Original Research Article

Prognostic value of vitamin D in patients with pneumonia: A systematic review and meta-analysis

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Abstract

Purpose: To investigate the prognostic role of vitamin D in pneumonia patients through meta-analysis.
Methods: PubMed and Embase were systematically searched for relevant studies that assessed the impact of vitamin D on the risk of adverse outcomes among patients with pneumonia. Risk ratios (RR) with 95 % confidence intervals (95 % CI) were pooled using meta-analysis. Q-test and I^2 statistics were used to evaluate between-study heterogeneity.
Results: Six studies were finally included in the meta-analysis. The results of meta-analysis of these studies indicated that low vitamin D status was associated with higher risk of mortality among pneumonia patients (RR = 2.59, 95 % CI = 1.32-5.08; p = 0.005). Results from meta-analysis of studies with adjusted estimates suggest that low vitamin D status was independently associated with higher risk of mortality among pneumonia patients (RR = 3.15, 95 % CI 1.54-6.44, p = 0.002). There was no significant risk of bias in the meta-analysis.
Conclusion: This study demonstrates that low vitamin D level is associated with a higher risk of adverse outcomes in patients with pneumonia.

Keywords: Pneumonia, Vitamin D, Prognosis, Meta-analysis, Systematic review

INTRODUCTION

Pneumonia is a common lung disease which is responsible for significant morbidity and mortality worldwide [1,2]. Community-acquired pneumonia (CAP) is the main type of pneumonia which can also result in high risk of mortality in critically-ill patients [3-5]. Risk stratification is crucial for the treatment of pneumonia, because it identifies patients with high risk of mortality for whom intensive care can be used [6,7]. Therefore, to improve the accuracy of risk stratification, there is need to find more appropriate factors for predicting the risk of mortality among pneumonia patients. Such findings will provide much help in developing some effective risk stratification tools

for evaluating the prognosis of pneumonia patients [8,9]. Currently, some blood biomarkers, such as C-reactive protein, procalcitonin and proadrenomedullin are thought to be associated with the survival of pneumonia patients [10-12].

Vitamin D plays important roles in regulating calcium homeostasis and immune response [13-16]. Results from previous studies suggest that vitamin D has a protective effect against respiratory tract infections [17,18]. It has been suggested that vitamin D may exert immuno-modulatory effects in patients with pneumonia [19,20]. Low vitamin D status or vitamin D deficiency is common in the elderly and in critically-ill patients, as well as in patients with

pneumonia [21-23]. Some studies reported that low vitamin D status was a risk factor for adverse outcomes among pneumonia patients, but results from some other studies were in disagreement with these reports [24-29]. Thus, in the present study, meta-analysis was carried out to quantitatively analyze published studies that assessed the prognostic role of vitamin D in pneumonia patients.

METHODS

Search strategy and selection criteria

Two investigators independently performed the literature search, which covered PubMed and Embase. The key search terms were vitamin D or 25-hydroxyvitamin D, respiratory tract infection and pneumonia. No restriction on publication date was applied. Studies were considered eligible and selected if they met all the conditions in the selection criteria i.e., (1) the studies were designed to assess the role of vitamin D in patients with pneumonia; (2) the patients were diagnosed with pneumonia; (3) studies that compared the risk of mortality of patients with or without lower vitamin D level; and (4) studies with data on outcomes, such as hazard ratios (HR) or risk ratios (RR) and their 95 % confidence intervals (95 % CI). Studies without any one of these conditions were excluded.

Data extraction and quality assessment

Two investigators independently extracted the following data from original studies: name of the first author, country of origin, type of study, sample size, types of pneumonia, type of outcomes, confounding factors and RRs of mortality. Study quality was evaluated according to Newcastle Ottawa Scale [30]. Quality was defined as high level or low level by the Newcastle Ottawa Scale.

Statistical analysis

STATA (Version 12.0, Stata Corporation, TX, USA) was used to perform statistical analyses. The Q-test and I^2 index were used to assess heterogeneity. For obvious heterogeneity (I^2 more than 50 %), random-effect meta-analysis (DerSimonian and Laird's method) was performed. For lack of heterogeneity (I^2 less than 50 %), fixed-effect meta-analysis (Mantel-Haenszel method) was done. Sensitivity analysis by omitting one study at a time was applied. Egger test and funnel plot were used to assess the risk of publications bias.

RESULTS

Included studies

Our database search revealed a total of 926 articles. However, after reading the titles and abstracts, only 12 studies were selected and then scrutinized by full-text reviews [24-29, 31-37]. Among these 13 studies, 7 studies were further excluded for not reporting data on the outcomes of interest [31-37]. Finally, 6 studies [24-29] fulfilled the eligibility criteria and were included. The characteristics of those 6 included studies are listed on Table 1.

Three studies were retrospective cohort studies, and the other 3 studies were prospective cohort studies. The included studies published from 1997 to 2016, and all were published in English. One study assessed the impact of rickets on mortality risk among pneumonia patients; rickets is associated with lack of vitamin D [24]. Five studies recruited adult patients, and one study recruited children patients. Four out of those 6 studies recruited patients with CAP. Four studies provided adjusted RRs, but there were inconsistencies in these values. By the Newcastle Ottawa Scale, four studies had high quality, while the other two studies had low quality.

Meta-analysis

The I^2 value in the meta-analysis of the 6 studies was 71.4 %. Meta-analysis of these 6 studies showed that low vitamin D status was associated with higher risk of mortality among pneumonia patients (RR = 2.59, 95 % CI = 1.32-5.08, *p* = 0.005) (Figure 1). Sensitivity analysis by omitting one study at a time, showed that the pooled RRs were not obviously changed by any single study. Besides, after excluding one study on the impact of rickets on mortality risk among pneumonia patients, low vitamin D status was associated with higher risk of mortality among pneumonia patients. Meta-analysis of the remaining 5 studies also proved that low vitamin D status was associated with higher risk of mortality among pneumonia patients (RR = 3.40, 95 % CI = 1.70 - 6.81, *p* = 0.001) (Figure 2). The I^2 value in the meta-analysis of the 5 studies was 36.7 %.

To assess whether low vitamin D status was an independent factor of mortality among pneumonia patients, a meta-analysis of studies with adjusted estimates was also performed. The pooled outcome suggested that low vitamin D status was independently associated with higher risk of mortality among pneumonia patients (RR = 3.15, 95 % CI = 54 - 6.44, *p* = 0.002) (Figure

3). The I^2 value in the meta-analysis of those 5 studies was 41.8 %.

Finally, there was no significant risk of bias in the meta-analysis (Figure 4), and the *p* value for Egger's test was 0.22.

DISCUSSION

Vitamin D has an important role in regulating biological functions, including immune response to infections. However, the roles of vitamin D in pneumonia are still largely unknown [14-16]. In this meta-analysis, the prognostic role of vitamin D in pneumonia patients was analyzed. The findings showed that low vitamin D status was associated with higher risk of mortality among pneumonia patients. Subsequent analyses also found that low vitamin D status was independently associated with higher risk of mortality among pneumonia patients. Thus, these outcomes indicate that vitamin D plays key roles in the development or progression of pneumonia, and low vitamin D level was significantly associated with higher risk of mortality in those patients.

Table 1: Characteristics of included studies on the prognostic role of vitamin D in pneumonia patients

Study	Study design	Country	Participants	Confounding factors	Quality
Muhe, (1997) [24]	Retrospective cohort	Ethiopia	521 children younger than 5 years with a diagnosis of pneumonia	None.	Low level
Leow (2011) [25]	Prospective cohort	New Zealand	112 patients admitted with community acquired pneumonia during winter	Sex, age, Charlson Index, CRP level and living in residential care were entered into the model	High level
Remmelts, (2012) [26]	Prospective cohort	Netherlands	272 hospitalized patients with CAP	Age and heart failure.	High level
Kim, (2015) [27]	Retrospective cohort	Korea	797 patients with community-acquired pneumonia	Pneumonia severity index.	High level
Haliloglu, (2016) [28]	Retrospective cohort	Turkey	44 patients with ventilator-associated pneumonia	None.	Low level
Holter, (2016) [29]	Prospective cohort	Norway	241 hospital survivors of CAP	Age, COPD, immuno-compromization and season.	High level

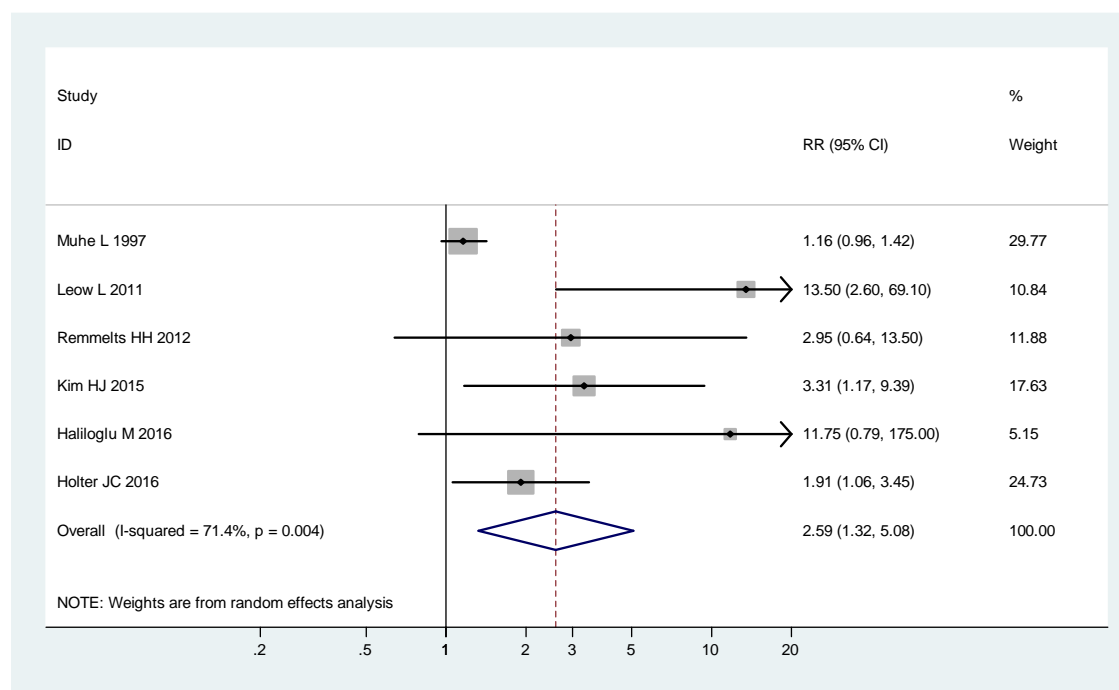*(CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein)*

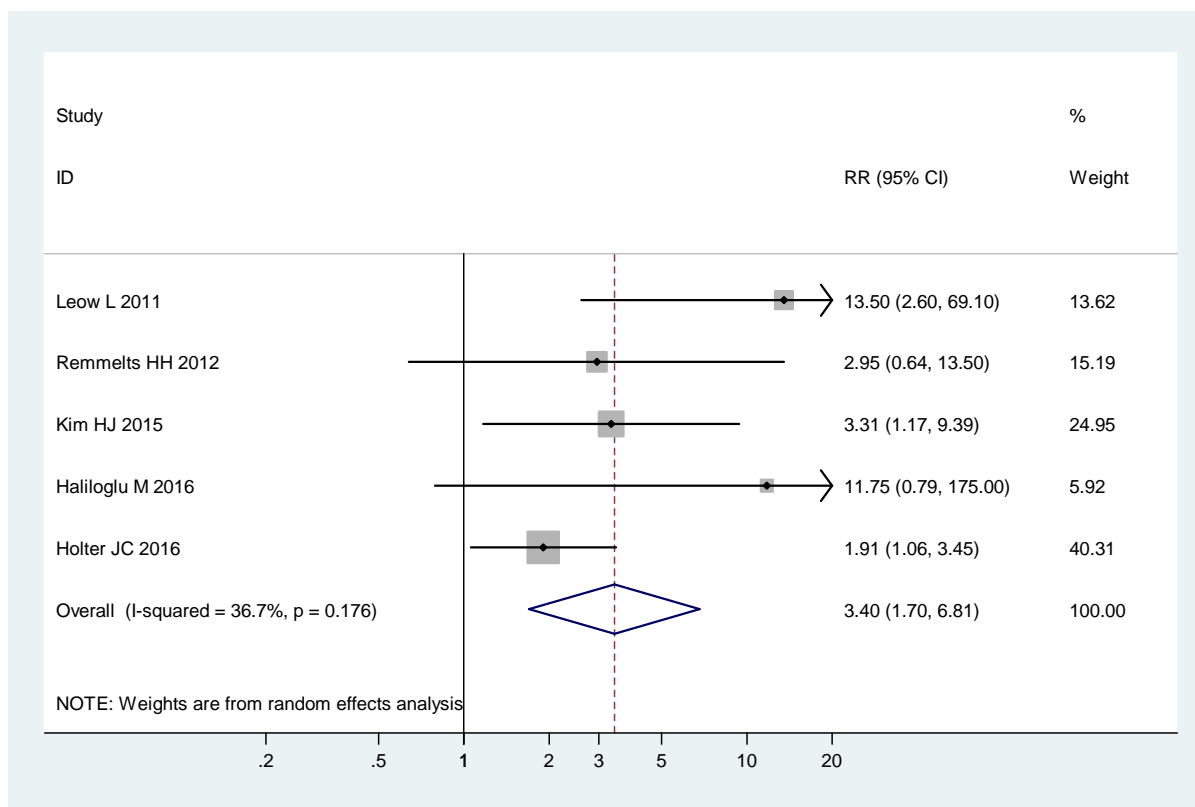**Figure 1:** Forest plot in the meta-analysis of total 6 included studies

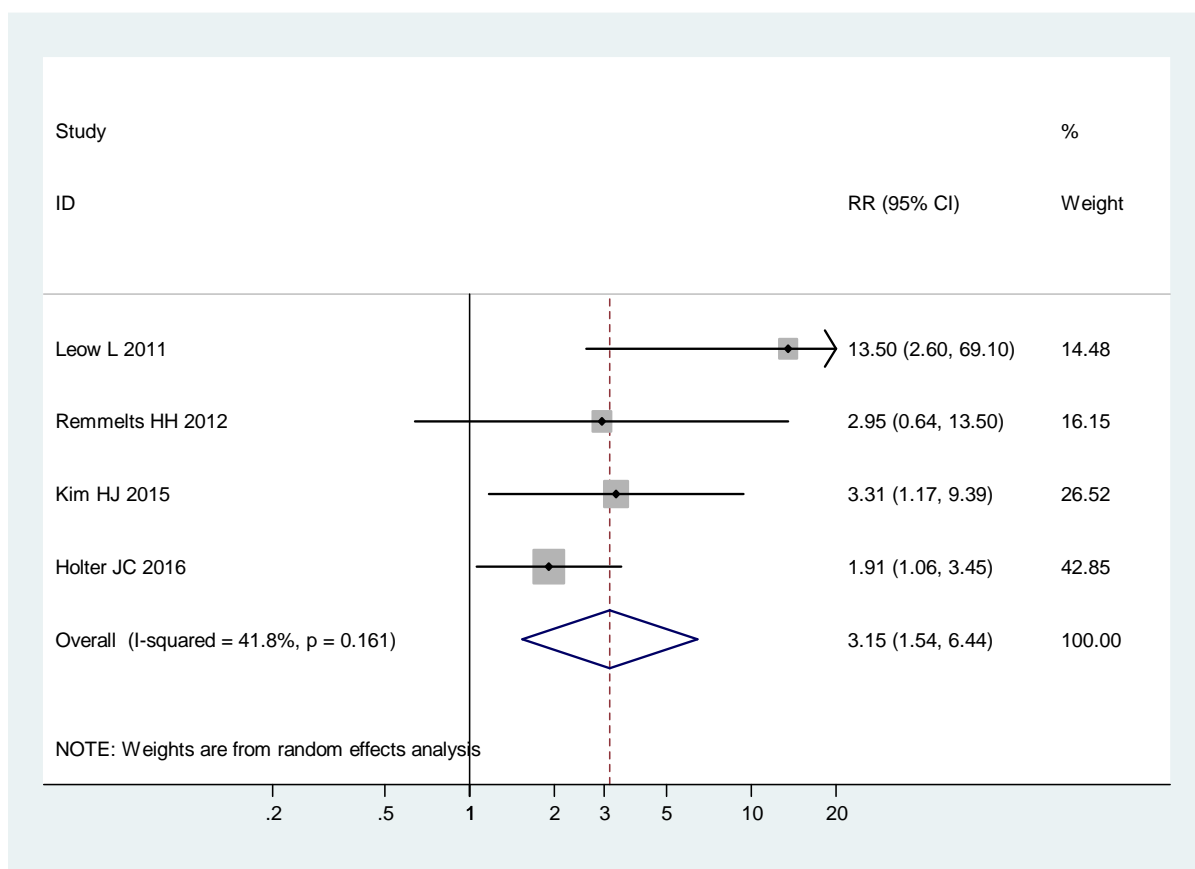**Figure 2:** Forest plot in the meta-analysis of five studies on the role of vitamin D in pneumonia patients

Figure 3: Forest plot in the meta-analysis of four studies reporting adjusted risk estimates
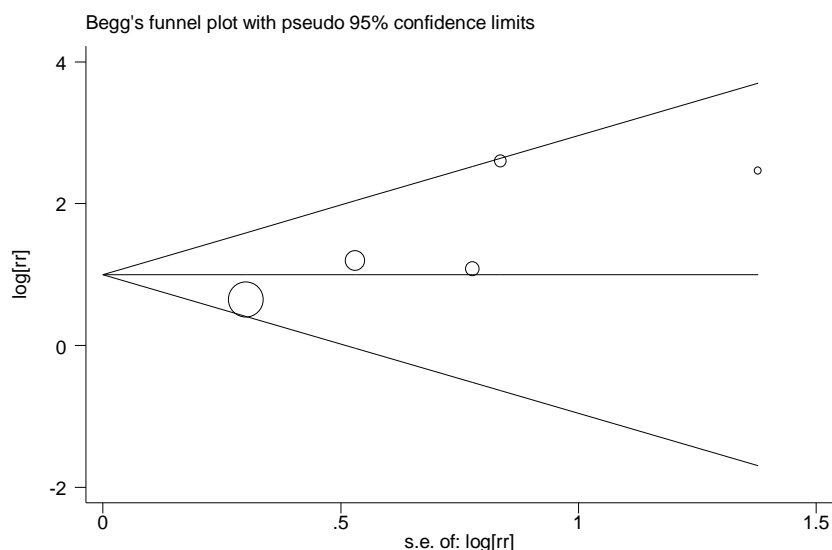
Figure 4: Funnel plot in the meta-analysis of five studies on the role of vitamin D in pneumonia patients

The role of vitamin D in pneumonia can be explained because the vitamin exerts some immuno-modulatory effects. Indeed, individuals with vitamin D deficiency have impaired immune function and thus are at higher risk of infections [38,39]. Some observational studies have found that patients with pneumonia usually have lower level of vitamin D than those without pneumonia, suggesting that vitamin D may be involved in vulnerability to pneumonia [32-34]. In the meta-analysis carried out in this study, it was directly established that vitamin D is a prognostic biomarker in pneumonia patients. This is new evidence for the role of vitamin D as an important immuno-modulatory factor in controlling infections.

Pneumonia is a common disease associated with high risk of morbidity and mortality. Risk stratification is crucial for the treatment of pneumonia. It is important to find more appropriate risk factors for predicting the risk of mortality among pneumonia patients, by improving the accuracy of risk stratification. The findings from this meta-analysis suggest that low vitamin D level is a good risk factor predicting the risk of mortality among pneumonia patients. This finding can be applied in clinical practice.

Apart from its prognostic role, the results from this study also suggest possible therapeutic effect of vitamin D in pneumonia. Since many pneumonia patients have vitamin D insufficiency, they may be treated with vitamin D supplements. Several studies have assessed the association between vitamin D status and pneumonia, but it was unclear whether vitamin D supplementation could improve the prognosis of pneumonia patients with vitamin D insufficiency [40-42].

Study limitations

This study had several limitations. Firstly, all the studies involved limited number of pneumonia patients. To improve the results, future studies with more pneumonia patients are needed. Secondly, some of those studies had a retrospective cohort design, and thus had high risk of bias. More studies with good quality are needed to provide new and strong evidence for the role of vitamin D in pneumonia. Thirdly, few studies were available, especially among African or Asian populations. More studies from multiple countries are also needed. Finally, the impact of season was not analyzed in most studies. Sunlight and seasons have important impact on circulating vitamin D levels and thus may have some influence on the survival of pneumonia patients. Future studies need to control the impact of sunlight or season when investigating the roles of vitamin D in pneumonia patients.

CONCLUSION

This study demonstrates that low vitamin D level is associated with higher risk of adverse outcomes in patients with pneumonia. However, additional studies are needed to verify the prognostic role of vitamin D in pneumonia patients. In addition, the molecular mechanisms for the roles of vitamin D against infections are also unclear and need to be studied in future studies.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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