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Review Article

Vitamin D Supplementation in Critically Ill Patients with Sepsis and Septic Shock: A Protocol for Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Sepsis is a life-threatening condition that frequently leads to intensive care unit (ICU) admission and is characterized by organ dysfunction, high morbidity, and mortality. Severe cases may progress to septic shock, further increasing the risk of death. Vitamin D, especially in its active form, plays a critical role in modulating the immune response. Vitamin D deficiency is common in patients with sepsis and has been associated with worse outcomes. Despite emerging evidence suggesting that supplementation may improve clinical outcomes, results are inconsistent due to variability in study design, patient populations, dosing regimens, and outcome measures.

Methods: This protocol outlines a systematic review with potential meta-analysis if sufficient data are available. Randomized-controlled trials (RCTs) evaluating vitamin D supplementation in adult patients with sepsis or septic shock will be included. Primary outcomes will focus on all-cause mortality, while secondary outcomes will include ICU and hospital length of stay, duration of mechanical ventilation, change in sequential organ failure assessment (SOFA) score, and vasopressor requirements. A comprehensive literature search will be conducted in PubMed, Scopus, Embase, and Web of Science, with supplementary searches in grey literature and reference lists. Screening, data extraction, and quality assessment will be conducted independently by multiple researchers using predefined forms and the Cochrane Risk of Bias 2 (RoB2) tool. Data synthesis will include narrative summaries and meta-analysis when appropriate, using standardized statistical methods.

Results: This review will systematically synthesize the available evidence regarding the effectiveness of vitamin D supplementation in critically ill patients with sepsis and septic shock. If sufficient homogeneous data are available, a meta-analysis will be performed to generate pooled estimates for mortality and other clinically relevant outcomes.

Conclusion: This systematic review and meta-analysis will provide a comprehensive

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and up-to-date synthesis of evidence regarding vitamin D supplementation in sepsis and septic shock. The findings are expected to clarify the current evidence, identify knowledge gaps, and inform future clinical research and evidence-based practice.

Introduction

Sepsis, one of the leading causes of admission to the intensive care unit (ICU), is a life-threatening condition characterized by organ dysfunction and is associated with substantial morbidity and mortality [1]. Sometimes, it may be metaphorically described as a “three-headed dragon," reflecting its complex and dysregulated pathophysiology. Following infection, the host immune response becomes dysregulated, leading to a cascade of systemic processes, including hyperinflammation, coagulopathy, fibrinogenesis, and, paradoxically, fibrinolysis [2-3]. Globally, sepsis represents a major health and economic burden, with an estimated 49 million cases and approximately 13 million sepsis-related deaths reported annually [4]. In its severe form, sepsis may progress to septic shock, which is associated with even higher mortality rates [1,5-6].

Vitamin D, particularly its active form 1,25-dihydroxycholecalciferol (calcitriol), exerts multiple effects on the innate immune system. In immune cells such as monocytes and macrophages, pathogen recognition through Toll-like receptors (TLRs) activates the enzyme CYP27B1, which converts circulating 25-hydroxyvitamin D, the primary marker of vitamin D status, into its active form. Calcitriol subsequently enhances the expression of antimicrobial peptides, including human cathelicidin (hCAP-18), which is further processed into LL-37. This peptide plays a critical role in host defense by exerting broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria, viruses, and fungi [7-10].

A growing body of evidence indicates that vitamin D deficiency is highly prevalent among critically ill patients, especially those with sepsis, affecting nearly 60% of cases. Low vitamin D levels have been associated with increased morbidity and mortality [6-7,11]. Some studies have demonstrated that vitamin D deficiency in critically ill and sepsis patients may contribute to increased mortality, prolonged ICU and hospital stay, longer duration for vasopressor support, and mechanical ventilation [12-13]. Conversely, several observational and interventional studies have suggested that vitamin D supplementation can improve outcomes, including reducing mortality and shortening the duration of hospitalization. However, the existing evidence remains inconsistent, with variability in study type, patient populations, dosing regimens, and reported outcomes [7,11,14-17]. Given these discrepancies, the lack of a clear consensus regarding the clinical efficacy of vitamin D supplementation in sepsis, and the fact that no previous systematic review has comprehensively focused on randomized controlled trials (RCTs) in patients with sepsis and septic shock [5,18], the existing reviews were heterogeneous in study type and did not specifically target sepsis populations, making it difficult to extrapolate their findings and contributing to substantial heterogeneity.

We therefore plan to systematically review the existing literature and, if sufficient data are available, perform a meta-analysis to evaluate the effect of vitamin D supplementation on clinical outcomes in critically ill patients with sepsis and septic shock.

Methods and Analysis

Study method

This protocol outlines a systematic review, with meta-analysis planned if sufficient results are available. The study will be conducted in accordance with PROSPERO registration standards and the PRISMA 2020 statement to ensure rigorous and transparent reporting of the review objectives. Trial registration code: CRD420261325500. Available from: https://www.crd.york.ac.uk/PROSPERO/view/CRD420261325500.

Study criteria

Inclusion and exclusion criteria

Studies will be chosen according to predefined criteria concerning the target population, study design, language, and relevant outcomes.

Study types

This study will include RCTs reporting at least one of our outcomes of interest. Non-interventional studies and non-RCTs, such as observational studies, case reports, case series, review articles, abstracts, and conference proceedings without full-text availability, will be excluded.

Study population

We will include studies involving critically ill adult patients (≥18 years) with sepsis or septic shock. Studies including pediatric patients, neonates, non-septic patients, or non-critically ill patients will be excluded.

Intervention or exposure

We will include studies in which vitamin D, in any form and by any route (e.g., cholecalciferol, ergocalciferol, or calcitriol, administered orally or parenterally), was used.

Comparator or control

We will include all studies that used a placebo as a control group, compared to vitamin D.

Outcomes

Outcomes will be categorized as primary and secondary. Our primary outcome will focus on the effect of vitamin D supplementation on all-cause mortality at the longest follow-up reported (e.g., 28-, 30-, or 90-day), with priority given to 28-30-day mortality. Secondary outcomes will include ICU or hospital length of stay, duration of mechanical ventilation, change in sequential organ failure assessment (SOFA) score, and the need for vasopressor therapy.

Time frame

There will be no limitations on the time frame for study searches.

Language

No language restrictions will be applied when searching for articles.

Data sources

A comprehensive search will be performed across PubMed, Scopus, Embase, and Web of Science to identify eligible studies. To minimize publication bias, grey literature sources, including allconferences.com, conferencealerts.com, and ClinicalTrials.gov, will also be searched. In addition, the reference lists of all included studies will be reviewed to identify potentially relevant articles that may not have been retrieved through the electronic database searches. Any additional eligible studies identified through these supplementary searches will also be considered for inclusion.

Search strategy

The search strategies will use a combination of MeSH and non-MeSH keywords to identify relevant articles.

Search strategy development and peer review

Keywords will include: 1) "Vitamin D," "Vitamin D Deficiency," "Cholecalciferol," "Ergocalciferols," "vitamin D3," "calcitriol," "calcifediol," "25-hydroxyvitamin D," and "1,25-dihydroxyvitamin D"; 2) "Sepsis," "Septic Shock," "Critical Illness," "severe sepsis," "critically ill," "ICU," and "intensive care unit"; and 3) "Mortality," "death," "all-cause mortality," "Length of Stay," "ICU length of stay," "hospital stay," "Respiration, Artificial," "mechanical ventilation," "ventilation," "ventilator duration," "ventilator-free days," and "weaning from ventilation." An experienced researcher in scientific literature searches will guide the development of the search strategies, which will then be peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist to ensure their accuracy and comprehensiveness. Search sensitivity and specificity will be optimized through the use of Boolean operators (AND, OR) and truncation. The full search strategies for all databases will be provided in the Appendix, with the final search dates also reported there. Additionally, the reference lists of all included studies will be screened, and forward citation searching will be conducted to identify any further eligible studies.

Screening process

Three researchers will independently evaluate the titles and abstracts retrieved from the databases twice for eligibility, using a predefined checklist (Table 1).

Studies deemed potentially eligible will have their full-text retrieved and assessed against the established inclusion criteria.

Any disagreements arising after the full-text evaluation will be resolved through discussion or, if necessary, by consultation with a fourth person. Before initiating the formal screening, the researchers will perform a pilot calibration exercise on a sample of titles and abstracts to enhance consistency and standardize the application of the eligibility criteria.

All screening processes will be conducted using EndNote (version 21) and Excel (version 2019), and the reasons for excluding full-text articles will be recorded.

Data extraction

A preliminary data extraction process will be conducted on a representative sample of the included studies (around 10%) using a standardized Microsoft Word form (version 2019). In this initial stage, two investigators will independently perform data extraction to refine the data collection framework, harmonize the interpretation of study variables, and identify potential inconsistencies. Differences between reviewers will be addressed through consensus discussions, with input from a third investigator when required. After completion of the calibration process, the revised extraction template will be applied to all eligible studies for the final data collection procedure (Table 2).

Handling of missing or unclear data

In cases where data are incomplete or unclear, the corresponding authors of the studies will be contacted through email or social media (up to three attempts over a period of 2-4 weeks). To minimize exclusion of eligible studies due to non-response, predefined criteria will guide the decision-making process. A study will be considered for quantitative analysis only when the

required outcome data are obtainable from the original article or its accompanying supplementary files. If subgroup-level information cannot be obtained, the study will be retained for qualitative description and reported as an evidence limitation but will not contribute to the meta-analysis. Details of all author contact efforts, along with the rationale for final inclusion or exclusion decisions, will be systematically documented.

Quality assessment

The included articles will be assessed for risk of bias using the 2019 version of the Cochrane Risk of Bias Tool (RoB 2), which evaluates five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results.

Table 1- Predefined checklist for titles and abstracts.

Criteria	Description	Screening decision	Researcher 1	Researcher 2	Final decision
Population	Includes: • Adult patients (≥18 years) • Critically ill patients • Sepsis • Septic shock • ICU patients Excluded: • Pediatric patients • Neonates • Non-septic patients • Non-critically ill patients	Include Doubt Exclude			
Intervention	Includes: • Vitamin D supplementation • Cholecalciferol • Ergocalciferol • Calcitriol • Oral vitamin D • Parenteral vitamin D Excludes: • Other vitamins • Co-administration with other vitamins	Include Doubt Exclude			
Comparator	Includes: • Placebo	Include Doubt Exclude			
Study design	Includes: • Randomized-controlled trials Exclude: • Non-interventional studies and others	Include Doubt Exclude			

Table 2- Template for data extraction.

Extracted data	Study number 1 (year)	Study number 2 (year)	Study number 3 (year)	Study number 4 (year)
Author, year				
Design				
Sample size				
Population				
Intervention				
Patients' age				
Patients' gender				
Source of sepsis				
Route of administration				
Duration				
Baseline vitamin D level				
Change in vitamin D level				
28-30-day mortality				
90-day mortality				

ICU stay
Hospital stay
Duration of mechanical ventilation
30-day readmission
SOFA score
Duration of vasopressors

Each domain will be rated as low risk, some concerns, or high risk, and an overall risk-of-bias judgment will be assigned based on these domain assessments. All included trials in the quantitative analysis will be independently evaluated twice for quality by two researchers, with any disagreements resolved through discussion.

The overall certainty of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach following risk-of-bias evaluation and data extraction. Findings will be classified as high, moderate, low, or very low certainty. GRADE assessments will be performed independently by two reviewers, with any disagreements resolved through discussion or by a third reviewer.

Data analysis and synthesis plan

A meta-analysis will be performed when sufficient data are available for quantitative synthesis; otherwise, the findings will be presented as a narrative synthesis. Statistical analyses will be conducted using R software or another appropriate statistical package. For dichotomous outcomes, such as mortality, treatment effects will be reported as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). Continuous outcomes will be summarized using either mean differences (MDs) or standardized mean differences (SMDs), as appropriate for the available data and outcome reporting. Statistical heterogeneity will be assessed using the I^2 statistic. Publication bias will be evaluated using funnel plots and Egger's test (if sufficient studies are available). Selective reporting bias will be evaluated based on the comparison between reported outcomes and those described in the methods or protocols, where available.

If sufficient data are available, subgroup analyses (e.g., based on patient characteristics or intervention differences) and sensitivity analyses (e.g., excluding studies at high risk of bias) will be conducted to explore the robustness of the findings. Meta-regression may also be performed to investigate potential sources of heterogeneity. If data are insufficient, analyses will be performed qualitatively or not conducted, as appropriate.

Discussion

The rising incidence of sepsis and septic shock, along with their associated high morbidity and mortality, imposes a substantial economic burden on societies. Given the complex and multifaceted nature of sepsis, affecting multiple organ systems, an effective and definitive treatment has not yet been established [19-20]. Accordingly, several therapeutic strategies have been investigated to improve outcomes in sepsis, including advanced drug delivery technologies such as nanoparticle-based platforms, particularly ribonucleic acid (RNA)-loaded nanoparticles [21]. Among these emerging approaches, vitamin D has received increasing attention because of its immunomodulatory properties. Growing evidence suggests that vitamin D may influence key pathophysiological processes involved in sepsis, raising the possibility that supplementation could represent a valuable adjunctive therapeutic strategy [22]. Clinical studies have consistently shown that vitamin D deficiency is common among patients with sepsis and is associated with poorer clinical outcomes and an unfavorable prognosis [17,23-24].

The high prevalence of vitamin D deficiency in sepsis is likely the result of several interacting molecular and clinical mechanisms [22,25]. During the septic response, immune cells together with organs such as the liver and kidneys increase their utilization of vitamin D to generate its biologically active metabolite, 1,25-dihydroxyvitamin D (calcitriol), resulting in a rapid decline in circulating 25(OH)D concentrations [22,26-27]. At the same time, hepatic and renal dysfunction, which frequently accompany sepsis, can further impair the conversion of vitamin D into its active form [22,28]. Persistent systemic inflammation and cytokine release also interfere with vitamin D metabolism by suppressing vitamin D-activating enzymes and reducing the availability of vitamin D-binding proteins, ultimately decreasing circulating bioavailable vitamin D [28-30]. In addition, inadequate nutritional intake and limited sunlight exposure during prolonged ICU admission may further contribute to declining vitamin D levels. Together, these mechanisms help explain the high frequency of vitamin D deficiency in patients with sepsis and support the hypothesis that correcting this deficiency could enhance immune function and improve clinical outcomes, including survival [31].

Vitamin D, particularly in its active form calcitriol, may affect the course of sepsis through several complementary molecular mechanisms. After binding to vitamin D receptors (VDRs) expressed on immune cells, including monocytes, macrophages, neutrophils, and

lymphocytes, it stimulates the production of antimicrobial peptides such as cathelicidin and defensins, thereby strengthening antimicrobial defenses and facilitating pathogen clearance [8,22].

Furthermore, vitamin D inhibits the nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) signaling pathway, reducing the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) while increasing anti-inflammatory cytokines like IL-10, which may attenuate the severity of the cytokine storm [1,22]. In addition, vitamin D helps preserve endothelial function and reduce oxidative stress, thereby limiting capillary leakage and coagulopathy. It also modulates adaptive immunity by regulating T regulatory (T-reg) cells and balancing T helper 1 (Th1)-Th2-Th17 pathways. Its metabolic effects represent another supportive mechanism (Figure 1) [22,32-33].

These combined effects may explain why some studies have reported reduced mortality, shorter ICU stay, and decreased duration of mechanical ventilation among patients receiving vitamin D.

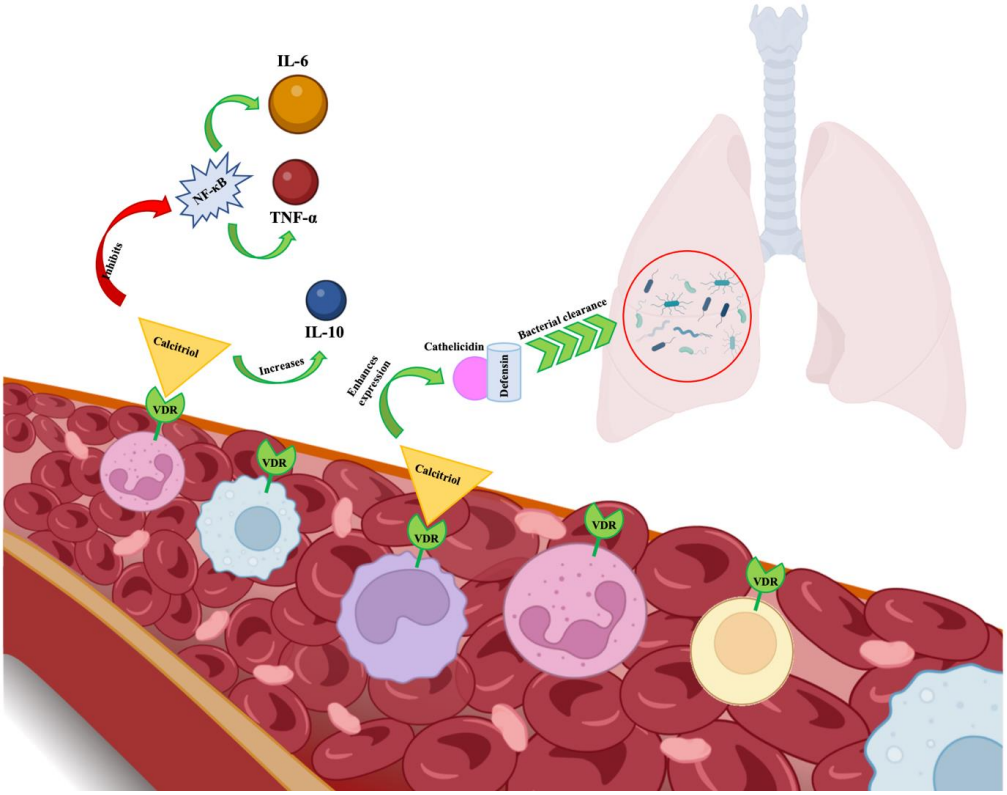

Figure 1- Proposed mechanism of vitamin D in sepsis.

However, clinical evidence remains limited and inconsistent. Variations in dosage, formulation, route of administration, timing of intervention, and patient characteristics have made direct comparisons across studies challenging. As a result, there is still no definitive consensus regarding the impact of vitamin D on clinical outcomes in patients with sepsis and septic shock.

Therefore, conducting a systematic review focused on RCTs, particularly those assessing outcomes such as mortality, ICU and hospital length of stay, and duration of mechanical ventilation, is essential.

Such an analysis would allow for a more precise evaluation of the clinical effects of vitamin D, help identify sources of heterogeneity and inconsistency in the existing literature, and provide a comprehensive synthesis of the available evidence to inform future clinical trials design.

Conclusion

Vitamin D supplementation has attracted considerable attention as a potential adjunctive treatment for patients with sepsis and septic shock; however, the available evidence remains inconsistent and difficult to interpret because of differences in study populations, intervention strategies, and outcome reporting. This systematic review and meta-analysis will comprehensively evaluate randomized controlled trials to determine the current evidence regarding the effectiveness of vitamin D supplementation on clinically relevant outcomes. The findings will help clarify existing uncertainties, highlight areas requiring further investigation, and provide an updated evidence base to support future research and

clinical decision-making in the management of critically ill patients with sepsis and septic shock.

Ethics approval and consent to participate

The study findings will be prepared for submission to a peer-reviewed journal in accordance with the PRISMA-P guidelines. The final review will be documented in accordance with the PRISMA 2020 guidelines.

The protocol of this study was registered in PROSPERO (CRD420261325500) and is available from https://www.crd.york.ac.uk/PROSPERO/view/CRD420261325500. The protocol was updated to improve clarity by reclassifying outcomes.

Authors' contributions

KS, FA, and MM conceptualized the study. KS and FA led protocol development and drafted the manuscript. KS, FA, AM, and LH will contribute to screening and data extraction. MM and AN provided overall supervision throughout protocol development. MM will serve as the third reviewer to adjudicate any unresolved disagreements that may arise during screening, data extraction, and risk-of-bias assessment. AM will lead data synthesis and analysis. All authors critically revised the manuscript and approved the final version.

Data availability

Available upon request.

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Appendix

Scopus syntaxes

- TITLE-ABS-KEY (("vitamin D" OR cholecalciferol OR ergocalciferol OR calcitriol) AND (sepsis OR "septic shock") AND ("intensive care" OR ICU OR "critical illness")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "cp")) AND (LIMIT-TO (SRCTYPE , "j") OR LIMIT-TO (SRCTYPE , "p"))
- TITLE-ABS-KEY (("vitamin D" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR calcifediol OR calcitriol) AND (sepsis OR "septic shock" OR "severe sepsis" OR "sepsis syndrome" OR "critical illness" OR "critically ill" OR ICU))
- TITLE-ABS-KEY (("vitamin D" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR calcifediol OR calcitriol) AND (sepsis OR "septic shock" OR "severe sepsis" OR "sepsis syndrome" OR "critical illness" OR "critically ill" OR ICU) AND (mortality OR "length of stay" OR "ICU length of stay" OR "mechanical ventilation" OR "ventilator duration"))
- TITLE-ABS-KEY (("vitamin D" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR calcifediol OR calcitriol OR "1,25-dihydroxyvitamin D" OR "25-hydroxyvitamin D") AND(sepsis OR "septic shock" OR "severe sepsis" OR "sepsis syndrome" OR "critical illness" OR "critically ill" OR ICU OR "intensive care unit" OR "intensive care" OR "life threatening infection")AND (mortality OR "all-cause mortality" OR "death rate" OR "length of stay" OR "hospital stay" OR "ICU stay" OR "ICU length of stay" OR "mechanical ventilation" OR "ventilator duration" OR "ventilator-free days"))
- TITLE-ABS-KEY (("vitamin D" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR calcifediol OR calcitriol OR "1,25-dihydroxyvitamin D" OR "25-hydroxyvitamin D" OR "active vitamin D" OR "vitamin D supplementation") AND(sepsis OR "septic shock" OR "severe sepsis" OR "sepsis syndrome" OR "critical

illness" OR "critically ill" OR ICU OR "intensive care unit" OR "intensive care" OR "life threatening infection" OR "multi-organ failure" OR "organ dysfunction" OR "systemic infection") AND(mortality OR "all-cause mortality" OR "death rate" OR "length of stay" OR "hospital stay" OR "ICU stay" OR "ICU length of stay" OR "mechanical ventilation" OR "ventilator duration" OR "ventilator-free days" OR "weaning from ventilation" OR "respiratory support duration"))

Web of sciences syntaxes

- TS=(("vitamin D" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR calcifediol OR calcitriol OR "1,25-dihydroxyvitamin D" OR "25-hydroxyvitamin D" OR "active vitamin D" OR "vitamin D supplementation") AND (sepsis OR "septic shock" OR "severe sepsis" OR "sepsis syndrome" OR "critical illness" OR "critically ill" OR ICU OR "intensive care unit" OR "intensive care" OR "life threatening infection" OR "multi-organ failure" OR "organ dysfunction" OR "systemic infection") AND (mortality OR "all-cause mortality" OR "death rate" OR "length of stay" OR "hospital stay" OR "ICU stay" OR "ICU length of stay" OR "mechanical ventilation" OR "ventilator duration" OR "ventilator-free days" OR "weaning from ventilation" OR "respiratory support duration"))
- TS=(("vitamin D" OR cholecalciferol OR calcitriol OR "vitamin D supplementation") AND (sepsis OR "septic shock" OR ICU OR "intensive care unit" OR "critically ill") AND(mortality OR "length of stay" OR "ICU stay" OR "mechanical ventilation" OR "ventilator duration"))
- TS=(("vitamin D" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR calcitriol OR "vitamin D supplementation") AND (sepsis OR "septic shock" OR "critical illness" OR "critically ill" OR ICU OR "intensive care unit") AND (mortality OR "all-cause mortality" OR "length of stay" OR "ICU stay" OR "mechanical ventilation" OR "ventilator duration"))
- TS=(("vitamin D" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR calcitriol OR "vitamin D supplementation" OR calcifediol OR "active vitamin D") AND (sepsis OR "septic shock" OR "critical illness" OR "critically ill" OR ICU OR "intensive care" OR "intensive care unit" OR "life-threatening infection" OR "multi-organ failure" OR "organ dysfunction") AND (mortality OR "all-cause mortality" OR "death rate" OR "length of stay" OR "hospital stay" OR "ICU stay" OR "ICU length of stay" OR "mechanical ventilation" OR "ventilator duration" OR "ventilator-free days" OR "weaning from ventilation"))
- TS=(("vitamin D" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR calcitriol OR calcifediol OR "1,25-dihydroxyvitamin D" OR "25-hydroxyvitamin D" OR "active vitamin D" OR "vitamin D supplementation") AND (sepsis OR "septic shock" OR "severe sepsis" OR "sepsis syndrome" OR "critical illness" OR "critically ill" OR ICU OR "intensive care" OR "intensive care unit" OR "life-threatening infection" OR "multi-organ failure" OR "organ dysfunction" OR "systemic infection" OR "organ failure") AND (mortality OR "all-cause mortality" OR "death rate" OR "length of stay" OR "hospital stay" OR "ICU stay" OR "ICU length of stay" OR "mechanical ventilation" OR "ventilator duration" OR "ventilator-free days" OR "weaning from ventilation" OR "respiratory support duration" OR "ventilator support"))
- TS=(("vitamin D" OR cholecalciferol OR calcitriol OR "vitamin D supplementation") AND (sepsis OR "septic shock" OR ICU OR "intensive care unit" OR "critically ill") AND (mortality OR "length of stay" OR "ICU stay" OR "mechanical ventilation"))

EMBASE syntaxes

- ('vitamin D'/exp OR 'vitamin D' OR cholecalciferol OR calcitriol OR 'vitamin D supplementation') AND ('sepsis'/exp OR sepsis OR 'septic shock'/exp OR 'septic shock' OR 'critical illness'/exp OR 'critical illness' OR ICU OR 'intensive care unit' OR 'critically ill') AND')mortality'/exp OR mortality OR 'length of stay'/exp OR 'length of stay' OR 'ICU stay' OR 'mechanical ventilation'/exp OR 'mechanical ventilation')
- ('vitamin D'/exp OR 'vitamin D' OR 'vitamin D3' OR cholecalciferol OR ergocalciferol OR calcitriol OR calcifediol OR '1,25-dihydroxyvitamin D' OR '25-hydroxyvitamin D' OR 'active vitamin D' OR 'vitamin D supplementation') AND('sepsis'/exp OR sepsis OR 'septic shock'/exp OR 'septic shock' OR 'severe sepsis' OR 'sepsis syndrome' OR 'critical illness'/exp OR 'critical illness' OR 'critically ill' OR ICU OR 'intensive care unit' OR 'intensive care' OR 'life-threatening infection' OR 'multi-organ failure' OR 'organ dysfunction' OR 'systemic infection')AND')mortality'/exp OR mortality OR 'all-cause mortality' OR 'death rate' OR 'length of stay'/exp OR 'length of stay' OR 'hospital stay' OR 'ICU stay' OR 'ICU length of stay' OR 'mechanical ventilation'/exp OR 'mechanical ventilation' OR 'ventilator duration' OR 'ventilator-free days' OR 'weaning from ventilation' OR 'respiratory support duration')
- ('vitamin D'/exp OR 'vitamin D' OR 'vitamin D3' OR cholecalciferol OR ergocalciferol OR calcitriol OR calcifediol OR '1,25-dihydroxyvitamin D' OR '25-hydroxyvitamin D' OR 'active vitamin D' OR 'vitamin D

supplementation') AND('sepsis'/exp OR sepsis OR 'septic shock'/exp OR 'septic shock' OR 'severe sepsis' OR 'sepsis syndrome' OR 'critical illness'/exp OR 'critical illness' OR 'critically ill' OR ICU OR 'intensive care unit' OR 'intensive care' OR 'life-threatening infection' OR 'multi-organ failure' OR 'organ dysfunction' OR 'systemic infection' OR 'organ failure')AND')mortality'/exp OR mortality OR 'all-cause mortality' OR 'death rate' OR 'length of stay'/exp OR 'length of stay' OR 'hospital stay' OR 'ICU stay' OR 'ICU length of stay' OR 'mechanical ventilation'/exp OR 'mechanical ventilation' OR 'ventilator duration' OR 'ventilator-free days' OR 'weaning from ventilation' OR 'respiratory support duration' OR 'ventilator support')

- ('vitamin D'/exp OR 'vitamin D' OR 'vitamin D3' OR cholecalciferol OR ergocalciferol OR calcitriol OR calcifediol OR '1,25-dihydroxyvitamin D' OR '25-hydroxyvitamin D' OR 'active vitamin D' OR 'vitamin D supplementation' OR calcitriol analogs)AND('sepsis'/exp OR sepsis OR 'septic shock'/exp OR 'septic shock' OR 'severe sepsis' OR 'sepsis syndrome' OR 'critical illness'/exp OR 'critical illness' OR 'critically ill' OR ICU OR 'intensive care unit' OR 'intensive care' OR 'life-threatening infection' OR 'multi-organ failure' OR 'organ dysfunction' OR 'systemic infection' OR 'organ failure' OR 'shock' OR 'severe infection')AND')mortality'/exp OR mortality OR 'all-cause mortality' OR 'death rate' OR 'length of stay'/exp OR 'length of stay' OR 'hospital stay' OR 'ICU stay' OR 'ICU length of stay' OR 'mechanical ventilation'/exp OR 'mechanical ventilation' OR 'ventilator duration' OR 'ventilator-free days' OR 'weaning from ventilation' OR 'respiratory support duration' OR 'ventilator support' OR 'ventilation support')
- ('vitamin D'/exp OR 'vitamin D' OR 'vitamin D3' OR cholecalciferol OR ergocalciferol OR calcitriol OR calcifediol OR '1,25-dihydroxyvitamin D' OR '25-hydroxyvitamin D' OR 'active vitamin D' OR 'vitamin D supplementation' OR calcitriol analogs)AND ('sepsis'/exp OR sepsis OR 'septic shock'/exp OR 'septic shock' OR 'severe sepsis' OR 'sepsis syndrome' OR 'critical illness'/exp OR 'critical illness' OR 'critically ill' OR ICU OR 'intensive care unit' OR 'intensive care' OR 'life-threatening infection' OR 'multi-organ failure' OR 'organ dysfunction' OR 'systemic infection' OR 'organ failure' OR 'shock' OR 'severe infection')AND('mortality'/exp OR mortality OR 'all-cause mortality' OR 'death rate' OR 'length of stay'/exp OR 'length of stay' OR 'hospital stay' OR 'ICU stay' OR 'ICU length of stay' OR 'mechanical ventilation'/exp OR 'mechanical ventilation' OR 'ventilator duration' OR 'ventilator-free days' OR 'weaning from ventilation' OR 'respiratory support duration' OR 'ventilator support')

PubMed syntaxes

- ("Vitamin D"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh]m OR "vitamin D" OR "vitamin D3" OR cholecalciferol OR ergocalciferol OR calcitriol OR calcifediol OR "25-hydroxyvitamin D" OR "1,25-dihydroxyvitamin D")AND("Sepsis"[Mesh] OR "Septic Shock"[Mesh] OR "Critical Illness"[Mesh] OR sepsis OR "septic shock" OR "severe sepsis"OR "critical illness" OR "critically ill" OR ICU OR "intensive care unit") AND("Mortality"[Mesh] OR mortality OR death OR "all-cause mortality" OR "Length of Stay"[Mesh] OR "length of stay" OR "ICU length of stay" OR "hospital stay" OR "Respiration, Artificial"[Mesh] OR "mechanical ventilation" OR ventilation OR "ventilator duration" OR "ventilator-free days" OR "weaning from ventilation")
- ("Vitamin D"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcitriol"[Mesh] OR "vitamin D"[tiab] OR "vitamin D3"[tiab] OR "vitamin D2"[tiab] OR cholecalciferol[tiab] OR ergocalciferol[tiab] OR calcitriol[tiab] OR calcifediol[tiab]OR "25-hydroxyvitamin D"[tiab] OR "25(OH)D"[tiab] OR "1,25-dihydroxyvitamin D"[tiab] OR "1,25(OH)2D"[tiab] OR "active vitamin D"[tiab] OR "vitamin D supplementation"[tiab])AND ("Sepsis"[Mesh] OR "Septic Shock"[Mesh] OR "Critical Illness"[Mesh] OR "Intensive Care Units"[Mesh] OR sepsis[tiab] OR "septic shock"[tiab] OR "severe sepsis"[tiab] OR "critical illness"[tiab] OR "critically ill"[tiab] OR ICU[tiab] OR "intensive care"[tiab] OR "intensive care unit"[tiab] OR "life-threatening infection"[tiab] OR "systemic infection"[tiab] OR "organ failure"[tiab] OR "multi organ failure"[tiab] OR "organ dysfunction"[tiab]) AND("Mortality"[Mesh] OR mortality[tiab] OR death[tiab] OR "all-cause mortality"[tiab] OR "Length of Stay"[Mesh] OR "length of stay"[tiab] OR "ICU length of stay"[tiab] OR "hospital length of stay"[tiab] OR "ICU stay"[tiab] OR "Respiration, Artificial"[Mesh] OR "mechanical ventilation"[tiab] OR ventilation[tiab] OR "ventilator duration"[tiab] OR "ventilator-free days"[tiab] OR "duration of ventilation"[tiab] OR "weaning from ventilation"[tiab] OR "respiratory support"[tiab])
- ("Vitamin D"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcitriol"[Mesh] OR "vitamin D"[tiab] OR "vitamin D3"[tiab] OR cholecalciferol[tiab] OR ergocalciferol[tiab] OR calcitriol[tiab] OR calcifediol[tiab] OR "25-hydroxyvitamin D"[tiab] OR "1,25-dihydroxyvitamin D"[tiab]) AND("Sepsis"[Mesh] OR "Septic Shock"[Mesh] OR "Critical Illness"[Mesh] OR "Intensive Care Units"[Mesh]OR sepsis[tiab] OR "septic shock"[tiab] OR "severe sepsis"[tiab] OR "critical illness"[tiab] OR "critically

ill"[tiab]m OR ICU[tiab] OR "intensive care unit"[tiab]) AND("Mortality"[Mesh] OR mortality[tiab] OR death[tiab]OR "Length of Stay"[Mesh] OR "length of stay"[tiab] OR "ICU stay"[tiab] OR "Respiration, Artificial"[Mesh] OR "mechanicalventilation"[tiab] OR "ventilator duration"[tiab] OR "ventilator-free days"[tiab])

- ("Vitamin D"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcitriol"[Mesh] OR "vitamin D"[tiab] OR cholecalciferol[tiab] OR ergocalciferol[tiab] OR calcitriol[tiab] OR calcifediol[tiab] OR "25-hydroxyvitamin D"[tiab] OR "1,25-dihydroxyvitamin D"[tiab])AND("Sepsis"[Mesh] OR "Septic Shock"[Mesh] OR sepsis[tiab] OR "septic shock"[tiab] OR "severe sepsis"[tiab]) AND("Mortality"[Mesh] OR mortality[tiab] OR death[tiab] OR "Length of Stay"[Mesh] OR "length of stay"[tiab] OR "ICU stay"[tiab] OR "Respiration, Artificial"[Mesh] OR "mechanical ventilation"[tiab] OR "ventilator duration"[tiab] OR "ventilator-free days"[tiab])
- ("Vitamin D"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcitriol"[Mesh] OR "vitamin D"[tiab] OR cholecalciferol[tiab] OR calcitriol[tiab] OR "25-hydroxyvitamin D"[tiab]) AND("Sepsis"[Mesh] OR "Septic Shock"[Mesh] OR sepsis[tiab] OR "septic shock"[tiab]) AND("Mortality"[Mesh] OR mortality[tiab] OR "Length of Stay"[Mesh] OR "ICU length of stay"[tiab] OR "Respiration, Artificial"[Mesh] OR "mechanical ventilation"[tiab] OR "ventilator duration"[tiab])