Systematic Review and Meta-Analysis

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Vitamin D status was associated with sepsis in critically ill children

A PRISMA compliant systematic review and meta-analysis

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Abstract

Background: Sepsis leads to the high mortality in critically ill infants and children. It is still controversial whether vitamin D deficiency was associated with the incidence of sepsis. Thus we designed the systematic review and meta-analysis.

Methods: The Ovid Medline, Embase, PubMed, and Cochrane library were systematically searched until April 5, 2020. The 25 hydroxyvitamin D (25-OHD) level was recorded and set 20 ng/mL as cut-off in cohort study to divide the lower and higher 25-OHD group. The odds ratio (OR) and 95% confidence intervals (CIs) were calculated for comparing the impact of vitamin D deficiency on the incidence of sepsis in critically ill children.

Results: A total of 27 studies were included with 17 case-control studies and 10 cohort studies. In those case-control studies, the maternal 25-OHD level and neonatal 25-OHD level in sepsis group was significant lower than non-sepsis group ($P < .001$). The percentage of severe vitamin D deficiency was significant higher in sepsis group comparing to non-sepsis group (odds ratio [OR] = 2.66, 95% CI = 1.13–6.25, $P < .001$). In those cohort studies, the incidence of sepsis in lower 25-OHD group was 30.4% comparing with 18.2% in higher 25-OHD level group. However, no statistical significant difference in terms of mechanical ventilation rate and 30-day mortality.

Conclusion: We demonstrated that critically ill infants and children with sepsis could have a lower 25-OHD level and severe vitamin D deficiency comparing to those without sepsis. Future studies should focus on the association of vitamin D supplement and the occurrence of sepsis in critically ill children.

Abbreviations: 25-OHD = 25 hydroxyvitamin D, CI = confidence interval, DCs = dendritic cells, MeSH = Medical Subject Heading, MODS = multiple organ dysfunction syndrome, NOS = the Newcastle-Ottawa Quality Assessment Scale, OR = odds ratio, PICU = pediatric intensive care unit, PRISMA = systematic review and meta-analysis, RR = relative risks, SD = standard deviations, SMD = standard mean difference, VDBP = vitamin D specific binding protein, VDR = vitamin D receptor.

Keywords: children, infant, sepsis, vitamin D deficiency

1. Introduction

Vitamin D is an important nutrient for the human body and it was first discovered in 1921. At first, it focused on the role of calcium and phosphorus metabolism and bone growth and development and therefore it was mainly used to resist rickets.[1] Until the 1980s, its extra-osseous role became research hotspots, studies have found that vitamin D can affect cell proliferation and mutation, hormone secretion regulation and immune regulation, and its role in many acute and chronic diseases has been confirmed and recognized, including infectious diseases, autoimmune diseases, cancer, Type 2 diabetes, cardiovascular diseases, and infectious diseases.[2–5] The biologically active form of vitamin D is 1,25 $(OH)_2$ D3, but the concentration of 25 hydroxyvitamin D (25-OHD) is easy to detect and stable in blood, which could represent the vitamin D level in human body.[6] Recent studies showed that 25-OHD deficiency is widespread in children and adults worldwide, and the 25-OHD deficiency rate in critically ill patients is as high as about 30% to 70%.[7–10]

Sepsis was first defined as a systemic inflammatory response caused by infection in 1991. When combined with organ dysfunction, it was defined as severe sepsis.[11] Sepsis develops fiercely and is prone to be complicated by multiple organ damage which has the characteristics of high mortality, long hospital stay, and high cost of treatment.[12] In 2016, the European Society of Critical Care Diseases redefined sepsis, emphasizing that infection is the cause of sepsis.[13] The unsteady-state host reaction caused by infection is extremely lethal, and the uncontrolled inflammation and immune function disorders are the key links. Sepsis has gradually become a high-risk species in

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All data generated or analyzed during this study are included in this published article [and its supplementary information files];

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the intensive care unit, and the disease is developing rapidly. If it is not effectively controlled, it can easily develop into multiple organ dysfunction syndrome (MODS), and the mortality rate of sepsis in children with pediatric intensive care unit (PICU) could reach as higher as 21.9%.[14]

Recent researches have shown that 25-OHD deficiency is an independent risk factor affecting the prognosis of sepsis adult patients.[15] And the mechanism related to sepsis may relate to the target of vitamin D treatment. Therefore, vitamin D supplementation may become a new method of adjuvant therapy for patients with sepsis. However, it is still controversial whether there is an association between vitamin D deficiency and sepsis in infant and children. Thereafter, we designed the systematic review and meta-analysis in assessing the vitamin D deficiency in associating with the occurrence of sepsis in children.

2. Methods

The ethical approval was waived from the local institution due to the study design and this study was designed in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.[16]

2.1. Search strategy

This study aimed to discuss the risk of blood vitamin D status in associating with the occurrence of sepsis in children. The Ovid Medline, Embase, PubMed, Cochrane Central Register of Controlled trials and Cochrane Database of Systematic reviews were systematically searched due to April 5, 2020. Moreover, grey literature was searched in related website and Google Scholar to find more related articles. The keywords and Medical Subject Heading (MeSH) were designed by an experienced librarian. Briefly, the MeSH and keywords included "sepsis," "septic shock," "vitamin D," "25-OHD." All the studies containing titles and abstracts were imported into Endnote for deleting the duplication and literature screening.

2.2. Criteria for inclusion and exclusion

All the studies discussing the risks of vitamin D status in occurrence of sepsis in children were included in the meta-analysis. The inclusion criteria were as follow: the study measured the 25-OHD in either maternal or neonatal level, or the study classified the vitamin D level into severe, deficiency, or insufficiency; the sepsis occurrence was limited in infant or children, whose age <18-year old; the sepsis was diagnosed by blood test; the study type limited in case-control study or cohort study in discussing the relationship between vitamin D level and occurrence of sepsis. The other meta-analysis, reviews, letter, comment, and conference reviews were reading for the further inclusion of the studies.

The exclusion criteria were: case reports or the case sample <10; the study did not report the vitamin D level; the study did not limit in sepsis in infant or child; the study was without full data to extract the odds ratio (OR) or relative risks (RR); the study data overlapped with those of another study; the study was not written in English.

2.3. Literature screening, data extraction and quality assessment

Two investigators (W-jY and Q-lY) independently screened the titles and abstracts according to the inclusion and exclusion criteria. The full text was further assessed if the titles and abstracts could not be determined. The third investigator (Q-yH) was adapted for discussion if disagreement existed.

The data were extracted into a standard form and recorded the information as follow: the study characteristics (author, publish year, country, institution, recruitment period, study design, and etc), vitamin D deficiency definition, patient characteristics (birthweight, age, sex, APGAR score, maternal or neonatal 25-OHD level, and etc), and the outcome assessment (sepsis rate, mechanical ventilation rate, and mortality).

Two investigators (L-sH and WZ) independently assess the quality of the including papers. The cohort studies were assessed based on the Newcastle-Ottawa Quality Assessment Scale (NOS), with a high quality of 6 to 9, whereas low quality was scored as 0 to 5.[17]

2.4. Statistical analysis

The meta-analysis was performed with Stata 15.0 software (Stata Corporation, College station, TX). In terms of case-control study, the risks of vitamin D status in associating with the sepsis were compared using OR and 95% confidence interval (CI). Moreover, 25-OHD level was compared using standard mean difference (SMD) using mean and standard deviations (SD). If the data provided as medians and ranges, we converted medians and ranges into means and SD using the formula provided by Hozo et al.[18] For cohort study, the sepsis occurrence, mechanical ventilation rate, and 30-day mortality were compared using RR and 95% CI. All P value <.05 was considered to be statistical significance for all the analyses.

3. Results

3.1. Selection of included studies

A total of 1130 studies were found based on the search strategy. Four studies were identified through grey literature screening. And 917 studies were screened through abstracts and titles after deleting the duplication studies. Finally, a total of 27 studies were included based on the inclusion and exclusion criteria.[3,7–10,19–40] The flowchart of the literature screening was shown in Fig. 1.

3.2. Characteristics and meta-analysis in the case-control studies

Due to the different study group in case-control study and cohort study, we divided the included studies based on the study type. The characteristics of case-control study were shown in Table 1. A total of 17 case-control studies with 1358 sepsis children and 1956 non-sepsis children. The case-control studies covering 6 countries, including India, Turkey, Egypt, Thailand, China, and USA. The median birthweight in sepsis group was 2602 g (range from 1294 to 3454 g) while that was 2678 g (range from 1750 to 3223 g). 56.6% of children were boys in sepsis group comparing to 55.1% of which in non-sepsis group. The median 1 and 5 minutes APGAR score was 7.7 and 8.8 in sepsis group comparing to 8 and 9 in non-sepsis group.

The comparison of 25-OHD level between sepsis group and non-sepsis group was summarized in Fig. 2. The maternal 25-OHD level was 20.7 ng/mL in sepsis group, which is lower than non-sepsis group with 29.05 ng/mL (SMD = −1.58, 95% CI = −2.42 to −0.74, $P < .001$). Similarly, the neonatal 25-OHD level in sepsis group was significant lower than non-sepsis group

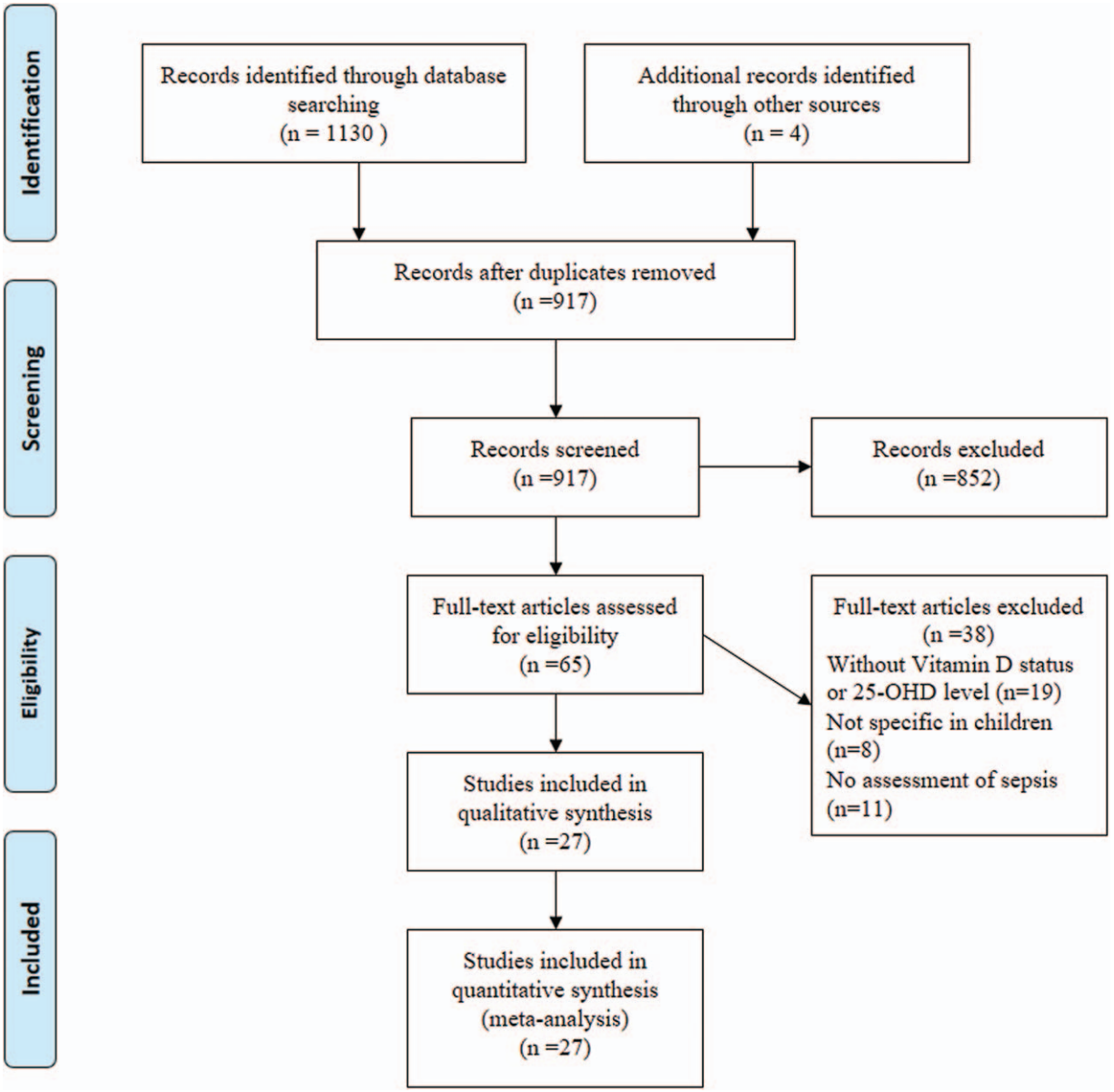

Figure 1. The flowchart of literature screening.

(SMD = –1.61, 95% CI = –2.09 to –1.10, $P < .001$). Based on the neonatal 25-OHD level in different children, several study classified the vitamin D deficiency into severe and insufficient vitamin D deficiency. The comparison of the percentage of severe and insufficient vitamin D deficiency was shown in Fig. 3. The percentage of severe vitamin D deficiency was significant higher in sepsis group comparing to non-sepsis group (OR = 2.66, 95% CI = 1.13–6.25, $P < .001$). However, no statistically difference was found in terms of insufficient vitamin D deficiency between 2 groups (OR = 1.04 95% CI = 0.76–1.41, $P = .364$).

3.3. Characteristics and meta-analysis in the cohort studies

Ten studies designed the cohort study to demonstrate the association between 25-OHD level and the outcome of critically ill children. The characteristics were summarized in Table 2. The publish year ranged from 2012 to 2020, and the recruitment year range from 2005 to 2017. Seven countries (China, Korea, India, Ireland, Spain, Australia, Canada) were covered. All the studies divided the cohort into lower 25-OHD level group and higher 25-OHD level group with cut-off of 20 ng/mL. A total of 925 patients were diagnosed as low 25-OHD level and 694 patients were high 25-OHD level. The percentage of boys was 59.5% in lower 25-OHD level group comparing to 56.9% in higher 25-OHD level group.

The comparison of the occurrence rate of sepsis, mechanical ventilation and 30-day mortality in critical children were summarized in Fig. 4. The sepsis rate was 30.4% in lower 25-OHD level group comparing to which was 18.2% in higher 25-OHD level group. Although the higher sepsis rate was found in lower 25-OHD level group, there was no statistically significance between 2 groups (RR = 1.24, 95%CI = 0.98–1.56, $I^2 = 28.7\%$, $P = .068$, Fig. 4A). The mechanical ventilation rate was 66.3% in

Table 1

The characteristics of included case-control study.

Author	Year	Recruitment year	Country	Vitamin D deficiency definition	NOS	Group	Sample	Birthweight	Male, %	APGAR score 1 min	APGAR score 5 min	Maternal 25-OHD levels	Neonatal 25-OHD levels	Deficiency in total	Severe vitamin D deficiency	Insufficiency vitamin D deficiency
Singh, P.	2020	2015–2016	India	Serum 25-OHD level: severe deficiency <11 ng/mL; insufficiency 11–32 ng/mL, and >32–100 ng/mL was adequate	8	Sepsis	70	2640±480	43 (61)	9 (9–10)	9 (9–10)	NG	16±10.5	56 (80)	29 (41)	27 (39)
						Non-sepsis	70	2580±370	40 (57)	9 (9–10)	9 (9–10)	NG	29.07±8.4	41 (59)	4 (6)	37 (53)
Dogan, P.	2020	2014–2015	Turkey	Serum 25-OHD level: severe vitamin D deficiency <5 ng/mL, insufficiency 5–15 ng/mL, sufficient >20 ng/mL	8	Sepsis	42	1294 (1018–1883)	18 (43)	7(5–8)	8 (7–9)	9.5 (8–13)	8.1 (5–9.5)	40 (95)	19 (45)	21 (50)
						Non-sepsis	66	1750 (1198–2290)	41 (62)	7(5–8)	8 (6–9)	14.1 (10.3–18)	12.2 (8.5–15.4)	49 (74)	14 (21)	35 (53)
Behera, C. K.	2020	2015–2016	India	Serum 25-OHD level: severe vitamin D deficiency <12 ng/mL, insufficiency 12–20 ng/mL, sufficiency > 20 ng/mL	8	Sepsis	40	2712±648	28 (70)	8±2	9±1	20.92±3.92	12.71±2.82	39 (98)	31 (78)	8 (20)
						Non-sepsis	40	2890±350	24 (60)	8±1	9±0	27.31±6.83	25.46±7.02	0 (0)	0 (0)	0 (0)
Ozdemir, A. A.	2019	2017–2018	Turkey	Serum 25-OHD level: severe vitamin D deficiency <12 ng/mL, insufficiency 12–20 ng/mL, sufficiency >20 ng/mL	6	Sepsis	51	NG	40 (78)	8±1	9±1	10.8±5.6	11.0±5.5	NG	NG	NG
						Non-sepsis	56	NG	26 (46)	8±1	9±1	14.9±10	13.8±10.6	NG	NG	NG
Hagag, A. A.	2019	2017–2019	Egypt	NG	5	Sepsis	60	2557±41		NG	NG	NG	16.95±2.60	NG	NG	NG
						Non-sepsis	30	2577±45		NG	NG	NG	24.36±3.35	NG	NG	NG
Agrawal, A.	2019	2016–2017	India	Serum 25-OHD level: severe vitamin D deficiency <5 ng/mL, insufficiency 5–15 ng/mL, sufficient >20 ng/mL	7	Sepsis	175	2441±670	81 (46)	NG	NG	NG	12.28±6.11	151 (86)	36 (21)	115 (65)
						Non-sepsis	50	2630±510	27 (54)	NG	NG	NG	14.88±7.2	37 (74)	7 (14)	30 (60)
Zheng, G.	2018	2015–2017	China	NG	6	Sepsis	75	NG	37 (49)	8.4±0.8	9.5±0.5	NG	14.85±6.14	NG	NG	NG
						Non-sepsis	100	NG	50 (50)	8.2±0.7	9.6±0.4	NG	26.38±6.56	NG	NG	NG
Tayel, S. I.	2018	2016–2017	Egypt	NG	7	Sepsis	49	3000±100	24 (49)	6.3±1.1	8.5±1.7	21.4±4.8	8.7±0.7	NG	NG	NG
						Non-sepsis	40	3000±100	17 (43)	9.3±0.6	10±0	36.9±4.2	19.1±4.7	NG	NG	NG
Li, W.	2018	2009–2011	China	Serum 25-OHD level: severe vitamin D deficiency <10 ng/mL, insufficiency 10–20 ng/mL, sufficient >30 ng/mL	5	Sepsis	433	NG	255 (59)	NG	NG	NG	15.96±9.03	NG	NG	NG
						Non-sepsis	785	NG	426 (54)	NG	NG	NG	31.71±14.82	NG	NG	NG
Dhandai, R.	2018	2015–2016	India	Serum 25-OHD level: vitamin D deficiency	6	Sepsis	60	2625.12±486.2	35 (58)	NG	NG	17.87±11.89	15.37±10	NG	NG	NG

(*continued*)

Table 1
(continued).

Author	Year	Recruitment year	Country	Vitamin D deficiency definition	NOS	Group	Sample	Birthweight	Male, %	APGAR score 1 min	APGAR score 5 min	Maternal 25-OHD levels	Neonatal 25-OHD levels	Deficiency in total	Severe vitamin D deficiency	Insufficiency vitamin D deficiency
				<120 ng/mL, insufficiency 20–30 ng/mL, sufficient >30 ng/mL												
						Non-sepsis	60	2495.58±490.1	42 (70)	NG	NG	23.65±9.55	21.37±9.53	NG	NG	NG
Gamal, T. S.	2017	2015–2016	Egypt	Serum 25-OHD level: severe vitamin D deficiency <12 ng/mL, insufficiency 12–20 ng/mL, sufficiency >20 ng/mL	6	Sepsis	50	NG	NG	NG	NG	42.5±20.7	6.4±1.8	NG	NG	NG
						Non-sepsis	30	NG	NG	NG	NG	50.4±21.4	24.6±2.2	NG	NG	NG
Korwutthikulrangsri, M	2015	NG	Thailand	NG	6	Sepsis	32	NG	NG	NG	NG	NG	16.6 (13.3–19.5)	NG	NG	NG
						Non-sepsis	36	NG	NG	NG	NG	NG	24.2 (21.0–27.9)	NG	NG	NG
Cizmeci, M. N.	2015	2011–2012	Turkey	Serum 25-OHD level: vitamin D deficiency <12 ng/mL, insufficiency 20–30 ng/mL, sufficient >30 ng/mL	6	Sepsis	40	2877±652	27 (68)	NG	NG	NG	NG	NG	NG	35 (87)
						Non-sepsis	43	3120±440	28 (65)	NG	NG	NG	NG	NG	NG	23 (53)
Cetinkaya, M	2015	2012	Turkey.	Serum 25-OHD level: severe deficiency <11 ng/mL; insufficiency 11–32 ng/mL, and >32–100 ng/mL was adequate	7	Sepsis	50	3454±460	26 (52)	8±3	8±2	22.2±6.8	8.6±3.1	NG	NG	NG
						Non-sepsis	50	3223±460	29 (58)	7±2	8±2	36.2±1.8	19.0±4.8	NG	NG	NG
Cekmez, F.	2014	2011–2012	Turkey	NG	5	Sepsis	40	2420±368	NG	NG	NG	NG	69±7.5	NG	NG	NG
						Non-sepsis	20	2520±280	NG	NG	NG	NG	35±19	NG	NG	NG
Aydemir, G.	2014	NG	Turkey	NG	5	Sepsis	40	NG	NG	NG	NG	NG	74±8	NG	NG	NG
						Non-sepsis	20	NG	NG	NG	NG	NG	28±12	NG	NG	NG
Madden, K.	2012	2009–2010	USA	Serum 25-OHD level: vitamin D deficiency <12 ng/mL, insufficiency 20–30 ng/mL, sufficient >30 ng/mL	5	Sepsis	51	NG	NG	NG	NG	NG	19.2 (12.6–24.8)	NG	NG	NG
						Non-sepsis	460	NG	NG	NG	NG	NG	22.5 (16.4–31.3)	NG	NG	NG

NOS = the Newcastle-Ottawa Quality Assessment Scale.

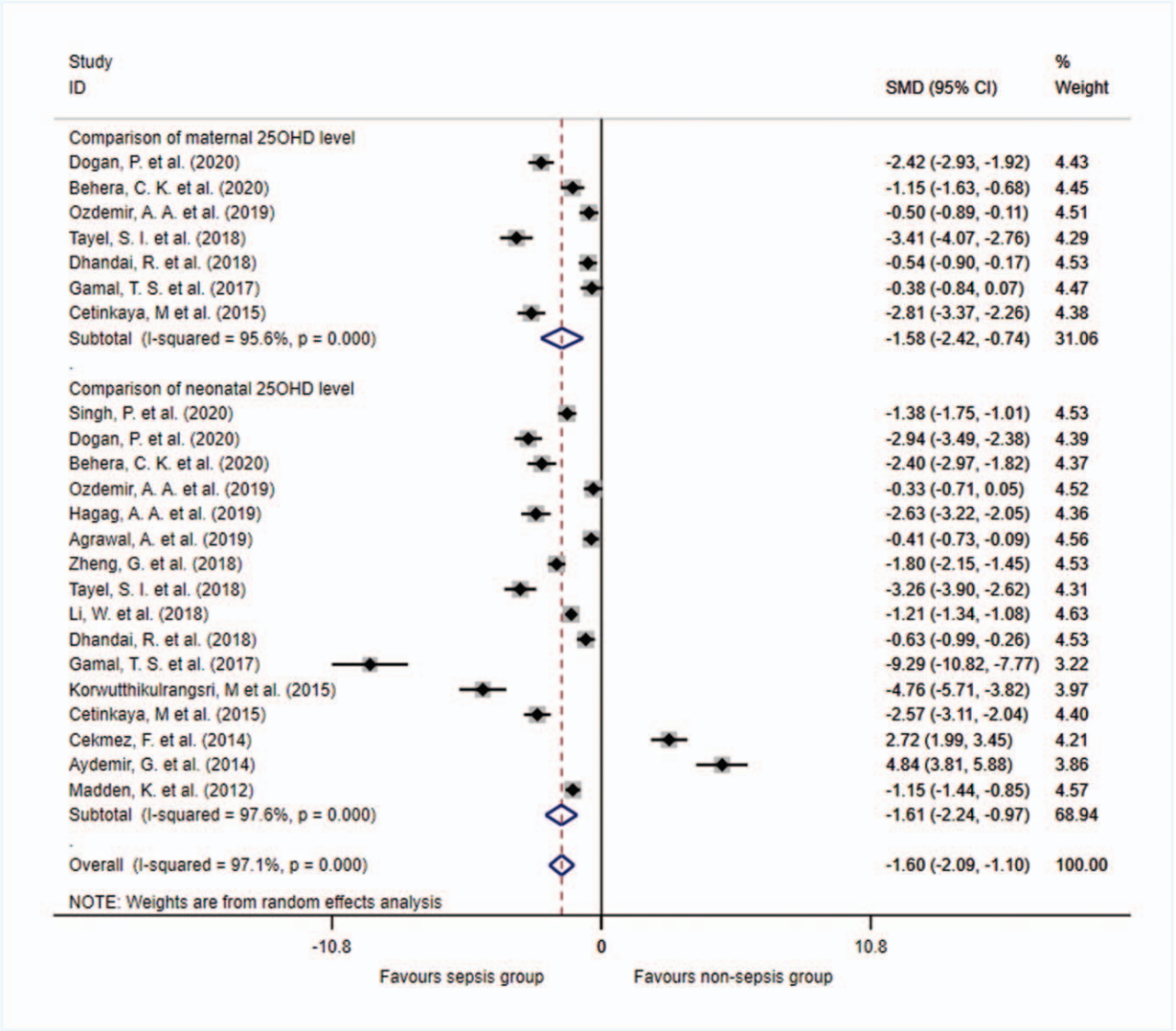

Figure 2. The comparison of maternal 25-OHD level and neonatal 25-OHD level in critically ill children with sepsis to those children without sepsis.

lower 25-OHD level group and 59.1% in higher 25-OHD level group, and no significant difference between 2 groups (RR = 1.07, 95% CI = 0.94–1.22, $I^2 = 31.6\%$, $P = .289$, Fig. 4B). Besides, the 30-day mortality was 29.1% in lower 25-OHD level group compared with 14.0% in higher 25-OHD level group, but without statistical difference (RR = 1.15, 95%CI = 0.83–1.59, $I^2 = 0\%$, $P = .398$, Fig. 4C).

3.4. Quality assessment in included studies

We assessed the quality of included studies based on the NOS approach, 12 studies were regarded as high quality in case-control study,[7,19,21,23,24,27,28,30,34,38–40] and all the cohort studies were regarded as high quality with NOS >6.[3,8,9,25,26,32,33,35–37]

4. Discussion

Our systematic review and meta-analysis demonstrated that both the maternal 25-OHD level and neonatal 25-OHD level were lower in infant with sepsis comparing to those infant without sepsis in PICU. Specially, the percentage of severe vitamin D deficiency was higher in sepsis group comparing to non-sepsis group. Although a higher rate of mechanical ventilation rate and 30-day mortality was found in lower 25-OHD level group in cohort study, there was no statistical significance between lower and higher 25-OHD level critically ill children.

Vitamin D can be ingested from food, but mainly from the body's own synthesis. 7-dehydrocholesterol isomerized in the skin under ultraviolet light (296–310 nm) to produce vitamin D3, which enters the blood circulation and binds to vitamin D specific binding protein (VDBP). It is transported to the liver and kidney successively and then hydroxylated by the action of 25-hydroxylase and 1-αhydroxylase into biologically active 1,25 (OH)D, and then carried by VDBP to various target organs through blood circulation, and vitamin D receptor (VDR) combines to play a biological role. The intestine, kidney, and bone are the main target organs. Most tissues and cells in the body can express VDR, and some contain the active enzyme

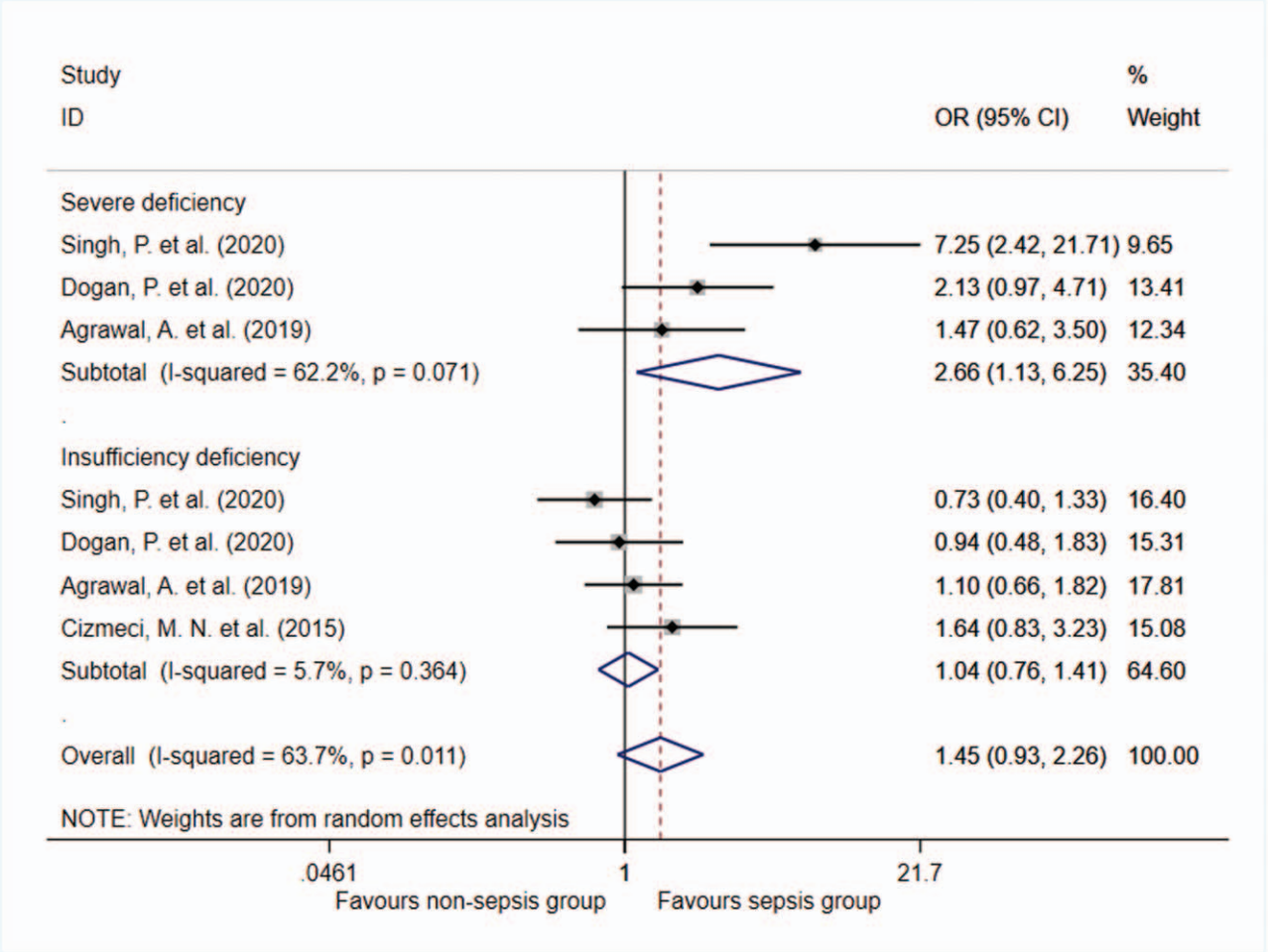

Figure 3. The comparison of severe vitamin D deficiency and insufficient vitamin D deficiency in critically ill children with sepsis to those children without sepsis.

Table 2

The characteristics of included cohort study (the cutoff of 25OHD level was defined as 20 ng/mL).

Author	Year	Recruitment year	Country	NOS	Group	Sample	Age, mo	Male, %	Sepsis, %	Mechanical ventilation	30 days mortality, %
Dang, H.	2020	2016–2017	China	8	Lower 25OHD group	116	21.5 (7–52.5)	67 (58)	NG	97 (84)	22 (19)
					Higher 25OHD group	180	19 (7–58)	99 (55)	NG	131 (73)	17 (9)
Kim, I.	2018	2013–2017	Korea	7	Lower 25OHD group	150	NG	84 (56)	26 (17)	NG	NG
					Higher 25OHD group	38	NG	15 (39)	3 (8)	NG	NG
Shah, S. K.	2016	NA	India	8	Lower 25OHD group	128	48 (6.5–108)	81 (63)	84 (66)	87 (68)	54 (42)
					Higher 25OHD group	26	9.5 (6–32)	21 (81)	16 (62)	22 (85)	14 (54)
Sankar, J.	2016	2013	India	8	Lower 25OHD group	75	NG	36 (48)	47 (63)	43 (57)	23 (31)
					Higher 25OHD group	26	NG	16 (62)	16 (62)	10 (38)	8 (31)
Prasad, S.	2015	2013–2014	India	8	Lower 25OHD group	67	12 (5–72)	46 (69)	9 (13)	30 (45)	NG
					Higher 25OHD group	13	13 (8–30)	9 (69)	2 (15)	3 (23)	NG
Onwuneme, C.	2015	2012–2015	Ireland	7	Lower 25OHD group	71	NG	NG	32 (45)	64 (90)	NG
					Higher 25OHD group	49	NG	NG	3 (6)	37 (76)	NG
Rey, C.	2014	NA	Spain	7	Lower 25OHD group	46	97 (44.5–145)	28 (61)	6 (13)	18 (39)	NG
					Higher 25OHD group	110	34 (14–98)	65 (59)	18 (16)	45 (41)	NG
Dayal, D.	2014	2012	India	6	Lower 25OHD group	23	NG	14 (61)	4 (17)	8 (35)	NG
					Higher 25OHD group	69	NG	53 (77)	5 (7)	13 (19)	NG
Rippel, C.	2012	2010–2011	Australia	7	Lower 25OHD group	24	29.1 (11.5–73.7)	16 (67)	5 (21)	18 (75)	1 (4)
					Higher 25OHD group	82	24.1 (16.3–35.5)	53 (65)	16 (20)	67 (82)	5 (6)
McNally, J. D.	2012	2005–2008	Canada	6	Lower 25OHD group	225	3.9 (0.5–13.1)	114 (51)	33 (15)	NG	NG
					Higher 25OHD group	101	2.5 (0.6–11.5)	53 (52)	15 (15)	NG	NG

NOS = the Newcastle-Ottawa Quality Assessment Scale.

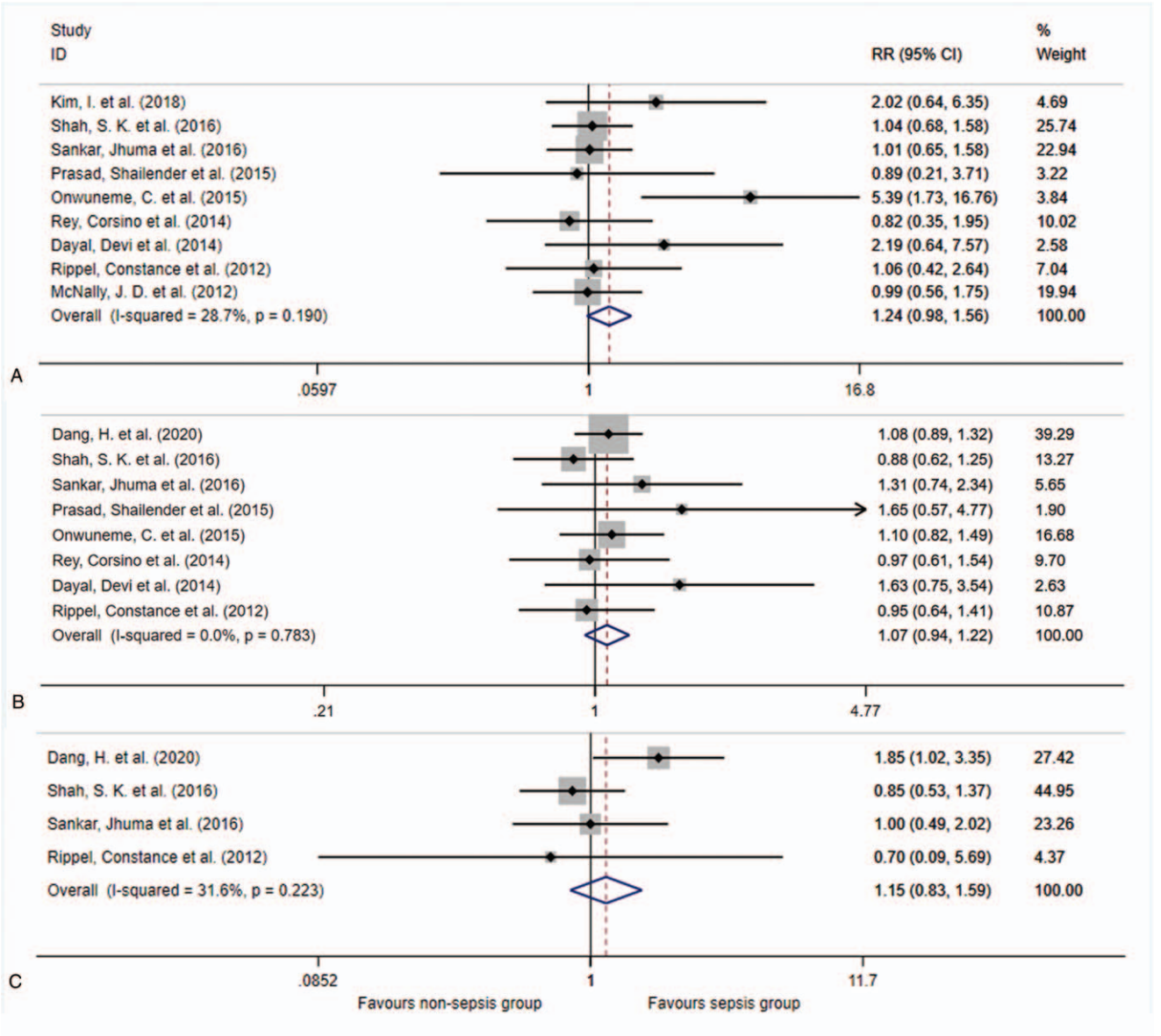

Figure 4. The comparison of the incidence of sepsis (A), mechanical ventilation (B), and 30-day mortality (C) in lower 25-OHD level group and higher 25-OHD level group.

required for the hydroxylation of vitamin D in the body, which generates 1,25$(OH)_2$D3 by itself. On this basis, vitamin D plays an important role in extra-osseous diseases, such as infectious diseases, autoimmune diseases, diabetes, cancer, cardiovascular diseases, and etc.[1,2] Vitamin D levels are affected by various factors such as sex, age, season, geographic location, disease, drugs, and etc, and healthy children also have vitamin D deficiency and deficiency.[41] Vitamin D is a nutritional vitamin, but surveys have shown that children with critical illness have a high incidence of nutritional risk, and children with sepsis have a high incidence of nutritional risk of 86.4%.[40] In our meta-analysis, we demonstrated that critically ill children with sepsis might have a lower 25-OHD level than those without sepsis.

However, the mechanism of vitamin D deficiency to increase the sepsis rate and mortality in children is not yet clear. In recent years, several studies confirmed the regulatory effect of vitamin D on the immune system. Some studies suggested that the lack of 25-OHD will reduce immune function, affect hormone metabolism, lead to an increase in the incidence of various infections and critical illnesses, thereby increasing mortality. Sepsis involves pathological and physiological changes such as uncontrolled inflammatory response, immune dysfunction, high metabolic state, and multiple organ damage, or may become the target of vitamin D treatment.[42] Moreover, studies have shown that VDR is expressed on the surface of immune cells such as mononuclear macrophages, T cells, and B cells. 25-OHD may affect the occurrence and development of sepsis by regulating immune function.[43] Moreover, vitamin D can enhance the body's resistance to pathogen invasion, suppress adaptive immune response, protect the body from various autoimmune diseases, and limit the rejection of grafts. Biological functions have been widely recognized.[44] Studies have found that VDR is expressed in most immune cells, including T cells, B cells, monocytes, and antigen-presenting cells, such as macrophages and dendritic

cells.[45] Because the regulation of vitamin D is mediated by VDR, this further confirms that vitamin D has a wide range of regulatory effects on the immune system. $1,25(OH)_2D3$ can inhibit the maturation and differentiation of dendritic cells (DCs) through interaction with VDR[38]; it can also regulate the expression and secretion of cytokines and chemokines by DCs derived from monocytes: such as promoting IL-10, the secretion of IL-12 and IL-23 inhibits the secretion of TNF-α and IFN-γ. More importantly, $1,25(OH)_2D3$ can indirectly inhibit the function of B cells by changing the response of CD4 T lymphocytes and inhibiting monocyte/macrophage secretion of cytokines and therefore had an anti-infection effect for curing inflammation.

There was a slight difference between case-control study and cohort study. In the case-control study, we suggested that infants and children with sepsis may have a lower 25-OHD level and a higher severe vitamin D deficiency rate than those without sepsis, and the results were statistically difference. However, in those included cohort studies, although the results showed a higher occurrence of sepsis and 30-day mortality in lower 25-OHD level group, there were no statistically difference were found. For one reason, all the studies defined the cut-off of 25-OHD level was 20 ng/mL, which was higher than the definition of severe deficiency, and thus increase the sepsis rate in the higher 25-OHD level group. For another, most study in case-control group only included the infants with new born, while the cohort study included more children with an elder age, which may result to the difference between 2 study type. Nevertheless, future evidence still needed to be undertaken for evaluating the risks of 25-OHD level and the occurrence of sepsis in critically ill children.

There are some limitations in our study. Firstly, although we analyzed the relationship between vitamin D deficiency and the occurrence of sepsis in critically illness children in case-control study and cohort study separately, the variables, such as participants age, associated medical conditions and original diseases among studies could be fully balanced which may result in the bias among studies. Secondly, we only include the studies written by English which may increase the publication bias in some certain condition. Thirdly, due to the scarce of the studies discussing the vitamin D supplement in reducing the occurrence of sepsis in critically ill children, we could not analyze the effect of vitamin D supplement in treatment of critical ill children. More large-scale observational study and randomized control trials still needed for the further demonstration the effect of vitamin D in association with sepsis in critically ill children.

5. Conclusion

We demonstrated that critically ill infants and children with sepsis could have a lower 25-OHD level and severe vitamin D deficiency comparing to those without sepsis. Future studies should focus on the association of vitamin D supplement and the occurrence of sepsis in critically ill children.

Author contributions

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