

## Effects of vitamin D supplementation on mortality in critically ill patients: a systematic review and meta-analysis

### Efeitos da suplementação de vitamina D em pacientes críticos: revisão sistemática e metanálise

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#### Abstract

**Objective:** this study aimed to use a meta-analysis to evaluate whether vitamin D supplementation can improve critically ill patients' parameters. **Methodology:** a systematic literature review and meta-analysis were performed using the electronic databases PubMed, Cochrane, Medline, and Scielo. The selected studies are randomized controlled trials (RCTs) that evaluate the effect of vitamin D supplementation in critically ill patients over 18 years of age and are available in full. All the articles involved randomized clinical trials that analyzed vitamin supplementation's effects on mortality, ICU stay, hospital stay, and use of mechanical ventilation. **Results:** the meta-analysis revealed that vitamin D supplementation in critically ill patients could reduce mortality in 28-30 days [RR =0.76 (95%CI: 0.57-1.00, p=0.05)] (p=0.85), hospital mortality (p=0.14), length of ICU stay (p=0.11), length of hospital stays (p=0.08) and time of mechanical ventilation (p=0.32). **Conclusion:** based on previous randomized controlled trials, this meta-analysis demonstrates that critically ill adult patients received at least one dose of vitamin D 150.000 IU by of the routes (enteral or parenteral) to reduce mortality in 28-30 days. Future studies involving a more significant number of participants are desirable. This factor becomes essential to evaluate supplementation with high and low doses of vitamin D.

**Keywords:** Vitamin D; Intensive Care Unit; critical care; sepsis.

#### Resumo

**Introdução:** baixos níveis de vitamina D estão associados com fatores prognósticos na unidade de terapia intensiva. A suplementação de vitamina D poderia melhorar o prognóstico de pacientes criticamente doentes. **Metodologia:** uma revisão sistemática da literatura foi realizada usando os seguintes bancos de dados eletrônicos: PubMed, Cochrane, Medline, usando as seguintes palavras-chave: vitamin D, intensive care unit, critical care, sepsis, critical ill. **Resultados:** a suplementação de vitamina D em pacientes críticos pode reduzir a mortalidade em 28-30 dias. (RR 0,76 (IC 95%: 0,57-1,00, p = 0,05). Não houve diferença significativa entre os grupos em relação à mortalidade entre 84 e 90 dias (RR 1,09 (IC 95%: 0,45-2,62, p = 0,85 ), mortalidade hospitalar (RR = 0,84 (IC 95%: 0,66-1,06, p = 0,14), duração da internação na UTI (RR -1,44 (IC 95%: -3,19-0,31, p = 0,11), duração da internação ( RR -6,46 (IC 95%: -13,72-0,80, p = 0,08) e tempo de ventilação mecânica (RR -0,91 (IC 95%: -70,70-0,88, p = 0,32). **Conclusão:** esta metanálise baseada em estudos randomizados controlados anteriores, demonstra que pacientes adultos gravemente doentes receberam pelo menos uma dose de vitamina D de 150.000 UI, por uma das vias (enteral ou parenteral) para reduzir a mortalidade em 28-30 dias. Estudos futuros envolvendo um número mais significativo de participantes são desejáveis. De fato, esse fator se torna essencial para avaliar a suplementação com doses altas e baixas de vitamina D.

**Palavras-chave:** Vitamina D; Unidade de Terapia Intensiva; cuidados críticos; sepse.

#### INTRODUCTION

Vitamin D has a traditionally known role in regulating calcium and phosphorus metabolism and preventing and treating diseases such as osteoporosis, rickets, and osteocalcin<sup>1,2</sup>. More recently, many other conditions have been described as being associated with low vitamin D levels, such as systemic arterial hypertension (SH), acute

myocardial infarction (AMI), asthma, and autoimmune diseases, such as lupus, rheumatoid arthritis, and multiple sclerosis, and even with the risk for infections<sup>3</sup>. Currently, vitamin D has also been implicated in the scenario of critically ill patients<sup>4,5</sup>.

In this sense, several studies have already demonstrated the association between hypovitaminosis D and prognostic factors in critically ill patients<sup>6-8</sup>. There is a high prevalence of vitamin D deficiency in the critically ill population, with high mortality rates for patients with a vitamin D level <12 ng/mL (versus vitamin D levels ≥12 ng/mL) (32.2% vs. 13.2%, with an adjusted relative risk of 2.2

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(95% CI: 1.07-4.54,  $P < 0.05$ )<sup>9</sup>. This is appropriate as several studies in intensive care units have shown an association between vitamin D deficiency (serum levels lower than 20 ng/mL) and an increased length of hospital stay and increased sepsis and mortality<sup>5,10,11</sup>.

Clinical trials performed in intensive care units (ICUs) have shown that vitamin D supplementation changes important clinical outcomes, such as mortality, organ dysfunction, sepsis, ICU stay, hospital stay, and mechanical ventilation<sup>4,10-14</sup>.

Three meta-analyses on this topic were published recently, presenting contradictory results<sup>12-14</sup>. The authors argued that a limited number of participants in individual studies might be responsible for these findings.

Among the limitations highlighted in the meta-analyses already performed, in the study by Weng et al.<sup>14</sup> (2017), which was a letter to the editor with four studies included, Langlois et al.<sup>13</sup> (2018) did not specify the type of vitamin D used. Putzu et al.<sup>12</sup> (2017) included a study that did not have a critically ill patient and a study that presented only biochemical results, did not specify the types of mortality, and only emphasized mortality in general. These three meta-analyses also did not include the study by Ding et al. (2017)<sup>15</sup>.

Given these different studies with controversial outcomes, considering the relevance of the topic, which requires more discussions, it was shown that there is a need to broaden the search to include different studies that better elucidate understanding and guide decision-making that will have an impact on the clinical picture of the critically ill patient.

This study aimed to systematically review the literature and perform meta-analyses of the RCTs that evaluated vitamin D supplementation in critically ill patients.

## METHODOLOGY

A systematic review of the literature and meta-analysis of randomized clinical trials was performed on the mentioned studies in Figure 1 and described in Tables 1 and 2.

The selected studies are randomized controlled trials (RCTs) that evaluate the effect of vitamin D supplementation in critically ill patients over 18 years of age and are available in full. The eligible studies followed the PICOS criteria, as indicated by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)<sup>16,17</sup>. All of the articles involved randomized clinical trials that analyzed vitamin supplementation's effects on mortality, ICU stay, hospital stay, and use of mechanical ventilation.

The articles were analyzed according to each item's available data as described in the meta-analysis charts. Uniformity cannot be maintained in the analyses due to the data provided in some articles corresponding to zero. The articles by Qurishi et al. and Han et al. were subdivided into the graphs analyzed according to the dose used, justifying the number of articles analyzed as variable.

Any other type of study and those not meeting the qualitative evaluation criteria were excluded from this review.

We searched the electronic databases at the following sites for randomized clinical trials: Scielo (<http://www.scielo.br>), PubMed/Medline ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)), and Cochrane/Bireme (<http://cochrane.bireme.br/portal/php/index.php>). The period established for the searches of the publications was between January 2000 and July 2017.

From 2018 to 2022, meta-analyses were found, and their findings were added to the discussion for comparison with the studied findings.

We used the keywords or Medical Subject Headings Terms (Mesh terms) in the referred sites: PubMed/Medline and Cochrane/Bireme: vitamin D, intensive care unit, critical care, sepsis, critically ill or using the Boolean connective and in different highlighted combinations as follows: vitamin D and intensive care unit, vitamin D and critical care, vitamin D and sepsis, vitamin D and critically ill.

The selected articles' references were also evaluated to identify other studies not visualized in the initial search.

The evaluation of the eligibility criteria and assessment of the studies' quality occurred through individual searches of two researchers (NBSL and JFC) and a later revision for consensus on selecting articles to be included in the study.

The articles' information was categorized in a matrix of measurements of the data, which included the items: the authorship, the number, the rule, the publication in which it was published, the number of patients, and summarization measures.

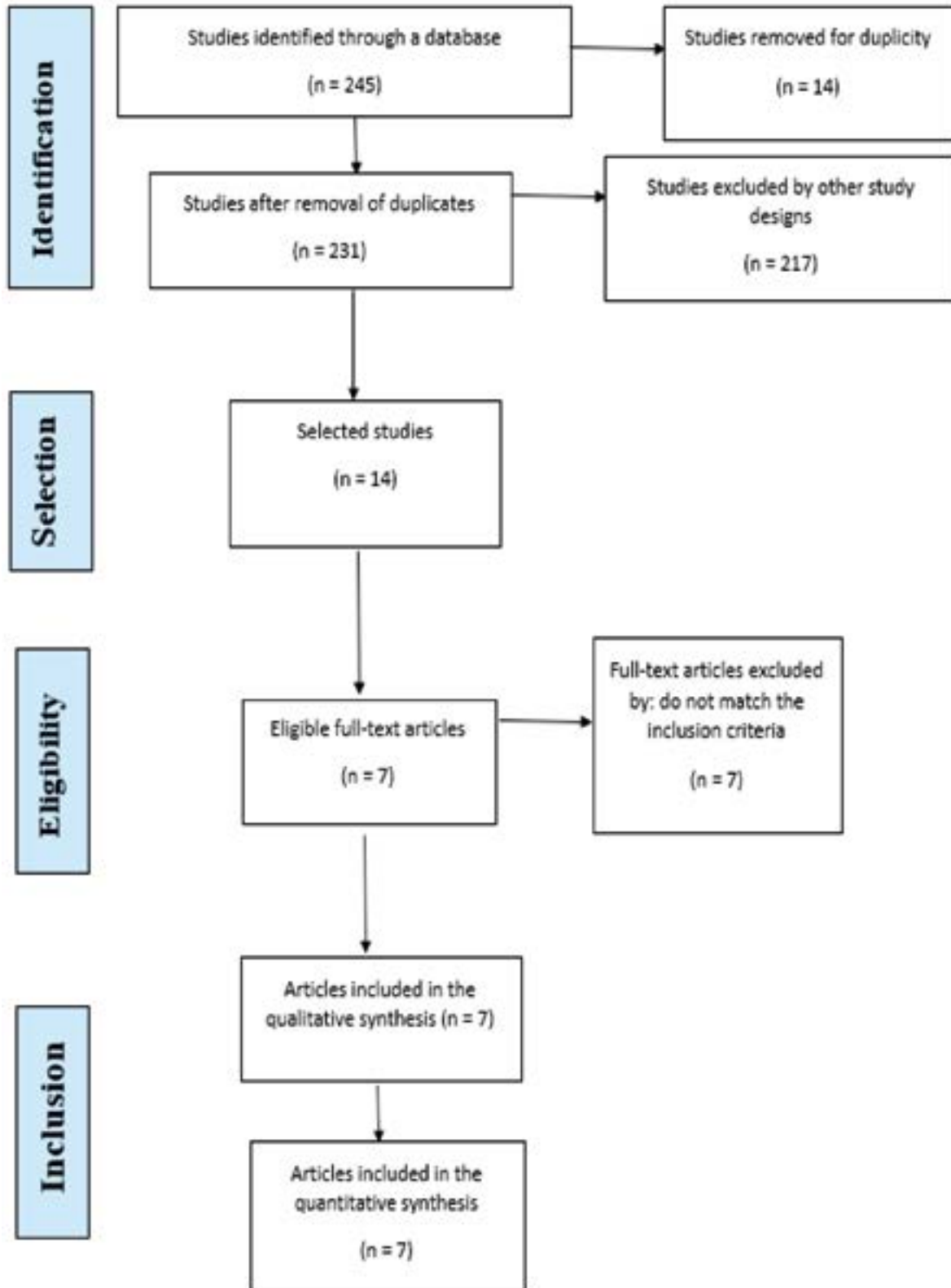
The selected article's qualitative evaluation was performed using the Jadad and Downs & Black scales<sup>18,19</sup>.

The relative risk was used to measure the effect of the meta-analyses on mortality. In contrast, for the meta-analyses of the hospitalization times and mechanical ventilation, the non-standardized mean difference was used to measure the effect since the unit of measurement for these was the same for the different studies. A  $P$  value of  $\leq$

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The  $I^2$ ,  $\tau^2$  and  $Q$  of Cochran statistics were calculated. Values of the  $I^2$  between 25% and 50% were considered indicators of moderate inconsistency between studies, and values above 50% indicated significant discrepancies between them<sup>21</sup>. Fixed-effect models were used when the  $I^2$  statistic was less than 25%, and random-effect models were used when the  $I^2$  was more significant than or equal to 25%. The weights of the studies' contributions to the summary measures were estimated using the inverse of the variance<sup>22</sup>.

Figure 1 - Flowchart of the methodology adopted for the selection of the articles included in the review.



Source: Source: self-authored  
self-authored

The publication bias analysis was performed by visually examining the funnel plot. For the publication bias, a sensitivity analysis was performed by the withdrawal and reintroduction of variables and observing their influence on the effect measures.

## RESULTS

### Systematic review

Regarding the quality of the studies included in the present meta-analysis, all of them<sup>5,10,11,15,23-25</sup> had a Jadad scale score greater than three and a Downs & Black scale score greater than 75%, demonstrating a high quality of the studies (Table 1).

In the present study, seven studies<sup>5,10,11,15,23-25</sup> published from 2011 to 2017 were included and evaluated 752 patients. Most of the participants were male ( $n = 472$ , 62.8%), and the ages of the participants ranged from 54 years to 68.9 years (Table 1).

Of the seven studies surveyed, six were prospective, randomized, and double-blind<sup>5,10,11,15,24,25</sup>, and one was an open study<sup>23</sup>. There were five unicentric studies<sup>5,11,18,23,25</sup> and two multicentric studies (Table 1)<sup>10,24</sup>.

Four of the studies included patients with sepsis or SIRS (18.26 to 28), and the three other studies evaluated

the patients with a dose of 25 (OH) D <20 ng/mL remaining greater than or equal to 48 h in the ICU<sup>5,10,11</sup>. The doses of vitamin D ranged from 540.00 IU to 150.000 IU, and the route of administration was orally or by a nasogastric tube in four of the studies<sup>5,10,11,25</sup>. One study had an intravenous route of administration<sup>24</sup>, and the other two used an intramuscular administration route (Table 1)<sup>15,23</sup>.

Regarding the vitamin D3 type, six studies used cholecalciferol 5,10,11,15,23,25 and one used calcitriol (2 mcg)<sup>24</sup>. Five of the studies administered a single dose of vitamin D; with the other two, one administered a total of 500,000 IU divided over five consecutive days. Another study performed an attack dose of 540,000 IU followed by 28 days of a monthly replacement regimen using 90,000 IU for another five doses (Table 1)<sup>5</sup>.

All studies produced elevated vitamin D levels compared to the baseline levels after the supplementation. Adverse events were identified in two studies, and the hypercalcemia observed in the first study was not clinically significant (4 patients out of 752 patients, 0.53%)<sup>5,23</sup>. From this total of four patients, one had previous hyperparathyroidism<sup>5</sup>, and the other three had mild hypercalcemia with no change in the total calcium and without any clinical repercussions (Table 1)<sup>23</sup>.

**Table 1 - List the studies included in this meta-analysis on vitamin D use.**

Author year	N, gender	First Name	Age years	Kind of study	Inclusion	Intervention, route of administration	Change of 25OHD	Adverse effects	Classification of Jadad and Downs Black
Amrein et al., 2011	25 (19 men)	Graz, Austria	62 ± 16	Prospective randomized double-blind placebo controlled uniconcentric	25OHD <20 ng/mL and> 48 h ICU	-540,000 IU cholecalciferol (n = 12) -Placebo (n = 13) -VO or VSNG -Single dose	Day 0: 13.1 ng/mL Day 7: 38.2 ng/mL, p <0.005	N = 0	Jadad: 4 DB: 24
Amrein et al., 2014	492 (309 men)	Graz, Austria	64.6 ± 14.7	Prospective randomized double-blind placebo-controlled uniconcentric	25OHD <20 ng/mL above 18 years of age and> 48 h ICU	-540,000 IU cholecalciferol G dose attack and after 28 days 90,000 IU / month for 5 months (n = 237) -Placebo (n = 238) -VO or VSNG	Day 0: 13.0 ± 4.1 ng/mL Day 7: 35.5 ± 18.7 ng/mL, p <0.001	N = 1 (0.04%) (Hypercalcemia in a patient with previous hyperparathyroidism)	Jadad: 5 DB: 27
Leaf et al., 2014	67 (37 men)	Boston, United States	Vitamin D: 68 (54-70) Placebo: 58 (49-69)	Prospective randomized double-blind placebo controlled multicentre (n = 2)	-Age > 18 years, severe sepsis or septic shock, central or arterial catheter	-2 mcg single dose calcitriol -Placebo (n = 238) -Endovenous -Single-dose	Weather 0: ND 6 h after: 75.7 (52.1-115.5) ng/mL	AT	Jadad: 5 DB: 25
Quraishi et al., 2015	30 (18 men)	Boston, United States	64 (IQR 58-68)	Prospective randomized double-blind uniconcentric	-Age ≥18 years, sepsis (<24 h)	-200,000 IU cholecalciferol (n = 10) -Group 1 -400,000IU Colecalciferol (n = 10) - Group 2 -Placebo (n = 10) -VO or VSNG -Single-dose	-Group 1: 45 (40-70) % -Group 2: 69 (55-106) % -Placebo: 3 (-3-8) %	N = 0	Jadad: 3 DB: 23
Nair et al., 2015	50 (36 men)	Sydney, Australia	54 ± 17.7	Prospective randomized uniconcentric open	-3/4 Criteria for SIRS within 24 h of admission, remaining ICU ≥48 h	-300,000 IU cholecalciferol (n = 25) -150,000IU Colecalciferol (n = 25) -Intramuscular -Single-dose	Elevation of 23.3 (95% CI: 11.5-35.1) nmol/L on day 14 in both groups	N = 3 mild ionic hypercalcemia N = 0 total hypercalcemia 0 IM injection complications	Jadad: 3 DB: 23
Han et al., 2016	31 (20 men)	Atlanta, United States	-250,000 IU: 56.4 ± 15.4 -500,000: 68.9 ± 18.6 -Placebo: 64.8 ± 17.5	Prospective randomized double-blind placebo controlled multicentre (n = 2)	-Age ≥ 18 years, mechanical ventilation ≥ 72 h, expected survival ≥ 96 h	-250,000 IU cholecalciferol (n = 9) -500,000 IU cholecalciferol (n = 11) -Placebo (n = 10) -VO or VSNG -Divided into 5 consecutive days	-250,000 IU: 23.2 ± 7.8 → 45 ± 20 ng/mL -500,000IU: 20 ± 7.3 → 55 ± ng/mL -Place: 21.5 ± 12.2 → ND	N = 0	Jadad: 5 DB: 25
Ding et al., 2017	57 (33 men)	Liaoning, China	57.40 ± 15.25	Prospective randomized double-blind placebo-controlled uniconcentric	-SIRS Sepsis -> 48 h	300,000 IU Colecalciferol (n = 29) -Placebo (n = 28) -Intramuscular Route -Single dose	ND	AT	Jadad: 4 DB: 22

Source: Research data.

DB: Downs-Black scale; h: time; IM: intramuscular; ND: not described; NA: not evaluated; SIRS: systemic inflammatory response syndrome; VO: oral; VSNG: via nasogastric tube; ICU: intensive care unit; 25OHD: 25-hydroxy-vitamin D.

**Table 2 - Outcomes analyzed from studies evaluating vitamin D supplementation in critically ill patients.**

Author/year	Mortality at 84 or 90 days, n (%)			Mortality 28-30 days, n (%)			Hospital mortality, n (%)			Mortality at 84 or 90 days, n (%)			Length of ICU stay, days			Length of hospital stay, days			Time of mechanical ventilation, days		
	Grupo I	Grupo C	P/HR	Grupo I	Grupo C	P/HR	Grupo I	Grupo C	P/HR	Grupo I	Grupo C	P	Grupo I	Grupo C	P	Grupo I	Grupo C	P	Grupo I	Grupo C	P
Amrein et al., 2011	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	13,4 ± 11,7	14 ± 16,3	0,54	23,7 ± 24,7	23,2 ± 21,2	0,97	10,57 ± 7,96	13,49 ± 14,23	0,88
Amrein et al., 2014	54 (22,8%)	63 (26,5%)	0,97 (0,67-1,39) P = 0,86	67 (28,3)	84 (35,3)	0,81 (0,58-1,11) P = 0,18	52 (21,9)	68 (28,6)	0,76 (0,53-1,09) P = 0,14	N/D	N/D	N/D	15,7 ± 20,9	17,3 ± 22,3	0,38	26,7 ± 25,3	26,7 ± 24,3	0,98	11,58 ± 14,03	13,3 ± 17,23	0,62
Leaf et al., 2014	7 (19%)	6 (19%)	1,00	8 (22)	7 (23)	1,00	6 (17)	7 (23)	0,56	N/D	N/D	N/D	13,3 ± 14,7	11,2 ± 9,1	0,83	25,9 ± 18,9	22,2 ± 19	0,89	8,30 ± 11	7,27 ± 7,08	0,33
Qurashi et al., 2015	N/D	N/D	N/D	N/D	200mU: 3 (30%) 400mU: 2 (20%)	N/D	200mU: 3 (30%) 400mU: 2 (20%)	3 (30%)	0,18	N/D	N/D	N/D	200mU: 8 ± 8	10 ± 5	0,83	200mU: 9 ± 8	37 ± 30	0,03	N/D	N/D	N/D
Nair et al., 2015	4 (16%)	5 (20%)	0,62	5 (20%)	5 (20%)	0,92	N/D	N/D	N/D	N/D	5 (20%)	0,72	14,5 ± 16,7	18,2 ± 8,91	0,98	45,5 ± 12	40,5 ± 44,5	0,83	N/D	N/D	N/D
Han et al., 2016	N/D	N/D	N/D	250mU: 0 500mU: 1 (10%)	1 (10%)	0,76	N/D	N/D	N/D	N/D	250mU: 1 (11%) 500mU: 4 (36%)	0,33	250mU: 15 ± 10 500mU: 17 ± 14	23 ± 14	0,30	250mU: 25 ± 14 500mU: 18 ± 11	36 ± 19	0,03	250mU: 12 ± 10 500mU: 14 ± 10	20 ± 15	0,29
Ding et al., 2017	N/D	N/D	N/D	N/D	10,34%	N/D	10,34%	17,86%	0,414	N/D	N/D	N/D	5,48 ± 4,08	6,68 ± 4,87	0,318	N/D	N/D	N/D	69,45 ± 87,51	77,64 ± 76,04	0,515

Source: Research data.

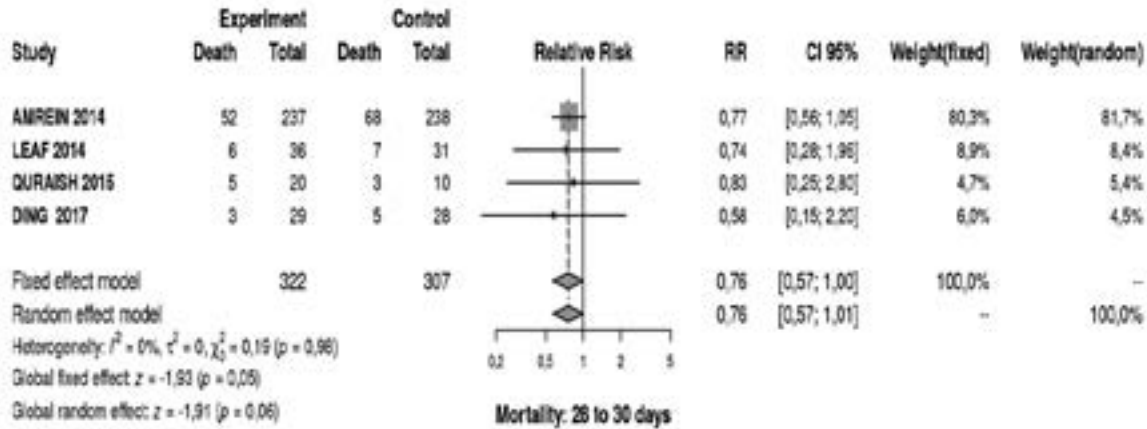
NA: not evaluated; Group C: Control group; Group I: intervention group; P (value), HR: hazard ratio. In Nair et al., the Intervention group is equivalent to 300,000 IU of vitamin D and the control group is equivalent to 150,000 IU; mU: one thousand units of vitamin D supplementation.

Meta-analysis

Figure 2 demonstrates the meta-analysis of the mortality in the 28-30 days variable, which included four studies<sup>5,15,24,25</sup>. The relative risk was 0.76 (95% CI: 0.57-

1.00,  $p = 0.05$ ), and in this case, there was a significant 24% reduction in mortality in 28-30 days in the vitamin D group. Regarding the studies' heterogeneity, the analysis revealed that it was absent ( $I^2 = 0\%$ ,  $p = 0.98$ ).

Figure 2 – Forest plot and meta-analyses on mortality in 28-30 days.

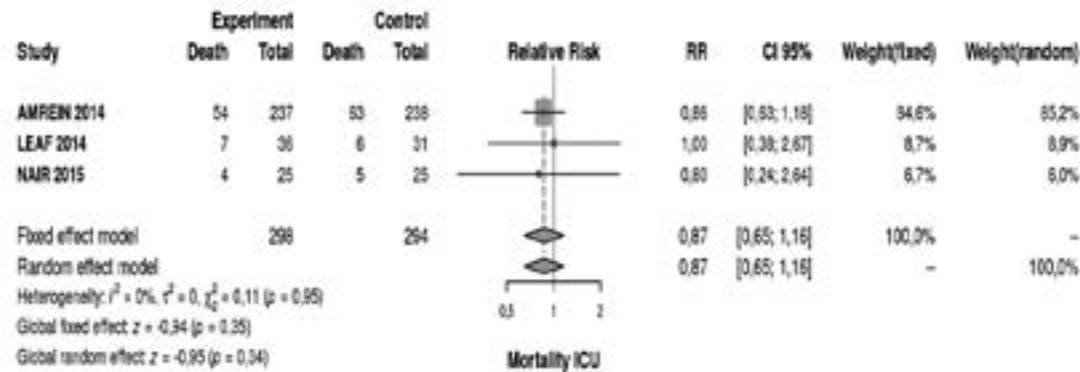


Source: self-authored

The analysis of the ICU mortality (Figure 3) included three studies<sup>5,23,24</sup>. The relative risk was 0.87 (95% CI: 0.65-

1.16,  $p = 0.35$ ) and therefore did not reach statistical significance. There was no heterogeneity ( $I^2 = 0\%$ ,  $p = 0.95$ ).

Figure 3 – Forest plot and meta-analyses on ICU mortality.

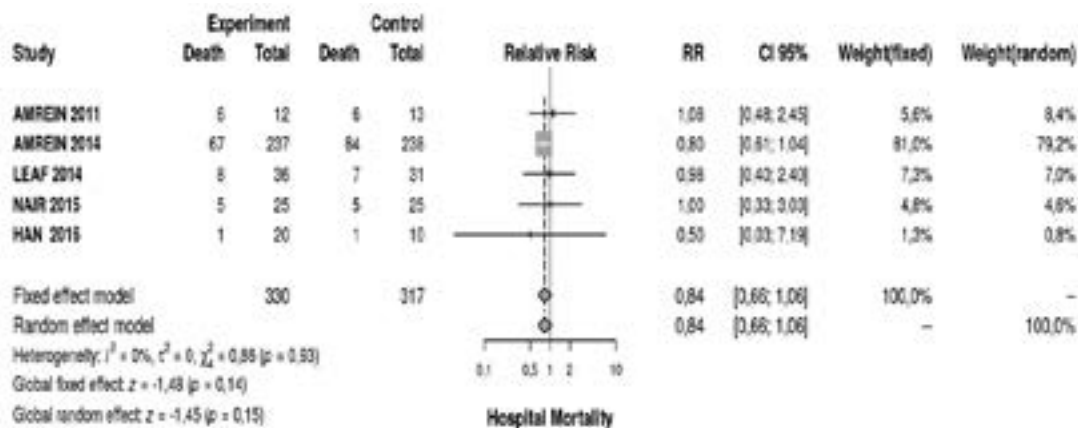


Source: self-authored

The analysis of hospital mortality (Figure 4) included five studies<sup>5,10,11,23,24</sup>, presenting a relative risk of 0.84

(95% CI: 0.66-1.06,  $p = 0.14$ ) and no heterogeneity ( $I^2 = 0\%$ ,  $p = 0.93$ ).

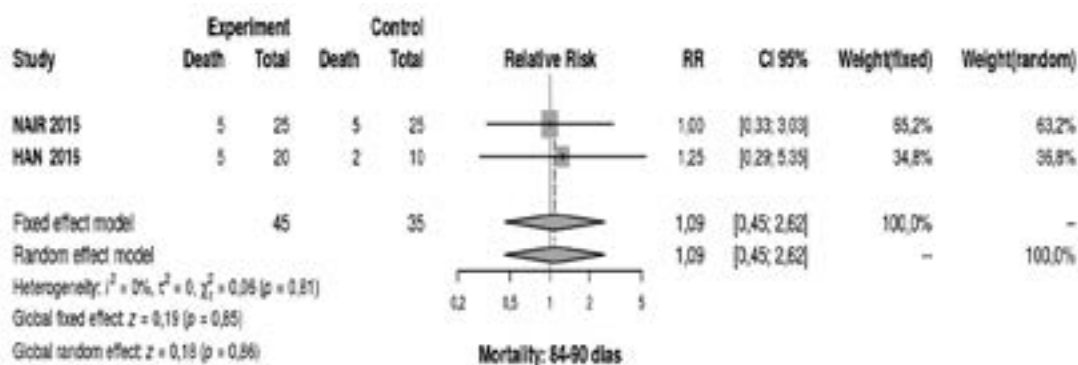
Figure 4 – Forest plot and meta-analyses on hospital mortality



Source: self-authored

Regarding the mortality in 84-90 days (Figure 5), which included two studies<sup>10,23</sup>, the relative risk was 1.09 (95% CI: 0.45-2.62,  $p = 0.85$ ), with no heterogeneity in the studies ( $I^2 = 0\%$ ,  $p = 0.81$ ).

Figure 5 – Forest plot and meta-analyses on mortality in 84-90 days.

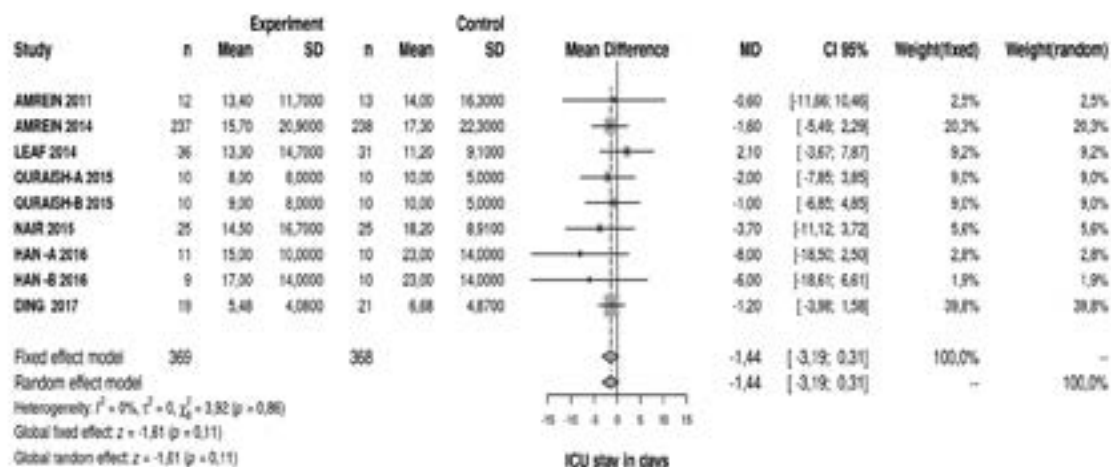


Source: self-authored

Observing Figure 6, which evaluated the variable of the time of hospitalization in the ICU, which included seven studies<sup>5,10,11,15,23-25</sup>, the difference in the mean number of days in the ICU stay was -1.44 days (95% CI: -3.19-0.31,  $p = 0.11$ ), which did not reach statistical significance and did not have heterogeneity in the studies ( $I^2 = 0\%$ ,  $p = 0.86$ ). The variable of the length of hospital stay was analysed in six of the studies<sup>5,10,11,23-25</sup>, and the mean difference in the number of days of the ICU stay was -6.46 days (95% CI: -13.72-0.80,  $p = 0.08$ ) and was similar among the two groups that received and did not receive vitamin D.



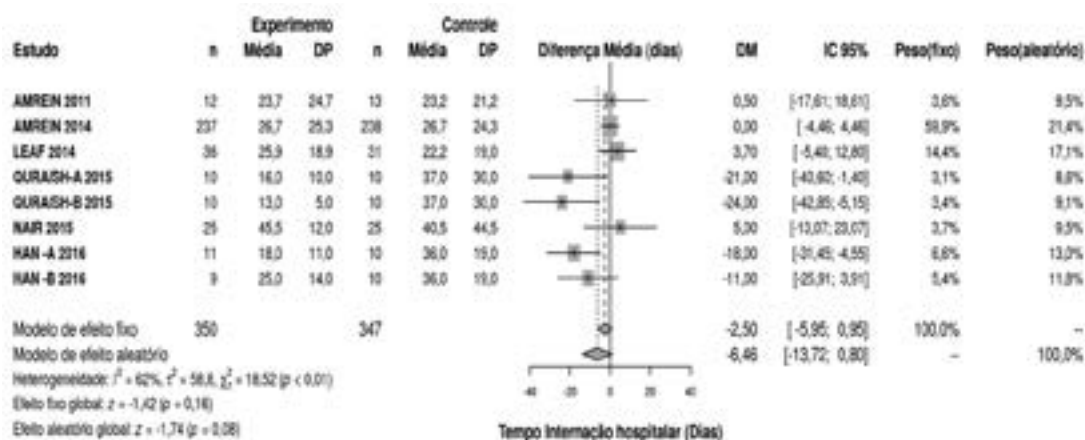
Figure 6 – Forest plot and meta-analyses on the length of ICU stay (in days).



Source: self-authored

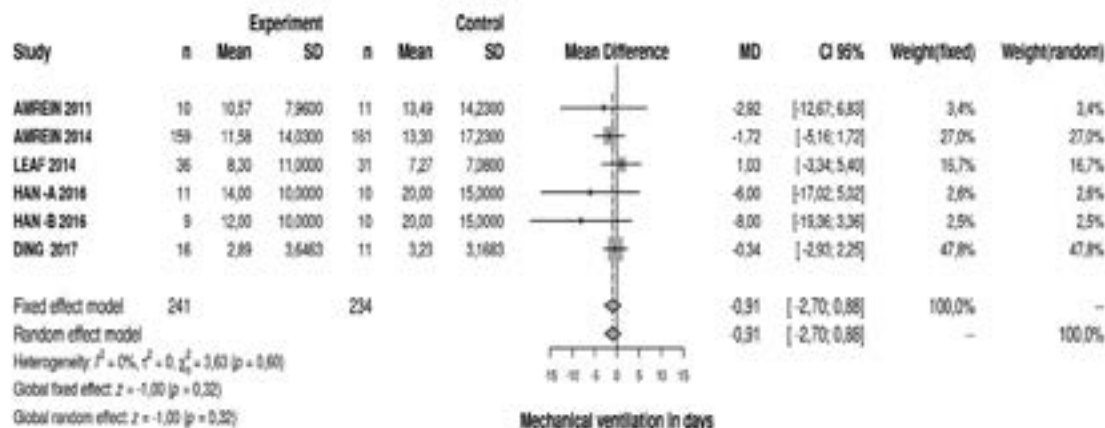
Although, the heterogeneity analysis of the studies revealed that they were not homogeneous ( $I^2 = 62\%$ ,  $p < 0.01$ ) (Figure 7).

Figure 7 – Forest plot and meta-analyses on the length of hospital stay (in days).



Source: self-authored

Lastly, concerning the time on mechanical ventilation, this variable waers <sup>5,10,11,15,24</sup>, and the groups did not differ significantly. The RR was -0.91 (95%: 2.70-0.88,  $p = 0.32$ ), and they did not present heterogeneity ( $I^2 = 0\%$ ,  $p = 0.60$ ) (Figure 8).

**Figure 8** – Forest plot and meta-analyses D on the mechanical ventilation time (in days).

Source: self-authored

## DISCUSSION

The present systematic literature review and meta-analysis revealed that critically ill patients' vitamin D supplementation could reduce mortality by 28-30 days.

This study's advantages are the inclusion of high-quality studies, all of which obtained a score of at least three on the Jadad scale and a score of over 75% on the Downs-Black scale, which assesses the quality of studies<sup>18,19</sup>. Along the same line, many of the studies were prospective, randomized, and double-blind, confirming the excellent scientific level of the studies analyzed. A real benefit is performing a statistical analysis using the meta-analysis method. In fact, in several international classifications of study quality, meta-analysis is always the best study design and is used as a clinical management parameter<sup>17</sup>. The primary justification for this article was the controversial results of previous meta-analyses.

The correlation between vitamin D and critically ill patients has been increasingly studied due to the essential immunomodulatory role of vitamin D, which regulates the innate and adaptive immune responses, acts in the suppression of inflammatory cytokines, especially in that of IL-6, and exerts fundamental activity in response to clinical treatment instituted through its supplementation in these patients<sup>2</sup>. Vitamin D's role in regulating the innate and adaptive immune systems has been recognized for some time. The mechanisms responsible include the direct expression of antimicrobial peptides that stimulate the production of suppressor T cells and suppress pro-inflammatory T cells. Vitamin D deficiency of <50 nmol/L represents a severe risk factor for infection, sepsis, and mortality in critically ill patients, as it increases susceptibility to severe infections and mortality<sup>26-29</sup>.

Regarding the serum vitamin D levels in critically ill patients, a meta-analysis published in 2014 that included 9,715 critically ill patients and different concentrations of 25-hydroxyvitamin D3 suggested that vitamin D deficiency

increases the susceptibility of critically ill patients to severe infections and mortality<sup>8</sup>.

Regarding vitamin D supplementation in critically ill patients, three meta-analyses are published in the literature on the topic. The first online study was published in October 2016 as a letter to the editor and included four randomized controlled trials and 602 patients. In this study, the authors did not observe significant differences concerning hospital mortality in the ICU at 30 days, at 84 days, and after six months. However, a shorter hospitalization time was found<sup>4</sup>.

The second meta-analysis, published in April 2017, included seven studies published between 2011 and 2016 and 716 patients. One of these studies did not address critically ill patients. It was found that in critically ill patients, vitamin D administration may be associated with significantly lower mortality compared to placebo and without significant adverse events<sup>12</sup>. In this study, the authors did not evaluate the different types of mortalities (hospital and ICU in 28-30 days and six months); they just evaluated mortality, and there were no descriptions of the methodology for which the parameters were used<sup>12</sup>.

The most recent meta-analysis published in May 2017 inserted six randomized clinical trials published between 2000 and 2016 that included 695 critically ill patients to compare vitamin D administration to placebo. It showed no reduction in mortality, the length of stay in the ICU and hospital, and no reduction in mechanical ventilation, justifying that the insufficient number of clinical trials<sup>13</sup> can explain the statistical inaccuracy. One limitation of this study was that the authors did not describe the type of vitamin D they evaluated (cholecalciferol or calcitriol). Furthermore, none of these previous meta-analyses was included in the study by Ding et al.<sup>15</sup> (2017).

In the meta-analysis of the present study, unlike the other meta-analyses above, a Chinese double-blind ECR study published in the year 2017 was included, which had a sample size of fifty-seven patients with sepsis who

were admitted to the ICU and observed the relationship between vitamin D3 and severity, as well as its relationship with the prognosis of the patients with sepsis, as an objective. In this study, vitamin D supplementation did not change mechanical ventilation parameters, ICU stays, and mortality in 28 days compared to the placebo group<sup>15</sup>.

Regarding the adverse effects, only 4/752 (0.53%) of the patients included in the current meta-analysis presented mild hypercalcemia without clinical repercussions. Notably, three of them had ionic hypercalcemia with no repercussions in the total calcium, and the only patient presented with total calcium elevation also presented with primary hyperparathyroidism. These findings powerfully demonstrate the safety of vitamin D use even at high doses (all received a dose above 150,000 IU) in critically ill patients<sup>30</sup>.

Several RCR analyze the impacts of vitamin D supplementation on critical illness in ICU patients. Deficiency of this vitamin has been pointed out as one of the main risks for developing pulmonary diseases. In many cases, administering high doses is effective for improving patients.

Regarding the studies published between 2018 and 2022, reported in the following paragraphs, negative results were identified concerning the dose of vitamin D supplementation in critically ill patients and unsatisfactory results regarding mortality.

To determine the effects of vitamin D supplementation in ICU patients at the Imam Hussein Hospital, during a single-center double-blind clinical trial, it was found that in the group that received the intervention with vitamin D, the need for mechanical ventilation reduced by 27 for 17 days. However, the incidence of respiratory tract bacterial infections has not shown significant changes. The study concluded that vitamin D deficiency leads to greater ventilator dependence and increased mortality rate in ICU patients. Furthermore, high-dose injections can increase the survival rate of patients<sup>31</sup>.

Another early randomized double trial was performed at Shohaday-e-Tajrish and Loghman-e-Hakim hospitals to study the effects of intramuscular vitamin D administration on the prognosis and mortality of patients diagnosed with ventilator-associated pneumonia. The individuals selected to compose the sample were patients over 18 years of age who had symptoms of fever, purulent respiratory secretion, leukocytosis or leukopenia. The study indicated that high-dose vitamin D supplementation decreases serum IL-6 levels in patients with VAP and proves to be an effective therapeutic intervention<sup>32</sup>.

Likewise, a study with 35 patients between 16 and 65 years old who suffered head trauma and were admitted to the ICU of Hospital Dr Ram Manohar Lohia in India revealed that vitamin D supplementation positively affects levels of consciousness and time spent on mechanical ventilation. Due to its wide availability, low cost and noticeable results, early treatment with vitamin D has been shown to be adequate<sup>33</sup>.

On the other hand, a study conducted between April 2017 and July 2018 in 44 hospitals in the United States with patients with severe vitamin D deficiency admitted to the ICU indicated that the administration of a single dose of 540,000 IU of the vitamin corrected the deficiency, however, supplementation of large doses of vitamin D3 did not show clinically significant differences and did not reveal an association between treatment and the decrease in mortality. The results of this study conclude that early supplementation with high dosages is not recommended in critically ill patients<sup>34</sup>.

Similar results were found in a study in three large hospitals in the United Kingdom. The investigators concluded that a single dose of cholecalciferol administered preoperatively was insufficient to reduce the EVLWI in cases of lung injury<sup>35</sup>.

By analyzing the effects of administering oral and injectable vitamin D in patients with traumatic injuries admitted to the ICU between August 2017 and May 2018, a randomized clinical study concluded that there was a significant reduction in the oxidation of stress biomarkers and the need for mechanical ventilation, as well as length of stay<sup>36</sup>. Likewise, other studies have not identified improvements in patients' conditions after administration of the vitamin<sup>37,38</sup>.

After studying the reaction of 86 patients hospitalized at El-Demedash Cardiac Academy Hospital after administration of vitamin D, researchers concluded that treatment with cholecalciferol caused a decrease in the rate of postoperative infection and ICU stay but did not impact the incidence of myocardial infarction, bleeding and mortality<sup>37</sup>.

In a randomized study with 24 critically ill ICU patients, it was observed that vitamin D modulates innate immunity; however, it was not possible to observe the effects of low-dose vitamin D supplementation. Therefore, it is not advantageous, as it did not affect the metabolism or the 25 (OH) D<sup>38</sup> concentration.

## CONCLUSION

This study has some limitations. The first one was that it did not separate high doses and low doses of vitamin D; when this analysis was performed, the number of participants was drastically reduced, thus leading to substantial heterogeneity. Therefore, it was decided to maintain the data's homogeneity by keeping the groups without this division. Another possible problem is that the vitamin D route of administration was not performed in the present study since it has been demonstrated that there is no difference in the pathways in the previous studies. However, for critically ill patients, it is well known in the literature that the gastrointestinal tract may be in hypofunction, limiting the absorption of vitamin D<sup>30</sup>, so the best route theoretically would be parenteral.

In conclusion, based on previous randomized controlled trials, this meta-analysis demonstrates that criti-

cally ill adult patients received at least one dose of vitamin D 150,000 IU by of the routes (enteral or parenteral) to reduce mortality in 28 -30 days. Future studies involving a more significant number of participants are desirable. In fact, this factor becomes essential to evaluate supplementation with high and low doses of vitamin D.

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