SYSTEMATIC REVIEW

Does Vitamin D Improve All-cause Mortality in Critically Ill Adults? An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials

Manpreet Kaur[1], Kapil Dev Soni[2], Anjan Trikha[3]

Abstract

Introduction: Vitamin D deficiency is an amendable risk factor linked to increase in mortality in critically ill patients. The aim of this systematic review was to evaluate if vitamin D supplementation reduced the mortality, and length of stay (LOS) in intensive care units (ICU) and hospitals in critically ill adults including coronavirus disease-2019 (COVID-2019) patients.

Materials and methods: We searched the literature using the PubMed, Web of Science, Cochrane and Embase databases until January 13, 2022, for RCTs comparing vitamin D administration to placebo or no treatment in ICUs. The fixed-effect model was used for the primary outcome (all-cause mortality) and the random effect model for secondary objectives (LOS in ICU, hospital, mechanical ventilation). Subgroup analysis included ICU types and high vs low risk of bias. Sensitivity analysis compared severe COVID-19 vs no COVID disease.

Results: Eleven RCTs (2,328 patients) were included in the analysis. Pooled analysis of these RCTs, showed no significant difference in all-cause mortality between the vitamin D and placebo groups [odds ratio (OR) 0.93, $p = 0.47$]. Inclusion of COVID-positive patients did not change the results (OR 0.91, $p = 0.37$). No significant difference was observed between the vitamin D and placebo groups in LOS in ICU ($p = 0.34$); hospital ($p = 0.40$) and mechanical ventilation duration ($p = 0.7$). In the subgroup analysis, there was no improvement in mortality in medical ICU ($p = 0.36$) or surgical ICU ($p = 0.03$). Neither low risk of bias ($p = 0.41$) nor high risk of bias ($p = 0.39$) reduced mortality.

Conclusion: Vitamin D supplementation in the critically ill did not have statistically significant benefits on clinical outcomes in terms of overall mortality, duration of mechanical ventilation, and LOS in ICU and hospital.

Keywords: Critical illness, Intensive care units, Mechanical ventilation, Vitamin D deficiency, Vitamin D supplementation.

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Highlights

- Vitamin D deficiency has been associated with metabolic alterations during critical illnesses.
- The possible role of Vitamin D supplementation on mortality and the ICU admission of COVID-19 patients or critically ill patients needs to be evaluated.
- In the present meta-analysis, there is no survival benefit with the addition of vitamin D in critically ill patients (whether COVID positive or negative)
- There was no benefit in the duration of mechanical ventilation, length of ICU, and hospital stay in patients who received vitamin D.

Introduction

Vitamin D deficiency has been associated with metabolic alterations during critical illnesses.[1] The prevalence of vitamin D deficiency [25(OH)D levels <20 ng/mL] in critically ill patients ranges from 40 to 70%.[2] Vitamin D receptors are present in various tissues, conferring its diverse biological functions in the human body.[3] It is becoming increasingly evident that in critically ill patients, vitamin D has potential effects on infectious, immunologic, neurologic, cardiovascular, and respiratory disorders.[4–6] Depletion of vitamin D and other trace elements has been implicated in systemic inflammation, oxidative stress and multiorgan failure.[3,7,8] Several observational studies have demonstrated that deficiency of vitamin D results in poor outcomes in terms of morbidity and mortality in critically ill patients.[2,9,10]

[1]Department of Anaesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, New Delhi, India

[2]Department of Critical and Intensive Care, JPN Apex Trauma Center, All India Institute of Medical Sciences, New Delhi, India

[3]Department of Anaesthesiology, All India Institute of Medical Sciences, New Delhi, India

Corresponding Author: Kapil Dev Soni, Department of Critical and Intensive Care, JPN Apex Trauma Center, All India Institute of Medical Sciences, New Delhi, India, Phone: +91 9718661658, e-mail: kdsoni111@gmail.com

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Multiple factors in ICU result in the high rate of vitamin D deficiency in the critically ill. As such prevalence of vitamin D deficiency in India [25(OH)D levels <20 ng/mL] is 50 to 94% based on community-based Indian studies.[11] Decreased sun exposure, decreased dietary intake, preexisting malnutrition, inflammation, disturbed metabolism, decreased synthesis of vitamin D-binding protein due to liver dysfunction, fluid resuscitation, increased vascular permeability, renal vitamin D wasting, decreased renal conversion to 1,25(OH)D3 and increased tissue conversion of 25(OH)D3 to 1,25(OH)D3. Liver, parathyroid and kidney dysfunction

Table 1: PICOS data extraction framework

PICOS framework	
Participants/population	Intensive care, Critically ill patients, critical illness, sepsis, trauma, ARDS, shock, injury, ventilated
Intervention(s), exposure(s)	Vitamin D, Vitamin D3, Vitamin D2, cholecalciferol, calcitriol oral, enteral or parenteral Vit D (1,25)-dihydroxyvitamin D or 25-hydroxy vitamin D or any other form of vitamin D
Comparator(s)/control	With or without any other treatment modality, Placebo as control
Outcome	Primary: All-cause mortality as reported Secondary: Length of ICU and hospital stay (days), length of mechanical ventilation, the incidence of adverse events related to intervention, infectious complications as reported in the trials
Study design	Comparative trials: prospective trials

increase the risk of developing vitamin D deficiency.[12] To add to it, very low 25(OH)D concentrations in critically ill patients result in reduced responses to vitamin D replacement which instead is converted into alternate metabolites.[13,14] Vitamin D deficiency is a modifiable factor and its correction if reduces morbidity in intensive care patients can have a promising role.

Many observational studies and meta-analyses conducted on critically ill patients have shown that there is mortality associated with low serum vitamin D levels. However, the causality between mortality and worse outcomes has not been confirmed owing to varied results.[9,15–18] The largest randomized controlled trial on 475 patients, the VITdAL-ICU (Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency) trial did not show any mortality benefit but its secondary analysis proposed improvement in severely deficient patients (i.e., 25-dihydroxy-vitamin D <12 ng/mL).[19,20] These results and the results of previous meta-analyses in critical illness emphasize the benefits of vitamin D supplementation.[21,22] Hence, it is still inconclusive whether vitamin D deficiency is associated with increased mortality in critically ill patients and whether vitamin D supplementation might be beneficial thereby supporting the need for this meta-analysis. A larger trial including 1,360 patients has recently been published by the PETAL clinical trials network wherein the administration of high-dose enteral vitamin D3 did not offer a 90-day mortality benefit.[9] This study has not been incorporated into any published meta-analysis. Hence, the present meta-analysis was designed to pool all the randomized controlled trials to assess whether vitamin D improves all-cause mortality in critically ill adults compared to placebo or no vitamin D3. In addition, vitamin D has been used at different doses and via different routes in various studies.[9,23] Optimal dosing, the timing of administration, and the form of vitamin D are still unanswered questions.

With the emergence of COVID-19, Vitamin D deficiency has been suspected to be a possible promoting factor for COVID susceptibility and severity. Vitamin D supplementation reduces respiratory tract infection and mortality risk in noncritical ill patients; however, whether it is useful in acute settings remains unclear. With conflicting data regarding the role of vitamin D in COVID-19,[24–26] we performed a sensitivity analysis to the assessment of the plausible role of vitamin D in ameliorating COVID-19 which has never been performed in any of the published meta-analyses.

Materials and Methods

Protocol and Registration

This meta-analysis was done in accordance with the PRISMA-P statement.[27] The protocol for this meta-analysis was registered with Prospero which can be accessed at the Prospero site (registration number of CRD42020163692).

Eligibility Criteria

We applied the population, intervention, control and outcome study design (PICOS) approach for trial identification and define the final selection criteria (Table 1). We included prospective randomized control trials that administered vitamin D in any form or route compared to placebo in critically ill intensive care patients on all-cause mortality in this meta-analysis. We excluded trials that utilized observational, quasi-experimental and cross-over designs.

Information Sources

Two reviewers (MK and KDS) independently searched the online literature available on PubMed, Embase, Web of Science and Cochrane Central Register of Controlled for potentially eligible published manuscripts until January 13, 2022. We did not execute any language or date restrictions on the search strategy. We searched the references of the previously published meta-analyses to determine trial eligibility. If there was any query about the publication, the corresponding author was contacted for additional information.

Search Strategy

The keywords used to search the database were: "randomized controlled trial, critically ill, intensive care, sepsis, ARDS, vitamin D/D2/D3, and mortality". Details of the PUBMED and EMBASE search strategies are provided in Supplementary File 1. We did not impose any language or age limits on our search strategy.

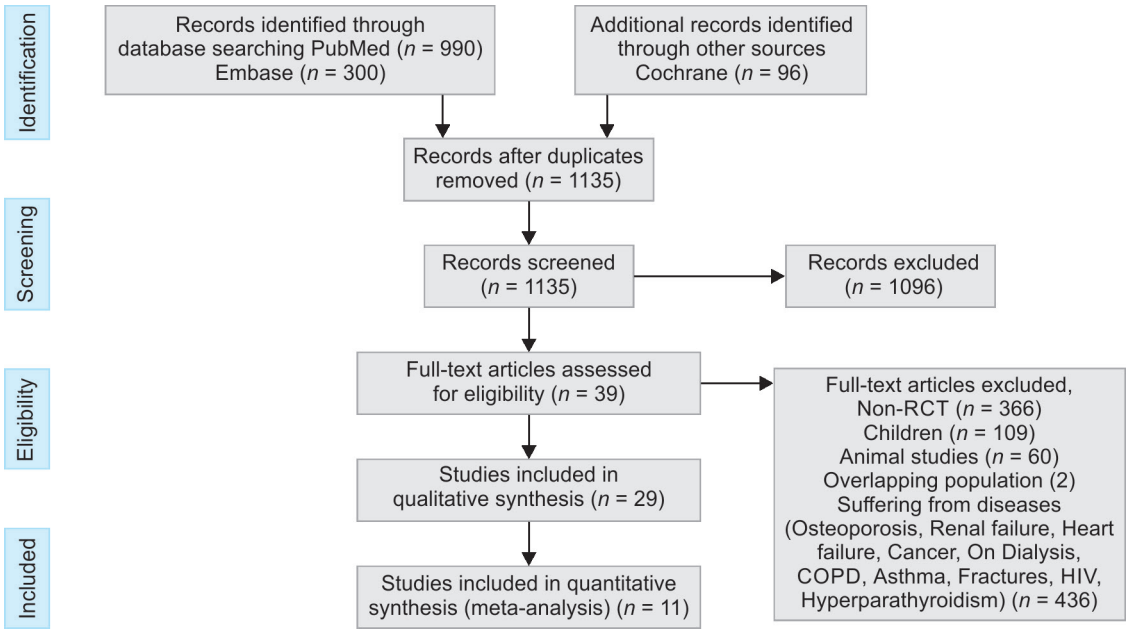
Study Selection

Two authors (MK and KDS) independently screened and evaluated titles and available abstracts. The full text of the eligible articles was retrieved and evaluated for eligibility. All collected data were tabulated in Microsoft Excel™ Version 1908 datasheet (Microsoft Corp., Redmond, Washington). Any dispute between the two authors was resolved by discussion with a third author (AT) who cross-checked the data before analysis (AT).

Data Collection

Two reviewers (MK and KDS) retrieved essential data independently from the eligible RCTs and tabulated the data in a Microsoft Excel™ Version 1908 (Microsoft Corp., Redmond, Washington) datasheet. Any disputes between the two authors were resolved by discussion with a third author (AT) who cross-checked this data before analysis (AT).

Flowchart 1: Preferred reporting items for systemic reviews and meta-analysis (PRISMA) algorithm for trial selection



Data Items

The data extracted from individual trials were tabulated in a standardized format which included: first author, year of publication, city, country of work, center/setting, sample size, patient demographic profile, characteristics of included patients, study design, intervention details, and outcome data. Outcome data included: all-cause mortality (as reported in the trial), length of ICU and hospital stay (days), length of mechanical ventilation, the incidence of adverse events related to intervention, and infectious complications as reported. We resolved all disagreements through a discussion with the arbitrator (AT) to achieve consensus.

Bias Risk in Individual Studies

Two authors (MK and KDS) used the Cochrane Collaboration tool to independently assess the methodological quality of the included studies. The potential risk of bias was rated as "low", "high" or "unclear" risk of bias. Reviewers resolved the disagreement by a discussion with an arbitrator (AT) who helped in getting a consensus about any unresolved disagreements.

These studies were searched in methodology for methodology included (yes, no or uncertain): Method of randomization, allocation concealment, blinding (participants, personnel, outcome assessment), missing data reporting, selective reporting, or any other bias.

Additional Analysis

We further analyzed studies by subgrouping studies into low risk and high risk of bias studies. Other subgroup analyses included characteristics of the studied patient population i.e. medical or surgical ICU. We did a sensitivity analysis by incorporating patients with COVID-19 receiving vitamin D admitted to ICU.

Results

Study Identification and Selection

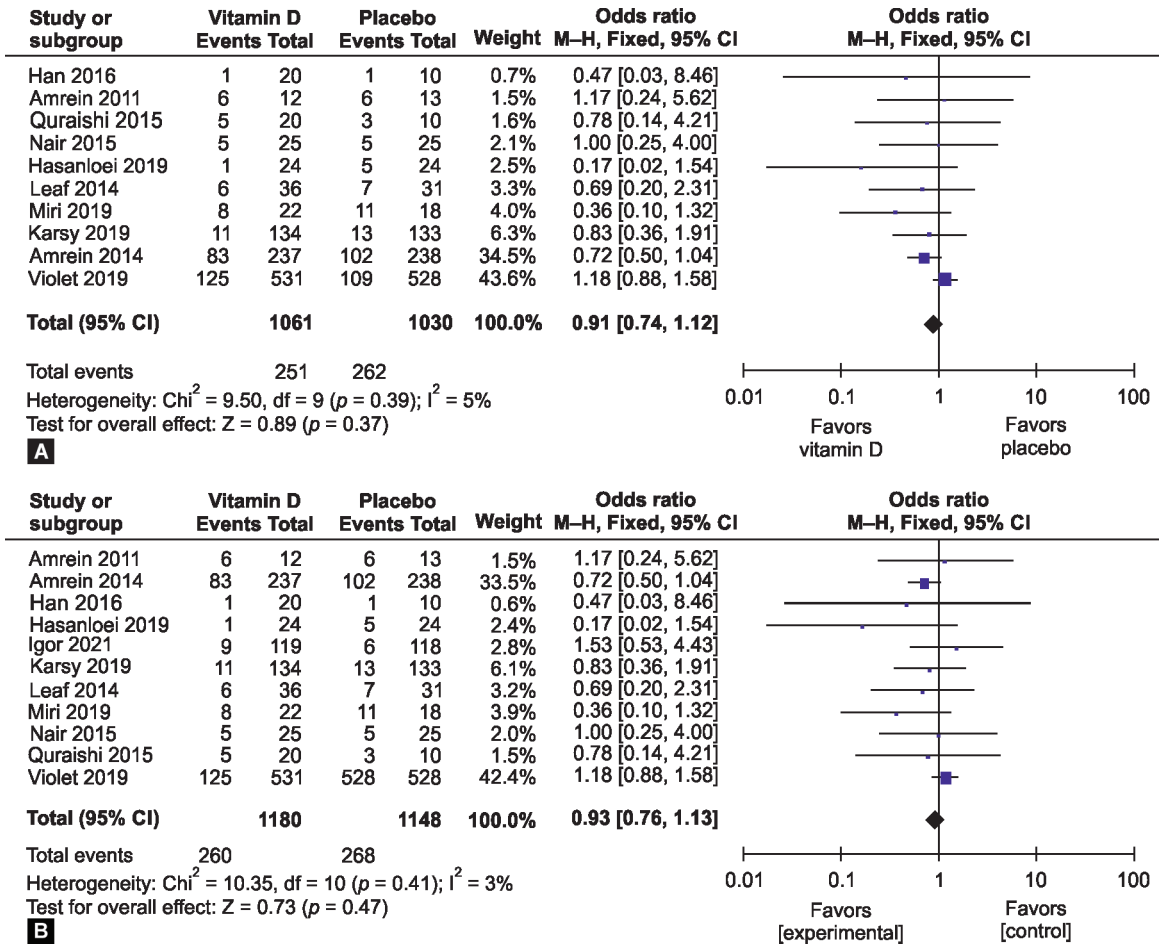
An initial comprehensive database search of PubMed, EMBASE, web of science and Cochrane for potentially eligible published manuscripts revealed 1,386 articles. After removal of the duplication using EndNote software (X9), 1,135 enrolled studies were screened (title and abstract) for identification of potentially eligible trials. Articles were excluded if they were nonrandomized control trials, wrong population (children), animal studies, suffering from diseases (Osteoporosis, renal failure, heart failure, cancer, chronic obstructive pulmonary disease, asthma, hyperparathyroidism, osteoporosis, fractures or were on dialysis), Non-ICU patients, biochemical outcomes only, lack of mortality data or were irrelevant. Finally, 36 full-text articles were assessed for suitability and ten trial data were excluded because of the dearth of mortality data. We excluded two trials which were retrospective studies, and one of which included diabetic patients with a lack of mortality data. Finally, 11 studies (10 Non-COVID and 1 COVID) were included in the meta-analysis quantitative synthesis.[10,15,16,23,28–34] A PRISMA flow diagram depicting studies selected is shown in Flowchart 1. A summary of the risk of biases statement for included studies has been shown in Figure 1.

Summary Measures and Result Synthesis

The primary outcome was "mortality at the longest follow up" while the secondary outcomes were duration of mechanical ventilation, length of ICU and hospital stay.

Primary Outcome Measures

Primary outcomes i.e. mortality were extracted as dichotomous outcomes from the relevant studies. The results were calculated as the odds ratios for each trial. The pooled odds ratio was calculated using the fixed-effect mantel hazel method or random effect. Continuous outcome variables were abstracted in the form of mean and standard deviation for both groups. Results were pooled across the studies based upon weighted mean differences. All statistical variables were calculated with a 95% confidence interval (95% CI). Q test and I^2 statistic were used to analyze heterogeneity and based on I^2 statistic findings, a fixed-effect model was used for analysis assuming an absence of within-study heterogeneity. Pooled analysis was done in RevMan software Review Manager (RevMan) [Computer program]. Version 5.4. Copenhagen: The Nordic



Figs 1A and B: Forest plot for an odds ratio of mortality pooled analysis level

Cochrane Centre, The Cochrane Collaboration, 2014). Publication bias was assessed by funnel plot.

Data Pooled analysis from 11 trials[10,15,16,23,28–34] (Table 2) found that vitamin D administration has no benefit in terms of all-cause ICU mortality compared to placebo or no agent being administered to critically ill patients (Odds ratio 0.93, 95% CI 0.76, 1.13 $p = 0.47$) (M-H fixed effect model) (Fig. 1B).

Secondary Outcome Measures

Duration of mechanical ventilation: Pooled analysis from four trials (570 patients) showed that the duration of mechanical ventilation was not statistically different in patients receiving vitamin D from placebo [Mean difference −1.08; 95% CI −7.12, 4.96 ($p = 0.73$); inverse variance, random effect model] (Fig. 2).

Length of ICU stay and hospital stay: Seven trials (935 patients) reported length of ICU stay, which was similar in both the groups (Mean difference −2.22 days, 95% CI −6.81, 2.37 days, $p = 0.34$; inverse variance, random effect model). Seven trials reported length of hospital stay which was also similar in both the groups (Mean difference −1.25, 95% CI −4.17, 1.68 days, $p = 0.40$; inverse variance, random-effect model) (Fig. 2).

Subgroup Analyses

In this meta-analysis, vitamin D administration did not reduce mortality in 1,376 patients admitted in medical ICUs (OR = 1.13, 95% CI: 0.87, 1.48, $p = 0.36$; M-H fixed-effect model), or in 590 patients admitted in surgical ICUs (OR = 0.68, 95% CI: 0.48, 0.96, $p = 0.03$; M-H fixed-effect model).

Neither low risk of bias in 1,993 patients (OR = 0.93, 95% CI: 0.75, 1.14, $I^2 = 3\%$, $p = 0.41$; M-H fixed effect model) nor high risk of bias (ROB) in 98 patients (OR = 0.55, 95% CI: 0.18, 1.64, $I^2 = 46\%$, $p = 0.39$ M-H fixed effect model) reduced mortality (Fig. 3).

Sensitivity Analysis

Pooled data analysis from 10 trials (without including severe COVID patients) found that vitamin D had no benefit in terms of mortality at longest follow-up in comparison to placebo for critical illness (Odds ratio 0.91, 95% CI 0.74, 1.12 $p = 0.37$, M-H fixed-effect model). Only 1 trial by Igor et al. done in COVID patients satisfied the inclusion criteria and pooled analysis of 11 trials on vitamin D showed no mortality benefit compared to placebo/no agent in critically ill patients (Odds ratio 0.93, 95% CI 0.76, 1.13 $p = 0.47$, M-H fixed-effect model) (Fig. 3).

Assessment of Risk of Bias

Study quality assessment was done using guidelines laid down by the Cochrane Collaboration and a summary of the risk of biases across different studies is depicted in Figure 4. We used Revman Version 5.4.1 (Cochrane Collaboration) for this evaluation and image generation. In most of the studies, attrition bias and reporting bias were unclear. There were only two studies (Hasanloei et al. and

Table 2: Characteristics of the randomized control trials included in the systemic review

Study/trial	*City, country*	*Center/ setting*	*Population*	*Vitamin D3 regimen*	*Mortality*	*Sample size*	*Endpoints*
Han et al., 2016	USA	2 centers/ ICU	Age >18 years; expected ventilation for at least 72 hours; expected to survive and remain in the ICU for at least 96 hours	50,000 IU vit D3 or 100,000 IU vit D3 daily for five consecutive days enterally	12 weeks	31	Length of stay (hospital, ICU), mortality (ICU, hospital, 28 days)
Amrein et al., 2011			Patients with vitamin D deficiency [25-hydroxyvitamin (25(OH)D) <20 ng/mL] and expected stay in ICU >48 hours	540,000 IU vit D (cholecalciferol ¼ 13, 5 mg) dissolved in 45 mL herbal oil vs Placebo (herbal oil) enterally or orally		25	
Quraishi et al., 2015	Boston, USA	Medical, surgical ICUs	All adults >18 years admitted within 24 hours of new-onset sepsis	Placebo vs 200,000 IU vs 400,000 IU	30 days	30 (10/10/10)	Length of stay (hospital and ICU) and mortality (30 days)
Nair et al., 2015	Australia		Patients with three of four SIRS criteria within 24 hours admission, expected ICU stay for at least 48 hours	Single i/m dose of either 150,000 IU or 300,000 IU cholecalciferol		50 (25/25)	
Hasanloei et al., 2019	Urmia University of Medical Sciences, Iran	Trauma ICU	Adult (18–65 years) with expected mechanical ventilation for at least 48 hours and at least 7 days' stay in the ICU, patients, 25(OH)D serum (10–30 ng/mL), Glasgow Coma Scale (GCS) score >9.	50,000 IU pearl cholecalciferol daily for 6 days, 1 intramuscular injection of 300,000 IU of cholecalciferol, control group: did not receive supplement		80 (26/27/27)	Biochemical, ICU, intubation days, and mortality
Leaf et al., 2014	Boston, USA	Single/mixed ICU	Age ≥18 years, severe sepsis or septic shock, and presence of an arterial or central venous catheter	Calcitriol (2 mg intravenously) vs placebo	28 days	67 (36/31)	Length of stay (hospital and ICU) and mortality (ICU, hospital, 28 days), leukocyte cathelicidin mRNA expression, plasma cytokine levels (IL-10, IL-6, tumor necrosis factor-α, IL-1b, and IL-2), and urinary kidney injury markers.
Miri et al., 2019	Iran	Single	Mechanically ventilated, adult patients (18–65 years)	300,000 IU vitamin D i/m and identical placebo	28 days	44	(APACHE II), sequential organ failure assessment (SOFA) score and clinical pulmonary infection score (CPIS)
Karsy et al., 2019	University of Utah Hospital, Utah	Neurocritical care patients	Age ≥18 years, neurosurgery or neurology patient, expected ICU stay of ≥48 hours, and vitamin D deficiency, specifically measured by 25-hydroxyvitamin D (defined as ≤20 ng/mL).	Vitamin D3 (cholecalciferol, 540,000 IU)	30 days	274 (134/133)	Hospital length of stay (LOS) was the primary outcome; secondary outcomes included intensive care unit (ICU) LOS, repeat vitamin D levels, patient complications, and patient disposition. Exploratory analysis evaluated specific subgroups of patients by LOS, GCS score, and simplified acute physiology score (SAPS II).

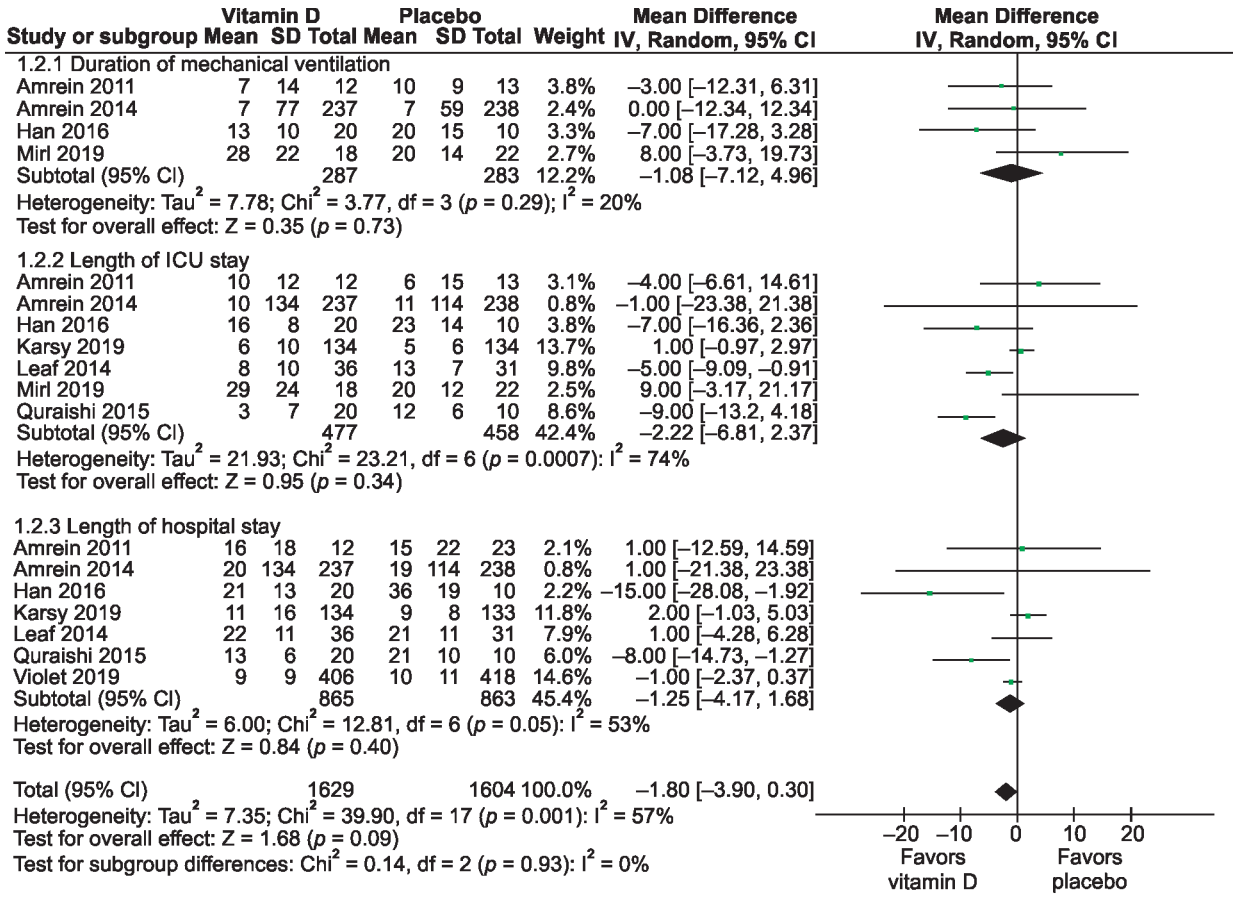


Fig. 2: Forest plot for secondary outcomes: The duration of mechanical ventilation, length of ICU stay, length of hospital stay and pooled analysis level

Nair et al.) that had a high risk of bias(selection and performance bias) and performance and detection bias), respectively (Fig. 5).[10,15] Publication bias funnel plot for "mortality at longest follow-up" is depicted in the supplementary file (Fig. 6).

Discussion

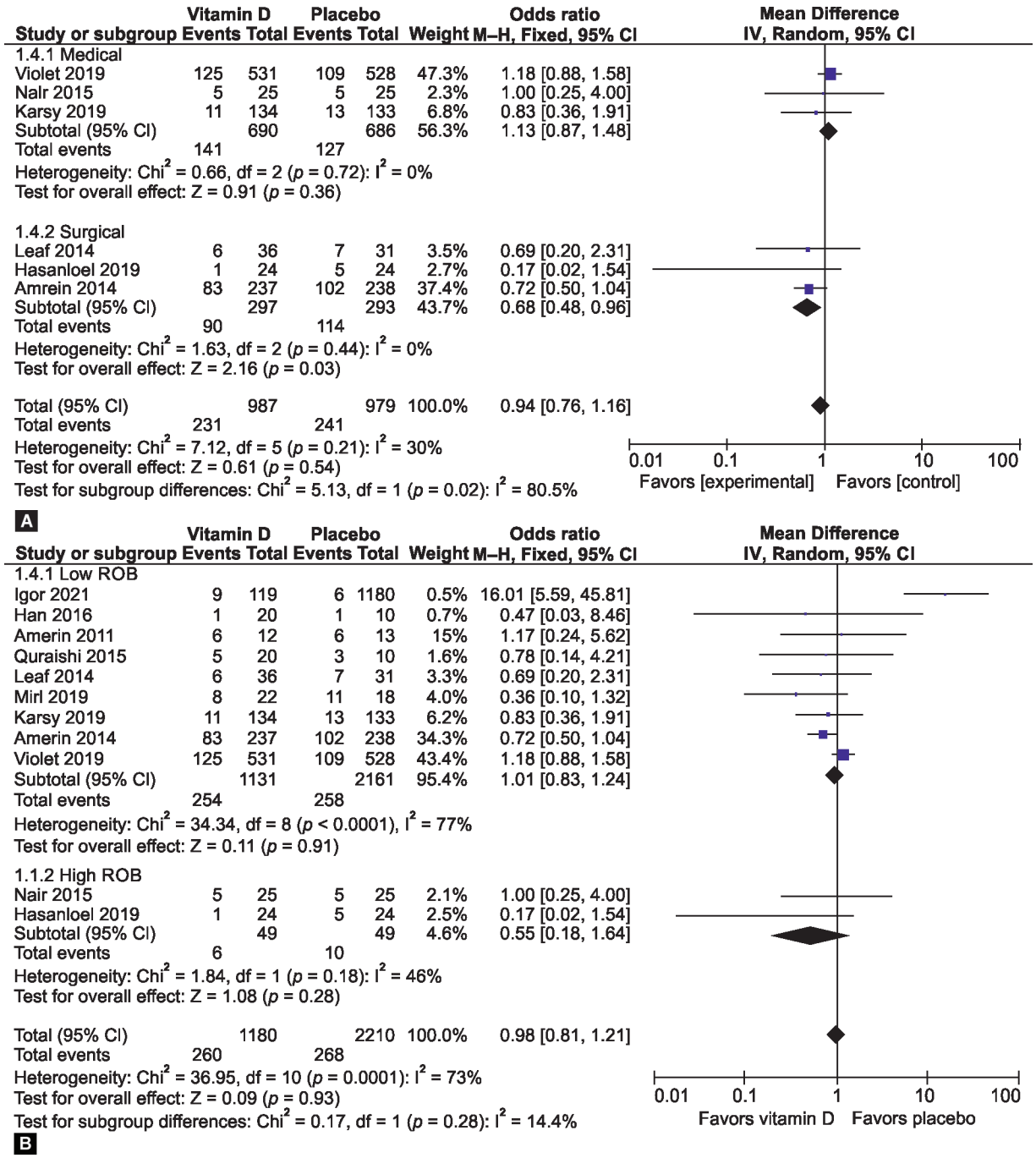
The principal findings of this meta-analysis are the absence of survival benefits with the addition of vitamin D in critically ill patients. Also, there was no benefit in terms of duration of mechanical ventilation, length of ICU and hospital stay in patients who received vitamin D. The physiological rationale for not finding a beneficial role could be implicated in inadequate bolus doses, selection of population without vitamin D deficiency and a few trials with too low sample size for assessment of primary outcome. When variability (heterogeneity) more choice is random effect model while when the heterogeneity was less fixed-effect model was used.

Several randomized controlled trials (RCTs) and meta-analyses did to assess vitamin D supplementation on the outcomes of critically ill patients demonstrated conflicting results. Some studies show positive effects of vitamin D administration on reducing the length of hospital stay,[28] duration of mechanical ventilation (MV),[15,32] and carry mortality benefits.[22,32] However, some studies and meta-analyses demonstrated no change in critically ill patient outcomes.[9,19,31,35–37] The largest trial, the VITdAL-ICU trial, did not show any improvement in hospital length of stay, hospital mortality, or 6-month mortality and lower mortality after vitamin D supplementation was only observed in severely vitamin D deficient patients.[19]

Since the potential role of vitamin D supplementation on mortality and the need for ICU admission of COVID-19 patients has inconsistent results, additional meta-analyses are needed to confirm the actual role of Vitamin D.

The major finding of this meta-analysis is that vitamin D supplementation might reduce all-cause mortality, duration of mechanical ventilation, length of ICU and hospital stay for the critically ill. The diamond of the forest plot of vitamin D role indicates the possibility of favoring vitamin D but since it is touching the horizontal line, the possibility of vitamin D having no effect cannot be ruled out either and it is difficult to say that administering vitamin D might have how much clinically significant effect on the mortality. Hence, though there is a signal of the benefit of using vitamin D in critically ill patients on mortality, we can't be certain of the clinical efficacy of vitamin D supplementation in the critically ill. Hence, vitamin D supplementation in the critically ill did not have statistically significant benefits on clinical outcomes in the present meta-analysis.

Other meta-analyses published include meta-analysis by Putzu et al.,[22] Langlois et al.,[3] Weng et al.,[21] Tentolouris et al.,[38] Lan et al.[37] Meta-analysis by Putzu et al. had limitations in that one of its studies evaluated biochemical outcomes and one of



Figs 3A and B: Forest plot for subgroup analysis. (A) Type of intensive care unit; (B) Subgrouping based on the risk of bias

the trials had included non-critically ill patients. Our meta-analysis results are different from the results of Putzu et al. where found vitamin D supplementation significantly reduced mortality compared to placebo (OR = 0.70, 95% CI 0.50–0.98, $p = 0.04$, $I^2 = 0\%$) while the secondary endpoints: length of hospital stay, length of intensive care unit stay, length of mechanical ventilation, and adverse events had no statistically significant difference. A meta-analysis by Tentolouris et al.[38] investigated vitamin D administration on mortality and admission to ICU of COVID-19 patients but had a majority of data from retrospective or observational trials and only one prospective RCT by Murai et al.[34] which has been included in our RCT as well.

The subgroup analyses have found irrespective of the type of ICU (medical/surgical), risk of bias (low or high), the role of vitamin D in reducing mortality seems to be inconclusive.

Major Strengths of this Meta-analysis

Present meta-analysis aggregates data from recently published RCTs on vitamin D supplementation in the critically ill by Hasanloei et al., Miri et al. and Violet et al.[15,32,33] which have not been included

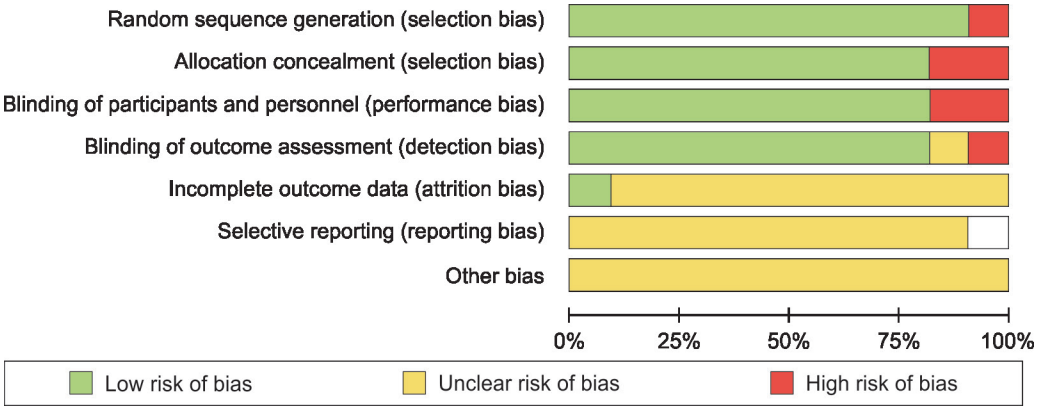


Fig. 4: Risk of bias–summary of all analyzed studies as per the Cochrane Collaboration reformations

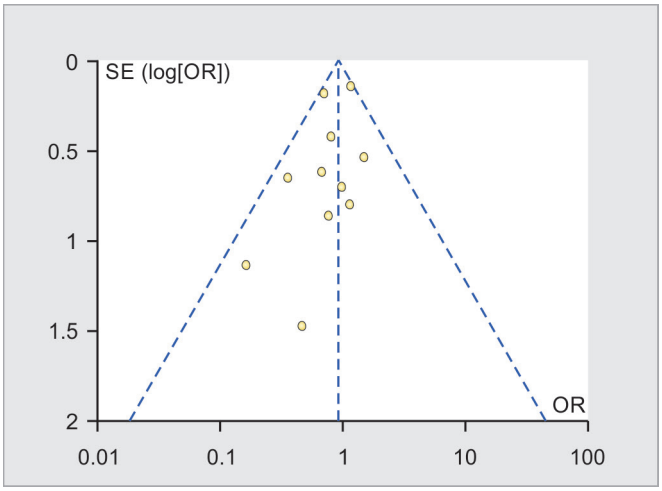


Fig. 5: Risk of bias–summary

in any recently published meta-analysis. Analyzing the risk of bias figure, a lot of domains allocated have a low risk of bias in the studies included within the meta-analysis, indicating that the overall results of the meta-analysis will have a low bias risk. Studies included in the meta-analysis were similar and combining them in the meta-analysis was appropriate as studies had I^2 low (5%). We also did subgroup analysis and sensitivity analysis which adds significantly to the meta-analysis results. Future directives are that more RCT are required to better identify subgroups which may benefit from vitamin D supplementation.

Major Limitations

Most of the studies included in the meta-analysis have long confidence intervals indicating less reliable results. Some of the upper confidence intervals of studies include no effect. Only Amrein et al. and Violet et al. have large sample sizes but opposing effects of vitamin D administration on overall mortality.[19,33]

Conclusion

Vitamin D supplementation in the critically ill did not have statistically significant benefits on clinical outcomes in terms of overall mortality, duration of mechanical ventilation, length of ICU and hospital stay in the present meta-analysis. Such findings could be corroborated by COVID-19 patients as well.

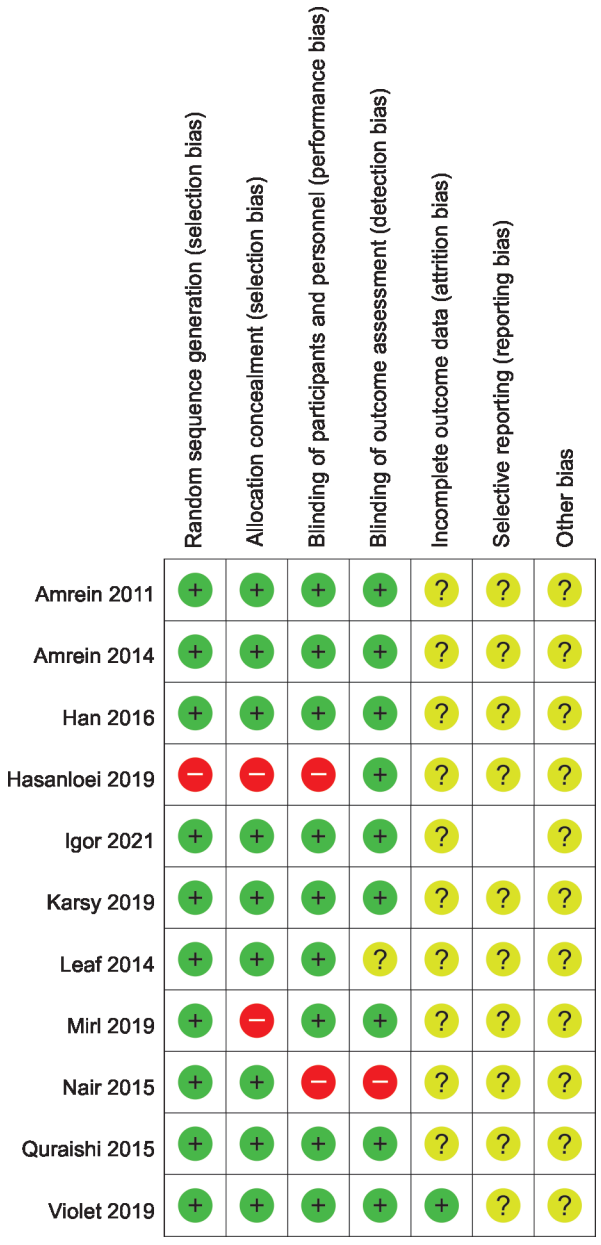


Fig. 6: Funnel plot for publication bias for "mortality at longest follow-up"

Orcid

Manpreet Kaur https://orcid.org/0000-0003-3069-1562
Kapil Dev Soni https://orcid.org/0000-0003-1214-4119
Anjan Trikha https://orcid.org/0000-0002-6001-8486

Supplementary Materials

All the supplemental materials are available online on the website of www.IJCCM.org.

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