

This Provisional PDF corresponds to the article as it appeared upon acceptance. Fully formatted PDF and full text (HTML) versions will be made available soon.

## Association between vitamin D deficiency and mortality in critically ill adult patients: a meta-analysis of cohort studies

*Critical Care* 2014, **18**:684 doi:10.1186/s13054-014-0684-9

Yan-Peng Zhang (1650394713@qq.com)  
You-Dong Wan (wanyoudong130@163.com)  
Tong-Wen Sun (suntongwen@163.com)  
Quan-Cheng Kan (1017361289@qq.com)  
Le-Xin Wang (LWang@csu.edu.au)

Published online: 12 December 2014

**ISSN** 1364-8535

**Article type** Research

**Submission date** 30 August 2014

**Acceptance date** 20 November 2014

**Article URL** <http://ccforum.com/content/18/6/684>

Like all articles in BMC journals, this peer-reviewed article can be downloaded, printed and distributed freely for any purposes (see copyright notice below).

Articles in BMC journals are listed in PubMed and archived at PubMed Central.

For information about publishing your research in BMC journals or any BioMed Central journal, go to <http://www.biomedcentral.com/info/authors/>

# Association between vitamin D deficiency and mortality in critically ill adult patients: a meta-analysis of cohort studies

Yan-Peng Zhang<sup>1,†</sup>  
Email: 1650394713@qq.com

You-Dong Wan<sup>1,†</sup>  
Email: wanyoudong130@163.com

Tong-Wen Sun<sup>1\*</sup>  
\* Corresponding author  
Email: suntongwen@163.com

Quan-Cheng Kan<sup>2\*</sup>  
\* Corresponding author  
Email: 1017361289@qq.com

Le-Xin Wang<sup>3\*</sup>  
\* Corresponding author  
Email: LWang@csu.edu.au

<sup>1</sup> Department of Integrated Intensive Care Unit, the First Affiliated Hospital, Zhengzhou University, 1 Jianshe East Road, Zhengzhou 450052, China

<sup>2</sup> Pharmaceutical Department, the First Affiliated Hospital, Zhengzhou University, 1 Jianshe East Road, Zhengzhou 450052, China

<sup>3</sup> School of Biomedical Science, Charles Sturt University, Wagga Wagga, NSW 2650, Australia

† Equal contributors.

## Abstract

### Introduction

Vitamin D deficiency is common in critically ill patients, and was reported to be associated with adverse outcomes. However, the effect of vitamin D deficiency on mortality in critically ill patients remains unclear.

### Methods

We searched PubMed and EMBASE from the inception to July 2014 for cohort studies to assess the effect of vitamin D deficiency on the incidence of mortality in critically ill patients. Mortality-specific odds ratio (OR) with 95% confidence interval (CI) were pooled with a random- or fixed-effect models when appropriate.

## Results

Seven cohort studies with a total of 4,204 participants including 1,679 cases of vitamin D deficiency were included in this meta-analysis. Vitamin D deficiency was significantly associated with an increased hospital mortality (OR 1.76; 95% CI, 1.38 to 2.24;  $P < 0.001$ ), with very low heterogeneity ( $I^2 = 2.3\%$ ;  $P = 0.402$ ). The finding of increased hospital mortality in critically ill adult patients was consistently found in every stratum of our subgroup analyses.

## Conclusions

This meta-analysis suggests that vitamin D deficiency is associated with increased incidence of hospital mortality in critically ill adult patients.

## Introduction

Vitamin D is a group of fat soluble vitamins that play a significant role in the regulation of bone metabolism [1], it also plays a major role in extra-skeletal metabolic processes, such as glucose metabolism, and in many aspects of cellular functions [2,3]. Vitamin D deficiency is associated with various disorders such as diabetes, infections, myocardial infarction, autoimmune disease, chronic obstructive pulmonary disease, tuberculosis, and excess mortality in general population [4]. The incidence of vitamin D deficiency has been reported to range from 26% to 82% in critically ill patients [5,6], and mounting evidence indicates that vitamin D deficiency is associated with adverse outcomes such as increased infection rates, prolonged length of ICU stay [7], higher in-hospital mortality [8], and increased health care costs [9]. However, Ralph et al. [10] did not observed an association between low levels of vitamin D and increased risk of mortality in critically ill patients, but they did find that patients with above physiological vitamin D levels had higher mortality and illness severity scores.

At present, the effect of vitamin D deficiency on outcomes such as mortality and morbidity in critically ill patients is not clear. We conducted a meta-analysis of 7 cohort studies to investigate the effect of vitamin D deficiency on clinical outcomes such as hospital mortality, ICU mortality and length of ICU stay in critically ill adult patients.

## Materials and methods

### Search strategy

The search was carried out in keeping with the statement of Meta-analysis of Observational Studies in Epidemiology (MOOSE) [11]. Without language restrictions, the literature from the inception to July, 2014 was searched in PubMed and EMBASE. The following search terms were used: “Vitamin D”, “cholecalciferol”, “hydroxycholecalciferols”, “ergocalciferol”, “25-hydroxyvitamin D<sub>2</sub>”, “dihydrotachysterol”, “critical ill” and “critically ill”. Furthermore, we reviewed the reference lists in the retrieved articles and recent reviews to identify other potential relevant studies.

## Study selection

A published study was included if it: 1) was a cohort design; 2) explored the effect of vitamin D deficiency on mortality in the critically ill adult patients; 3) reported the adjusted effect size and its 95% confidence intervals (CIs). In case of duplicate publication, we only included studies of the most informative and complete.

## Data extraction and quality assessment

The following information was abstracted from all the included studies by using a standardized data collection form: study name (together with the first author's name and publication year), study design, country, population characteristics, number of patients, number of vitamin D deficiency cases, gender composition in patients, mean age of the patients, severity of illness by Simplified Acute Physiology Score (SAPS) or Acute Physiology and Chronic Health Evaluation (APACHE) scores, definition of vitamin D deficiency, major clinical outcomes, and quantity score. We also checked the supplementary files, and contacted the authors for more detailed information where necessary.

We assessed the authenticity and quality of the included studies by Newcastle-Ottawa Scales (NOS) [12], in which a study was judged on 3 broad perspectives consisting of 8 items. We assigned risk of bias categories in accordance with the number of adequate items of Newcastle-Ottawa Scales (NOS) that judged in each study. As following categories: low risk of bias (6–8 adequate items), medium risk of bias (4–5 adequate items), high risk of bias (less than 4 adequate items), very high risk of bias (no description of methods).

Two investigators (YP Zhang and YD Wan) carried out the literature search, study selection, data extraction and quality assessment independently. Any Discrepancies were resolved by consensus.

## Statistical analysis

To compute a summary odds ratio (OR), we used the adjusted odds ratio (OR) and its 95% CI in all analyses. Hazard ratio (HR) was considered as odds ratio (OR) directly. Heterogeneity test was conducted using the Cochran Q statistic at the  $P < 0.10$  level of significance. We also quantify the  $I^2$  statistic, which describes the inconsistency due to the heterogeneity across studies [13-15].  $I^2$  value  $> 50\%$  indicates a significant heterogeneity. The appropriate pooling method was decided according to the value of the  $I^2$  statistic: fixed-effects models for  $I^2 < 50\%$  and random-effects models for  $I^2 \geq 50\%$  [13-15]. Prespecified subgroup analyses were performed according to minimum serum 25-hydroxyvitamin D level as the threshold to define vitamin D deficiency (20 ng/ml, 15 ng/ml, 12 ng/ml, 10 ng/ml) to examine the influence of this clinical factor on the overall risk estimation. We also conducted a sensitivity analysis by changing the pooling model (fixed-effects model or random-effects model) and using the one-study-out method and applying various exclusion criteria to test the robustness of the pooled estimate. Potential publication bias was assessed by Egger linear regression test [16].  $P < 0.05$  was considered to be representative of a significant statistical publication bias, except where otherwise specified. All statistical analyses were performed by using STATA, version 11.0 (Stata Corp).

# Results

## Study selection and study characteristics

Our initial search yielded 98 potentially relevant publications, 3 of which were excluded for duplicate publications. We excluded 62 studies based on title and abstract review. After reviewing the full text of the remaining 33 studies, we identified 7 cohort studies in this present meta-analysis [8,17-22]. The reasons for excluding studies in the final review included: reviews and editorial articles, small sample size ( $n < 100$ ), not relevant to our analysis, and studies did not report adjusted ORs of risk estimates and its 95% CIs (see the detail in Figure 1).

---

### Figure 1 Flow chart of article selection.

---

The main characteristics of the seven studies included in this meta-analysis are shown in Table 1. In total, 4,204 participants including 1,679 cases of vitamin D deficiency were enrolled in this meta-analysis. The study-design types were as follows: single center studies ( $n = 4$  [8,18,19,22]), multi center studies ( $n = 3$  [17,20,21]), retrospective studies ( $n = 3$  [8,17,22]), and prospective studies ( $n = 4$  [18-21]). Six studies presented outcome of hospital mortality [8,17,18,20-22], and only two studies presented outcome of ICU mortality [19,22]. As for length of ICU stay, one study provided data expressed as mean  $\pm$  SD [8], two studies did not report it [17,20], and the rest four described the data as median [18,19,21,22]. Every single study was matched or adjusted for a wide range of potential confounders. There is no consistent definition on vitamin D deficiency between included studies. The average NOS score of the included studies was 6.6 (range from 6 to 7). An additional table file shows this in more detail [see Additional file 1].

**Table 1 Main characteristics included in the meta-analysis**

First author/Year of publication (reference)	Amrein. et al./2014 [22]	Aygenel. et al./2013 [19]	Hu. et al./2013 [18]	Nair. et al./2012 [21]	Higgins. et al./2012 [20]	Venkatram. et al./2011 [8]	Braun. et al./2011 [17]
<b>Study design</b>	single-center, retrospective	single-center, prospective	single-center, prospective	multi-center, prospective	multi-center, prospective	single-center, retrospective	multi-center, retrospective
<b>Country</b>	Austria	Turkey	China	Australia	Canada	USA	USA
<b>Patients</b>	Neurologic (30.2%), Cardiac surgery (15.0%), Respiratory disease (8.1%), Trauma (5.8%), Brain surgery (5.0%), Infectious diseases, including sepsis at admission (4.4%)	Respiratory insufficiency (45%), Organ dysfunctions (44%), Invasive mechanical ventilation (44%), Sepsis/septic shock (35.8%), Renal replacement therapy (34%), Nosocomial infection (35%)	Severe pneumonia with respiratory failure (47.2%), Acute exacerbations of chronic obstructive pulmonary disease (19%), Intra-abdominal infection (15.3%), Mechanical ventilation (85.6%)	Cardiac (30%), Infection/sepsis (26%), Heart/lung/bone marrow transplant (21%), Trauma (9%), Metabolic (7%), Neurological (7%)	Cardiovascular (14%),Respiratory (29%),Neurological (7%),Metabolic (7%),Gastrointestinal (3%), Sepsis (5%), Postoperative (35%)	Cardiac (4.8%), Gastrointestinal (10.7%), Metabolic (11.4%), Neurological (12.5%), Obstructive airway disease (13.7%), Pulmonary (18.3%), Others (10.9%), Renal (5%), Sepsis/Septic shock (12.3%)	Medical (58.3%) Surgical (41.7%)
<b>No. patients</b>	655	201	216	100	196	437	2,399
<b>No. case patients (%)</b>	394(60.2%)	139(69.2%)	95(44.0%)	24(24.0%)	50(25.5%)	340(77.8%)	637(26.6%)
<b>No. male patients (%)</b>	412 (62.9%)	113 (56.0%)	120(55.6%)	65(65.0%)	121(62.0%)	208 (47.5%)	1,030 (43.0%)
<b>Mean age, y</b>	65 (22) <sup>a</sup>	66 (21) <sup>a</sup>	64(25) <sup>a</sup>	52 ± 17 <sup>b</sup>	64 ± 14 <sup>b</sup>	56.6 ± 17.1 <sup>b</sup>	64.9 ± 16.6 <sup>b</sup>
<b>Severity of illness</b>	26 (16) <sup>a</sup> (SAPS II)	23(11) <sup>a</sup> (APACHE II)	21(8) <sup>a</sup> (APACHE II)	21 ± 8 <sup>b</sup> (APACHE II)	20.2 ± 7.8 <sup>b</sup> (APACHE II)	67.0 ± 27.5 <sup>b</sup> (APACHE IV)	/
<b>Definition of Vitamin D deficiency, insufficiency and sufficiency</b>	deficient (<20 ng/ml), insufficient (≥20 and <30 ng/ml), normal (≥30 ng/ml)	insufficient (<20 ng/ml), sufficient (≥20 ng/ml)	deficient (<20 ng/ml), insufficient (≥20 and <30 ng/ml), sufficient (≥30 ng/ml)	deficient (<10 ng/ml), insufficient(10–20 ng/ml), sufficient(>20 ng/ml)	deficient (≤12 ng/ml), insufficient (>12 to ≤24 ng/ml), sufficient (>24 ng/ml)	deficient (<20 ng/ml), insufficient (≥20 and <30 ng/ml), sufficient (≥30 ng/ml)	deficient(≤15 ng/mL, insufficient (16 –29 ng/mL, sufficient (≥30 ng/ mL)
<b>Major Clinical Outcomes</b>	ICU and hospital mortality, ICU and hospital LOS	ICU mortality	hospital mortality	hospital mortality, ICU and hospital LOS	hospital mortality, time-to-alive ICU discharge	hospital mortality, hospital LOS	30-day, 90-day, 365-day, and in-hospital mortality
<b>Quality score<sup>c</sup></b>	7	6	6	7	7	6	7

SAPA, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, Intensive Care Unit; LOS, length of stay. a, median (interquartile range); b, mean ± standard deviation; c, Newcastle-Ottawa Scales (NOS).

## Overall results

Combined by fixed-effects model, the multivariable-adjusted ORs of hospital mortality and ICU mortality for each study are shown in Figures 2, 3, respectively. Results from six studies showed that vitamin D deficiency is associated with an increased risk of hospital mortality (OR 1.76; 95% CI, 1.38–2.24;  $P < 0.001$ ), with very low heterogeneity among the studies ( $I^2 = 2.3\%$ ;  $P = 0.402$ ). For ICU mortality, there was not enough evidence to conclude that vitamin D deficiency was not associated with increased incidence of ICU mortality in critically ill adult patients (OR 1.43; 95% CI, 0.76–2.70;  $P = 0.271$ ). The data of length of ICU stay for every individual study is presented in Table 2.

**Figure 2 Forest plot showing the effect of vitamin D deficiency on hospital mortality.**

**Figure 3 Forest plot showing the effect of vitamin D deficiency on ICU mortality.**

**Table 2 ICU length of stay (LOS) among studies**

Study	Year	Vitamin D classification	ICU LOS (days)
Amrein. et al. [22]	2014	deficiency, <20 ng/ml	6.9 (9.8) <sup>a</sup>
		insufficiency, 20–30 ng/ml	4.9 (7.7) <sup>a</sup>
		sufficiency, >30 ng/ml	5.2 (6.5) <sup>a</sup>
Aygençel.et al. [19]	2013	insufficiency, <20 ng/ml	9 (5, 14) <sup>b</sup>
		sufficiency, ≥20 ng/ml	8 (5, 13) <sup>b</sup>
Hu. et al. [18]	2013	deficiency, <20 ng/ml	10.5 (6.8, 25.3) <sup>b</sup>
		insufficiency, 20–30 ng/ml	8.6 (6.9, 20.5) <sup>b</sup>
		sufficiency, >30 ng/ml	15.2 (10.3, 23.6) <sup>b</sup>
Nair.et al. [21]	2012	deficiency, <10 ng/ml	12 (2, 14) <sup>b</sup>
		Insufficiency, 10–20 ng/ml	7 (4, 15) <sup>b</sup>
		sufficiency, >20 ng/ml	4 (3, 10) <sup>b</sup>
Higgins.et al. [20]	2012	deficient, ≤12 ng/ml	10.6 ± 8.4 <sup>c</sup>
		insufficient, 12–24 ng/ml	6.8 ± 6.0 <sup>c</sup>
		sufficient, >24 ng/ml	5.9 ± 5.4 <sup>c</sup>
Venkatram. et al. [8]	2011	deficiency, <20 ng/ml	4.3 ± 4.5 <sup>c</sup>
		insufficiency, 20–30 ng/ml	3.7 ± 3.9 <sup>c</sup>
		sufficiency, >30 ng/ml	4.2 ± 3.7 <sup>c</sup>
Braun.et al. [17]	2011	-	-

a, median(interquartile range); b, median(Q1,Q3); c, mean ± standard deviation.

## Subgroup and sensitivity analyses

Table 3 shows the results of subgroup and sensitive analyses. Definition of vitamin D deficiency varies between studies, which may impact the overall estimates. We therefore stratify mortality rates across different studies based on vitamin D thresholds as a continuum, and the finding of increased incidence of hospital mortality in critically ill adult patients was consistently found in each stratum. Our sensitivity analyses suggested that the overall estimates did not materially altered by changing pooling models (fixed-effects model: OR 1.76; 95%CI, 1.38—2.24 and random-effects model: OR 1.76; 95% CI, 1.37—2.26), and also did not materially altered all along with any single study removed in each turn, with a range from 1.67 (95% CI:1.30–2.15) to 1.82 (95% CI:1.42–2.34).

**Table 3 Subgroup and sensitive analyses for hospital mortality**

Analyses	No. studies	OR (95% CI)	<i>P</i> <sub>heterogeneity</sub>	<i>I</i> <sup>2</sup>
<i>Subgroup analysis</i>				
<b>Total</b> [8,17-22]	7	1.76 (1.38-2.24)	0.402	2.3%
<b>25(OH)D level as a cutoff for vitamin D deficiency</b>				
<b>20 ng/ml</b> [8,18,22]	3	2.12 (1.35-3.34)	0.198	38.3%
<b>15 ng/ml</b> [17]	1	1.72 (1.27-2.33)	-	-
<b>12 ng/ml</b> [20]	1	1.12 (0.45-2.70)	-	-
<b>10 ng/ml</b> [21]	1	1.13 (0.18-7.27)	-	-
<i>Sensitive analysis</i>				
<b>Multi-center</b> [17,20,21]	3	1.63 (1.23-2.17)	0.623	0.0%
<b>Prospective cohort</b> [18,20,21]	3	1.83 (1.03-3.24)	0.241	29.7%
<b>One-study-out method</b>				
<b>Amrein</b> [22]	1	1.79 (1.23-2.70)	0.284	20.5%
<b>Hu</b> [18]	1	1.67 (1.30-2.15)	0.511	0.0%
<b>Nair</b> [21]	1	1.77 (1.39-2.26)	0.298	18.3%
<b>Higgins</b> [20]	1	1.82 (1.42-2.34)	0.396	1.8%
<b>Venkatram</b> [8]	1	1.72 (1.35-2.19)	0.571	0.0%
<b>Braun</b> [17]	1	1.82 (1.23-2.70)	0.281	21.0%
<b>Fixed-effects vs. random-effects model method</b>				
<b>Fixed-effects model</b>	6	1.76 (1.38-2.24)	0.402	2.3%
<b>Random-effects model</b>	6	1.76 (1.37-2.26)	0.402	2.3%

25(OH)D, 25-hydroxyvitamin D.

## Publication bias

Publication bias was assessed, but the low power with only seven studies limited the interpretability of the finding.

## Discussion

### Main findings

To the best of our knowledge, this is the first meta-analysis to explore the effect of vitamin D deficiency on mortality in critically ill adult patients. This study suggests that vitamin D deficiency is associated with an increased hospital mortality in the critically ill adult patients. The effect of vitamin D deficiency was observed in every stratum of our subgroup analyses. In addition, a relatively small number of samples (only two studies [19,22]) provided data on ICU mortality, and the final estimate showed there was not enough evidence to conclude that vitamin D deficiency was not associated with increased incidence of ICU mortality in critically ill adult patients (OR 1.43; 95% CI, 0.76-2.70; *P* =0.271).

### Possible mechanism

Although vitamin D deficiency may increase the incidence of hospital mortality in the critically ill adult patients, the reason remains unclear and can be explained by several different mechanisms. Firstly, a range of biological responses involving immune system functions and processes in cellular growth, proliferation, and apoptosis may be influenced by vitamin D [1,23]. Vitamin D regulates the expression of the antimicrobial peptides cathelicidin (LL-37) and  $\beta$ -defensin, both of which have functional effectors within the



immune system [24,25]. Cathelicidin can fight against a broad spectrum of infectious agents, including Gram-negative and -positive bacteria, as well as fungi [24]. Secondly, as vitamin D is a known link between toll-like receptors (TLR) activation and innate immunity [26], and vitamin D receptors are expressed in T cells [27], activated B cells [28], and dendritic cells [29], vitamin D deficiency may increase the risk of inflammation and sepsis in the critically ill by the suppression of immune reactivity and stimulatory effects on innate immunity [30-32]. Thirdly, vitamin D has also been found to down-regulate proinflammatory cytokines such as interferon- $\gamma$ , tumor necrosis factor- $\alpha$ , and interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, as well as T helper 1 cells and B cells in the adaptive immune system [33,34]. At the same time, vitamin D up-regulates anti-inflammatory cytokines, such as IL-4, IL-5 and IL-10. It promotes the expression of T-regulatory cells, which turn off the adaptive immune response [35]. These studies suggest that vitamin D deficiency disturbs the innate immunity system and compromises the ability of critically ill patients to down-regulate the adaptive immune response. In addition, the tissue requires more vitamin D in critically ill patients, and vitamin D deficiency may result in wide spread tissue dysfunction [36]. These effects may explain an increasing mortality results from systemic inflammatory response syndrome, organ failure and metabolic dysfunction in critically ill patients.

## **Clinical implications**

Our findings may have several implications. As vitamin D deficiency impacts on mortality in critically ill patients, vitamin D levels may be used to predict the outcomes in critically ill patients. Unlike markers such as C-reactive protein (CRP), procalcitonin, D-dimer and leucocyte counts, which have been shown to predict disease severity in critically ill patients [37], vitamin D levels may not only predict disease severity and outcomes but also contribute to the co-morbidities commonly seen in critically ill patients. Our meta-analysis may offer possibilities of therapeutic exploitation of vitamin D supplementation in critically ill patients. A recent randomized clinical trial by Amrein and colleagues [38] suggested that administration of high-dose vitamin D<sub>3</sub> compared with placebo did not improve hospital length of stay and hospital mortality for vitamin D deficient ( $\leq 20$  ng/mL) patients who are critically ill. However, lower hospital mortality was observed in a subgroup of patients with severe vitamin D deficiency ( $\leq 12$  ng/mL) [38]. These findings should be interpreted with caution and researchers should probe further into the effect of vitamin D supplementation on adverse outcomes, as well as the assessment of its dosing efficacy and safety.

## **Strengths and limitations**

The generalizability of our meta-analysis has been enhanced by its exhaustive search without language restrictions and by using the MOOSE guidelines as our systematic review methods. Also, we are able to enhance the precision of the risk estimates with our strict inclusive criteria. We included seven cohort studies with high quality, which minimized the likelihood of recall interviewer and selection biases that can be a concern in epidemiological studies. We did not find any significant heterogeneity between the studies included in our meta-analysis.

Several limitations should be acknowledged. Firstly, some studies in this analysis did not utilize liquid chromatography-tandem mass spectrometry (LC-MS/MS) to determine 25(OH) D levels [39], which may potentially impact on the overall results. Secondly, vitamin D levels have seasonal variations, which has the highest mean values in August and the lowest mean levels in March [22]. Only the study by Amrein and colleagues [22] took seasonal influence

into account, so we could not adjust this factor. Thirdly, most studies were conducted in some specific ICUs, such as surgical ICU or medical ICU, which may not represent all ICU patients. Fourthly, the definition of vitamin D deficiency in critically ill patients remains inconsistent, and in our meta-analysis, different criteria of vitamin D definition was used among the studies.

## **Conclusions**

This study showed that vitamin D deficiency is associated with an increased hospital mortality in critically ill adult patients. However, there is not enough evidence to conclude that vitamin D deficiency is not associated with increased ICU mortality in critically ill adult patients, which need more studies to probe further into it in the future.

## **Key messages**

- Vitamin D deficiency is associated with increased incidence of hospital mortality in critically ill adult patients.
- Current evidence about vitamin D deficiency and increased ICU mortality is still not enough to draw a conclusive conclusion.
- More studies should probe further into the effect on ICU mortality in critically ill adult patients.

## **Abbreviations**

25(OH)D: 25-hydroxyvitamin D; APACHE: Acute physiology and chronic health evaluation; CI: Confidence interval; CRP: C-reactive protein; HR: Hazard ratio; ICU: Intensive care unit; LC-MS/MS: Liquid chromatography-tandem mass spectrometry; LOS: Length of stay; MOOSE: Meta-analysis of observational studies in epidemiology; NOS: Newcastle-Ottawa scales; OR: Odds ratio; SAPS: Simplified acute physiology score; SD: Standard deviation; TLR: Toll-like receptors.

## **Competing interests**

The authors declare that they have no competing interests.

## **Authors' contributions**

YPZ conceived the study, participated in the design, collected the data, and drafted the manuscript. YDW collected the data, and performed statistical analyses. KQC helped to collect the data. YDW and TWS conceived the study, participated in the design, and helped to draft the manuscript. Le-Xin Wang edited and checked the manuscript. All authors read and approved the final manuscript.

# Acknowledgements

## Source of funding

This study was supported by the National Natural Science Foundation of China (Grant No. 81370364), Innovative investigators project grant from the Health Bureau of Henan Province, Program Grant for Science & Technology Innovation Talents in Universities of Henan Province (2012HASTIT001), Henan provincial science and technology achievement transformation project (122102310581), Henan province of medical scientific research project (201203027), China.

## References

1. Holick MF: **Vitamin D deficiency.** *N Engl J Med* 2007, **357**:266–281.
2. Adams JS, Hewison M: **Update in Vitamin D.** *J Clin Endocrinol Metab* 2010, **95**:471–478.
3. Holick MF: **Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis.** *Am J Clin Nutr* 2004, **79**:362–371.
4. Lee P, Nair P, Eisman JA, Center JR: **Vitamin D deficiency in the intensive care unit: an invisible accomplice to morbidity and mortality?** *Intensive Care Med* 2009, **35**:2028–2032.
5. Lucidarme O, Messai E, Mazzoni T, Arcade M, du Cheyron D: **Incidence and risk factors of vitamin D deficiency in critically ill patients: results from a prospective observational study.** *Intensive Care Med* 2010, **36**:1609–1611.
6. Matthews LR, Ahmed Y, Wilson KL, Griggs DD, Danner OK: **Worsening severity of vitamin D deficiency is associated with increased length of stay, surgical intensive care unit cost, and mortality rate in surgical intensive care unit patients.** *Am J Surg* 2012, **204**:37–43.
7. McKinney JD, Bailey BA, Garrett LH, Peiris P, Manning T, Peiris AN: **Relationship between vitamin D status and ICU outcomes in veterans.** *J Am Med Dir Assoc* 2011, **12**:208–211.
8. Venkatram S, Chilimuri S, Adrish M, Salako A, Patel M, Diaz-Fuentes G: **Vitamin D deficiency is associated with mortality in the medical intensive care unit.** *Crit Care* 2011, **15**:R292.
9. Peiris AN, Bailey BA, Manning T: **The relationship of vitamin D deficiency to health care costs in veterans.** *Mil Med* 2008, **173**:1214–1218.
10. Ralph R, Peter JV, Chrispal A, Zachariah A, Dian J, Sebastian T, Venkatesh B, Thomas K: **Supraphysiological 25-hydroxy vitamin D3 level at admission is associated with**

**illness severity and mortality in critically ill patients.** *J Bone Miner Metab* 2014, DOI 10.1007/s00774-014-0585-7.

11. Rajasekhar A, Lottenberg R, Lottenberg L, Liu H, Ang D: **Pulmonary embolism prophylaxis with inferior vena cava filters in trauma patients: a systematic review using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines.** *J Thromb Thrombolysis* 2011, **32**:40–46.

12. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P: **The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.** Available: [www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) (accessed 2014 October 16).

13. DerSimonian R, Laird N: **Meta-analysis in clinical trials.** *Control Clin Trials* 1986, **7**:177–188.

14. Higgins JP, Thompson SG, Deeks JJ, Altman DG: **Measuring inconsistency in meta-analyses.** *BMJ* 2003, **327**:557–560.

15. Begg CB, Mazumdar M: **Operating characteristics of a rank correlation test for publication bias.** *Biometrics* 1994, **50**:1088–1101.

16. Egger M, Davey SG, Schneider M, Minder C: **Bias in meta-analysis detected by a simple, graphical test.** *BMJ* 1997, **315**:629–634.

17. Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y, Giovannucci E, Christopher KB: **Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill\*.** *Crit Care Med* 2011, **39**:671–677.

18. Hu J, Luo Z, Zhao X, Chen Q, Chen Z, Qin H, Qin Y, Liang X, Suo Y: **Changes in the calcium-parathyroid hormone-vitamin D axis and prognosis for critically ill patients: a prospective observational study.** *PLoS One* 2013, **8**:e75441.

19. Aygencel G, Turkoglu M, Tuncel AF, Candır BA, Bildacı YD, Pasaoglu H: **Is vitamin D insufficiency associated with mortality of critically ill patients?** *Crit Care Res Pract* 2013, **2013**:1–9.

20. Higgins DM, Wischmeyer PE, Queensland KM, Sillau SH, Sufit AJ, Heyland DK: **Relationship of vitamin D deficiency to clinical outcomes in critically ill patients.** *Jpen-Parenter Enter* 2012, **36**:713–720.

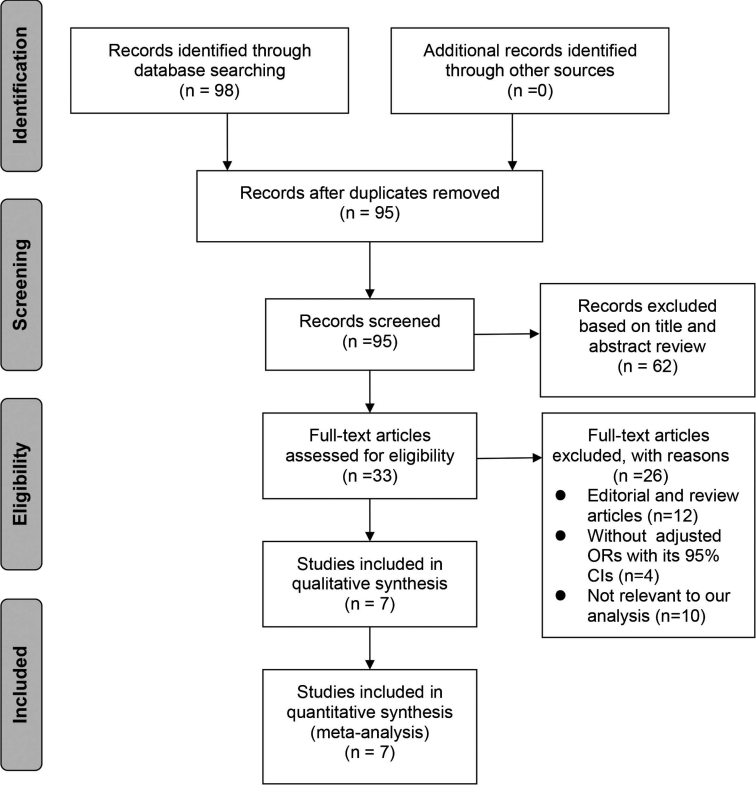
21. Nair P, Lee P, Reynolds C, Nguyen ND, Myburgh J, Eisman JA, Center JR: **Significant perturbation of vitamin D–parathyroid–calcium axis and adverse clinical outcomes in critically ill patients.** *Intens Care Med* 2013, **39**:267–274.

22. Amrein K, Zajic P, Schnedl C, Waltensdorfer A, Fruhwald S, Holl A, Purkart T, Wunsch G, Valentin T, Grisold A, Stojakovic T, Amrein S, Pieber TR, Dobnig H: **Vitamin D status and its association with season, hospital and sepsis mortality in critical illness.** *Crit Care* 2014, **18**:R47.

23. Arnson Y, Amital H, Shoenfeld Y: **Vitamin D and autoimmunity: new aetiological and therapeutic considerations.** *Ann Rheum Dis* 2007, **66**:1137–1142.
24. Durr UH, Sudheendra US, Ramamoorthy A: **LL-37, the only human member of the cathelicidin family of antimicrobial peptides.** *Biochim Biophys Acta* 2006, **1758**:1408–1425.
25. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, Tavera-Mendoza L, Lin R, Hanrahan JW, Mader S, White JH: **Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression.** *J Immunol* 2004, **173**:2909–2912.
26. Liu PT, Stenger S, Tang DH, Modlin RL: **Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin.** *J Immunol* 2007, **179**:2060–2063.
27. Mahon BD, Wittke A, Weaver V, Cantorna MT: **The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells.** *J Cell Biochem* 2003, **89**:922–932.
28. Heine G, Anton K, Henz BM, Worm M: **1alpha,25-dihydroxyvitamin D3 inhibits anti-CD40 plus IL-4-mediated IgE production in vitro.** *Eur J Immunol* 2002, **32**:3395–3404.
29. Adorini L, Penna G, Giarratana N, Roncari A, Amuchastegui S, Daniel KC, Uskokovic M: **Dendritic cells as key targets for immunomodulation by Vitamin D receptor ligands.** *J Steroid Biochem Mol Biol* 2004, **89–90**:437–441.
30. Deluca HF, Cantorna MT: **Vitamin D: its role and uses in immunology.** *FASEB J* 2001, **15**:2579–2585.
31. Mora JR, Iwata M, von Andrian UH: **Vitamin effects on the immune system: vitamins A and D take centre stage.** *Nat Rev Immunol* 2008, **8**:685–698.
32. Kankova M, Luini W, Pedrazzoni M, Riganti F, Sironi M, Bottazzi B, Mantovani A, Vecchi A: **Impairment of cytokine production in mice fed a vitamin D3-deficient diet.** *Immunology* 1991, **73**:466–471.
33. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C: **Vitamin D: modulator of the immune system.** *Curr Opin Pharmacol* 2010, **10**:482–496.
34. Baeke F, Gysemans C, Korf H, Mathieu C: **Vitamin D insufficiency: implications for the immune system.** *Pediatr Nephrol* 2010, **25**:1597–1606.
35. Hewison M: **Vitamin D and the immune system: new perspectives on an old theme.** *Endocrinol Metab Clin North Am* 2010, **39**:365–379.
36. Lee P: **Vitamin D metabolism and deficiency in critical illness.** *Best Pract Res Clin Endocrinol Metab* 2011, **25**:769–781.
37. Nylen ES, Alarifi AA: **Humoral markers of severity and prognosis of critical illness.** *Best Pract Res Clin Endocrinol Metab* 2001, **15**:553–573.

38. Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, Urbanic PT, Waltensdorfer A, Munch A, Warnkross H, Stojakovic T, Bisping E, Toller W, Smolle KH, Berghold A, Pieber TR, Dobnig H: **Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU Randomized Clinical Trial.** *JAMA* 2014, **312**:1520–1530.

39. Roth HJ, Schmidt-Gayk H, Weber H, Niederau C: **Accuracy and clinical implications of seven 25-hydroxyvitamin D methods compared with liquid chromatography-tandem mass spectrometry as a reference.** *Ann Clin Biochem* 2008, **45**:153–159.



Identification

Screening

Eligibility

Included

Records identified through database searching (n = 98)

Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 95)

Records screened (n = 95)

Records excluded based on title and abstract review (n = 62)

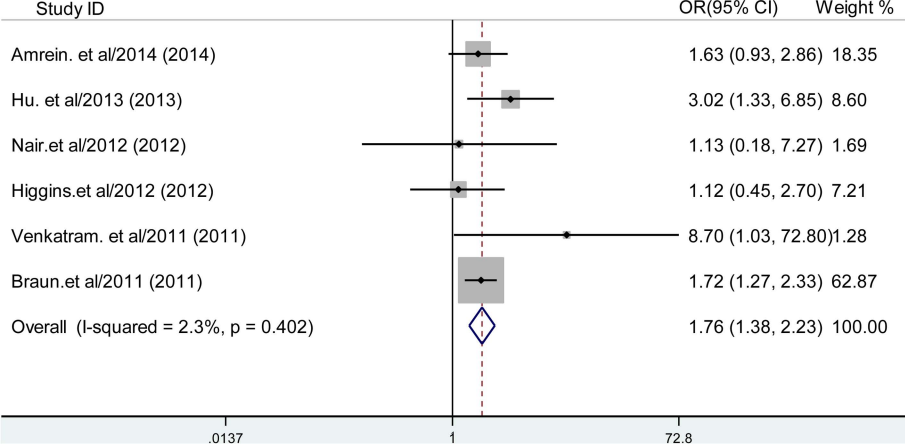
Full-text articles assessed for eligibility (n = 33)

Full-text articles excluded, with reasons (n = 26)

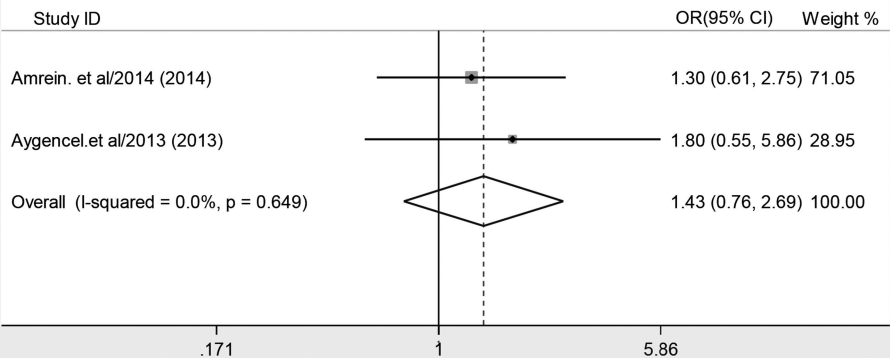
- Editorial and review articles (n=12)
- Without adjusted ORs with its 95% CIs (n=4)
- Not relevant to our analysis (n=10)

Studies included in qualitative synthesis (n = 7)

Studies included in quantitative synthesis (meta-analysis) (n = 7)







## **Additional files provided with this submission:**

**Additional file 1.** Methodological quality assessment (risk of bias) of included studies by Newcastle-Ottawa Scales (30k)  
<http://ccforum.com/content/supplementary/s13054-014-0684-9-s1.doc>