Vitamin D and outcomes in adult critically ill patients. A systematic review and meta-analysis of randomized trials

Alessandro Putzu, Alessandro Belletti, Tiziano Cassina, Sara Clivio, Giacomo Monti, Alberto Zangrillo, Giovanni Landoni

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TITLE PAGE

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Vitamin D and outcomes in adult critically ill patients. A systematic review and meta-analysis of randomized trials

Authors

[1] Alessandro Putzu, alessandroputzu@ymail.com

[2] Alessandro Belletti, belletti.ale@gmail.com

[1] Tiziano Cassina, tiziano.cassina@cardiocentro.org

[1] Sara Clivio, sara.clivio@cardiocentro.org

[2] Giacomo Monti, monti.giacomo@hsr.it

[2, 3] Alberto Zangrillo, zangrillo.alberto@hsr.it

[2, 3] Giovanni Landoni, landoni.giovanni@hsr.it

Affiliations:

1 Department of Cardiovascular Anesthesia and Intensive Care, Fondazione Cardiocentro Ticino, Lugano, Switzerland

2 Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy

3 Vita-Salute San Raffaele University, Milan, Italy

Corresponding author

Prof. Giovanni Landoni

Department of Cardiothoracic Anesthesia and Intensive Care

Ospedale San Raffaele

Via Olgettina 60, Milano, 20132 Italy

Tel: +39-02-26436154

Fax +39-02-26437178

Email: landoni.giovanni@hsr.it

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Keywords

Vitamin D; critical illness; critical care; mortality; survival

ABSTRACT

Purpose

Low Vitamin D blood levels are associated with high mortality in critically ill patients. There is controversy about Vitamin D supplementation in this population. The objective of this meta-analysis was to evaluate if Vitamin D administration reduces mortality in critically ill patients.

Materials and Methods

Online databases were searched up to September 1st 2016 for randomized placebo-controlled trials on the use of Vitamin D in adult patients with critical illness. The primary endpoint was mortality among trials with low risk of bias. The secondary endpoints were: length of hospital stay, length of intensive care unit stay, length of mechanical ventilation, and adverse events.

Results

Seven studies published between 2011 and 2016, for a total of 716 patients, were included in the analysis. Vitamin D administration was associated with significantly lower mortality compared to placebo (101/320 [32%] in the Vitamin D group versus 123/307 [40%] in the placebo group, OR = 0.70 [95% CI, 0.50, 0.98], $p = 0.04$, $I^2 = 0\%$). No differences in adverse events and other secondary endpoints were found.

Conclusions

In critically ill patients, Vitamin D administration might be associated with a reduction in mortality without significant adverse events. A large multicenter randomized trial should conclusively confirm these findings.

INTRODUCTION

Millions of patients receive Vitamin D supplementation every year [1,2] and more than one third of the US adult population take Vitamin D supplements [2]. Beside its involvement in bone metabolism and calcium and phosphorus homeostasis, Vitamin D is widely recognized to have other nonskeletal pleiotropic effects, including immunomodulatory, anti-microbial, cardiovascular, and muscular effects [3,4].

Hypovitaminosis D is common in the general population [1] and increases up to 82% in critically ill patients [5–8]. Unfortunately, Vitamin D deficiency is associated with increased mortality both in the overall population [4,9] and in critically ill patients [5–7,10–13]. Low Vitamin D plasma levels are also associated with an increased susceptibility to sepsis [14] and with an increased mortality in septic patients [5,11,12]. Low Vitamin D plasma levels were found to be associated with the intensive care unit (ICU) and hospital length of stay in patients undergoing cardiac surgery [15] or with sepsis [5].

Vitamin D is considered biologically inactive until it undergoes two enzymatic hydroxylation reactions: the first reaction takes place in the liver forming 25-OH Vitamin D and the second takes place in the kidney forming the biologically active hormone, calcitriol (1,25-OH Vitamin D) [16]. Vitamin D levels are affected by several factors, such as vitamin D intake, sun exposure, adiposity, age, and skin melanin content in the overall population [4,17]. Notably, vitamin D levels are worsened by immobilization, kidney disease, fluid overload, and inflammation, conditions which occur frequently in critically ill patients [15,18,19].

Millions of patients per year are admitted in the ICU [20], and even more are admitted to an intermediate care unit or an acute medical unit. Despite improvement in technology and patients' care, mortality in critically ill patients remains high. Interventions aimed at reducing

mortality are strongly warranted and even a small reduction in mortality can save thousands of patients worldwide. To this aim, there is controversy about Vitamin D supplementation in critically ill patients [9,21,22]. Several studies have found that Vitamin D supplementation might be associated with a reduction in all-cause mortality in various settings, including healthy subjects and cancer patients [23–25]. The largest randomized controlled trial (RCT) performed so far in critically ill patients was underpowered to detect differences in mortality but found promising effects of Vitamin D supplementation in the subgroup of patients with severe Vitamin D deficit [22]. Therefore, we performed a systematic review with meta-analysis of randomized literature to test the hypothesis that Vitamin D, as compared to placebo, reduces mortality in critically ill patients.

MATERIALS AND METHODS

Eligibility criteria

Eligible studies met the following PICOS criteria: 1) Population: adult hospitalized critically ill patients; 2) Intervention: administration of Vitamin D; 3) Comparison intervention: placebo-control; 4) Outcome: mortality; 5) Study design: RCT. There was no restriction on Vitamin D formulation and dose or time of administration. The exclusion criteria were: overlapping populations and pediatric studies.

Search Strategy

Two investigators independently searched BioMedCentral, PubMed, EMBASE, and the Cochrane Central Register of clinical trials (last updated September 1st, 2016) for appropriate articles. The full PubMed search strategy is available in the Supplementary Material 1. Abstracts from recent international conferences and references of retrieved articles were searched for additional relevant studies. No language restriction was enforced.

Study Selection and Data Abstraction

References obtained from searches were first independently examined at an abstract level by two investigators and then, if potentially relevant, collected as complete articles. Two authors independently extracted data from eligible studies and collected potential sources of significant clinical heterogeneity. If the article did not include data on mortality, the corresponding author was contacted for further data.

The primary endpoint of the present review was mortality at the longest follow-up available among trials with lower risk of bias. The secondary endpoints were: length of hospital stay, length of ICU stay, length of mechanical ventilation (MV), and adverse events related to the interventions. The secondary endpoints were reported as per-author definition.

We independently rated the overall quality of evidence for outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [26].

Risk of Bias Assessment

The validity of each trial included was evaluated for bias according to The Cochrane Collaboration methods [26]. We rated the potential risk of bias by applying a rating of "Low", "High" or "Unclear" to each study.

Data Analysis and Synthesis

To analyze the binary outcome we calculated odds ratio (ORs) and 95% confidence intervals (CI). In cases of statistical significance, we calculated the Number Needed to Treat (NNT). Standardized Mean Difference (SMD) and 95% CI were computed for continuous variables with fixed effect model. In the adverse events analysis, we calculated risk difference (RD), because trials with zero total event or low event rates have a much higher weight in the pooled estimate of RD compared to the other measures[27]. Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. To assess the between-study heterogeneity, we used Cochran's Q statistic and the I^2 statistic. We used a fixed effect model in case of low statistical inconsistency ($I^2 \leq 25\%$) or a random-effect model in case of significant statistical inconsistency ($I^2 > 25\%$). If 10 or more trials were included in the study [26], publication bias was assessed by visually inspecting the funnel plot of the primary outcome. Post-hoc sensitivity analyses were performed: analyzing data with a fixed effect versus random effects model; changing summary statistic (OR, RD, Risk Ratio [RR]); removing each study in turn; and including all the trials regardless of the risk of bias [26]. We performed a post-hoc subgroup analysis to determine a possible class effect of Vitamin D3.

The present systematic review was conducted in keeping with Cochrane methodology [26] and PRISMA (Preferred Reporting Items Systematic Reviews and Meta-Analysis) guidelines

[28] (Supplementary Material 2). The meta-analysis was performed using Review Manager [29].

RESULTS

Literature search

The search strategy yielded 7262 citations (Figure 1) and a total of 23 studies were assessed in detail. Major exclusions were due to pediatric setting (n = 5) [30–34], overlapping populations (n = 5) [35–39], lack of a randomized design (n = 3) [40–42], abstract-only publications with lack of mortality data (n = 2) [43,44], and absence of control group (n = 1) [45]. Finally, seven articles [22,46–51] (716 participants) were included in the systematic review (Table 1).

Study characteristics and quality

The characteristics of the seven included studies are shown in Table 1 and Supplementary Material 3. Manuscripts were published between 2011 and 2016. Five studies were single-center [22,47–50] and two studies were two-centers [47,51]. In one case [51] we received further data from the authors.

Six studies administered Vitamin D3 (also known as cholecalciferol) and one study administered calcitriol [46]. All the studies had placebo as comparator. Two studies administered Vitamin D supplements in patients with a vitamin deficit (defined as Vitamin D level ≤20 ng/ml) [22,48].

Five trials were considered to carry a low risk of bias in all bias domains, one trial was of unclear risk of bias [50], and one trial was judged at high risk of bias [51] (Supplementary Material 4). The GRADE level of evidence for each outcome is presented in the Supplementary Material 5.

Vitamin D administration in critically ill patients: mortality

Analysis including low-risk of bias trials showed that the administration of Vitamin D in critically ill patients was associated with a significant reduction in mortality at the longest follow-up available (101 of 320 [31.56%] patients in the Vitamin D group vs. 123 of 307 [40.07%] in the placebo-control group, OR = 0.70 [95% CI, 0.50, 0.98], $p = 0.04$, NNT = 12) (Figure 2) with five studies included [22,46–49]. The data were homogenous (p for heterogeneity = 0.68, $I^2 = 0\%$).

The significant effect on mortality was confirmed when including all eligible RCTs regardless of risk of bias (7 trials, 716 patients, OR = 0.71 [95% CI, 0.51, 0.98], $p = 0.04$, $I^2 = 0\%$) and when analyzing data using a random effect model or changing summary statistics. However, two studies [22,49] altered the results when removing a single study at a time (Supplementary Material 6). No differences were found when analyzing trials that administered enteral Vitamin D3 (560 patients, OR = 0.70 [95% CI, 0.50, 0.99], $I^2 = 0\%$, $p = 0.05$) [22,47–49] (Supplementary Material 6). The overall quality of evidence for mortality was moderate.

Vitamin D administration in critically ill patients: clinical outcomes

Five studies reported length of ICU and hospital stay [22,47–49,51] and three trials reported length of MV [22,48,51]. Data analysis showed no significant difference between groups (Figure 3). The overall quality of evidence for these outcomes was low to moderate.

Adverse events and safety of Vitamin D administration in critically ill patients

All trials reported no serious adverse events related to Vitamin D administration and five of them reported that significant adverse events did not occur at all [46–49,51]. One trial [50], not included in the primary analysis for mortality, did not specify whether adverse events were present. According to Vitamin D physiology, the supposed adverse events were mainly related to mineral metabolism (e.g., calcium and phosphate homeostasis).

Five trials [22,46,48,49,51] evaluated the serum total calcium level, two trials [22,48] the serum ionized calcium level, and four trials [22,46,48,51] the serum phosphate level in both groups: no significant differences were found between Vitamin D and placebo (total calcium: SMD = 0.00 [95% CI, -0.16, 0.16], $p = 0.99$, $I^2 = 51\%$; ionized calcium: SMD = -0.13 [95% CI, -0.30, 0.05], $p = 0.16$, $I^2 = 0\%$; phosphate: SMD = 0.06 [95% CI, -0.11, 0.22], $p = 0.49$, $I^2 = 73\%$; median follow-up = 7 days) (Supplementary Material 7).

The rate of hypercalcemic and hyperphosphatemic events where reported respectively in three [22,46,48] and two trials [22,46]. The intention-to-treat analysis of the cumulative event rate at longest follow-up available showed no significant difference between Vitamin D and placebo: RD = 0.01 [95%CI, -0.01, 0.03], $p = 0.40$, $I^2 = 0\%$ for hypercalcemia; RD = 0.00 [95% CI, -0.06, 0.07], $p = 0.89$, $I^2 = 0\%$ for hyperphosphatemia (Supplementary Material 7).

The serum level of 25-OH Vitamin D was evaluated in all the trials and was significantly higher in Vitamin D group versus placebo (SMD = 1.20 [95% CI, 1.04, 1.37], $p < 0.00001$, $I^2 = 79\%$, p for heterogeneity < 0.0001, median follow-up = 7-days). The results were confirmed when including only trials that administered enteral Vitamin D3 (5 trials, SMD = 1.32 [95% CI, 1.14, 1.49], $p < 0.00001$). Higher level was evidenced in all the trials excluding the one [46] where calcitriol, the activated form of 25-OH Vitamin D, was administered. The serum level of calcitriol was evaluated in three trials [22,46,48] with significant higher values in Vitamin D group versus placebo (SMD = 0.22 [95% CI, 0.04, 0.39], $p = 0.01$, $I^2 = 78\%$, p for heterogeneity = 0.01, median follow-up = 7-days) (Supplementary Material 7).

The overall quality of evidence for these outcomes was moderate.

DISCUSSION

The most important findings of our meta-analysis are that Vitamin D supplementation might reduce mortality in critically ill patients and that enteral administration is effective in increasing Vitamin D blood levels compared to placebo, without major adverse events. No statistically significant differences in length of ICU and hospital stay were found.

The underlying mechanisms by which critically ill patients may benefit from Vitamin D supplementation remain to be investigated. Vitamin D affects various biological processes [3,4]. The immunomodulatory effects of Vitamin D on adaptive and innate immune system were extensively investigated [52–55]. A potential role of Vitamin D supplementation in supporting immune-function and host defense in critically ill patients has been suggested also by small randomized human trials: Vitamin D supplementation increases serum levels of cathelicidin, a peptide with strong bactericidal properties [43,47], can increase the leukocyte mRNA expression of anti-inflammatory cytokines [46], and decreases production of inflammatory cytokines [47].

It is widely recognized that Vitamin D deficiency is common in critically ill patients and associated with increased mortality [5–7,10–12]. Previous publications demonstrated a significant decrease in vitamin D status during ICU stay [15,56] and low serum levels of Vitamin D within 24 hours of ICU admission identify patients at high risk for prolonged hospitalization and mortality [57]. Conversely, patients taking Vitamin D supplementation before ICU admission were found to have lower mortality compared with patients who did not take any supplements in a non-randomized study [11]. All these non-randomized findings suggest that Vitamin D supplementation could be beneficial in all critically ill patients, regardless of the pre-illness vitamin status. The largest RCT performed so far focused on the

correction of vitamin D deficiency in 475 critically ill patients through enteral administration of Vitamin D3 [22]. This trial had length of hospital stay as primary endpoint and was not powered enough to reach definitive conclusions on survival, even if Vitamin D was significantly associated with a 18% relative risk reduction of death in a subgroup of patients with severe vitamin D deficit (Vitamin D level ≤ 12 ng/ml) [22].

Notably, this is the first meta-analysis of RCTs that suggested a potential survival benefit of Vitamin D in critically ill patients, even if several reviews and trials suggested to investigate the tangible role of Vitamin D in this setting [5,7,11,22,57]. The potential beneficial effects of Vitamin D supplementation on survival in critically ill patients are in accordance with evidences coming from other settings, such as long-term treatment in the general population [23,58], cancer patients [24], and elderly people [25].

Vitamin D supplements are inexpensive, with few side effects reported in the general population [21,59,60]. Mild hypercalcemia has been reported to be the most common side effect in critically ill patients [21]. Conversely, our analysis found no difference in the rate of hypercalcemia or hyperphosphatemia and no significant differences in calcium and phosphate serum levels.

Enteral administration of Vitamin D was the preferred route of administration in the trials included in our systematic review. However, it must be underlined that an important proportion of these patients could present critical illness-induced malabsorption [61] or impaired gastric emptying [62]. Conversely, our findings indicated significant increase in Vitamin D levels as a result of enteral supplementation, suggesting the effectiveness of enteral administration in this population. Low-dose intravenous Vitamin D3 did not normalize vitamin D status in critically ill patients [41] and there is currently no commercially available high-dose intravenous form, although high-dose intramuscular form may be an option in

selected patients (e.g., not anticoagulated patients) [45,50]. On the other hand, intravenous calcitriol, the activated form of Vitamin D3 employed in some patients with late-stage chronic kidney disease, could be an option in patients with enteral system disorders but the safety profile of this form should be systematically evaluated in critically ill patients, even if a small RCT did not reported any adverse events in severe sepsis patients [46].

A major strength of this systematic review is that we assessed mortality, the most important clinical outcome. All the randomized trials included in the primary analysis were placebo-controlled, with low risk of bias, generally small in size, but showed statistical heterogeneity as low as 0%. We recognize the difference in length of follow-up and differences in baseline population characteristics between trials as a limitation, even though all trials included in the mortality analysis showed an overall mortality rate ≥ 19% at the 1-month follow-up.

A major limitation of our study is that a single trial [22] included almost twice the total number of subjects in all the other trials combined and therefore the weight in the pooled analysis is high. Nevertheless, as meta-analyses should be considered hypothesis-generating rather than confirming, results of our study provides an interesting spark for future investigation on interventions aimed at reducing mortality in critically ill patients. There is now compelling need for a large, multi-center, adequately powered RCT to provide definitive evidence on the effect of Vitamin D on survival and to explore the fact of whether the whole critically ill population or only Vitamin D -deficient patients could benefit from supplementation.

CONCLUSIONS

Current randomized evidence suggests that the administration of Vitamin D could reduce mortality in critically ill patients. Considering the absence of major side effects, the effectiveness in increasing Vitamin D blood levels, and the possible effect on survival, Vitamin D supplementation is a very attractive intervention for future investigations aimed at reducing mortality in critically ill patients. A multi-center randomized placebo-controlled trial adequately powered for mortality should finally elucidate if Vitamin D could improve survival in these patients.

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FIGURE LEGENDS

Figure 1: Flow diagram for the selection of studies.

Figure 2: Impact of Vitamin D administration on mortality in critically ill patients.

Figure 3: Impact of Vitamin D administration on length of hospital stay, length of intensive care unit stay, and length of mechanical ventilation.

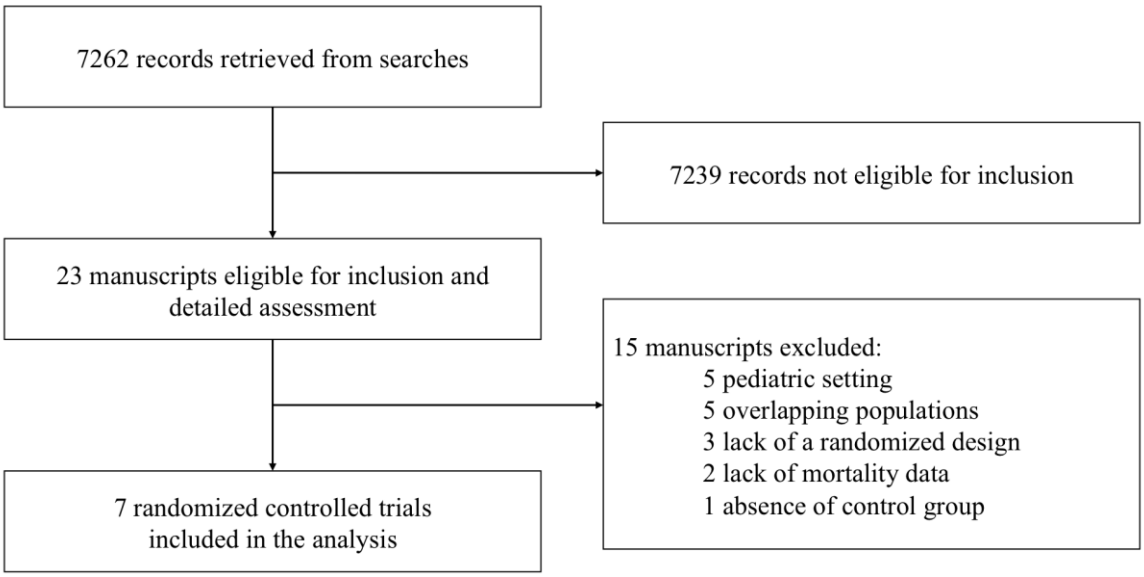

Fig. 1

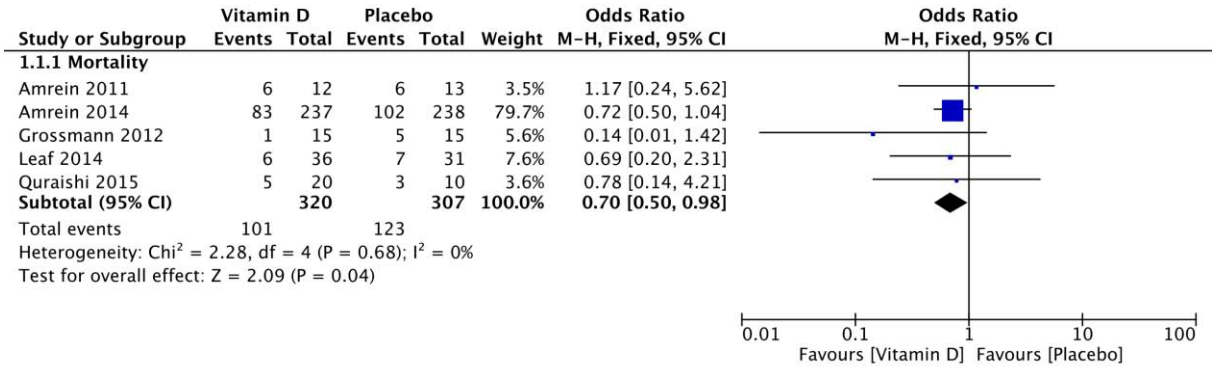

Fig. 2

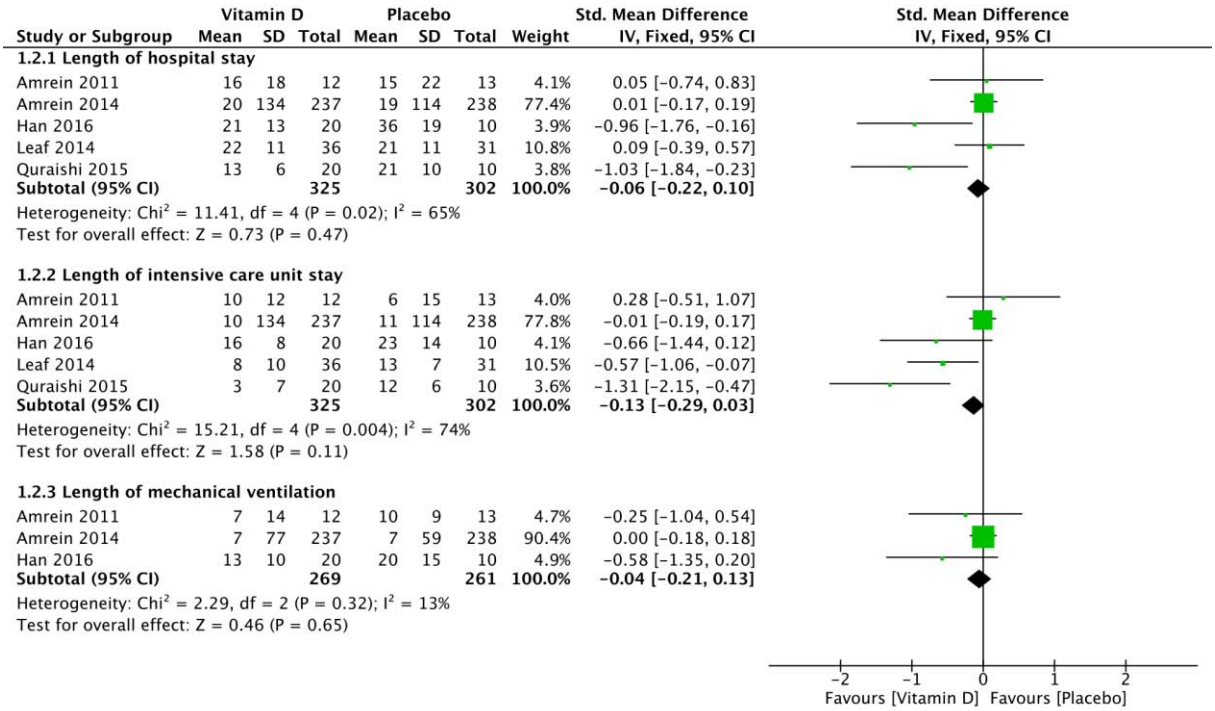

Fig. 3

TABLE

Table 1 – Characteristics of the randomized placebo-controlled trials included in the systematic review.

Trial	City, Country	Number of centers	Setting	Sample size (n)	Overall mortality (n, %)	Vitamin D dose and formulation	Adverse events	Longest follow-up for mortality
Alizadeh 2016	Tehran, Iran	Single-center	Surgical ICU patients	59	3 (5%)	Single intramuscular dose of Vitamin D3 600,000 IU	Not reported	7-days
Amrein 2011	Graz, Austria	Single-center	Multidisciplinary ICU patients	25	12 (48%)	Single enteral dose of Vitamin D3 540,000 IU	None	In-hospital
Amrein 2014	Graz, Austria	Single-center	Multidisciplinary ICU patients	475	185 (39%)	Single enteral dose of Vitamin D3 540,000 IU and monthly maintenance dose of 90,000 IU	No serious adverse events. At 6 months follow-up, 4 of 37 patients	6-months

						for 5 months	(11%) of the patients in the vitamin D group had total serum calcium levels > 10.6 mg/dL, versus 1 of 43 patients (2%) in the placebo group.	
Grossman n 2012	Atlanta, USA	Single-center	Acute pulmonary exacerbation in cystic fibrosis patients	30	6 (20%)	Single enteral dose of Vitamin D3 250,000 IU	None	3-months
Han 2016	Atlanta, USA	Two-centers	Ventilated ICU patients	30	7 (23%)	Different Vitamin D3 enteral doses	None	84-days

						divided over 5 consecutive days (250,000 IU or 500,000 IU)		
Leaf 2014	Boston, USA	Two-centers	Severe sepsis and septic shock ICU patients	67	13 (19%)	Single intravenous dose of Calcitriol 2 mcg	None	28-days
Quraishi 2015	Boston, USA	Single-center	Severe sepsis and septic shock ICU patients	30	8 (27%)	Single enteral dose of Vitamin D3 200,000 IU or 400,000 IU	None	30-days

ICU, intensive care unit.