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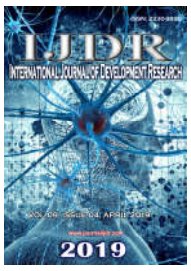

RESEARCH ARTICLE OPEN ACCESS

VITAMIN D IN INTENSIVE THERAPY IN TREATMENT OF ADULT PATIENTS: A METHANALYSIS OF CLINICAL TESTING

***[1,2,4]Eliza Miranda Ramos, [3]Matheus Dullius de Lima, [5]Jéssica Eloy Cunha Gonzalez, [3]Dr. Gilberto Gonçalves Facco and [1,2,4]Dr. Valter Aragão do Nascimento**

[1]Post-Graduate Program in Health and Development in the Midwest Region, Dr. Hélio Mandetta Medical School, Federal University of Matogrosso do Sul, Campo Grande, MS, Brazil
[2]Federal University of Matogrosso do Sul, Campo Grande, MS, Brazil
[3]AnhangueraUniversity - UNIDERP, Nursing Department, Campo Grande, MS, Brazil
[4]Laboratory of Mineral Metabolism and Biomaterials, Dr. Hélio Mandetta Medical School, Federal University of Matogrosso do Sul, Campo Grande, MS.
[5]Federal University of Matogrosso do Sul, Department of Nursing, Campo Grande, MS, Brazil

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ABSTRACT

Introduction: In Brazil, sepsis is one of the diseases with a high death rate in intensive care. **Objectives:** to gather information available from the authors to verify the efficacy of vitamin D supplementation in intensive care patients with sepsis. **Methods:** Analytical and observational through a meta-analysis. **Results:** 18 randomized studies were included in this meta-analysis, observational and experimental studies in humans from January 2000 to December 2018, totaling 10,011 patients evaluated. **Conclusion:** The prevalence of vitamin D deficiency in studies is high in patients diagnosed with sepsis.

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INTRODUCTION

Sepsis is a critical illness as the leading cause of death in intensive care in Brazil (Ramos *et al*, 2019). In recent years, Brazil has been presenting a high rate of sepsis death in intensive care units (Hamada and Fukagawa, 2007) which has been surpassing deaths due to stroke and infarction in intensive care units (Ramos *et al* 2019), that is, annually approximately 230,000 adult patients being treated in the units of intensive care has sepsis and an estimated 55.7% of hospitalized patients (Arnson *et al*, 2012) with sepsis is dead in relation to the age profile sepsis affects 40% of the adult population (Amrei *et al*, 2011) with 35 or more years of intensive care in Brazil (Lee, 2011).

***Corresponding author*: Eliza Miranda Ramos,**
Post-Graduate Program in Health and Development in the Midwest Region, Dr. Hélio Mandetta Medical School, Federal University of Matogrosso do Sul, Campo Grande, MS, Brazil

Although the introduction of early protocols to improve the clinical situation occurs (Holick, 2007), the success of continuous treatment is a challenge for health professionals (Ponsonby *et al*, 2008) who rapidly depend on the elimination of the microorganisms responsible for the change as well as the treatment of support (Jeng *et al*, 2009).In relation to vitamin D deficiency, it is characterized by a low serum concentration of 25-hydroxyvitamin D3 (25 (OH) D) (Adorini and Penna, 2008) with a level lower than 50 nmol / L and has a high prevalence in patients admitted to intensive care (Ross *et al*, 2011). Previous studies suggest that Vitamin D is a key regulator of the innate and adaptive immune system (Zivin *et al*, 2001; Ramos *et al*, 2019).However, the serum concentration of 25-hydroxyvitamin D3 25 (OH) D3 is considered a major risk factor for susceptibility to infection and the development of sepsis (Nierman and Mechanick,

1998). The patient in intensive care with sepsis has a high prevalence of vitamin D deficiency (Lee *et al*, 2009). Previous epidemiological studies have led to vitamin D deficiency as a risk factor for sepsis (Van Den *et al*, 2003).Because the low serum levels of Vitamin D (Ramos *et al*, 2019) binding protein (DBP) (Berwick and Kesler, 2005), which is the main carrier of Vitamin D (Ramos *et al*, 2019), is decreased in sepsis with very low levels of 25 (OH) D3 (Santos *et al*, 2007).Some previous studies have evaluated the role of Vitamin D in the treatment of sepsis in an experimental animal model (Van Den *et al*, 2003), which has demonstrated the regulation of levels of systemic inflammatory cytokines, such as TNF-α and IL-6 (Abdelfatah *et al*, 2015), and these vitamin D effector functions are important in pathogenic development of sepsis (Flynn *et al*, 2012).A current study has theorized about the onset and progression of sepsis (Chen *et al*, 2015), which focuses on the deregulation of inflammatory responses, which includes the large and uncontrolled release of pro-inflammatory mediators to initiate a chain of events leading to generalized tissue lesions (Amrein *et al*, 2014). Generally, the degree of immune dysfunction is related to the severity of sepsis, since cells of the innate and adaptive immune system express the vitamin D receptor (VDR) in counterpart with the inhibitory role in adaptive immunity (Han *et al*, 2016). Vitamin D is a potent activator of the system immune (Leaf *et al*, 2014), being absolute component of the natural mechanisms of defense against the microbial invasion (Nair *et al*, 2015). This study was registered and authorized in the Center for Reviews and Dissemination - PROSPERO with the code: CRD42019121732. Therefore, this meta-analysis gathered information available from the authors to verify the efficacy of vitamin D supplementation in intensive care patients with sepsis.

MATERIALS AND METHODS

This study used an analytical and observational method when developing in meta-analysis context after a systematic review on the efficacy of vitamin D supplementation in patients with sepsis in Brazilian intensive care. The search strategies used were with opposite specificity and sensitivity, as suggested by the American Society for Parenteral and Enteral Nutrition, including the randomized clinical trials which were identified in the Medline, Lilacs, PubMed, Scielo, Scopus and Web databases of Science. The period was 2000 to the first half of 2018, published in English, Portuguese and Spanish in the adult population in intensive care. Relevant randomized clinical trials were identified according to the database cited and the specific terms were used with the following strategy: Type of publication: (randomized clinical trial OR controlled clinical trial and Vitamin D supplementation), MeSH: (random allocation OR method double blind and sepsis), MeSH 2: (simple concealment method and Sepsis and Vitamin D Supplementation) and MeSH 3: (Epidemiology and Vitamin D).Two different methods were used to evaluate the quality of the clinical studies, in the case of JADAD and Down & Black (De-la-Torre-Ugarte-Guanilo *et al*, 2011). Four pairs of reviewers participated in the study, who worked independently. The application of the Down & Black method was performed by two health professionals, specialized in clinical epidemiology, in the same place and year, which served as a comparison parameter for another instrument. We used the instrument presented by Downs and Black, which consists of 27 questions regarding the quality of information of the articles, internal validity (Bias and confounding) (Santos *et al*, 2007), external validity, and statistical power, giving rise to a score ranging from zero to twenty-seven points (Santos *et al*, 2007). Any of the articles was classified according to quality and evidence and not the exclusion factor, because, evaluating the available evidence regarding the topic and relating to the results found has a higher factor in the systematic review and mainly metanalysis (De-la-Torre-Ugarte-Guanilo *et al*, 2011).The articles were classified as follows: excellent (24 to 27), good (20 to 23), reasonable (15 to 19) and bad (14 or less) (Santos *et al*, 2007), this classification pattern was adopted in other review studies (De-la-Torre-Ugarte-Guanilo *et al*, 2011).The percentages obtained and standardized in each system were categorized as follows (De-la-Torre-Ugarte-Guanilo *et al*, 2011): Class I - 0 to 20%, class II - 21% to 40%, class III - 41% to 60%, class IV - 61% to 80%, class V - 81% to 100%.Spearman's correlation coefficient was calculated for the quality percentages obtained by the reviewers (Santos *et al*, 2007). This method of classification focuses mainly on the internal validity of the study, its form of randomization, and how it diverted or minimized biases and used evaluative methods like others (De-la-Torre-Ugarte-Guanilo *et al*, 2011). It is an investigative structured instrument (De-la-Torre-Ugarte-Guanilo *et al*, 2011).The JADAD system includes three topics which are related to bias reduction (centered on internal validity) (Santos *et al*, 2007). The questions have the yes / no choice (De-la-Torre-Ugarte-Guanilo *et al*, 2011). And it maintains a quality score which has five points (Santos *et al*, 2007): three times a point for the yes and two additional points for appropriate randomization and allocation methods. Because they were several instruments of evaluation, we chose to use these two methods, by numbering quite different items, with a weighted or non-punctuated form, which were clearly complementary (Santos *et al*, 2007). In order to include the evaluation of a greater number of characteristics that makes up the methodology of the randomized clinical trials. The quality score calculations for each system were performed according to their weighted and original value (Jadad and Black & Down) (De-la-Torre-Ugarte-Guanilo *et al*, 2011).

In order to compare the different systems with each other, these obtained quality scores were transformed into a percentage in relation to the maximum score of each quality evaluation system (Santos *et al*, 2007). Some meetings were subsequently held for consensus to the definite score of each randomized controlled clinical study (Santos *et al*, 2007). Regarding the analysis of the effect of intervention against and nonintervention, it was determined that it was considered preferable to those studies that obtained a score equal to or better than 50% of the possible (De-la-Torre-Ugarte-Guanilo *et al*, 2011), in use of each instrument, in at least one quality of use instrument (Santos *et al*, 2007) . The Review Manager 5.3 statistical package was used for meta-analysis. The relative risk was calculated in a 95% confidence interval because only dichotomous variables were used. According to the heterogeneity identified among the included clinical studies, a random effect model was used to perform the meta-analysis. The studies were organized in code according to Table 01.

RESULTS

A total of 357 studies were selected and identified, 339 were excluded by the following criteria: irrelevant articles (n = 135), samples with very small sampling design (n = 5), pediatric studies (n = 102), articles by (n = 24), studies whose objective was only to analyze the metabolism of vitamin D in the body (n = 34), studies that did not report sepsis (n = 39).

Table 1. Identification code of the studies included in the meta-analysis on the efficacy of vitamin D supplementation in patients with sepsis in intensive care

Author	Year	Code
Abdelfatah *et al*	2015	A
Alves *et al*	2015	B
Amrein *et al*	2014	C
Cameron *et al*	2017	D
Chen *et al*	2015	E
De Pascale*et al*	2016	F
Flynn*et al*	2012	G
Han*et al*	2016	H
Jeng*et al*	2009	I
Lasky-Su*et al*	2017	J
Leaf *et al*	2014	K
Moromizato *et al*	2014	L
Nair *et al*	2015	M
Parekh*et al*	2017	N
Quraishi *et al*	2013	O
Quraishi *et al*	2015	P
Rech*et al*	2014	Q
Zittermann *et al*	2016	R

Table 2. Classification of the quality level of the studies included in the systematic review and meta-analysis according to its evidence. 2019

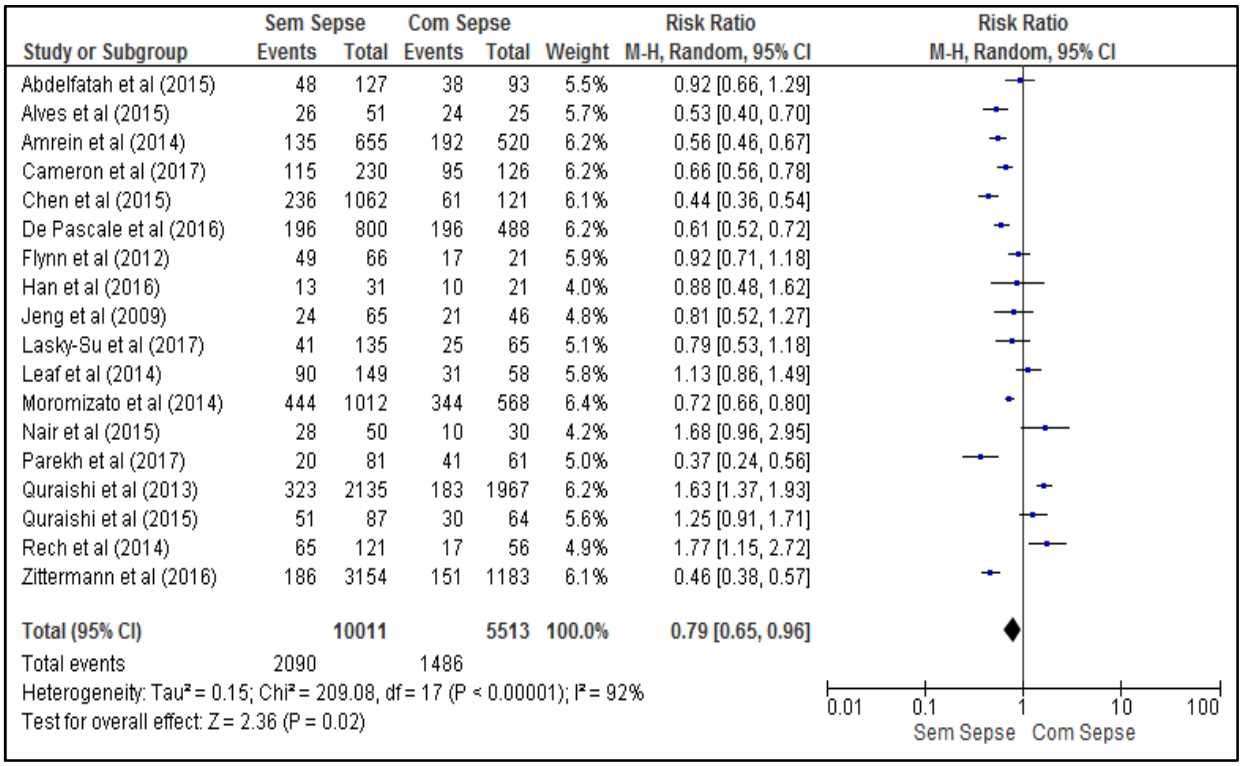
Study Code	Type of Publication / Periodical	Language of Publication	City / Country of Origin	Study QualityLevel
A	Article/BMJ Journals	English	Ohio/EUA	IV
B	Article/Rev. Bras. Terapy Intensive	Portuguese	Brazil	V
C	Article/Critical Care	English	Austria	III
D	Article/BMJ Open	English	London/England	III
E	Article/The Journal of Clinical Endocrinology and Metabolism	English	GuangxiProvince/China	III
F	Article/ClinicalMicrobiologyInfection	English	Rome/Italy	IV
G	Article/American journal of surgery	English	Detroit/USA	III
H	Article/Critical Care Medicine	English	Virginia/USA	IV
I	Article/Journal of Translational Medicine	English	Georgia/USA	IV
J	Article/Critical Care (London, England)	English	Boston/USA	III
K	Article/American Journal of Respiratory and Critical Care Medicine	English	Boston and Colorado/USA	IV
L	Article/Critical Care Medicine	English	Boston/USA	V
M	Article/Critical Care Medicine	English	Sydney/Autralia/Munich/Germany/QLD/Australia	V
N	Article/Critical Care Medicine	English	London/England	IV
O	Article/The American Journal of Clinical Nutrition	English	Boston/USA	V
P	Article/Critical Care Medicine	English	Boston/USA	V
Q	Article/American Journal of Critical Care: An Official Publication, American Association of Critical-Care Nurses	English	Boston/USA	IV
R	Article/PloSOne	English	BadOeynhausen/ Germany	III

Were included 18 randomized, observational and experimental studies in humans from January 2000 to December 2018, totaling 10,011 patients. The average of the supplementation was at the dose (vitamin D) for human serum in the 18 included studies of 50 nmol / L. Sepsis occurred on average at an incidence of 55% of the patients in the included studies (n = 5513) (Table 03). The characteristics and level of quality of the articles were presented in Table 02. Regarding mortality, 60.0% (n = 10) of the studies obtained a mean mortality in the period of 30 days of hospitalization. Regarding vitamin D levels and presence of sepsis, the studies were grouped and compared to the effect of deficiency levels (sufficient levels of Vitamin D (25 (OH) D)) using a method of inverse variance in random models which may generate a 95% confidence interval (IC). A random model was used, since the sample had a heterogeneous characteristic, the variances used for subgroups were sepsis and mortality (Figure 01 and Figure 02). Unfortunately, approximately 40% of the studies (n = 7) did not report the exact dose used in vitamin D supplementation, although subgroup analysis was performed based on the design of the studies and in order to determine the results of these studies and the graph was used forest plot.

Five of the eighteen studies reported the presence of sepsis (Quraishi *et al*., 2013), Rech *et al* (2014), Leaf *et al*. (2014), Quraishi (2015), Nair *et al*. (2015), when grouping the risk difference for the effect of vitamin D supplementation without developing sepsis was included 3338 patients grouped. The risk of pooled difference was 0.79 (95% IC 0.65 to 0.96).When comparing studies with vitamin D levels in intensive care were deficient and supplementation was required, a lower risk was found to develop infectious diseases such as sepsis (p <0.00001 (95% CI)). Vitamin D supplementation used in the 18 articles was performed by Vitamin D3 and significantly reduced the risk of developing sepsis in long periods of hospitalization and intensive care (greater than or equal to the 30-day intensive care stay (I2 = 92%).Observational data in the studies demonstrated an inverse association between vitamin D supplementation and sepsis in two articles (Zittermann *et al*., 2016 and Quiraishi *et al*., 2013), however, reverse causality is possible, for example, some patients develop vitamin D deficiency due to the hospitalization process, as opposed to the vitamin D deficiency caused by sepsis, although the randomized clinical trials included in this meta-analysis had a low risk of viral load, and the results were

Table 3. Sepsis prevalence in patients with vitamin D deficiency in intensive care according to included studies. 2019

Codes of Study	Adults with Sepsis and Vitamin D Deficit	Population Incidence
A	74/271	27.3%
B	26/51	50.9%
C	135/655	20.6%
D	115/230	50.0%
E	236/1062	22.2%
F	196/800	24.5%
G	49/66	74.2%
H	13/31	41.9%
I	24/65	36.9%
J	135/235	57.4%
K	90/149	60.4%
L	444/1012	43.8%
M	28/50	56.0%
N	20/81	24.6%
O	323/2135	15.1%
P	51/87	58.6%
Q	65/121	53.7%
R	186/3154	5.89%



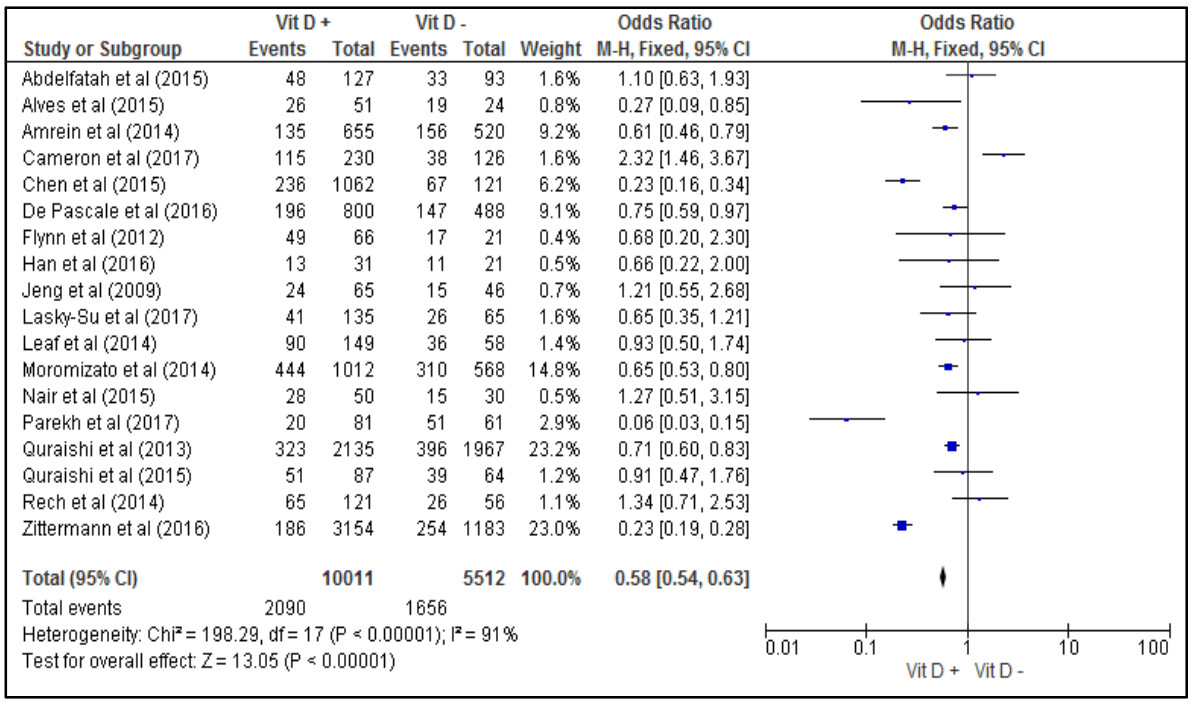
(IC: confidence interval (IC), inverse variance, absence of sepsis, presence of sepsis, sufficient level of vitamin D supplementation).

Figure 1. Comparison of studies on the use of vitamin D supplementation (Vitamin D Dosage = 50 nmol / L) with presence of sepsis. 2019

carefully analyzed because of the low number of probabilities of the analyzed subgroup and mode of intervention. Therefore, the combination of the 18 randomized clinical trials demonstrated the existence of a clinically relevant benefit in the use of Vitamin D Supplementation in intensive care in the control of sepsis with no statistically significant difference between the vitamin D group without sepsis (use of Vitamin D) and (Control - without use of Vitamin D) P <0.02 (Test for overall effect - Z = 2.36 (P <0.02). Data on death related to vitamin D deficiency (Vit-) were collected from 18 randomized clinical trials totaling 1656 patients. The comparison was significant and favored the use of Vitamin D in intensive care patients with reduced sepsis death (OR 0.58, 95% IC 0.54 to 0.63, P <0.00001) (I^2 = 91%). Thus, it is observed that the second intervention, in this case, the presence of Vitamin D, decreases the chances of occurrence of the researched outcome, in the case of death.

DISCUSSION

The objective of the present study was to verify the efficacy of the use of Vitamin D through the supplementation in patients in intensive care with sepsis in order to contribute to decisions and clinical protocols in the intensive care in relation to sepsis. This study aimed mainly at the descriptive analysis of the randomized clinical trials regarding the dosage of Vitamin D and main clinical alterations, such as vitamin D dosage and death. To our knowledge, this is the first metanalysis of clinical and randomized studies investigating major changes (clinical improvement and death) in the development of sepsis after vitamin D supplementation. Our main findings indicate that dosage in vitamin D supplementation in intensive care patients equal to 50 nmol / L (Alves *et al*, 2015) has a trivial and positive effect on the development of sepsis and death in intensive care with hospitalization time greater than 30 days



(IC: confidence interval (IC), inverse variance, absence of Vitamin D, Presence of Vitamin D, Death by sepsis).

Figure 2. Comparison of the studies in the use of Vitamin D supplementation (Vitamin D Dosage = 50 nmol / L) with presence of Death by Sepsis. 2019

due to the similarity of the studies involved in the meta-analysis (Zittermann *et al*, 2016; Quiraishi *et al*, 2013). It is worth noting that the use of Vitamin D with a dose equivalent to 50 nmol / L (Chen *et al*, 2015) was superior to that of 20 nmol / L in the treatment of an infectious process in patients undergoing long-term intensive care (greater than or equal to 30 days) (Jeng *et al*, 2009) with 88% of possibility of obtaining balance in the response of the immune system, however with significant difference (De Pascale *et al*, 2016).Vitamin D deficiency is capable of leading to imbalance of the immune system (Cameron *et al*, 2017), Vitamin D plays a primary role in defense against bacterial and viral agents and this defense occurs by the stimulation (Chen *et al*, 2015) of antimicrobial peptides which can intensify the reduction of cathelicidins and the level of vitamin D concentrations are more significant (Lasky-Su *et al*, 2017), for example, in samples from intensive care patients with sepsis in reference to non-sepsis patients (Chen *et al*, 2015). In this context, the role of Vitamin D as an Immunomodulators is reinforced (Parekh *et al*, 2017), since Vitamin D identifies and nullifies the action of inflammatory cytokines mainly to interleukins 6 (IL-6) (Leaf *et al*, 2014), which induces systemic inflammatory response syndromes (Moromizato *et al*, 2014).

When we compare the serum level of Vitamin D during the intensive care admission process of the sepsis patient (Nair *et al*, 2017), an increase in the probability of developing organic disease is observed (Jeng *et al*, 2009). In the comparison between dosages of less than 20 nmol / L, the study Morimazato *et al*. (2014) showed inferiority to the supplementation dosage higher than 40 nmol / L (Alves *et al*, 2015) (P = 0.65).Similar result was found among other authors Zittermann *et al* (2016) and Quiraishi *et al* (2013). This difference may be in the limitation of morbidity when aggregating longevity in the general population (Quraishi *et al*, 2013), because lower levels of Vitamin D (Zittermann *et al*, 2016), such as 17.8 ng / mL serum have been used to increase the frequency by 26% of risk of death (Rech *et al*, 2014) by some infectious process when not performed Vitamin D supplementation (Quraishi *et al*, 2015). It is emphasized that the main intensive care centers in Brazil do not routinely perform the routine evaluation of the serum level of the vitamin D sequence in intensive care patients (Alves *et al*, 2015).This meta-analysis reaffirmed that insufficient high prevalence of serum vitamin D (89%) in patients in intensive care triggers changes in the immune system such as sepsis (Ramos *et al*, 2019). The results of this meta-analysis combined with blood serum vitamin D levels lower than 20 ng / mole showed an improvement in patients in intensive care (Cameron *et al*, 2017), in this case, related to mortality (Death) (Ramos *et al*, 2019), since patients without routine use of Vitamin D (dosage of 50 nmol / L) in the intensive care unit presented a lower result (P <0.00001), for example, the study by Amrein *et al* (2014) presented 30% (n = 156) mortality in the absence of vitamin supplementation D (dosage - 50 nmol / L).Vitamin D supplementation (Dosage - 50 nmol / L) evidenced in the study by Cameron *et al* (2017) the reliability of reducing mortality and increasing immune resistance in intensive care patients (Chen *et al*, 2015). De Pascale *et al*. (2016) pointed out that patients with a positive indicator of prolonged admission to intensive care, in the case of survival, showed significant and elevated serum levels of vitamin D during hospitalization compared to patients who presented mortality (Flynn *et al*, 2012). Rech *et al*. (2014) reinforces in his final remarks in the article selected to qualify Vitamin D supplementation (40 nmol / L dosing interval at 50 nmol / L) with the best result being the most efficient amount whose blood values normalize in 7 days of hospitalization in intensive care, because the improvement of the serum level of Vitamin D accelerates avoids the disorders of serious diseases such as sepsis (Rech *et al*, 2014). Four authors (Alves *et al* (2015), Rech *et al* (2014), Flynn *et al* (2012) and Jeng *et al* (2009)) pointed out that patients with a higher magnesium concentration index demonstrated an inverse relationship between the index of circulating concentration of Vitamin D and mortality (Jeng *et al*, 2009). Therefore, Vitamin D is the

main component in the influence between the kidney (Jeng *et al*, 2009), bones and the parathyroid hormone (PTH) and the intestine which regulates the homeostasis of calcium and phosphorus (Alves *et al*, 2015). This meta-analysis reinforces that the negative effects correlated with vitamin D deficiency and PTH elevation are the cause of increased mortality observed in 75% of the studies analyzed (n = 13) in intensive care patients, that is, of vitamin D deficiency in relation to the impairment of PTH response (De Pascale *et al*, 2016) in intensive care patients may be a reflection of the organism in the effort to protect against the adverse effect of the calcium-PTH-calcium axis (Rech *et al*, 2014), which can significantly increase through the sensitive calcium receptor in the parathyroid glands and confirms compatibility in the most effective control of the synthesis of PTH secretion by low ionized calcium (Zittermann *et al*, 2016). Let's remember that Vitamin D is calcium-conductive in the percentage of 10% to 15% of the diet by the small intestine (Quraischi *et al*, 2015), for example, in a normal person without changes in the immune system and with serum vitamin D normality the small intestine absorbs about 30% calcium (Quraishi *et al*, 2013) in the diet and in important physiological processes such as gestation (Rech *et al*, 2014), lactation, growth or development of infectious processes there is an increase of 80% to obtain efficiency (Nair *et al*, 2015).

In pulmonary dysfunctions Vitamin D can be associated with death, because the study suggests that there is a correlation in vitamin D deficiency with neurological (Flynn *et al*, 2012), cardiac and (Lasky-Su *et al*, 2017), especially, in the immune system (Han *et al*, 2016), which presents as sepsis outcome (Ramos *et al*, 2019). Jeng *et al* (2009) pointed out in a previous study that high rates of vitamin D deficiency present a 2.8 fold increased risk of developing cerebrovascular accident and 3,4 times more lung disorders (Ramos *et al*, 2019), such as pneumonia compared to normal levels or whether the mortality in this study due to respiratory and neurological changes was significantly affected by the Vitamin D condition (Figure 01) (Ramos *et al*, 2019).From the results found in this meta-analysis, the following evidence was observed regarding the efficiency of the use of vitamin D supplementation in intensive care: Evidence is sufficient to state that the efficacy of vitamin D supplementation (50nmol / L dosage) is higher than lower doses (Nair *et al*, 2015). A discrete superiority in the use of vitamin D supplementation should be considered when correlating death in sepsis-intensive therapy (Leaf *et al*, 2014), as evidenced by the meta-analysis. Therefore, studies are necessary to confirm this hypothesis, the research justifies the need for clinical change in relation to the use of vitamin D supplementation (50 nmol / L) (Ramos *et al*, 2019) in patients with sepsis in intensive care when compared to other doses of vitamin D presented a significant change in the maintenance of the patient in intensive care (Flynn *et al*, 2012). However, when the dose was compared with the risk of death (Chen *et al*, 2015), vitamin D supplementation was observed with a dose of 50 nmol / L with a statistically significant difference simplifying its indication (Cameron *et al*, 2017).

Conclusion

This meta-analysis review which included the prevalence of vitamin D deficiency in studies is high in intensive care patients with a diagnosis of sepsis with high-level evidence from a randomized clinical trial conducted in the intensive care setting revealed that vitamin supplementation D (50 nmol / L) is more effective than 20 nmol / L, dosages of vitamin D supplementation of less than 50 nmol / L are less effective in the development of diseases such as sepsis.

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