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Efficacy of High-Dose Vitamin D Supplementation as an Adjuvant Treatment on Pneumonia: Systematic Review and a Meta-Analysis of Randomized Controlled Studies

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Abstract

The purpose of this meta-analysis was to summarize randomized controlled trial (RCT) evidence and evaluate the efficacy and safety of vitamin D (VD) supplementation as an adjunct to antibiotics for the treatment of pneumonia. Data sources published from the inception dates up to January 2020 were searched. RCTs of VD supplementation of any duration, age, and dosing regimen type were eligible for inclusion if data on pneumonia were collected. Thirteen studies (4786 randomized participants) fulfilled eligibility criteria. VD supplementation significantly increased levels of serum 25(OH)D (mean difference = 15.97; 95% CI, 7.49–24.44; $P = .002$) and reduced incidence of repeat episodes of pneumonia (risk ratio [RR] = 0.68; 95% CI, 0.50–0.93; $P = .02$). Subgroup analysis revealed VD supplementation had more reducing effects on repeat episodes of pneumonia among participants in trials in which the population were children (RR = 0.66; 95% CI, 0.48–0.90), duration <3 months (RR = 0.55; 95% CI, 0.33–0.91), or dose of VD <300,000 IU (RR = 0.51; 95% CI, 0.29–0.89). Although our results suggested that VD supplementation had a positive effect on recovery rate of pneumonia (RR = 1.28; 95% CI, 0.94–1.74; $I^2 = 13\%$), there was no statistical difference ($P = .12$). High-dose VD intervention may have an effect on reducing the incidence rate of repeat episodes of pneumonia by enhancing immune efficacy, although more population studies are needed to support that VD supplementation has therapeutic effects on pneumonia itself. (*Nutr Clin Pract.* 2020;0:1–17)

Keywords

immunologic adjuvants; meta-analysis; pneumonia; vitamin D

Introduction

Lower respiratory tract infections, including pneumonia, were the third most common cause of death globally in 2015, exceeded only by ischemic heart disease and cerebrovascular disease.[1] Pneumonia is an acute lower respiratory tract infection that primarily affects the lungs.[2] Pneumonia as a pulmonary infectious disease is the leading cause of mortality among young children.[3,4] Forty-three million new pneumonia cases are diagnosed, with a mortality rate of 322 per 100,000, in the population under 5 years old every year globally.[3,5] In addition, pneumonia more frequently becomes the direct cause of death among the elderly, as they are more prone to the disease.[6,7] Pneumonia affects older persons more because there is a relative decline in immune function caused by aging, malnutrition, various chronic diseases, and other factors.[8] Community-acquired pneumonia (CAP) is the eighth leading cause of death in the United States and in adults aged 65 years and older.[9,10] Pneumonia, especially pneumococcal CAP, causes significant morbidity and economic burden in adults.[11] The new coronavirus disease 2019 (COVID-19) outbreak across the world now directly leads to lung infection and rapid respiratory failure. Computed tomography findings of COVID-19 pneumonia with a detailed analysis were well

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described in the current study,[12] and in the study by Chung et al,[13] researchers could have described specific patterns of lung abnormalities, including organizing pneumonia, bilateral bronchopneumonia, and diffuse alveolar damage patterns.

Despite advances in the management of pneumonia,[14] there is a need for effective novel therapies.[15,16] Recently, the role of vitamin D in host defense against infection h much attention from researchers. Vitamin D has pleiotropic immunomodulatory properties besides its classic function in calcium-phosphate homeostasis. Several studies have shown an association between vitamin D deficiency and increased the susceptibility to pneumonia.[17–19] In accordance with the definition of vitamin D deficiency being a 25(OH)D of <20 ng/mL, vitamin D deficiency is common in Europe, North America, Australia, the Middle East, India, Africa, and South America and is common not only in elderly people but also in children and the young, middle-aged, and adults.[20] A recent meta-analysis of observational studies supported the evidence that there is an association between vitamin D deficiency and an increased risk of CAP patients.[21] However, there is limited evidence of observational studies regarding the effect of vitamin D on pneumonia treatment, as there is a major limitation of confounding risk caused by inadequate adjustment.

Two systematic reviews have summarized randomized controlled trials (RCTs) on the use of vitamin D to treat pneumonia.[22,23] One of 2 reviews did not perform a meta-analysis, as only 2 RCTs met the inclusion criteria.[22] Another more recent systematic review and meta-analysis, which included 7 randomized placebo-controlled studies, reported the effects of vitamin D on the following outcomes were inconclusive when compared with control: time to resolution of acute illness (hours), mortality rate, duration of hospitalization, and time to resolution of fever.[23] Both reviews included only children under 5 years old only and showed a marked paucity of studies numbers and clinical heterogeneity among the included trials.

Since publication of the last meta-analysis,[23] dozens of other randomized trials studying the adjuvant treatment effect of vitamin D on pneumonia have been reported. The lack of consistent findings and new available evidence justifies another systematic review and meta-analysis to assess potential benefit.

Hence, the present study assessed the effect of vitamin D supplementation as adjuvant therapy on pneumonia in not only children but also adults by comparing the primary outcomes (ie, time to resolution of pneumonia, duration of hospitalization, recovery rate of pneumonia, and change in serum levels of 25[OH]D) and the main secondary outcomes (ie, incidence rate of repeat episodes of pneumonia, mortality of pneumonia, rate of intensive care unit [ICU]/hospital admission, rate of complications, time to resolution of fever, and change in levels of serum procalcitonin [PCT] and high-sensitivity C-reactive protein [hs-CRP]).

The goal of this systematic review was to summarize the RCT evidence and to evaluate the efficacy and safety of vitamin D supplementation as an adjunct to antibiotics for the treatment of pneumonia.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[24]

Search Strategy

A literature search was performed in PubMed, Cochrane Central, Scopus, and Web of Science from the inception dates to January 2020. Databases were systematically searched by 3 independent investigators. The keywords included ("vitamin D" OR "25OHD" OR "25(OH)D" OR cholecalciferol OR ergocalciferol) AND ("respiratory tract infections" OR "acute respiratory infection" OR bronchiolitis OR pneumonia). Moreover, the reference or citation lists from the retrieved articles were checked to search for further relevant studies. The search was limited to studies in humans published in English.

Inclusion Criteria and Exclusion Strategy

Studies were included if they met the following criteria: (1) Patients were hospitalized with a clinical diagnosis of pneumonia. Pneumonia was defined according to World Health Organization (WHO) acute respiratory infection guidelines.[25] (2) The interventions consisted of treatment with vitamin D as an adjunct to antibiotics and other supportive measures. We considered any dose schedule (low vs high dose, daily dose vs bolus dose), any duration, and any route (oral or injection) of vitamin D. (3) Outcome measures frequently used to determine the clinical efficacy of any pneumonia treatment were time to recovery, duration of hospitalization, repeat episodes of pneumonia, adverse events, or death and hematology indicators (25[OH] vitamin D, procalcitonin, hs-CRP, etc). Nonclinical studies, uncontrolled trials, and trials with insufficient data from which one cannot evaluate outcomes were excluded from the meta-analysis. We excluded studies that included patients with other debilitating diseases, asthma, or other respiratory diseases and postoperative conditions. Two authors examined the full-text reports for compliance with eligibility criteria independently. Inconsistencies were resolved by discussion until a consensus was reached.

Definition of Outcomes

The primary outcome of the meta-analysis was time to resolution of pneumonia, duration of hospitalization,

recovery rate of pneumonia, and change in serum levels of 25(OH)D. Secondary outcomes were incidence rate of repeat episodes of pneumonia, mortality of pneumonia, rate of ICU/hospital admission, complications rate, time to resolution of fever, and change in serum levels of PCT and hs-CRP.

We defined the time to resolution of pneumonia by referring to the original article—that is, achievement of the following parameters from the time of initiation of treatment: respiratory rate less than the age-specific cutoffs, no danger signs or hypoxia, no lower-chest indrawing, and ability to feed. These parameters were present for at least 2 consecutive days or 48 hours. We defined the duration of hospitalization as the time period between study enrollment and discharge. We defined repeat episodes of pneumonia as episodes occurring 15 days or more after the first; however, only an episode happening within 14 days was judged to be a continuation of the previous episode.

Data Extraction and Quality Assessment

Data extraction was conducted independently by 2 investigators using a standardized data collection method. We designed the data extraction and extracted the following information from included studies: author; year; location (country); participants (age, sex, sample size, type or degree of pneumonia, and baseline 25[OH]D); intervention (dosage, duration, frequency, and cointervention, if any); and outcomes (primary and secondary outcomes, unit of measurement).

Assessment of study quality was independently performed by 2 reviewers using the Cochrane Collaboration tool for assessing risk of bias in RCTs version 5.1.0.[26] The Cochrane tool has 7 domains: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. Each item was classified as low, high, or an unclear risk of bias (if there was insufficient information).[27] If studies presented different research outcomes from the same study data, we regard them as different studies.[28,29] Inconsistencies were resolved by discussion with the third review author until a consensus was reached. For scoring the quality of studies more intuitively, the Jadad score also was used. It is based on randomization, concealment of treatment allocation, blinding, completeness of follow-up, and the use of intention-to-treat analysis.[30]

Quantitative Data Synthesis

We extracted and entered outcome data into Review Manager 5 software for statistical analysis using the standard methods of the Cochrane to synthesize data. For dichotomous data (incidence rate of repeat episodes of pneumonia, rate of recovery, rate of ICU/hospital admission, mortality rate, and complications rate), we extracted the number of events and the total number of participants in each group. For continuous data (time to resolution of pneumonia, duration of hospitalization, duration of resolution of fever, and change in levels of serum 25[OH]D, PCT, and hs-CRP), we used the mean and SD for each group together with the number of participants in each group. If a 95% CI was provided instead of SD for continuous data, we extracted the mean and SD from the 95% CI. If a study reported a standard error, we converted it to an SD using the following formula: [SD = SEM × square root (n)]. If medians were used, we extracted the median and the interquartile range. Then, we calculated the corresponding mean and SD according to the available statistical methods.[31,32]

Statistical Analysis

The meta-analysis was performed on RevMan 5.3 (Cochrane Collaboration, London, UK). For continuous data, we calculated mean differences (MDs) with 95% CI to estimate the treatment effect. For dichotomous data, we calculated a pooled estimate of the treatment effect for each outcome using risk ratio (RR) with 95% CI. Q test and I^2 index were used to assess the heterogeneity among the included studies. Substantial heterogeneity was indicated as $P < .05$ in the χ^2 test and an I^2 of $\geq 25\%$.[26] The fixed-effect models and random-effects models were used according to the level of heterogeneity. If significant heterogeneity was present (I^2 statistics no less than 25%), then a random-effects model was used. We performed a sensitivity analysis by removing 1 study at a time and analyzed the rest to evaluate whether the results could have been affected markedly by a single study. The role of several potential sources of heterogeneity was examined by subgroup analysis. It should be emphasized that to ensure the effectiveness of subgroup analysis, only the primary or secondary outcomes combined from >3 studies were included in the subgroup analysis. The publication bias assessed by using Begg's and Egger's test (significant level = .05) was conducted to quantitatively explore the possible publication bias, using STATA SE (StataCorp LP, College Station, TX, USA). All tests were 2-tailed, and $P < .05$ was considered significant for all included studies.

Results

Study Selection and Characteristics

For the present meta-analysis, our search identified a total of 282 studies that were assessed for eligibility; of these, 13 studies[28,29,33–43] with a total of 4786 randomized participants fulfilled the eligibility criteria (Figure 1). Although

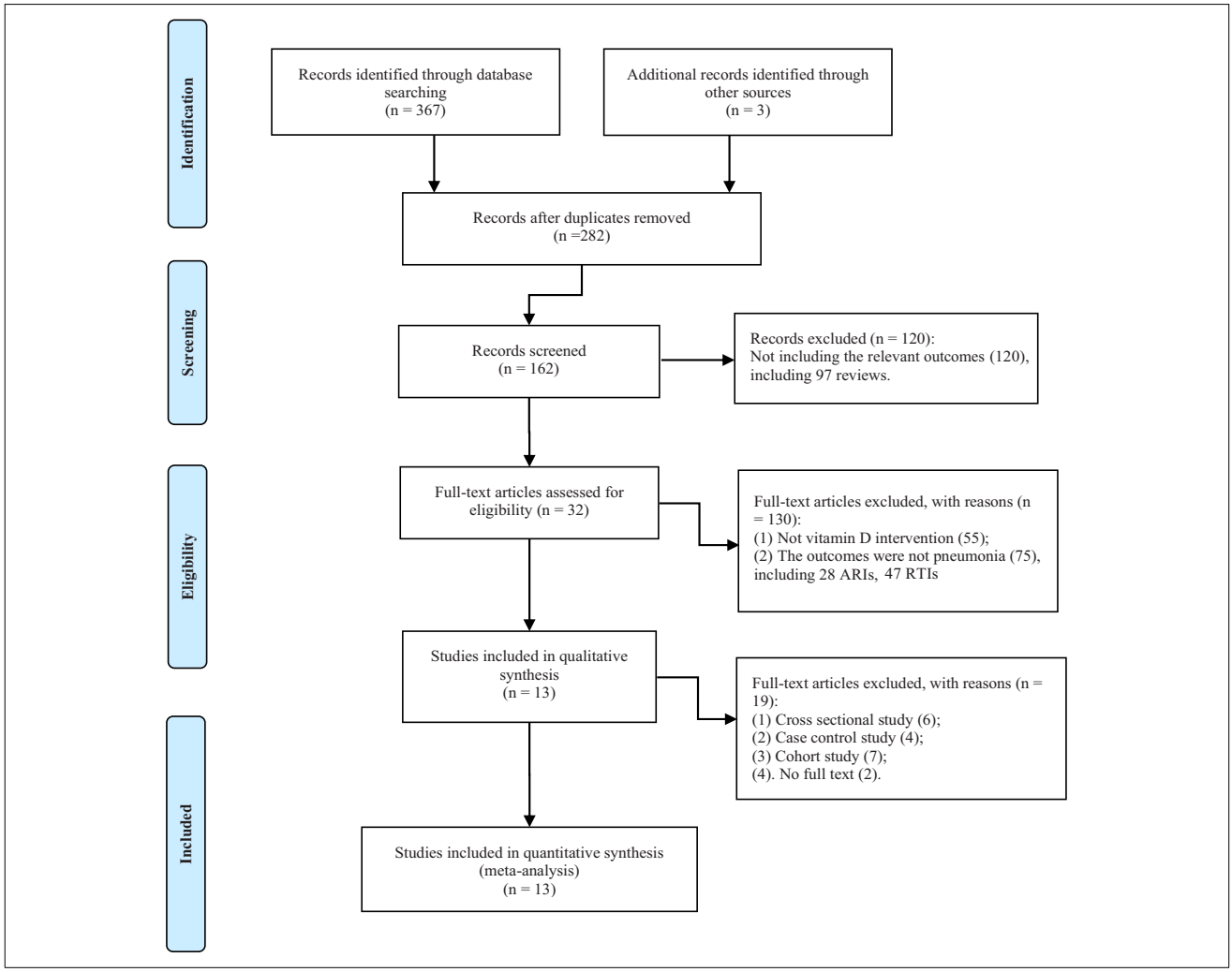

Figure 1. Flow diagram of the systematic search of the literature. ARI, acute respiratory infection; RTI, respiratory tract infection.

3 studies[19,34,38] were extracted from records, identified through a systematic review,[23] we did not extract any valid data from the study conducted by Rajshekhar et al.[19]

Characteristics of studies contributing data to this meta-analysis and their participants are presented in Table 1. Trials were conducted in 6 different countries (India, Iran, Pakistan, Afghanistan, New Zealand, and China) on 2 continents and enrolled participants of both children (2 months to 72 months) and adults (>50 years). Twelve studies were conducted in Asia; 1 was conducted in Oceania.[40] Baseline serum 25(OH)D concentrations were reported in 4 out of 13 trials; of these, 3 studies were vitamin D deficiency, and the mean baseline 25(OH)D concentration ranged from 17.12 to 49.4 nmol/L. Eight studies administered oral vitamin D_3 to participants in the intervention arm; the remaining 5 trials administered intramuscular vitamin D_3: vitamin D was given as single high doses in 12 studies and as mild doses in 1 study. Study duration ranged from 2 weeks to 20 months. The studies differed in terms of inclusion criteria, dose, and duration of vitamin D use. Nine studies presented primary outcomes including time to resolution of pneumonia,[33,35,37,39] duration of hospitalization,[33,34,40,42,43] and change in serum levels of 25(OH)D.[28,35,40] Twelve studies provided secondary outcomes; only 1 article[34] did not provide secondary outcomes.

Risk of Bias Within Studies

Details of the risk-of-bias assessment are provided as shown in Table 1 and Table 2. All trials were assessed as being at a low risk of bias according to the Jadad score, in which 4–7 is considered high quality: 3 studies[34,39,41] got a score of 4, 3[38,42,43] got a score of 5, and the remaining 7 got a score of 7. Eight studies[28,29,33,35–37,40] used sequentially numbered,

Table 1. Characteristics of Randomized Controlled Trials on Vitamin D Supplementation and Pneumonia Included in the Present Meta-Analysis.

Authors (y)	Country	Duration	Participants (percentage male) (I:C)	Baseline 25(OH)D	I (IU)	Outcome	Jadad score
Manaseki-Holland et al (2010)[37]	Afghanistan	90 d	A total of 453 children with nonsevere or severe pneumonia Age: 1–36 mo Male: 56.7%I vs C: 224:229	NR	I: a single 100,000-IU dose of oral vitamin D_3 at onset of pneumonia C: a single 2-mL dose of olive oil at onset of pneumonia	Primary: Time to resolution of pneumonia/recovery for 48 consecutive hours, and treatment failure. Secondary: Risk of children having a repeat episode of pneumonia during the 90-d posttreatment period. Risk of survival without experiencing a repeat episode of pneumonia.	7
Choudhary et al (2012)[33]	India	>90 d	A total of 200 children with severe pneumonia Age: 2 mo to 5 y Male: 60%I vs C: 100:100	NR	I: vitamin D_3 for 5 d at doses of 1000 IU for children aged up to 1 y and 2000 IU for children aged over 1 y C: lactose (200 mg) once daily for 5 d	Primary: Time to resolution of severe pneumonia. Secondary: Duration of hospitalization, time to resolution of tachypnea, fever, hypoxia, chest retraction, and inability to feed/lethargy.	7
Manaseki-Holland et al (2012)[36]	Afghanistan	18 mo	3046 children Age: 1–11 moI vs C: 1542:1522	NR	I: 100,000 IU (2.5 mg) of oral vitamin D_3 once every 3 mo in olive oil C: placebo (olive oil)	Primary: The first or only episode of radiologically confirmed pneumonia. Secondary: Incidence rate of repeat episodes of pneumonia.	7
Dhungel et al (2015)[34]	Pakistan	3 mo	A total of 200 children with nonsevere and severe pneumonia Age: 2–60 mo, (mean), (I) 8.1 ± 11.0 mo, (C) 6.9 ± 10.1 mo Male: 61%I vs C: 100:100	NR	I: a single 100,000-IU dose of intramuscular vitamin D_3 was given within 24 h of admission C: none (only standard care including antibiotics)	Primary: Duration of hospitalization. Secondary: The risk of children having a repeat episode of pneumonia during the 3-mo posttreatment period.	4

(*continued*)

Table 1. (continued)

Authors (y)	Country	Duration	Participants (percentage male) (I:C)	Baseline 25(OH)D	I (IU)	Outcome	Jadad score
Gupta et al (2016)[35]	India	180 d	A total of 324 children with WHO-defined severe pneumonia Vitamin D deficient: 126 (39%) were (serum 25[OH]D < 12 ng/mL) Age: 6 mo to 5 y (median [IQR]: 12 [7–19.8] mo)I vs C: 162:162	NR	I: 100,000 IU of oral vitamin D_3 in single dose on the day of enrollment C: placebo in single dose	Primary: Change in serum levels of 25(OH)D. Time to resolution of severe pneumonia and proportion of children having recurrence of pneumonia in next 6 mo. Secondary: Time taken for overall resolution of illness.	7
Rahmati et al (2016)[38]	Iran	12 mo	100 children with community-acquired pneumonia Age: 2–72 mo, (mean) (I) 17.6 mo, (C) 16.8 mo Male: (I) 54%, (C) 61.2%I vs C: 50:50	NR	I: oral vitamin D_3 with 50,000 IU/d for 2 d C: placebo (olive oil)	Primary: Duration of hospitalization/antibiotic therapy. Duration of fever.	5
Miroliaee et al (2017)[28]	Iran	28 d	A total of 46 patients with vitamin D deficiency and VAP Age: (I) 57.83 ± 18.84; (C) 56.45 ± 20.70 Male: 63%I vs C: 24:22	I: 17.12 ± 6.11 C: 19.5 ± 4.60 (ng/mL)	I: 300,000 units of intramuscular vitamin D_3 within 48 h after diagnosis of VAPC: placebo	Primary: The studied markers PCT, SOFA score, and CPIS. Secondary: The morality rate among study participants.	7
Somnath et al (2017)[43]	India	12 mo	154 children with acute LRTI Age: 2 mo to 5 y, (mean) 13 mo Male: treatment: 69.2%; C: 65.8%I vs C: 78:76	Total: 18.356 ± 12.88 I: 17.97 ± 11.35 C: 18.75 ± 14.35 (ng/mL)	I: a single 100,000-IU dose of oral vitamin D on first day of admission + standard care therapy C: standard care therapy alone	Primary: Median duration of hospital stays. Secondary: Mortality, PICU admission, complications, and recurrence of respiratory infections within 90 d of discharge.	5
Slow et al (2018)[40]	New Zealand	6 wk	117 adults with community-acquired pneumonia Age: (mean) 63 y; (I) 65.0 ± 14.5 y; (C) 60.9 ± 17.3 y Male: 63.2%I vs C: 60:57	I: 47.9 ± 22.0 C: 49.4 ± 21.6	I: a single oral dose of 200,000-IU vitamin D_3 immediately following enrollment into the studyC: placebo	Primary The complete resolution of chest radiograph infiltrate at 6-wk poststudy treatment. Secondary: Length of hospital stay. Intensive care admission and return to normal activity.	7

(*continued*)

Table 1. (continued)

Authors (y)	Country	Duration	Participants (percentage male) (I:C)	Baseline 25(OH)D	I (IU)	Outcome	Jadad score
Miroliaee et al (2018)[29]	Iran	28 d	46 vitamin D–deficient patients with VAP Age: (I) 57.83 ± 18.84; (C) 56.45 ± 20.70 Male: 63%I vs C: 24:22	I: 17.12 ± 6.11 C: 19.5 ± 4.60 (ng/mL)	I: 300,000 units of intramuscular vitamin D_3C: placebo	Primary: The selected markers, CRP, and plasma level of vitamin D. Secondary: Long-term outcome, ie, patient mortality.	7
Singh et al (2019)[39]	India	20 mo	A total of 100 children under 5 y old with pneumonia Age: <5 y Male: 58%I vs C: 50:50	NR	I: standard treatment + quarterly doses of oral vitamin D_3 (300,000 IU) for 1 y C: standard treatment	Secondary: Outcome variables were documented in terms of the number of episodes (URTI and LRTI), hospital admissions, duration, severity, and complications.	4
Anwar et al (2019)[42]	Pakistan	3 mo	A total of 200 children with pneumonia and low vitamin D level (<20 ng/mL) Age: (mean) 7.5 mo, 2–59 mo Male: 61%I vs C: 100:100	NR	I: antibiotics + intramuscular 1 lakh units of vitamin D_3 (100,000 IU) on the first day of hospital treatmentC: antibiotics	Primary: The duration of hospitalization. Secondary: The repeat episode of pneumonia.	5
Wang et al (2019)[41]	China	14 d	A total of 124 patients with chronic obstructive pulmonary disease with infectious pneumonia Age: (I) 54.17 ± 6.02; (C) 53.89 ± 5.37	NR	I: Symbicort combined with azithromycin + vitamin D_3 (300,000 units of intramuscular vitamin D_3/d [acute phase]; 0.25 μg calciferol/d [stationary phase] for 14 d) C: Symbicort combined with azithromycin	Secondary: The levels of PCT and hs-CRP index were measured before and after treatment.	4

C, control; CPIS, Clinical Pulmonary Infection Score; hs-CRP, high-sensitivity C-reactive protein; I, intervention; IQR, interquartile range; LRTI, lower respiratory tract infection; NR, not reported; PCT, procalcitonin; PICU, pediatric intensive care unit; SOFA, Sequential Organ Failure Assessment; URTI, upper respiratory tract infection; VAP, ventilator-associated pneumonia; WHO, World Health Organization.

Table 2. Risk-of-Bias Summary: Review Authors' Judgements About Each Risk-of-Bias Item for Each Included Study.

Study	Random sequence generation	Allocation sequence concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential sources of bias
Manaseki-Holland et al (2010)	L	L	L	U	L	U	L
Choudhary et al (2012)	L	L	L	L	L	U	L
Manaseki-Holland et al (2012)	L	L	L	U	L	U	L
Dhungel et al (2015)	U	U	U	U	U	U	L
Gupta et al (2016)	L	L	L	U	L	U	L
Rahmati et al (2016)	L	U	U	U	L	L	L
Miroliaee et al (2017)	L	L	L	U	L	U	L
Somnath et al (2017)	L	L	H	L	L	L	L
Slow et al (2018)	L	L	L	U	U	L	L
Miroliaee et al (2018)	L	L	L	U	L	U	L
Singh et al (2019)	L	U	U	U	L	U	L
Anwar et al (2019)	L	U	U	U	L	U	L
Wang et al (2019)	L	U	U	U	L	U	L

H, high; L, low; U, unclear.

sealed envelopes or codes for allocation of participants to the 2 groups and were assessed as being at low risk of bias. Five studies[34,38,39,41,42] did not mention the method for allocation and were assessed as being at unclear risk of bias. Blinding of participants and caretakers was conducted in 8 studies[28,29,33,35–37,40,43] through kee appearance, color and even tasteWping similar in terms of appearance, color, and even taste. Six studies[28,29,33,35–37,40] describe methods of blinding to prevent performance bias and were assessed as being at low risk of bias. Of these, 2 studies[33,35] reported the code key would be opened only after administration of the intervention, duration of follow-up, data collection, and tabulation were completed, thus preventing detection bias; these studies were assessed as being at low risk of bias for this domain. Five studies[34,38,39,41,42] did not describe methods to prevent detection bias and were assessed as being at unclear risk of bias. However, Somnath et al[43] were unblinded, presenting a high risk of performance bias. We assessed 12 studies as being at low risk for attrition bias (incomplete outcome data); however, the study by Dhungel et al[34] was assessed as being at unclear risk of bias because of it did not provide this information. Slow et al[40] reported an attrition rate of 13.3%, but the rest of the studies reported an attrition rate of <10%. In the domain of selective reporting, we assessed 4 studies[35,38,40,43] as being at low risk of reporting bias, as they were registered in the clinical trial registry. In addition, we found there were no other potential sources of bias in the included studies.

Primary outcomes.

Time to resolution of pneumonia (hours). The results for time to resolution of pneumonia were reported in 3 comparisons including 935 participants (Figure 2A). The pooled result from 3 studies showed no significant difference for time to resolution of pneumonia (MD = −1.02; 95% CI, −5.74 to 3.70; $P = .67$; $I^2 = 12\%$; $P_{\text{for heterogeneity}} = .32$). Egger's linear regression (intercept = −0.21, $P = .87$) and Begg's rank correlation ($z = 0.00$, $P = 1.00$) suggested no publication bias in the meta-analysis.

Duration of hospitalization (hours). The protective effects of vitamin D supplementation were not seen in the analysis of duration of hospitalization (MD = −1.40; 95% CI, −9.53 to 6.73; $P = .74$; $I^2 = 12\%$; $P_{\text{for heterogeneity}} = .2$) in 1152 participants in 6 studies (Figure 2B). Similarly, subgroup analysis revealed no protective effect of vitamin D supplementation among individuals at 4 potential factors (Table 3). However, duration and dosing regimen type as factors could explain heterogeneity, for I^2 value declined in both subgroups. No publication bias was found in the

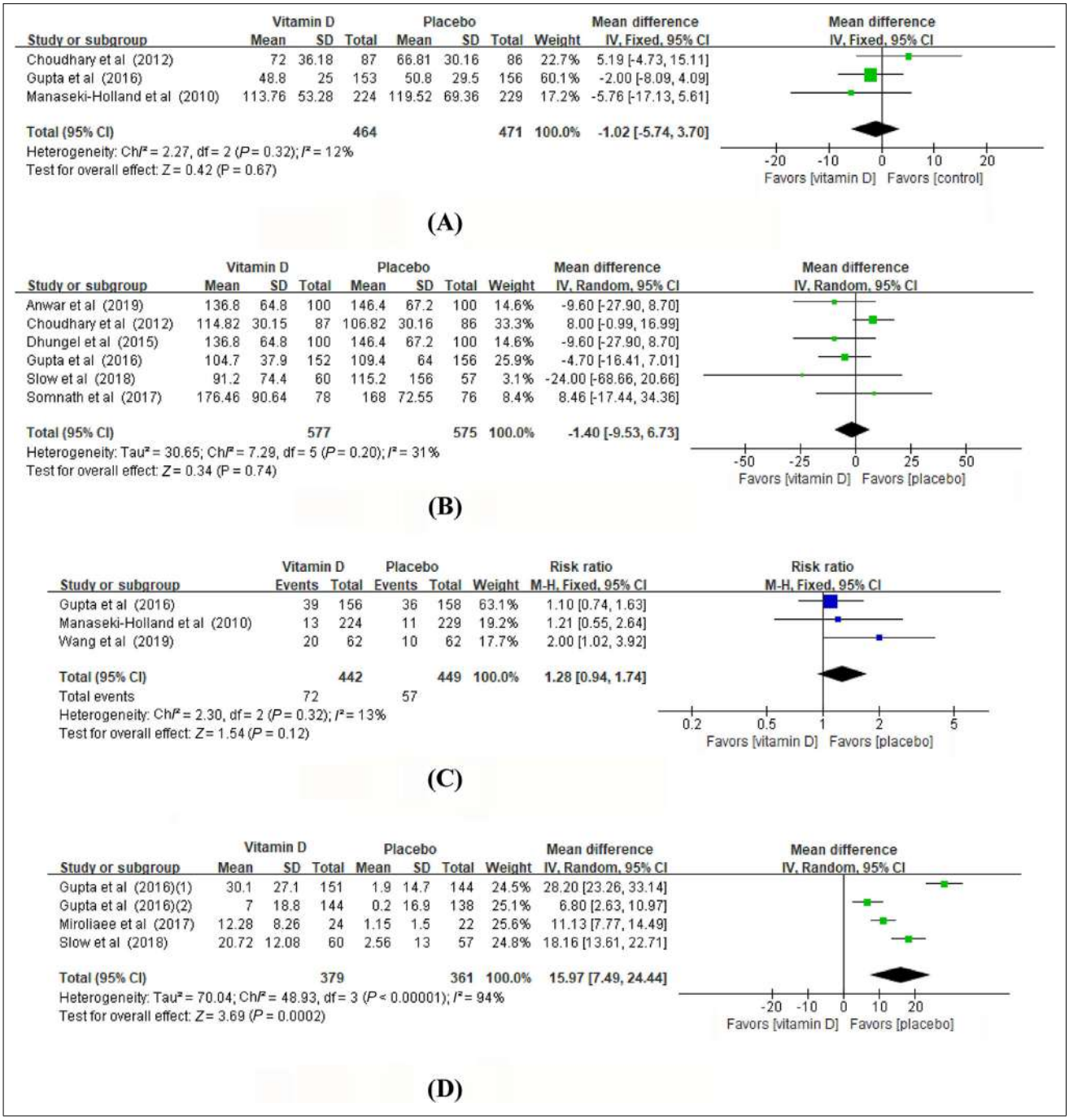

Figure 2. Effect of vitamin D supplementation on (A) time to resolution of pneumonia; (B) duration of hospitalization; (C) recovery rate of pneumonia; (D) change in levels of serum 25(OH)D. Different annotations were explained. (1) and (2) represent different intervention times. M-H, Metropolis Hastings.

meta-analysis (Egger's: intercept = 1.39, $P = .24$; Begg's: $z = 0.573$, $P = .21$).

Recovery rate of pneumonia. The pooled summary estimate of 3 studies showed a marginal change (1.28 times) in the recovery rate of pneumonia in the vitamin D group (RR = 1.28; 95% CI, 0.94–1.74; $I^2 = 13\%$) compared with that in the placebo group, which was not statistically different ($P = .12$) (Figure 2C). No subgroup analysis was conducted because we were limited by the small combined number of studies. No publication bias was found (Egger's: intercept = 2.17, $P = .86$; Begg's: $z = 0.00$, $P = 1.00$).

Change in levels of serum 25(OH)D. Three studies including 740 participants assessed the effects of vitamin D supplementation on change in levels of serum 25(OH)D (Figure 2D). Results showed vitamin D supplementation significantly increased the change in levels of serum 25(OH)D (MD = 15.97; 95% CI, 7.49–24.44; $P = .002$), with a higher heterogeneity ($I^2 = 94\%$, $P_{\text{for heterogeneity}} < .0002$). Subgroup analysis revealed a strong effect of vitamin D supplementation on increasing levels of serum 25(OH)D among adults (n = 2; MD = 14.47; 95% CI, 7.59–21.35, $P < .001$; $I^2 = 83\%$; $P_{\text{for heterogeneity}} < .001$) and no statistically significant effect among children (n = 2; MD = 17.46; 95% CI, −3.51 to 38.43; $P = .10$; $I^2 = 98\%$, $P_{\text{for heterogeneity}} < .001$). For other stratifications, subgroup analysis showed a significant difference in change in levels of serum 25(OH)D in vitamin D intervention compared placebo groups (Table 3). However, no predetermined factors could explain heterogeneity. No publication bias was found (Egger's: intercept = −0.81, $P = .50$; Begg's: $z = 1.02$, $P = .31$).

Secondary outcomes.

Incidence rate of repeat episodes of pneumonia. The pooled summary estimate of 10 comparisons in 6 studies showed an incidence rate of repeat episodes of pneumonia in the vitamin D group that was 0.68 times (RR = 0.68; 95% CI, 0.50–0.93; $I^2 = 83\%$) that was 0.68 times the rate in the placebo group, which was statistically significant ($P < .001$) (Figure 3A). Subgroup analysis revealed that such a protective effect was seen among participants in trials in which the population were children (n = 9; RR = 0.66, 95% CI, 0.48–0.90; $P = .0009$; $I^2 = 64\%$), follow-up duration was <3 months (n = 6; RR = 0.55; 95% CI, 0.33–0.91; $P = .22$; $I^2 = 93\%$), or dose of vitamin D was <300,000 IU (n = 6; RR = 0.51; 95% CI, 0.29–0.89; $P = .02$; $I^2 = 93\%$). Whether dosing regimen type was oral or intramuscular, protective effect was statistically significant (Table 3). Dosing regimen type as factors could explain heterogeneity, for the I^2 value declined in both subgroups. No publication bias was found in the meta-analysis (Egger's: intercept = −0.27, $P = .56$; Begg's: $z = 0.72$, $P = .47$).

Rate of ICU/hospital admission. The results for rate of ICU/hospital admission were reported in 6 comparisons in 3 studies including 362 participants (Figure 3B). The pooled result showed a rate of ICU/hospital admission in the vitamin D group that was 0.67 times (RR = 0.67; 95% CI, 0.38–1.20; $I^2 = 0\%$) the rate in the placebo group, which was not statistically significant yet ($P = .18$). However, subgroup analysis revealed a statistically significant declined rate of ICU/hospital admission (n = 2; RR = 0.26; 95% CI, 0.07–0.99; $P = .05$; $I^2 = 0\%$) comparing the vitamin D group with placebo in the stratification of follow-up duration <3 months. Egger's linear regression (intercept = −0.79, $P = .45$) and Begg's rank correlation ($z = 0.75$, $P = .45$) suggested no publication bias in the meta-analysis.

Complications rate. The protective effect of vitamin D supplementation were not seen in the analysis of complications rate (RR = 0.61; 95% CI, 0.20–1.86; $P = .38$; $I^2 = 35\%$, $P_{\text{for heterogeneity}} = .22$) in 933 pneumonia participants in 3 studies (Figure 3C). Subgroup analysis revealed no protective effect of vitamin D supplementation among individuals at 4 potential factors (Table 3). No publication bias was found in the meta-analysis (Egger's: intercept = −0.17, $P = .78$; Begg's: $z = 0.49$, $P = .62$).

Mortality of pneumonia. The protective effect of vitamin D supplementation was not seen in the analysis of pneumonia mortality (RR = 0.61; 95% CI, 0.20–1.86; $P = .38$; $I^2 = 35\%$, $P_{\text{for heterogeneity}} = .22$) in 163 participants in 2 studies (Figure 3D). No publication bias was found (Begg's: $z = 0.00$, $P = 1.00$).

Time to resolution of fever (hours). The results for time to resolution of fever were reported in 5 comparisons including 708 pneumonia participants (Figure 4A). The pooled result from these studies showed no significant difference for time to resolution of fever (MD = −3.06; 95% CI, −11.62 to 5.51; $P = .48$; $I^2 = 79\%$, $P_{\text{for heterogeneity}} = .32$) in vitamin D supplementation compared with the placebo group. Subgroup analysis revealed no effectiveness of oral vitamin D supplementation (dose of 300,000 IU) on time to resolution of fever in children with pneumonia (n = 4; for stratification of children, ≥300,000 IU stratification, >3 months' stratification, oral route stratification: MD = 1.74; 95% CI, −2.31 to 5.79; $P = .4$; $I^2 = 0\%$). Egger's linear regression (intercept = −0.16, $P = .88$) and Begg's rank correlation ($z = 0.24$, $P = .81$) suggested no publication bias in the meta-analysis.

Change in levels of serum PCT and hs-CRP. The pooled summary estimate of 3 studies showed no statistically significant difference for change in levels of serum PCT (MD = −0.20; 95% CI, −1.02 to 0.62; $P = .63$; $I^2 = 91\%$, $P_{\text{for heterogeneity}} < .001$) and hs-CRP (MD = −4.07; 95% CI, −19.23 to 11.08; $P = .60$; $I^2 = 85\%$, $P_{\text{for heterogeneity}} = .09$) in the vitamin D group compared with placebo (Figure 4B and C). No subgroup analysis was conducted because we were limited by the small combined numbers of studies. No publication bias was found (for PCT, Begg's: $z = 0.00$, $P = 1.00$; for hs-CRP, Begg's: $z = 0.00$, $P = 1.00$).

Sensitivity Analyses

As described in the Methods, we carried out a sensitivity analysis by excluding 1 study at a time and calculating the pooled results for the rest of the studies. For example, we

Table 3. Subgroup Analysis on Vitamin D Supplementation as an Adjuvant Treatment on Pneumonia.

Subgroups	N	Estimated value, MD or RR [95% CI]	*P*-value	I^2 (%)	Statistical method	$P_{\text{subgroup differences}}$
Duration of hospitalization (MD = 1.40; 95% CI, −9.53 to 6.73; I^2 = 31%)						
Patients						
Children	5	−0.65 [−8.84 to 7.55]	.88	35%	Random	.31
Adults	1	−24.00 [−68.66 to 20.66]	.29	None	Random	
Duration of follow-up						
<3 mo	3	−10.71 [−23.14 to 1.71]	.09	0%	Fixed	.08
≥3 mo	3	3.23 [−6.01 to 12.46]	.49	33%	Random	
Dose of vitamin D						
<300,000 IU	6	−1.40 [−9.53 to 6.73]	.74	31%	Random	—
≥300,000 IU	—	—	—	—	—	
Dosing regimen type						
Intramuscular	2	−9.60 [−22.54 to 3.34]	.15	0%	Fixed	.16
Oral	4	1.98 [−7.70 to 11.66]	.69	32%	Random	
Change in serum 25(OH) vitamin D (MD = 15.97; 95% CI, 7.49–24.44; I^2 = 94%)						
Patients						
Children	2	17.46 [−3.51 to 38.43]	.1	98%	Random	.79
Adults	2	14.47 [7.59–21.35]	<.001	83%	Random	
Duration of follow-up						
<3 mo	2	17.46 [−3.51 to 38.43]	.1	98%	Random	.79
≥3 mo	2	15.97 [7.49–24.44]	<.001	94%	Random	
Dose of vitamin D						
<300,000 IU	3	17.66 [5.52–29.81]	.004	95%	Random	.31
≥300,000 IU	1	11.13 [7.77–14.49]	<.001	—	Random	
Dosing regimen type						
Intramuscular	3	17.66 [5.52–29.81]	.004	95%	Random	.31
Oral	1	11.13 [7.77–14.49]	<.001	—	Random	
Time to resolution of fever (MD = −3.06; 95% CI, −11.62 to 5.51; I^2 = 79%)						
Patients						
Children	4	1.74 [−2.31 to 5.79]	.4	0%	Fixed	<.001
Adults	1	−13.92 [−20.26 to −7.58]	<.001	—	Fixed	
Duration of follow-up						
<3 mo	1	−13.92 [−20.26 to −7.58]	<.001	—	Fixed	<.001
≥3 mo	4	1.74 [−2.31 to 5.79]	.4	0%	Fixed	
Dose of vitamin D						
<300,000 IU	4	1.74 [−2.31 to 5.79]	.4	0%	Fixed	<.001
≥300,000 IU	1	−13.92 [−20.26 to −7.58]	<.001	—	Fixed	
Dosing regimen type						
Intramuscular	1	−13.92 [−20.26 to −7.58]	<.001	—	Fixed	<.001
Oral	4	1.74 [−2.31 to 5.79]	.4	0%	Fixed	
Incidence rate of repeat episodes of pneumonia (RR = 0.69; 95% CI, 0.51–0.94; I^2 = 83%)						
Patients						
Children	9	0.66 [0.48–0.90]	.009	64%	Random	.02
Adults	1	0.93 [0.86–1.01]	.11	—	Random	
Duration of follow-up						
<3 mo	6	0.55 [0.33–0.91]	.02	93%	Random	.11
≥3 mo	4	0.89 [0.66–1.20]	.42	8%	Random	
Dose of vitamin D						
<300,000 IU	6	0.51 [0.29–0.89]	.02	93%	Random	.07
≥300,000 IU	4	0.91 [0.69–1.20]	.50	10%	Random	
Dosing regimen type						
Intramuscular	3	0.28 [0.17–0.45]	<.01	0%	Fixed	<.01
Oral	7	0.86 [0.76–0.97]	.02	25%	Fixed	

(*continued*)

Table 3. (continued)

Subgroups	N	Estimated value, MD or RR [95% CI]	*P*-value	I^2 (%)	Statistical method	$P_{\text{subgroup differences}}$
Rate of ICU/hospital admission (RR = 0.67; 95% CI, 0.38–1.20; $I^2 = 0\%$)						
Patients						
Children	5	0.76 [0.42–1.38]	.37	0%	Fixed	.26
Adults	1	0.14 [0.01–2.57]	.18	—	Fixed	
Duration of follow-up						
<3 mo	2	0.26 [0.07–0.99]	.05	0%	Fixed	.1
≥3 mo	4	0.92 [0.47–1.78]	.80	0%	Fixed	
Dose of vitamin D						
<300,000IU	2	0.56 [0.13–2.53]	.45	27%	Fixed	.76
≥300,000IU	4	0.73 [0.35–1.51]	.39	15%	Random	
Dosing regimen type						
Intramuscular	—	—	—	—	—	—
Oral	6	0.67 [0.38–1.20]	.43	0%	Fixed	
Complications rate (RR = 0.67; 95% CI, 0.38–1.20; $I^2 = 0\%$)						
Patients						
Children	6	1.12 [0.83–1.51]	.37	0%	Fixed	—
Adults	—	—	—	—	—	
Duration of follow-up						
<3 mo	1	0.49 [0.05–5.21]	.55	—	Fixed	.49
≥3 mo	5	1.14 [0.84–1.54]	.40	0%	Fixed	
Dose of vitamin D						
<300,000 IU	2	1.19 [0.87–1.61]	.27	0%	Fixed	.20
≥300,000 IU	4	0.44 [0.10–1.94]	.28	0%	Fixed	
Dosing regimen type						
Intramuscular	—	—	—	—	—	—
Oral	6	1.12 [0.83–1.51]	.37	0%	Fixed	

ICU, intensive care unit; MD, mean difference; RR, risk ratio.

excluded low-score studies by considering the methodological quality, then calculated the pooled results as follows: The pooled results of duration of hospitalization and the heterogeneity remain stable (MD = −0.07; 95% CI, −9.04 to 8.90; I^2 = 34%) when excluding a study by Dhungel et al[34]; the pooled RR of complications rate was almost not changed (RR = 1.19; 95% CI, 0.87–1.61; I^2 = 0%) by excluding a study by Singh et al[39]; the pooled RR of incidence rate of repeat episodes of pneumonia and the heterogeneity also kept stable (RR = 0.61; 95% CI, 0.39–0.95; I^2 = 90%) by excluding the study by Singh et al[39]; similarly, the pooled RR of rate of recovery was still stable after excluding the study by Wang et al.[41] We equally considered that there were no changes in the overall heterogeneity and effect size when any study was excluded.

Discussion

In this meta-analysis of RCTs, vitamin D supplementation significantly increased levels of serum 25(OH)D (MD = 15.97; 95% CI, 7.49–24.44; P = .002) and reduced the incidence rate of repeat episodes of pneumonia (RR = 0.68; 95% CI, 0.50–0.93; $I^2 = 83\%$). Although our result indicates that vitamin D supplementation has a positive effect on recovery rate of pneumonia (RR = 1.28; 95% CI, 0.94–1.74; $I^2 = 13\%$), there is no statistical difference ($P = .12$). Subgroup analysis revealed such a protective effect on the incidence rate of repeat episodes of pneumonia was seen among participants in trials in which the population were children (n = 9; RR = 0.66; 95% CI, 0.48–0.90; $P = .0009$; $I^2 = 64\%$), duration was <3 months (n = 6; RR = 0.55; 95% CI, 0.33–0.91; $P = .22$; $I^2 = 93\%$), or dose of vitamin D was <300,000 IU (n = 6; RR = 0.51; 95% CI, 0.29–0.89; $P = .02$; $I^2 = 93\%$). In addition, subgroup analysis revealed a statistically significant decline in rate of ICU/hospital admission (n = 2; RR = 0.26; 96% CI, 0.07–0.99; $P = .05$; $I^2 = 0\%$), comparing the vitamin D group with placebo in the stratification of follow-up duration <3 months. Use of vitamin D was safe: potential adverse reactions were rare, and the complication events and rate were relatively low in the group randomized to intervention compared with the control arms.

The included studies differed in terms of inclusion criteria, dose, and duration of vitamin D use. We have reasons to believe that results differed owing to improper dose, different population, or mode of administration in

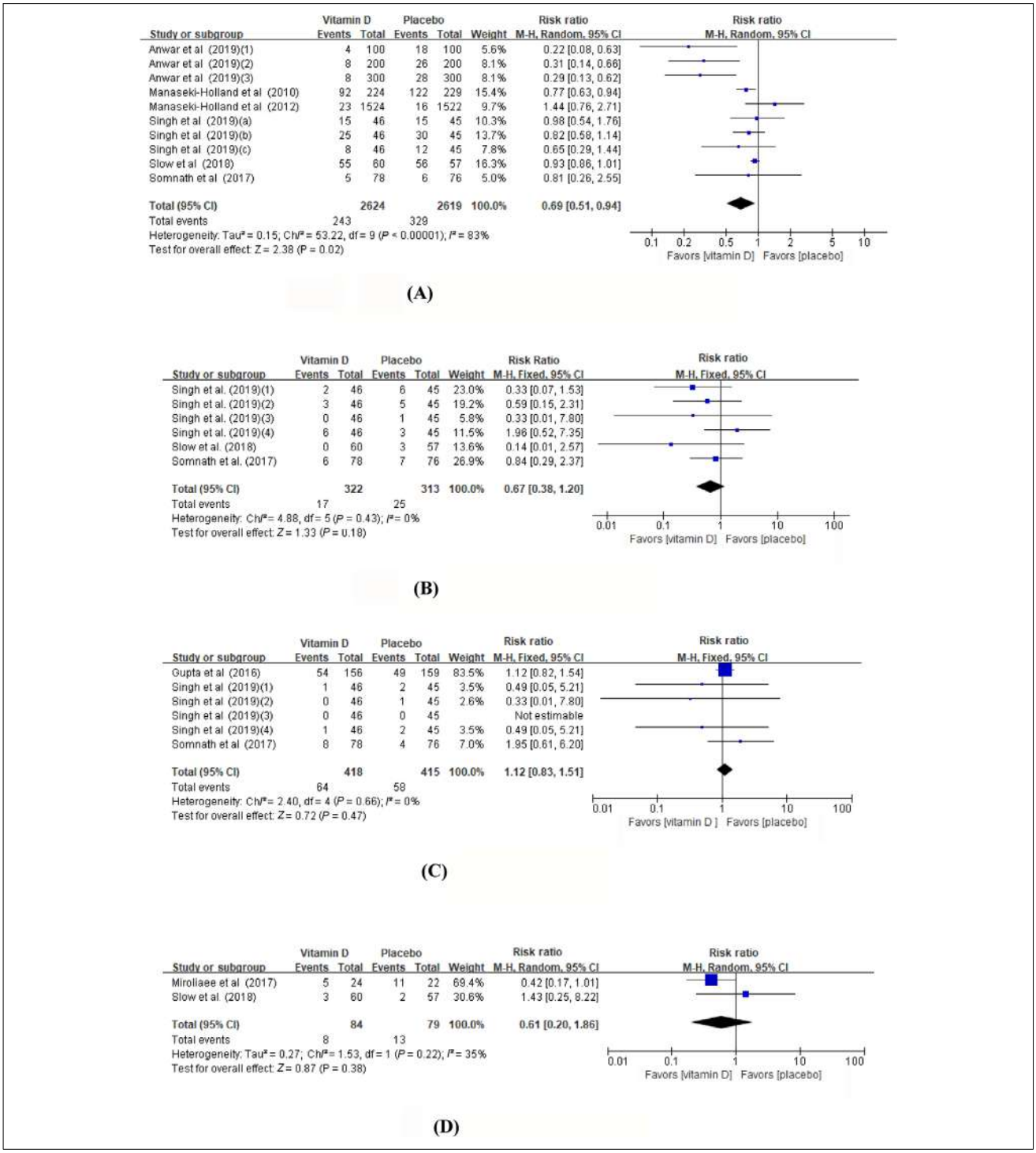

Figure 3. Effect of vitamin D supplementation on (A) incidence rate of repeat episodes of pneumonia; (B) rate of intensive care unit/hospital admission; (C) complications rate; (D) mortality of pneumonia. For Singh et al, (a), (b), and (c) represent severity of pneumonia, respectively; (1), (2), (3), and (4) represent different intervention times. For Anwar et al, (1), (2), and (3) represent different intervention times. M-H, Metropolis Hastings.

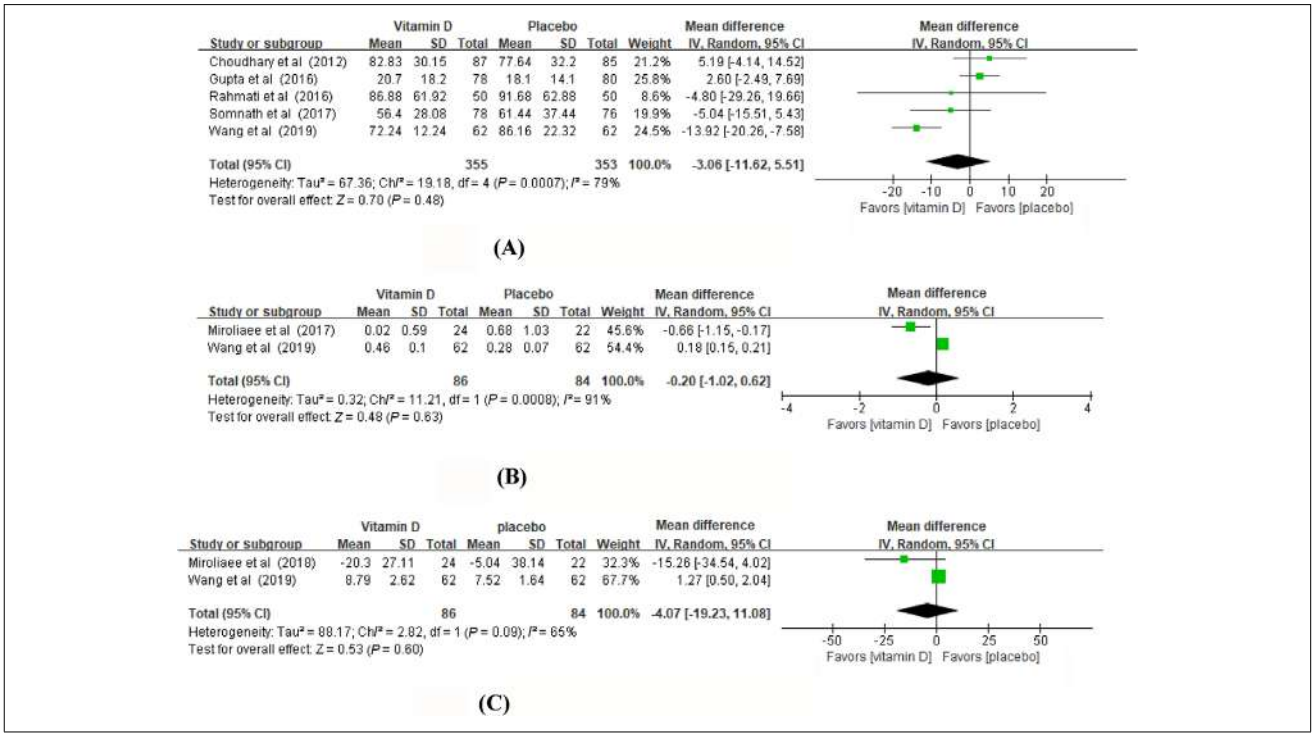

Figure 4. Effect of vitamin D supplementation on (A) time to resolution of fever; (B) change in levels of serum procalcitonin; (C) change in levels of serum high-sensitivity C-reactive protein. IV, xxxx.

pneumonia. The dose of vitamin D varied among included studies. One trial[33] used continuous doses varying from 2000 to 5000 IU for 5 days, another[41] used a continuously high dose of 300,000 IU for acute phase, and others used single high bolus doses ranging from 100,000 to 500,000 IU.

In fact, the dose of vitamin D has been concerning and controversial. Haeusler et al[44] reported that high- (75,000 IU/kg food) but not medium-dose vitamin D had caused mild hypercalcemia, which rendered T cells more prone to proinflammatory activation. Vos et al reported that once-monthly oral vitamin D supplementation (100,000 IU) after lung transplantation fails to demonstrate a significant difference in chronic lung allograft dysfunction prevalence, innate immunomodulatory, or a beneficial clinical effect compared with placebo.[45] Feige et al reported a patient with primary progressive multiple sclerosis (MS) who presented with generalized weakness caused by hypercalcemia after uncontrolled intake of >50,000 IU of cholecalciferol per day over several months.[46] de Vries et al also reported a single high (300,000 IU) or low dose (75,000 IU) of cholecalciferol does not seem to reduce arterial stiffness and leukocyte activation in overweight, vitamin D–deficient women.[47] However, Sharifi et al conducted a double-blind RCT to assess the effect of a single muscular injection of 7.5 mg vitamin D_3 (300,000 IU) on the serum levels of immune cytokines in ulcerative colitis patients and found serum tumor necrosis factor-α (TNF-α), Immune interferon-γ (IFN-γ), and Interleukin-12p70 (IL12p70) levels decreased significantly.[48] Vitamin D seems to inhibit helper T 1 (T_H1) immune responses and have no effect on T_H2 responses.

Our result revealed a single high dose (but <300,000 IU) of vitamin D was beneficial for decreasing the incidence rate of repeat episodes of pneumonia (RR = 0.68) within the observation period of <3 months. We hypothesized that a single high dose of vitamin D supplementation could decrease the incidence rate of repeat episodes of pneumonia by partly improving immune function. Sotirchos et al reported cholecalciferol supplementation with 10,400 IU daily is safe and tolerable in patients with MS and exhibits in vivo pleiotropic immunomodulatory effects in MS,[49] which is consistent with our study. A meta-analysis hypothesized similarly that vitamin D supplementation could exert immunomodulatory effects that strengthen resistance to acute infections, which would reduce the risk of death in debilitated individuals.[50]

Moreover, considering frequency of administration, another systematic review revealed the protective effect was larger in studies using once-daily dosing compared with large bolus doses.[51] In the present systematic review, patients in 11 of 13 included studies took single high doses of vitamin D, which might be a good explanation of a smaller effect of vitamin D when using a single large bolus schedule.

Another aspect that has to be considered was the prevalence of malnutrition, as underlying malnutrition may

affect the state of immunity and hence blunt the vitamin D effect. Of these, only 5 studies[34–36,39,40] did report the malnutrition situation in either vitamin D or control groups, causing difficulty in correlating the effect of vitamin D supplementation in malnourished patients. Low vitamin D status is an independent risk factor for treatment failure and delayed recovery from severe lower respiratory infections.[52] The level of serum vitamin D in patients with pneumonia was significantly low,[53] maybe because of a systemic inflammatory response in the host.[54,55]

In total, there remains little evidence to suggest that vitamin D supplementation has an effect on most outcomes, including time to resolution of pneumonia, duration of hospitalization, recovery rate of pneumonia, and the main secondary outcomes (including mortality of pneumonia, rate of ICU/hospital admission, complications rate, time to resolution of fever, and change in serum levels of serum PCT and hs-CRP), strengthening the hypothesis that low vitamin D status is a consequence of ill health rather than its cause.

Strengths and Limitations of This Study

Our study has several strengths. It is the first to include enough literature to evaluate the efficacy of vitamin D on primary and secondary outcomes; we obtained detailed information for all 13 trials identified by our search, and the score of literature quality evaluation is 3–7, indicating high quality; the proportion of randomized participants with missing outcome data was small; participants with diverse characteristics in multiple settings were represented; and most of the pooled results were low in heterogeneity. Our findings, therefore, have a high degree of validity. Moreover, the present subgroup was composed referring to the "credibility criteria" relating to study design, analysis, and context.[56]

However, our study has some limitations. In the subgroup analyses of the present meta-analysis, the risk of residual confounding for analyses was always present when relatively few trials were represented (eg, the subgroup analyses that were stratified by dosing regimen or region). A second limitation is that not all of the included studies reported the etiology of pneumonia. This is important for any differential therapeutic effect of vitamin D (if any) in bacterial or viral pneumonia. A third potential limitation is that not all of our studies provided baseline 25(OH)D levels, and we were unable to explore the effects of vitamin D treatment stratified at baseline 25(OH)D level in subgroup analysis. Future trials should report about the etiological/microbiological diagnosis of pneumonia. Simultaneously, they should measure the vitamin D level to corroborate the clinical findings. Besides these, data on prior antibiotic use, duration of pneumonia before vitamin D supplementation, and nutrition status should also be provided. Finally, an RCT of a multicenter large population (if possible) should also be conducted.

Conclusion

In summary, it seems that high-dose vitamin D intervention has an effect on reducing the incidence rate of repeat episodes of pneumonia by enhancing immune efficacy, although more population studies are needed to support that vitamin D supplementation has an effect as an adjuvant treatment on pneumonia itself, including time to resolution of pneumonia, duration of hospitalization, and recovery rate of pneumonia.

Statement of Authorship

C. Yang, Y. F. Lu, and M. Wan equally contributed to the conception and design of the research; C. Yang contributed to the design of the research; C. Yang, L Yang, and M. Wan contributed to the acquisition and analysis of the data; C. Yang, X. Yang, D. Xu, and S. Wang. contributed to the interpretation of the data; and C. Yang and G. Sun drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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