeneity was no longer observed (Chi2 $P = 0.53$, I2=0%) and the risk of developing a severe course of the disease in VDD patients remained significant [OR 2.47 (1.80, 3.37); $p < 0.00001$].

Finally, the analysis of the risk of mortality in patients with VDD (original article supplementary Fig. 2) also remained unchanged after the exclusion of the pre-print reference 55. Indeed, the analysis of the remaining 8 studies confirmed the absence of a significant increase in mortality risk in patients with VDD compared to patients with adequate 25(OH)D levels [OR 1.74 [0.84, 3.59]; $p = 0.14$] regardless of the cut-off values considered for deficiency (supplementary Fig. 2A). Heterogeneity between studies was found (Chi2 $P < 0.03$, I2=55%), and its origin was due to the study by Jain and colleagues (42) (Supplementary Fig. 2B). When this was excluded from the

A

Study or Subgroup	Severe Covid Mean	SD	Total	Non severe Covid Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
De Smet et al.	17.8	8.45	85	21.37	17.3	46	9.0%	-3.57 [-8.88, 1.74]
Faul et al.	10.8	4.8	12	16.4	7.6	21	9.8%	-5.60 [-9.84, -1.36]
Jain et al	14.35	5.79	63	27.89	6.21	91	11.1%	-13.54 [-15.46, -11.62]
Karanova et al.	11.9	6.4	25	18.5	14	55	9.6%	-6.60 [-11.07, -2.13]
Kerget et al.	16.8	10.5	35	21.8	15.8	53	8.8%	-5.00 [-10.49, 0.49]
Luo et al.	9.28	3.1	74	11.2	3.79	261	11.5%	-1.92 [-2.76, -1.08]
Panagiotou et al.	13.4	6.7	42	19.27	15.3	92	10.1%	-5.87 [-9.60, -2.14]
Pizzini et al.	20	9.6	53	23.2	10	56	10.1%	-3.20 [-6.88, 0.48]
Radujkovic et al.	18.2	13.1	93	21.3	11.5	92	10.2%	-3.10 [-6.65, 0.45]
Ye et al.	16.28	5.96	10	22.38	6.67	50	9.8%	-6.10 [-10.23, -1.97]
Total (95% CI)			**492**			**817**	**100.0%**	**-5.50 [-8.86, -2.14]**

Heterogeneity: Tau² = 25.51; Chi² = 122.99, df = 9 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.21 (P = 0.001)



B

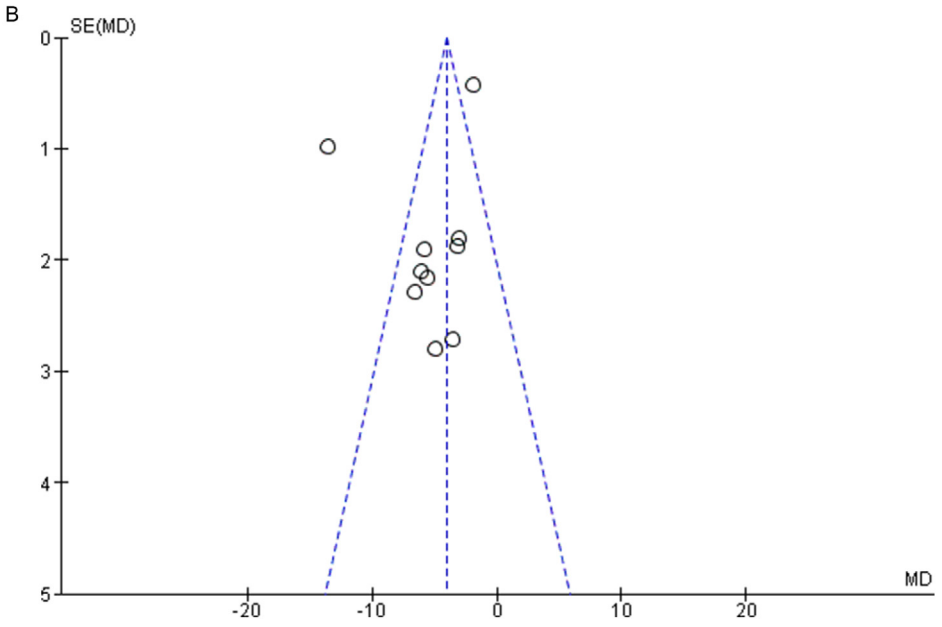


Fig. 3. Panel A. Forest plot of **s**tudies that assessed 25(OH)D levels as a continuous variable in patients with severe course of COVID-19 than those with mild course. **Panel B.** Funnel plot showing the source of heterogeneity of studies that evaluated 25(OH)D levels as a continuous variable in patients with severe course of COVID-19 than those with mild course. Serum 25(OH)D levels are expressed in ng/ml.

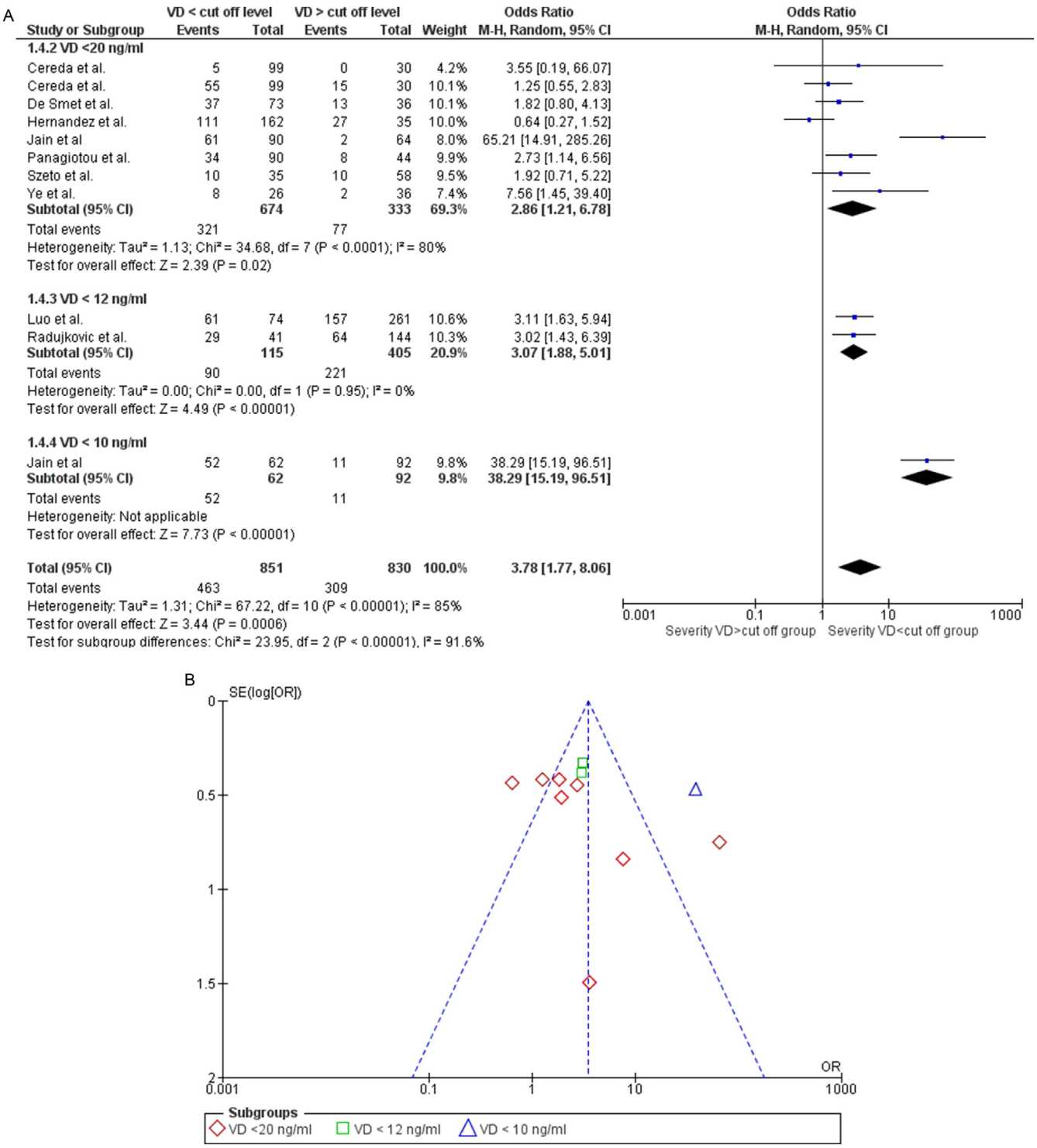


Fig. 5. Panel A. Forest plot of **s**tudies that assessed the risk of a severe course of disease in subjects with 25(OH)D values below or above a specified cut-off. The different cut-offs used by the studies allowed for subgroup analysis. Studies using cut-off values higher than those established by the Endocrine Society for the diagnosis of Vitamin D Deficiency (<20 ng/ml) were not included. **Panel B.** Funnel plot showing the source of heterogeneity of studies that evaluated the risk of a severe course of disease in subjects with 25(OH)D below or above a specified cut-off.

analysis, the Funnel Plot showed homogeneity among the remaining studies (Chi2 P = 0.15, I2=36%), and the increased risk of COVID-19 mortality in the presence of VDD was confirmed to be non-significant [OR 1.30 (0.83, 2.03); p = 0.25].

In conclusion, the results of this new analysis showed no difference compared to the original one. Therefore, the inclusion of pre-prints did not affect the results of our meta-analysis. After the exclusion of pre-prints, we may still hypothesize a role for low 25(OH)D levels in the risk of SARS-CoV-2 infection and the development of more severe forms of COVID-19.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101168.

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