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Vitamin D Deficiency and Acute Respiratory Distress Syndrome: A Systematic Review

Darius Hartanto[1*], Debby Claudi[1], Thamrin Ciatawi[1]

Faculty of Medicine, North Sumatera University, Medan, Indonesia[1]

Corresponding author: 1*

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ABSTRACT

Acute respiratory distress syndrome (ARDS) had been associated with high mortality and ICU admission. Several studies had found the association between vitamin D level and risk of ARDS. The objective of this systematic review was to determine the association between vitamin D deficiency and ARDS. This systematic review used online databases (Google Scholar, PubMed, Science Direct, and CENTRAL) in obtaining eligible journals. All published observational studies that determine the association between levels of vitamin D and the incidence or prevalence of ARDS were included. The search yielded 5 journals. Severe vitamin D deficiency was associated with a higher APACHE II score, SOFA score, and DCI score, lower PaO2/FiO2, higher duration of mechanical ventilation, and longer ICU hospitalization. Vitamin D level was significantly lower in ARDS patients with vitamin D deficiency, especially in severe deficiency group compared to the control group ($p < 0.005$). Severe vitamin D deficiency is associated with worse clinical outcomes and severe ARDS.

1. INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a disorder that causes progressive respiratory failure, characterized by reduced lung compliance, profound hypoxia, increased dead space, normal pulmonary capillary wedge pressure (PCWP), and bilateral lung infiltrates [1], [2]. ARDS is a form of non-cardiogenic pulmonary edema caused by an inflammatory process originating from the pulmonary or systemic affecting the alveolar-capillary membrane [3], [4]. There was high variability in the epidemiology of ARDS. In the US, a total of 1,151,969 cases of ARDS, ranging from 64.2 to 78.9 cases/100,000 people/years were diagnosed based on data from 2006 to 2014, while the incidence of ARDS in European countries was around 79 cases per 100,000 and was lower than US [5], [6], [7]. ARDS accounts for 10.4% of total intensive care units (ICU) cases, 23,4% required mechanical ventilation and the mortality rate was as high as 52% [8], [9]. Recently, several studies reported that one of the contributors to the high mortality and ICU admission in ARDS patients was vitamin D deficiency (VDD) [10]. VDD can be induced by certain comorbidities such as malignancies, metabolic disorders such as diabetes and hypertension, cardiovascular diseases, infections, and these conditions have been associated with poor prognosis [11]. VDD in critically ill patients caused massive cytokine production, undepressed local and systemic inflammatory responses,

which contributes to the severity of ARDS [12], [13]. These mechanisms occurred by suppressing the activation of T cell vitamin D receptor, which leads to the reduction of T-Helper (TH) 1 and TH2 proliferation, and regulatory T cell production. Besides, the production of cathelicidin, an antimicrobial peptide, that played a role in killing pathogen against virus and bacteria directly or via endotoxin, was suppressed in VDD [14]. Previous study showed that supplementation of vitamin D can significantly reduce the risk of acute respiratory tract infection and greater effect can be seen in 25-hydroxyvitamin D level below 25 nmol/L [15]. The objective of this systematic review of observational studies was to comprehensively determine the association between vitamin D deficiency and ARDS, while the secondary objective was to determine the baseline characteristic and difference of vitamin D level between ARDS and control groups.

2. METHODS

This systematic review answered key scientific questions about the association of vitamin D deficiency and ARDS and the comparison of vitamin D level between ARDS and control groups. The sources of this review were obtained by screening both national and international journals in Google Scholar, PubMed, Science Direct and Cochrane Central Register for Controlled Trials (CENTRAL) in The Cochrane Library databases from inception until January 2021. All published observational studies such as prospective cohort, retrospective cohort, case-control, and cross-sectional studies, that determine the association between levels of vitamin D (25(OH)D or 1,25-dihydroxyvitamin D [1,25(OH)2D]) and the incidence or prevalence of ARDS were included. Reviews, case reports, letters to editor, commentaries, abstracts, unpublished studies and journals that were not in English were not included. The search keywords consist of "Vitamin D", "25-hydroxyvitamin D", "25(OH)D", "Vitamin D and ARDS", "Vitamin D deficiency and ARDS", "acute respiratory distress syndrome", "ARDS", and "Acute respiratory failure". The criteria of participants were 18 years of age or older who had vitamin D levels (25(OH)D) measured before or during hospitalization and ARDS was diagnosed based on the Berlin criteria. We included all studies which defined vitamin D deficiency as plasma 25(OH)D level <20 ng/ml (50 nmol/L).

Table 1. Characteristic of included trials.

First Author (Year)	Country	Study Design	Sample Group	Sample Size	Vitamin D Categorization and Cut off	Outcomes
[16]	Birmingham, United Kingdom	Retrospective cohort study	• ARDS • Risk of ARDS	• 52 • 65	• Deficient: <50 nmol/L • Severe deficiency: <20 mmol/L	• Comorbidities • APACHE II • Length of hospital stay • PaO_2/FiO_2 ratio • Plasma 25(OH)D level

[17]	Italy	Retrospective, observational single center study	ARDS	42	• Insufficiency: 20-29 ng/ml • Moderate deficiency: 10-19 ng/ml • Severe deficiency: <10 ng/ml	• Comorbidities • SOFA score • PaO_2/FiO_2 ratio • ICU length of stay • Plasma 25(OH)D level
[18]	Boston, United States of America	Retrospective cohort study	• ARDS • Without ARDS	• 352 • 1634	• <10 ng/ml • 10-19.9 ng/ml (consider inadequacy) • 20-29.9 ng/ml • ≥ 30 ng/ml	• Comorbidities • Deyo-Charlson index (DCI) • Plasma 25(OH)D level
[19]	Brazil	Cross-sectional study	ARDS	71	Cut-off based on the previous study: • < 12 ng/ml • ≥ 12 ng/ml	• Comorbidities • APACHE II • SOFA score • DCI • Mechanic ventilation duration • ICU length of stay • Plasma 25(OH)D level
[20]	Korea	Retrospective Cohort study	ARDS	108	• Deficient: <20 ng/ml • Sufficient: ≥ 20 ng/ml	• Comorbidities and predisposing condition • APACHE II • ICU length of stay • Plasma 25(OH)D level

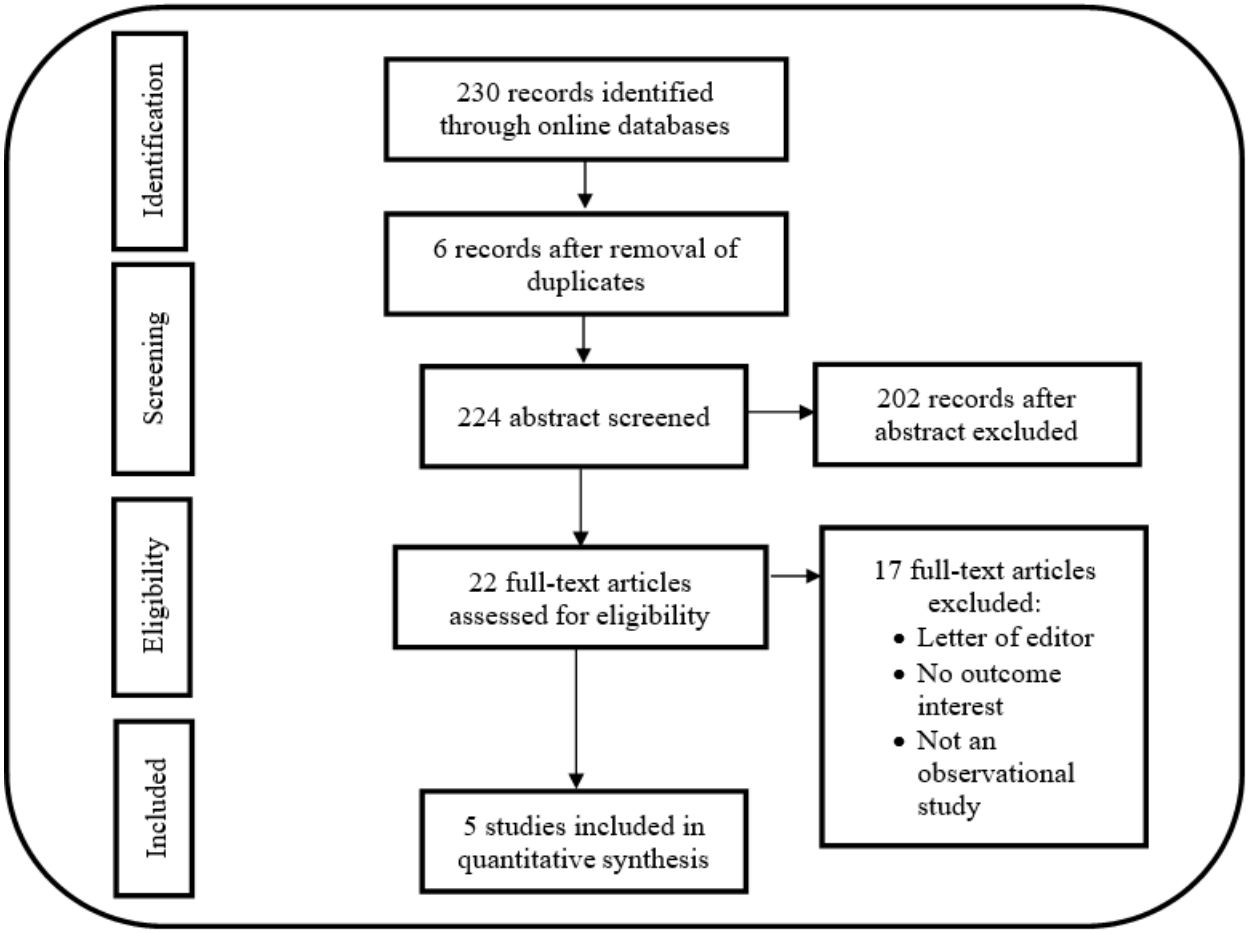

Figure 1. PRISMA diagram.

3. RESULTS

3.1 Baseline Characteristics

Based on the inclusion criteria, five journals were collected, including prospective, retrospective, and cross-sectional study which determine the association of vitamin D level and ARDS. Three of five journals described the comorbidities, while two journals described predisposing conditions of ARDS. According to those journals, the most common comorbidities of ARDS were malignancies, followed by metabolic syndromes such as hypertension and diabetes, then cardiovascular diseases, and chronic kidney disease. For predisposing condition, pneumonia (68% and 35%) and sepsis (19.4% and 46%) were reported as the most common conditions that caused ARDS. All these conditions were more common in the patient with VDD compared to sufficient group and based on the study of, only malignancies were significantly different between both groups. Three studies were found using APACHE II scoring system to determine the prognosis for ARDS patients. Based on the study by, APACHE II levels were a significant difference between both groups with the median values 24 and 12, respectively. These findings were different from the study by which showed no significant difference in APACHE II scores between patients with vitamin D levels <12 (23.17±10.93) and ≥12ng/mL (20.49±895). Also found no significant differences in vitamin D level between low vitamin D level (<20 ng/mL) and sufficient level (≥20ng/mL) groups. Along with the APACHE score results, only two studies which reported the PaO_2/FiO_2 ratio in ARDS patients with deficient and sufficient vitamin D levels. The study of showed that the higher PaO2/FiO2 ratio was found in patients who are at risk of ARDS, while the study of reported that the PaO2/FiO2 ratio was higher in the group of ARDS patients who were in severe deficiency groups, while none of the patients in vitamin D

sufficient group had PaO2/FiO2 ratio < 300. These results supported by the findings in, which reported that shorter duration of mechanical ventilation usage was found in ARDS patient with sufficient vitamin D (≥ 12 ng/ml).

Two studies found using DCI with different scoring categorizations. The study by divided the DCI by three scoring range, which was 0-3, 4-6, and >6, which mean the higher the score, the more likely the predicted outcome will result in mortality. The score of 0-3 was more common in patients without VDD, while the score of >6 was more common in patients with insufficient vitamin D (10-19.9 ng/ml), but there was no statistically significant difference between those groups. The same result was also found in the study of, in which the higher DCI scores were found on the vitamin D level <12 ng/ml group and there was a significant association between vitamin D level and DCI after adjusting the age, sex and body mass index of ARDS patients (p = 0.001). The study by analyzed the mean level of SOFA score in four groups of vitamin D level and found no differences between those groups with the lowest SOFA score was found in the vitamin D sufficient group. This finding was similar to study that also shown no significant difference in SOFA score between vitamin D level <12ng/mL and ≥ 12ng/mL groups. Four studies were found to state the length of ICU stay. The study by shown severe vitamin D deficiency had a shorter ICU length of stay compared to vitamin D level above 10 ng/ml for 8 days and 12,5 days respectively. This finding was different compared with three other studies. Reported that the median length of stay in ICU was higher in the vitamin D level <20 group compared to ≥20ng/mL group. Showed that patients with vitamin D level <12ng/mL had a longer length of stay compared to vitamin D level ≥12ng/mL group, but there was no significant difference between both groups. There was a significant difference in the median length of ICU stay in ARDS and non-ARDS groups (p = 0.025) with longer days were found in the ARDS group.

3.2 Vitamin D Levels and ARDS

All of these studies reported the same results where the plasma 25(OH)D level was found lower in ARDS patients with VDD, especially in severe deficiency group and there was a significant difference between both groups. The study of reported that most of the ARDS patients experienced hypovitaminosis (81%) and had vitamin D serum level < 10 ng/ml. On the study of, showed that the plasma 25 (OH)D was lower in ARDS patients who were non-survivor (7,7 ± 4,4 ng/ml) compared to ARDS survivor patients, but no significant difference was found between both groups. There was various result of odds ratio (OR) between these studies. The study of reported that the OR of VDD causing ARDS was 13.20 and 1.84 respectively.

4. DISCUSSION

This systematic review determining the association between vitamin D levels by assessing plasma 25(OH)D level and ARDS. Based on this study results, patients with severe vitamin D deficiency (25(OH)D <20 ng/mL) were more likely to cause severe ARDS, which lead to an increased number of non-survivor patients. The common predisposing conditions were pneumonia and sepsis, while the most common comorbidity was malignancies and metabolic syndrome. These results were also found in the study of, which reported that hypertension and diabetes, followed by chronic pulmonary disease and malignancies [21]. A previous study had reported that approximately 50-60% of patients admitted to the ICU had VDD. The cause of VDD in critically ill patients especially ARDS patients probably caused by decreased intake and absorption of vitamin D and end-organ resistance, which leads to decreased vitamin D production. Besides that, an increase of vitamin D requirement in critically ill patients leads to enhanced conversion of 25(OH)D to the active form of vitamin D (1,25 (OH)2D) [22]. Therefore, several studies showed that low vitamin D level can be used as a marker to predict organ dysfunction and mortality in critically ill patients [23]. Meta- analysis conducted by, showed that low 25(OH)D levels was correlated with bad prognosis and clinical outcomes, such as increased in mortality, length of hospital stays and complications during

hospitalization [24]. Vitamin D plays a role in innate immunity since its receptors can be found on monocytes. VDD is associated with the activation of inflammatory processes. In the condition of VDD, there was a lack of natural antibody production since it was stimulated by vitamin D. Vitamin D also plays a role in strengthening immunity by stimulating monocyte differentiation and suppressing the proliferation of lymphocytes. Besides that, vitamin D is also believed to increase the phagocytic activity of macrophages to produce an antimicrobial peptide, known as cathelicidin [25], [26]. Vitamin D supplementation has been shown to reduce circulating levels of inflammatory cytokines, such as IL-1, IL-6, and TNF [27]. Three studies gave varying results regarding their association with the APACHE II scoring system. APACHE (Acute Physiology and Chronic Health Evaluation) is a scoring system that consists of 12 clinical and laboratory parameters that are useful for assessing outcomes in patients admitted to the ICU and were assessed within 24 hours of the first ICU admission. Increased APACHE II scores in the range 0–71 were associated with hospital mortality [28], [29]. This study showed that APACHE II levels were higher in ARDS patients which in line with previous studies, where sepsis more likely to happen in ARDS and will increase the severity of illness scores [30]. However, two studies showed no significant difference between ARDS and the control group and there was no correlation between vitamin D level and APACHE II score. In contrast to the study of, showed that there was a poor negative significant correlation between vitamin D level and APACHE II score ($r = -0.05$, $p = 0.006$). This study concluded that the APACHE II score might be related to an increase in mortality in VDD ARDS patients [31].

As the diagnosis of ARDS was based on the Berlin definition, one of its components was the PaO2/FiO2 ratio. This study result showed that the ARDS with VDD had a higher PaO2/FiO2 ratio and associated with longer mechanical ventilation duration. The study of reported that patients with VDD (<12 ng/ml) were significantly associated with the use of mechanical ventilation and death (hazard ratio 6.12 and 14.73 respectively, $p = 0.004$) [32]. The same outcome was also found on the study of, showed that patient with VDD had a significantly shorter duration of free mechanical ventilation with median approximately 16 days [33]. The other marker to predict the severity of disease and mortality was DCI. A high DCI score has relations with the disease severity and higher mortality rate [34]. To predict 90-day mortality in ICU patients, it is better to use a combination of vitamin D and DCI levels than DCI alone [35]. The DCI was primarily used to assess the prognosis for malignancies and has not been assessed for ARDS, but several previous studies reported that DCI has shown to be a useful scoring system for assessing prognostic factors in ARDS [36]. Several studies also concluded that DCI score of 4 or more will increase ARDS patients' risk for developing multi- organ failure and poor prognosis [37]. SOFA is a scoring system that assesses various parameters of six organ systems to determine severe organ dysfunction [38], [39]. The SOFA score is commonly used in critically ill patients to assess the severity of organ failure [39]. This study result showed that there was no significant relationship between vitamin D levels and the SOFA score. The same result was also found in the previous study which stated that there was no association between SOFA score and vitamin D levels on day 1 and day 7.9 hospitalization. This result had the opposite result of other studies which stated that there was an increase in the SOFA score in patients after 24 hours of admission [40]. These differences may be caused by the SOFA score was only assessed once at the time of the first admission and no reassessment was carried out after. This concern can be a reason that further research is still needed. In terms of ICU length of stay, only one study found shorter ICU length of stay in patients with lower vitamin D levels. This finding might be the result of a high mortality rate in patients with severe vitamin D deficiency, while other studies concluded that low vitamin D level at ICU admission was correlated with higher in-hospital and one-year mortality [41]. Other study showed that patients with vitamin D deficiency had double the risk of staying 3 days longer in the ICU [42]. The results of this study still had several limitations, such as the small number of studies that met the inclusion criteria; other variables such as age, comorbidities, clinical complications which might be the cofounding factors.

5. CONCLUSION

The conclusion of this study was vitamin D deficiency especially plasma 25(OH)D <10 ng/ml is associated with worse clinical outcomes and severe ARDS. By having low plasma 25(OH)D, ARDS patients were associated with higher severity scores, longer hospitalization, and higher mortality.

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