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SYSTEMATIC REVIEW

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# Risk factors and outcomes of ventilator-associated pneumonia: an updated systematic review and meta-analysis

Paula Ochoa[1,2], Alejandro Rico Mendoza[3], Daniel Molano[4], Joan Ramon Masclans[5] and Henry Mauricio Parada-Gereda[6*]

## Abstract

**Background** Ventilator-associated pneumonia (VAP) is a common complication in intensive care unit (ICU) patients, which increases morbidity rates and adversely affects outcomes. The associated risk factors and outcomes remain controversial. The aim of the present study is to explore the risk factors and clinical outcomes of patients with VAP.

**Methods** Two investigators conducted independent systematic Literature searches of Pubmed, Cochrane Database, Scopus, Medline, Science Direct and Epistemonikos databases published from inception to November 2024. The Newcastle-Ottawa Scale (NOS) was used to assess study quality. A meta-analysis was performed using the random-effects Model. The systematic review protocol was registered in the CRDdatabase 42024538138 of the Prospective International Registry of Systematic Reviews (PROSPERO). A subgroup analysis, bivariate meta-regression, and sensitivity analysis were performed. Publication bias was assessed using a funnel plot and Egger's test. Certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology.

**Results** Twenty-two studies were included in the meta-analysis, with a total of 16,731 patients. Male gender odds ratio (OR) 1.30 (95% Confidence interval (CI) 1.18-1.44) $p<0.05$; the use of H2 blockers OR 2.24 (95% CI 1.50-3.37) $p<0.05$; tracheostomy OR 3.44 (95% CI 2.0-5.92) $p<0.05$; prior antibiotic treatment OR 1.52 (95% CI 1.08-2.15) $p<0.05$; reintubation OR 5.11 (95% CI 2.29-11.42) $p<0.05$; enteral feeding OR 4.73 (95% CI 2.54-8.78) $p<0.05$; Chronic Obstructive Pulmonary Disease (COPD) OR 1.52 (95% CI 1.10-2.09) $p<0.05$; impaired consciousness at hospital admission OR 3.14 (95% CI 1.28-7.69) $p<0.05$; nasogastric tube OR 2.94 (95% CI 1.56-5.53) $p<0.05$; use of neuromuscular blockers OR 1.30 (95% CI 1.13-1.49) $p<0.05$; trauma OR 1.47 (95% CI 1.12-1.93) $p<0.05$, and days of intubation prior to VAP OR 6.2 (95% CI 1.09-11.3). A $p<0.05$ significantly increased the risk of VAP. In patients with VAP, the average ICU stay was 12.7 days longer (95% CI: 9.6-15.8) $p<0.05$; the duration of mechanical ventilation was 12.3 days longer (95% CI: 9.27-15.34) $p <0.05$; the hospital stay was 16.1 days longer (95% CI: 10.8-21.5) $p <0.05$. The certainty of the evidence was low for most outcomes.

*Correspondence:
Henry Mauricio Parada-Gereda
maoparada1606@gmail.com
Full list of author information is available at the end of the article

**Conclusions** Male gender, use of H2 blockers, tracheostomy, prior antibiotic treatment, reintubation, enteral feeding, COPD, impaired consciousness at hospital admission, nasogastric tube, use of neuromuscular blockers, trauma and days of intubation prior to VAP significantly increased the risk of VAP. In patients with VAP, ICU stay, duration of mechanical ventilation, and hospital stay presented significant increases.

**Keywords** Intensive care units, Mortality, Pneumonia ventilator associated, Patient outcome assessment, Risk factors

## Background

Invasive mechanical ventilation (MV) is a cornerstone of care for critically ill patients in the ICU. However, its prolonged use comes with risks, one of the most concerning being VAP—a hospital-acquired infection that typically develops after at least 48 h of MV [1, 2]. VAP is among the most common ICU-acquired infections, contributing to higher morbidity, mortality [3–5], and healthcare costs [6, 7]. Its Reported incidence varies widely, from 5 to 40%, depending on the setting and diagnostic criteria [8, 9].

Globally, the estimated prevalence of VAP is approximately 15.6% [10], with incidence rates ranging from 8.0 to 28.8% among at-risk patients and event rates of 1.4 to 16.5 per 1,000 ventilator days [11]. These variations reflect differences in diagnostic criteria, institutional prevention strategies, and regional healthcare conditions [12, 13].

According to the National Healthcare Safety Network (NHSN) of the Centers for Disease Control and Prevention (CDC), the incidence of VAP has significantly decreased in medical and surgical ICU over the past 15 years [14]. Despite this progress, preventing and managing VAP remains a major challenge [15]. Standardised protocols, such as the *Neumonía Zero* initiative, have helped reduce VAP rates in many ICUs worldwide [16, 17].

Several risk factors have been linked to a higher likelihood of developing VAP, including older age, male sex, prolonged MV duration, impaired consciousness, comorbidities, severe burns, and prior antibiotic use [18]. However, findings across studies are often inconsistent, especially in different patient populations and ICU settings, including neonatal and specialised units [19]. Research into VAP risk factors in adults is ongoing [20, 21].

VAP is also associated with worse clinical outcomes, such as longer MV duration, extended hospital stays, and increased mortality—especially in cases involving Gram-negative bacilli [22–24]. While some multicentre prospective studies report high mortality rates linked to VAP, others have found no significant difference, highlighting the need for further research [25, 26].

A previous systematic review by Wang et al. [19] included 16 studies and Reported a pooled incidence of VAP of 22%. Significant risk factors identified were $H_2$ blocker use, nasogastric tube placement, enteral feeding, central venous catheterisation, and tracheostomy, whereas variables such as advanced age or reintubation were not consistently associated with VAP. Although the review suggested a potential association between VAP and increased Mortality, the analysis showed considerable heterogeneity. Importantly, that study did not include meta-regression analyses or an assessment of certainty using the GRADE approach, and its search period was Limited up to 2019, prior to the COVID-19 pandemic. These limitations highlight the need for an updated systematic review using more rigorous methodologies.

Building on these findings, our study expands the evidence base by incorporating recent publications, including those arising during the COVID-19 era, and by applying advanced methods such as meta-regression, sensitivity analyses, and GRADE assessment. This approach aims to provide a clearer understanding of the risk factors and clinical outcomes of VAP, thereby contributing to more effective preventive strategies and evidence-based management in critically ill patients.

## Methods

The methodology used in this systematic review and meta-analysis was adapted and summarised from procedures described in previous studies conducted by our research group [27]. This review included prospective and retrospective cohort studies, cross-sectional studies, and case–control studies of ICU patients aged 18 years and older with VAP. The protocol was registered in the PROSPERO database (CRD42024538138), and the review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28]. Importantly, this review is part of a broader research programme on ventilator-associated pneumonia. A previous systematic review by our group focused exclusively on patients with traumatic brain injury, whereas the present study addresses risk factors and outcomes of VAP in all critically ill adult populations.

Methodological quality was assessed independently by two investigators (PO, HMPG) using the Newcastle-Ottawa scale (NOS) [29]. Studies with seven stars or more are considered high quality, those with four to six stars moderate quality, and those with fewer than four stars of poor quality. The certainty of the evidence was evaluated using the GRADE (Grading of

Recommendations Assessment, Development, and Evaluation) methodology.

### Study question (PECO framework)

We addressed two complementary questions in adults (≥ 18 years) receiving invasive mechanical ventilation in the ICU.

First (**risk factors; PECO**), we compared *exposure* versus *non-exposure* to patient-related factors (e.g., male sex, COPD, impaired consciousness, trauma) and treatment-related factors (e.g., tracheostomy, reintubation, nasogastric tube, enteral feeding, $H_2$ blockers, neuromuscular blockers, prior antibiotic use, and duration of ventilation before VAP) for the *outcome* of VAP. A meta-analysis was performed for risk factors that were reported in at least three studies.

Second (**clinical impact; PECO**), we considered *exposure* as a diagnosis of VAP and the *comparator* as the absence of VAP, evaluating clinical *outcomes* including duration of mechanical ventilation, ICU length of stay, hospital length of stay, and mortality.

### Eligibility criteria

This systematic review and meta-analysis included prospective and retrospective cohort studies and cross-sectional studies of ICU patients aged ≥ 18 years with VAP. The studies had to report on the risk factors for VAP, clinical outcomes, or both. Full-text studies were required to fully access the results. Studies including paediatric patients were excluded. There were no restrictions on the date or language of the studies included.

### Search strategy

Two investigators (PO, HMPG) independently conducted systematic Literature searches of PubMed, Cochrane Database, Scopus, Medline Ovid, Science Direct, and Epistemonikos databases, published from inception to November 2024. Discrepancies between the investigators were resolved with the intervention of a third investigator (DMF), and manual searches were conducted by selecting reference lists of the articles included. The terms "ventilator associated pneumonia", "intensive care units", "risk factors", "patient outcome assessment", and articles in all languages were included; the full search strategy is described in Additional files 1.

### Inclusion criteria

The inclusion criteria for our study were as follows: all patients who had been on mechanical ventilation for More than 48 h were included; articles had to provide a clear operational definition and a diagnosis of VAP; articles had to report on risk factors or outcomes of VAP; studies had to be cohort, cross-sectional, or case-control; and the full text had to be available.

### Exclusion criteria

Systematic reviews, those whose unit of analysis was not the patient, case reports, editorials, correspondence, studies of patients without VAP.

### Statistical analysis

Review Manager Software (RevMan5.3; Cochrane Collaboration, Oxford, UK) was used to perform a meta-analysis of VAP risk factors and outcomes in VAP patients. Mean differences and 95% confidence intervals (95% CI) were calculated to compare the continuous variables. For count data, odds ratios (OR) and 95% CI were used. They were considered significantly associated with VAP when $p < 0.05$. Heterogeneity, calculated using the $I^2$ statistic, was considered to exist if $I^2 > 50\%$. Random-effects models were used for the meta-analysis. A subgroup analysis was conducted to identify sources of heterogeneity in clinical outcomes, considering age (> 60 years), study type, and methodological quality assessed with the NOS scale. Other subgroup analyses were performed for risk factors based on the nature of the study (prospective, retrospective, multicentre, and single-centre) and according to the diagnostic criteria for VAP. A sensitivity analysis was conducted by removing outliers for risk factors, and finally, a bivariate meta-regression analysis was carried out. Publication bias was assessed using a funnel plot and Egger's test with Stata 18 [30–32].

### Data synthesis and extraction

A set form was used to extract the following information from the articles included: name and country of first author, year of publication, type of study, sample size, patients with VAP, their sex and age, definition of VAP, risk factors, and clinical outcomes (mortality, duration of mechanical ventilation, ICU stay, hospital stay). Rayyan software was used for data extraction. Some studies presented continuous data using means and standard deviations or medians and first and third quartiles. To use these data in the meta-analysis, we converted the medians and first and third quartiles to means and standard deviations using the method described by Wan et al. [33]. Risk factors mentioned in at least three studies will be included in the analysis.

## Results

The initial search yielded 2096 citations from seven databases. A total of 2046 articles were excluded based on their titles and abstracts, while another 28 were excluded after full-text review, due to non-compliance with the inclusion criteria or presentation of at least one of the exclusion criteria. Ultimately, 22 studies were included in the meta-analysis, comprising a total of 16,731 patients (a detailed flow chart is shown in Fig. 1).

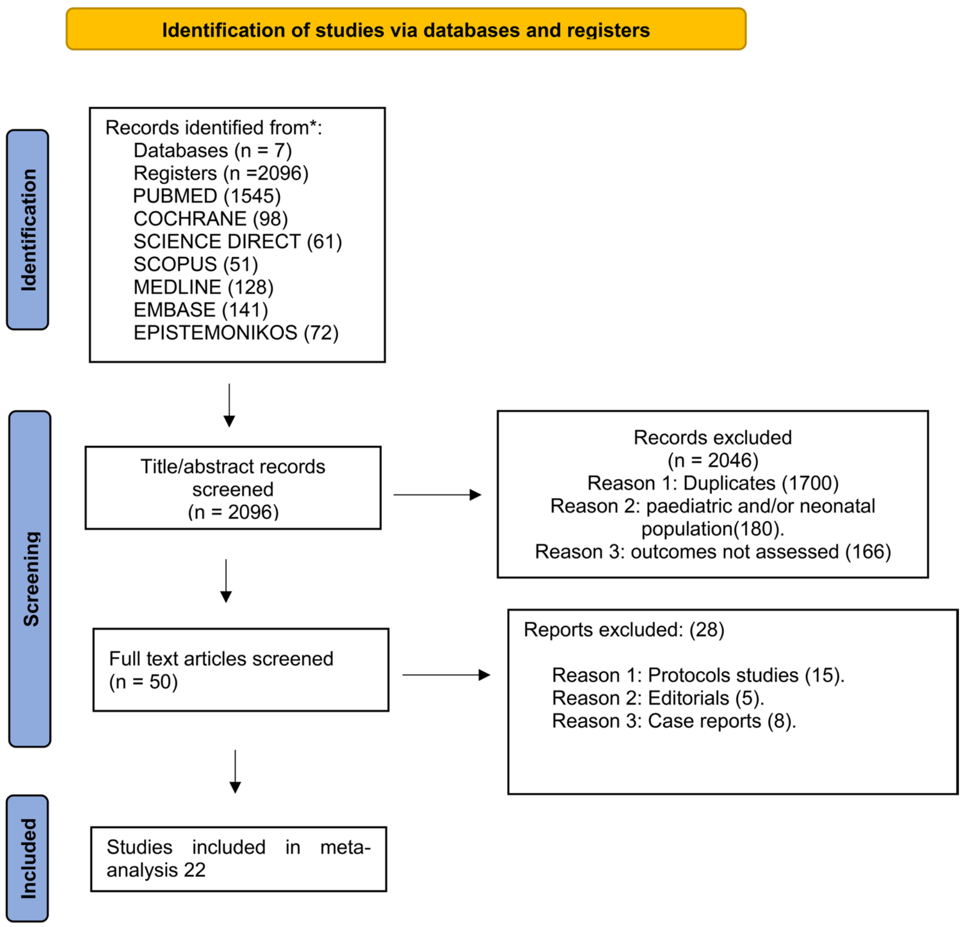


**Fig. 1** Study selection flowchart

## Characteristics of the studies included

The different characteristics of the studies are listed in Table 1. Eighteen studies were cohort studies [25, 26, 34–39]([40–49] and four case-control studies [50–53]. The studies were published between 2000 and 2023. In 18 studies, the definition of VAP was based on clinical, radiographic, and microbiological criteria [25, 26, 34, 35, 37–40, 42, 45–53]; one study used the Centers for Disease Control and Prevention (CDC) criteria [36]; two studies used the clinical pulmonary infection score (CPIS) [41, 44]; One study used the criteria of the American Thoracic Society/Infectious Diseases Society of America guidelines [43].

## Risk factors

### *Patient-related factors*

Twenty-four potential risk factors were identified and reported in at least three studies. Among patient-related factors, a significant association was observed between male sex and VAP (OR 1.30; 95% CI 1.18–1.44; $p < 0.05$; $I^2$ 0%; 16 studies, 11,177 patients). A history of COPD was also associated with increased risk (OR 1.52; 95% CI 1.10–2.09; $p < 0.05$; $I^2$ 75%; 10 studies, 10,227 patients). Impaired consciousness at hospital admission showed a strong association (OR 3.14; 95% CI 1.28–7.69; $p < 0.05$; $I^2$ 83%; 3 studies, 373 patients). Trauma as the reason for ICU admission was another risk factor (OR 1.47; 95% CI 1.12–1.93; $p < 0.05$; $I^2$ 0%; 3 studies, 345 patients). No significant associations were found for age, smoking, poisoning, diabetes, cardiac disease, APACHE II, SAPS II, immunosuppression, or chronic kidney disease.

### *Treatment-related factors*

Several treatment-related factors were significantly associated with VAP. The use of $H_2$ blockers was associated with increased risk (OR 2.24; 95% CI 1.50–3.37; $p < 0.05$; $I^2$ 0%; 6 studies, 957 patients). Tracheostomy showed a strong association (OR 3.44; 95% CI 2.0–5.92; $p < 0.05$; $I^2$ 77%; 10 studies, 2,821 patients), as did reintubation (OR 5.1; 95% CI 2.29–11.42; $p < 0.05$; $I^2$ 77%; 4 studies, 679 patients). Enteral feeding was another important factor (OR 4.7; 95% CI 2.54–8.78; $p < 0.05$; $I^2$ 57%; 5 studies, 1,894 patients), as well as nasogastric tube use (OR 2.94; 95% CI 1.56–5.53; $p < 0.05$; $I^2$ 20%; 5 studies, 671 patients). Neuromuscular blocker use was also significant (OR 1.30; 95% CI 1.13–1.49; $p < 0.05$; $I^2$ 0%; 3 studies,

**Table 1** Characteristics of the studies included

| Authors | Country | Design | *n* | Patients with VAP | Age VAP | Sex VAP (male/female) | Definition of VAP | Risk factors | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Sofianou et al. 2000 [25] | Greece | Prospective cohort | 198 | 67 | - | - | Clinical, radiographical, microbiological criteria | APACHE II, mechanical ventilation, length of ICU stay, $PaO_2/FiO_2$ ratio at admission | Mortality |
| Apostolopoulou E. et al. 2003 [34] | Greece | Prospective cohort | 175 | 56 | 52.5 ± 18.1 | 82/37 | Clinical, radiographical, microbiological criteria | Bronchoscopy, tube thoracostomy, tracheostomy, APACHE II score > 18, and enteral feeding. | Duration of mechanical ventilation. |
| Pawar M et al. 2003 [40] | India | Prospective cohort | 952 | 25 | 59.7 ± 12.7 | 21//4 | Clinical, radiographical, microbiological criteria | Emergency surgery, COPD, reintubation, coma, steroid treatment, intra-aortic balloon counterpulsation, enteral feeding, tracheostomy, acute physiology, age, APACHE II score, prior antibiotics, MV hours and steroids. | Total ventilation hours, ICU stay, hospital stay and mortality |
| Erbay RH et al. 2004 [53] | Turkey | Retrospective case-control study | 731 | 37 | 56.0 (25.0) | - | Clinical and microbiological findings | Respiratory failure, coma in admission (Glasgow coma scale < 9), depressed consciousness, enteral feeding and length of stay | Mortality |
| Nseir S et al. 2007 [51] | France | Retrospective case-control | 1402 | 177 | 59 ± 16 | 141/36 | Clinical, radiographical, microbiological criteria | Neurological failure, antibiotic treatment, COPD, male sex, and tracheostomy | Duration of MV, ICU stay and mortality |
| Rocha L de A et al. 2008 [50] | Brasil | Case-control study | 275 | 84 | 47.8 ± 17.4 | 54/30 | Clinical, radiographical, microbiological criteria | Duration of MV, tracheostomy and use of antibiotics prior to VAP. | Duration of MV, hospital stay and mortality. |
| Joseph NM et al. 2009 [47] | India | Prospective cohort | 200 | 36 | 41.4 ± 14.7 | 24//12 | Clinical, radiographical, microbiological criteria | Altered consciousness, tracheostomy, reintubation, emergency intubation and nasogastric tube | Mortality |
| Ranjit S et al. 2011 [26] | Nepal | Prospective cohort | 69 | 22 | 32.69 ± 23.75 | 10//12 | Clinical, radiographical, microbiological criteria | Reintubation, more invasive lines, H2 blockers and $PaO_2/FiO_2$. | Duration of mechanical ventilation, ICU stay. |
| Tamayo E et al. 2012 [49] | Spain | Prospective cohort | 1610 | 124 | 68.5 ± 10.03 | 46/78 | Clinical, radiographical, microbiological criteria | Immunosuppression, obesity, reintervention, COPD | Hospital stay and mortality. |
| Charles MP et al. 2013 [51] | India | Prospective cohort | 76 | 18 | 47.8 ± 17.8 | 15//3 | Use of the clinical pulmonary infection score (CPIS) clinical and microbiological criteria. | Chronic lung failure, H2 blockers usage, and supine position | Not studied |
| McGovern Murphy F et al. 2014 [52] | Canada | Case-control | 263 | 43 | 65 (53–73) | 33/14 | Clinical, radiographical, microbiological criteria | Charlson score ≥ 5, diabetes mellitus, APACHE II, SAPS II, reintubation, use of antibiotics at the beginning of MV, smoking, days of intubation. | Not studied |
| Ranjan N et al. 2014 [48] | India | Prospective cohort | 105 | 60 | - | 39/21 | Clinical, radiographical, microbiological criteria | Trauma, duration of MV, broad-spectrum antibiotics in the previous 7 days | Mortality |
| Karatas M et al. 2016 [36] | Turkey | Retrospective cohort | 1560 | 178 | 67.8 ± 21.1 | 102/76 | CDC criteria | APACHE II and Charlson comorbidity index scores, prolonged duration of hospitalisation and MV time, previous history of hospitalisation and antibiotherapy, reintubation, enteral nutrition, COPD, cerebrovascular disease, diabetes mellitus and organ failure. | Mortality |

**Table 1** (continued)

| Authors | Country | Design | *n* | Patients with VAP | Age VAP | Sex VAP (male/female) | Definition of VAP | Risk factors | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Six S et al. 2016 [39] | France | Retrospective cohort | 503 | 141 | 62 (51.5–74) | 102/39 | Clinical, radiographical, microbiological criteria | Number of days spent with hyperoxaemia, SAPS II, red blood cell transfusion and proton pump inhibitor use. | Duration of mechanical ventilation, ICU stay and mortality in the ICU |
| Othman et al. 2017 [46] | Egypt | Prospective cohort | 100 | 22 | 35.4 ± 13.7 | 16//6 | Clinical, radiographical, microbiological criteria | Smoking, altered consciousness, tracheostomy and reintubation. | Not studied |
| Xu Y. et al. 2019 [35] | China | Retrospective cohort | 901 | 156 | - | 136/20 | Clinical, radiographical, microbiological criteria | COPD, intensive care unit admission, MV methods, number of antibiotics administered, number of central venous catheters, duration of indwelling urinary catheter and use of corticosteroids prior to MV. | Length of stay in ICU and length of stay in hospital |
| Papakrivou E et al. 2020 [42] | Greece | Prospective cohort | 123 | 45 | 56.1 ± 3 | 35/10 | Clinical, radiographical, microbiological criteria | Intra-abdominal hypertension, ICU stay days, COPD, abdominal surgery | Mortality in ICU |
| Martínez-Martínez M et al. 2021 [43] | Spain | Prospective cohort | 353 | 100 | 61.5 (52.5–67) | 76/24 | American Thoracic Society/Infectious Diseases Society of America guidelines criteria | Admission to an open ICU, higher SOFA, treatment with corticosteroids and treatment with tocilizumab. | Duration of MV, ICU stay and mortality. |
| Teng G et al. 2022 [37] | China | Retrospective cohort | 89 | 40 | - | 23/17 | Clinical, radiographical, microbiological criteria | Therapeutic hypothermia and advanced age > 65 years | Duration of mechanical ventilation, ICU stay, hospital stay and 28-day mortality. |
| Pawlik J et al. 2022 [44] | Poland | Mixed prospective and retrospective cohort | 371 | 52 | - | - | Use of the clinical pulmonary infection score (CPIS) clinical and microbiological criteria. | Tracheostomy, age, sex, APACHE, antibiotic use prior to VAP | Duration of MV, ICU stay and mortality. |
| Garnier M et al. 2023 [38] | France | Prospective multicentre cohort | 3388 | 1523 | 63 (55–70) | 1195/328 | Clinical, radiographical, microbiological criteria | Male sex, concomitant bacterial pneumonia on ICU admission, $PaO_2/FiO_2$ ratio at intubation, neuromuscular blocking agents and corticosteroids. | Duration of mechanical ventilation, ICU stay, hospital stay and 28 and 90-days mortality. |
| Reyes LF et al. 2023 [45] | Colombia | Retrospective multicentre cohort | 3287 | 610 | 65.0 (57.0–72.0) | 442/168 | Clinical, radiographical, microbiological criteria | Prolonged stay under invasive mechanical ventilation, ARDS to admission and number of comorbidities. | Duration of MV, hospital stay and mortality. |

*SAPS II* Simplified Acute Physiology Score, *APACHE II* Acute Physiology and Chronic Health Evaluation, *COPD* Chronic Obstructive Pulmonary Disease, *SOFA* Sequential Organ Failure Assessment score, *ARDS* Acute Respiratory Distress Syndrome, *ICU* Intensive Care Unit, *MV* Mechanical Ventilation, *VAP* Ventilator Associated Pneumonia. $PaO_2/FIO_2$: arterial oxygen pressure/inspired oxygen fraction

4,126 patients), as was prior antibiotic treatment (OR 1.52; 95% CI 1.08–2.15; $p<0.05$; $I^2$ 57%; 5 studies, 2,382 patients). Finally, the duration of ventilation prior to VAP onset was strongly associated with risk (OR 6.2; 95% CI 1.09–11.3; $p<0.05$; $I^2$ 98%; 5 studies, 2,565 patients). No significant associations were identified for corticosteroid use, emergency intubation, or previous surgery.

The results of the meta-analysis of risk factors are displayed in Table 2, and the forest plots are provided in Supplementary File 1.

#### *Clinical outcomes*

The pooled results from 15 studies showed that VAP was not associated with Mortality, OR 1.24 (95% CI: 0.94–1.63), $p=0.12$, $I^2$ 87%. VAP was associated with a longer ICU stay, mean difference 12.74 (95% CI: 9.66–15.81), $p<0.05$, $I^2$ 95%; it significantly lengthened the duration of mechanical ventilation, mean difference 12.3 (95% CI: 9.27–15.34), $p<0.05$, $I^2$ 95%; finally, patients with VAP had a prolonged hospital stay, mean difference 16.17 (95% CI: 10.83–21.52), $p<0.05$, $I^2$ 96%, as shown in Figs. 2 and 3.

The differences between the findings of this updated meta-analysis and those of the previous systematic review by Wang et al. [19] can be seen in Table 3, which summarises the variations in study inclusion, identified risk factors, clinical outcomes, and methodological approaches.

### Publication bias

No publication bias was evident in any of the clinical outcomes. The results for publication bias were: mortality analysis, Egger's test ($p=0.13$), Begg's test ($p=0.74$); duration of mechanical ventilation, Egger's test ($p=0.24$), Begg's test ($p=0.43$); ICU stay, Egger's test ($p=0.01$), Begg's test ($p=0.47$); and hospital stay, Egger's test ($p=0.96$), Begg's test ($p=0.76$). A funnel plot is presented in Additional file.

### Assessment of the methodological quality of the studies

The results of the quality assessment of the studies included are shown in Supplementary Tables 1 and 2. Ten studies were of high quality [34, 35, 38, 42, 45, 46, 49–52]; eleven of moderate quality [25, 26, 36, 37, 39–41, 43, 44, 47, 53] and one study of low quality [48].

The certainty of the evidence was defined as follows:

- High for length of hospital stay in the case-control study.
- Moderate for duration of mechanical ventilation in the cohort.
- Low for mortality in cohort studies, duration of mechanical ventilation in case-control studies, ICU length of stay in case-control studies and cohorts, and hospital length of stay in cohort studies.
- Very low for mortality in the case-control studies (See supplementary files).

### Subgroup analysis, bivariate meta-regression, and sensitivity analysis

A subgroup analysis was performed for clinical outcomes. The subgroups used were: age over 60 years, study type, and quality assessment with the NOS. The analysis for the subgroup > 60 years found no reduction in heterogeneity in any of the outcomes measured: Mortality OR 1.32 (95% CI: 0.96–1.83), $p<0.05$, $I^2$ 89%; ICU length of stay MD 13.58 (95% CI: 8.68–18.47), $p<0.05$, $I^2$ 95%; duration of mechanical ventilation MD 14.74 (95% CI: 12.39–17.09), $p<0.05$, $I^2$ 88%; length of hospital stay MD 11.17 (95% CI: 10.83–21.52), $p<0.05$, $I^2$ 96%. Subgroup analysis by study type did not show a significant decrease in heterogeneity either; finally, analysis of methodological quality showed that in studies with Moderate methodological quality according to the NOS, VAP was significantly associated with Mortality, OR 1.68 (95% CI: 1.32–2.15), $p<0.05$, $I^2$ 17%.

No significant increase in Mortality was observed in studies with a VAP diagnosis based on clinical, radiographic, and microbiological criteria, showing high heterogeneity, OR 1.25 (95% CI: 0.94–1.65), $p=0.12$, $I^2$ 88%.

The subgroup analysis showed reductions in heterogeneity for corticosteroid use in multicentre studies, OR 1.03 (95% CI: 0.91–1.17), $p=0.62$, $I^2$ 0%; for COPD in multicentre studies, OR 1.11 (95% CI: 0.90–1.37), $p=0.32$, $I^2$ 0%; for diabetes mellitus, OR 1.14 (95% CI: 1.0–1.30), $p=0.05$, $I^2$ 16%; and for corticosteroid use in prospective studies, OR 1.03 (95% CI: 0.91–1.17), $p=0.59$, $I^2$ 0%; and a reduction in heterogeneity for enteral feeding in prospective studies, OR 4.54 (95% CI: 2.40–8.57), $p<0.55$, $I^2$ 0%.

The findings of the sensitivity analysis, after removing outliers, showed a reduction in heterogeneity for tracheostomy ($I^2$ 27%), prior antibiotics ($I^2$ 0%), reintubation ($I^2$ 38%), enteral feeding ($I^2$ 0%), impaired consciousness ($I^2$ 40%), corticosteroid use ($I^2$ 0%), COPD ($I^2$ 0%), APACHE II ($I^2$ 38%), and SAPS II ($I^2$ 0%).

Meta-regression analysis showed that age > 60 years did not have a significant impact on outcome, coefficient −0.007, z −1.33 (95% CI −0.01 to 0.003), $p=0.18$; additionally, study size was significantly associated with the log odds ratio observed in the studies examined, coefficient 0.54, z 2.0 (95% CI 0.02 to 1.06), $p=0.04$. Finally, higher quality studies tended to show smaller effect sizes than lower quality studies, coefficient −0.001, z −3.4 (95% CI −0.00 to −0.001), $p=0.001$. The sensitivity analysis for clinical outcomes did not reduce heterogeneity.

**Table 2** Risk factors for VAP analysed in the meta-analysis

| Risk Factors | # Studies | Heterogeneity $I^2$ (%) | Pooled OR/MD (95% CI) | *p* |
|---|---|---|---|---|
| **Patient-related factors** | | | | |
| Gender (male) | 16 | 0 | OR 1.30 (1.18, 1.44) | **< 0.05** |
| COPD | 10 | 75 | OR 1.52 (1.10, 2.09) | **< 0.05** |
| impaired consciousness at hospital admission | 5 | 83 | OR 3.14 (1.28, 7.69) | **< 0.05** |
| Poisoning | 6 | 0 | OR 1.04 (0.70, 1.53) | 0.86 |
| Smoking | 5 | 0 | OR 0.97 (0.78, 1.21) | 0.79 |
| Use of corticosteroids | 13 | 52 | OR 1.22 (0.99, 1.51) | 0.06 |
| Diabetes mellitus | 10 | 65 | OR 1.0 (0.79, 1.28) | 0.97 |
| Cardiac disease | 7 | 38 | OR 0.98 (0.76, 1.27) | 0.89 |
| Age | 14 | 84 | MD 0.04 (−1.57, 1.65) | 0.96 |
| Trauma | 7 | 0 | OR 1.47 (1.12,1.93) | **< 0.05** |
| Chronic kidney disease | 6 | 24 | OR 0.88 (0.68, 1.13) | 0.31 |
| APACHE II | 7 | 90 | MD 2.01 (0.60, 3.43) | < 0.05 |
| SAPS II | 4 | 85 | MD 0.70 (−2.84, 4.23) | 0.7 |
| **Treatment-related factors** | | | | |
| H2 blocker | 6 | 0 | OR 2.24 (1.50, 3.37) | **< 0.05** |
| Tracheostomy | 11 | 77 | OR 3.44 (2.00, 5.92) | **< 0.05** |
| Prior antibiotic treatment | 5 | 57 | OR 1.52 (1.08, 2.15) | **< 0.05** |
| Reintubation | 6 | 77 | OR 5.11 (2.29, 11.42) | **< 0.05** |
| Enteral feeding | 6 | 57 | OR 4.73 (2.54, 8.78) | **< 0.05** |
| Nasogastric tube | 5 | 20 | OR 2.94 (1.56, 5.53) | **< 0.05** |
| vNeuromuscular blocker use | 3 | 0 | OR 1.30 (1.13, 1.49) | **< 0.05** |
| Days of intubation prior to VAP | 5 | 98% | MD 6.20 (1.09,11.30) | **< 0.05** |
| Emergency intubation | 3 | 74 | OR 2.39 (0.36, 15.67) | 0.36 |
| Previous surgery | 10 | 13 | OR 1.09 (0.88, 1.34) | 0.43 |

*OR* Odds ratio, *MD* Mean difference, *APACHE* Acute Physiology And Chronic Health Evaluation, *SAPS II* Simplified Acute Physiology Score II, *COPD* Chronic Obstructive Pulmonary Disease, Values in bold indicate statistical significance

The forest plot of the subgroup analysis, bivariate meta-regression, and the sensitivity analysis can be seen in Supplementary file.

## Discussion

This systematic review and meta-analysis, including 22 studies and 16,731 patients, identified several significant risk factors for VAP, such as male sex, use of $H_2$ blockers, tracheostomy, prior antibiotic treatment, reintubation, enteral feeding, impaired consciousness at admission, nasogastric tube use, use of neuromuscular blockers, trauma, and prolonged duration of ventilation. Subgroup analyses based on age > 60, study design, and quality assessment did not substantially reduce heterogeneity, although moderate-quality studies according to NOS showed a significant association between VAP and mortality with low heterogeneity. Additional subgroup analyses of multicentre and prospective studies reduced heterogeneity for selected factors such as corticosteroid use, COPD, diabetes, and enteral feeding. Sensitivity analyses after removing outliers also improved consistency for tracheostomy, prior antibiotics, reintubation, enteral feeding, impaired consciousness, corticosteroid use, COPD, APACHE II, and SAPS II. Meta-regression indicated that sample size contributed to heterogeneity across studies. Patients with VAP had significantly longer durations of mechanical ventilation, ICU stay, and hospitalisation. Overall, study quality was high in ten studies, moderate in eleven, and low in one, but the certainty of the evidence for most outcomes remained low due to heterogeneity.

VAP is the most common infection acquired in the ICU [54]. Despite advances in microbiological diagnostics, its epidemiology and diagnostic criteria remain controversial, which complicates the interpretation of studies on treatment, prevention, and outcomes [9]. Identifying risk factors is therefore essential to enable closer monitoring and timely interventions. In this context, it is important to distinguish between modifiable and non-modifiable risk factors. Modifiable factors can potentially be addressed through preventive strategies, such as sedation management, ventilatory practices, and nutritional approaches [55, 56]. By contrast, non-modifiable factors—such as age, sex, comorbidities, and baseline severity—inform risk stratification and guide the intensity of surveillance [57].

Our results indicate that both patient- and treatment-related factors contribute to VAP risk. Male sex and the need for tracheostomy were significantly associated with increased risk, in agreement with a previous meta-analysis [58]. The use of neuromuscular blockers also showed a significant association, consistent with the findings of Garnier et al. [38]. Prior antibiotic exposure, a factor of ongoing international concern, was confirmed in our study as a significant risk factor for VAP, corroborating results from earlier reports [18, 59].

The causal association between enteral nutrition and VAP remains controversial. In our meta-analysis, enteral feeding emerged as a significant risk factor, consistent with previous studies [60, 61]. Several mechanisms have been proposed, including vomiting, aspiration, and gastrointestinal intolerance due to gastroparesis, which may lead to increased gastric volume and reflux [62] Although these mechanisms are biologically plausible, the evidence

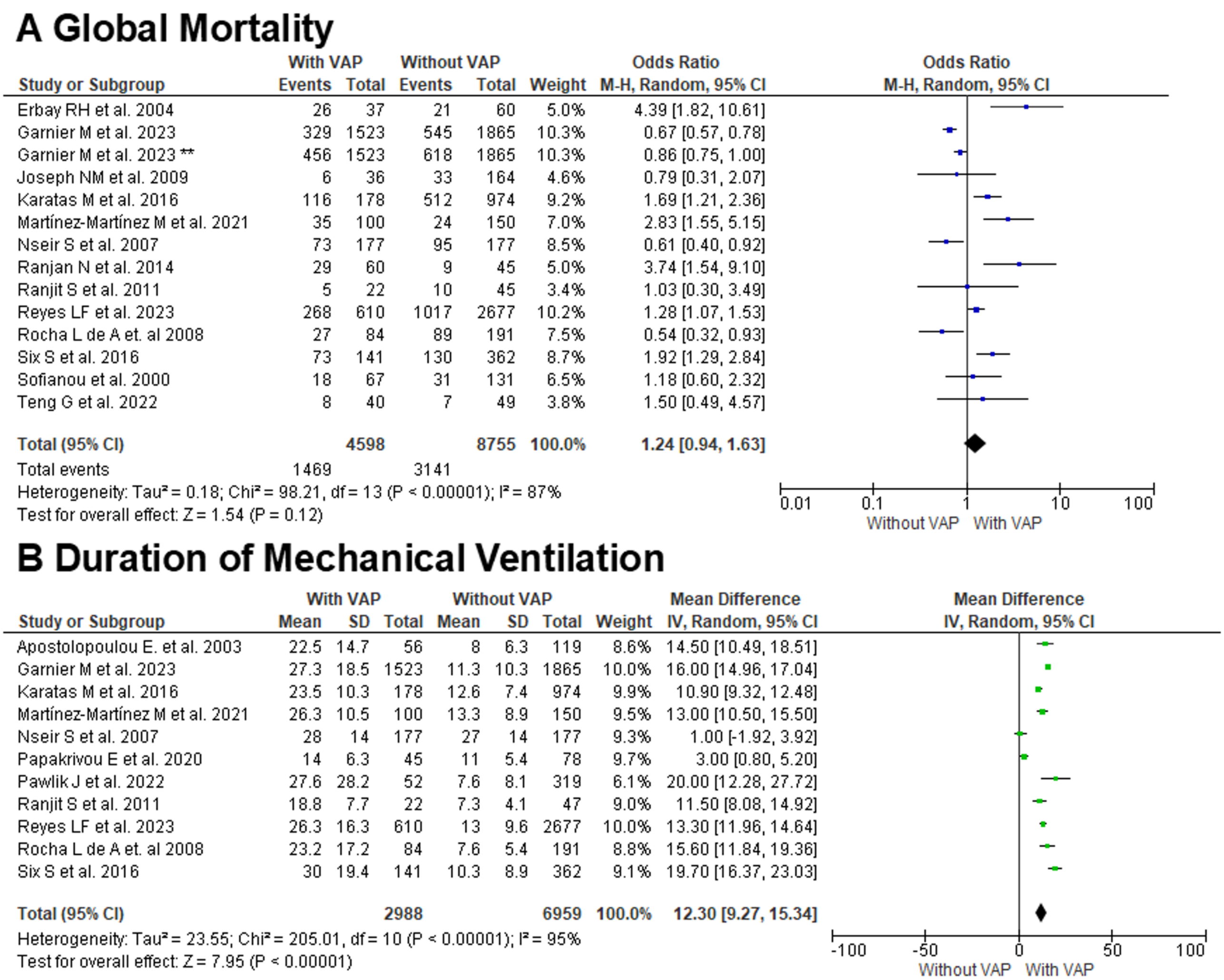


**Fig. 2** Forest plot of clinical outcomes. Garnier: 28-day mortality. Garnier**: 28-day mortality

remains inconsistent and further studies are required to clarify this association.

The role of the nasogastric tube as a potential confounder also deserves consideration. In our analysis, nasogastric tube use was significantly associated with VAP, in line with previous reports [18]. Permanent gastric tubes may impair sphincter function and facilitate bacterial colonisation of the pharynx and lower respiratory tract. Future research should therefore address whether the increased risk is primarily attributable to enteral nutrition itself or to the device. Recent recommendations from the *Neumonía Zero* project support the use of small-bore tubes advanced into the small intestine as a safer alternative [16].

Reintubation was significantly associated with VAP, consistent with previous studies [63].The transfer of organisms from the upper to the lower respiratory tract may explain this increased risk [64]. The use of $H_2$ blockers also showed a significant association, in line with earlier reports and possibly related to gastric alkalisation [65]. In addition, patient-related factors such as COPD and impaired consciousness were confirmed as significant contributors, consistent with prior findings [66, 67].

In agreement with previous studies [3, 44, 68], our meta-analysis confirmed that patients with VAP experience longer durations of mechanical ventilation, ICU stay, and hospitalisation. Although Mortality rates of up to 50% have been reported [9], the actual contribution of VAP to mortality in critically ill patients remains uncertain. Some studies suggest that VAP increases mortality [38, 45], but our analysis did not demonstrate a consistent association. The heterogeneity of results may account for these discrepancies. Interestingly, subgroup analyses based on NOS assessment indicated a significant association between VAP and mortality in studies of moderate quality, which may reflect potential biases in this subgroup.

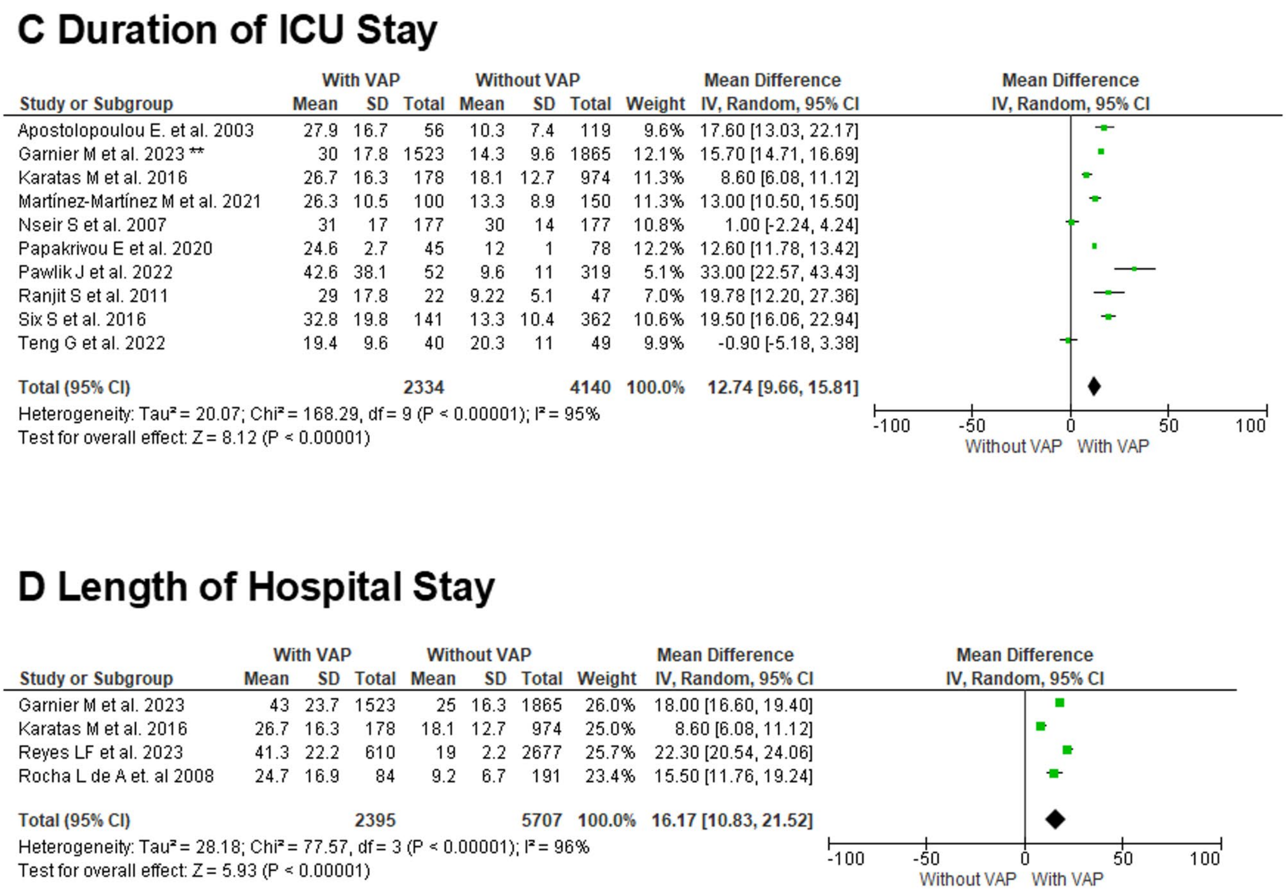


**Fig. 3** Forest plot of clinical outcomes. Garnier: 28-day mortality. Garnier **: 28-day mortality

**Limitations**

This meta-analysis has several limitations. Firstly, the diagnostic criteria for VAP used in the studies were inconsistent. It would be beneficial to establish a clear and uniform diagnostic standard for VAP in the future. Secondly, a high degree of heterogeneity was observed in the meta-analysis of some risk factors and clinical outcomes. Finally, the low rating of the certainty of clinical outcomes, in combination with the high heterogeneity observed in the meta-analysis, suggests that the results should be interpreted with caution and that further research is needed to clarify the outcomes of VAP.

**Strengths of the study**

Our study also has several strengths. Firstly, the number of studies included in the meta-analysis provides a broad and representative basis for the analysis. Secondly, the large number of patients studied enhances the robustness and generalisability of the results. Thirdly, the examination of a wide range of risk factors and clinical outcomes offers a comprehensive understanding of VAP. Additionally, the subgroup analyses and sensitivity analysis increase the study's methodological rigour. Finally, the careful formulation of the search strategies, study selection, and data entry and analysis ensures the accuracy and reliability of the findings.

**Implications for clinical practice**

This study has important implications for clinical practice, particularly in distinguishing modifiable from non-modifiable risk factors for VAP. While non-modifiable factors such as sex or underlying comorbidities support risk stratification and closer surveillance, modifiable factors—including reintubation, tracheostomy, sedation practices, and enteral nutrition strategies—represent actionable targets for prevention. Addressing these factors through evidence-based bundles and multidisciplinary protocols can reduce the incidence of VAP and improve patient outcomes. Recognising these risks is crucial not only for reducing the duration of mechanical ventilation, ICU stay, and hospitalisation, but also for enhancing overall recovery and quality of care in critically ill patients.

**Future directions**

Future research should focus on standardising the diagnostic criteria for VAP, assessing the interaction between risk factors and co-interventions, and exploring the role

**Table 3** Comparison between Wang et al. (2019) and the present updated meta-analysis

| Characteristic | Wang et al. (2019) | Present review |
|---|---|---|
| Number of studies included | 16 (12 meta-analysed) | 22 (all meta-analysed) |
| Search period | Up to August 2019 | Up to November 2024 |
| Population | Adults in ICU (multi-centre and single-centre studies) | Adults in ICU, including recent studies (COVID-19 included) |
| Significant risk factors | $H_2$ blocker use, nasogastric tube, enteral feeding, central venous catheter, tracheostomy | Male gender, the use of H2 blockers, tracheostomy, prior antibiotic treatment, reintubation, enteral feeding, COPD, impaired consciousness, nasogastric tube, use of neuromuscular blockers, trauma, days of intubation prior to VAP. |
| Significant outcomes | ↑ ICU stay, ↑ hospital costs (~$10,019) and ↑ mortality. | ↑ Duration of MV, ↑ ICU and hospital stay. |
| Sensitivity analysis | No | Yes |
| Meta-regression | No | Yes |
| GRADE assessment | No | Yes |
| Added value | First meta-analysis of incidence, risk factors and mortality | Update with larger number of studies, more rigorous methods and COVID-19 context. |

*COPD* Chronic Obstructive Pulmonary Disease, *MV* Mechanical Ventilation, *ICU* Intensive Care Unit, *GRADE* Grading of Recommendations Assessment, Development and Evaluation

of emerging technologies to monitor and prevent complications associated with mechanical ventilation. In addition, well-designed, prospective multicentre studies are needed to clarify the true contribution of controversial factors, such as enteral nutrition and prior antibiotic exposure, to the development of VAP.

## Conclusions

Male gender, the use of H2 blockers, tracheostomy, prior antibiotic treatment, reintubation, enteral feeding, COPD, impaired consciousness at hospital admission, nasogastric tube use, use of neuromuscular blockers, trauma and days of intubation prior to VAP significantly increased the risk of VAP. In patients with VAP, ICU stay, duration of mechanical ventilation and hospital stay were significantly increased.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03932-2.

Supplementary Material 1. Supplementary materials include: the search strategy, a forest plot of risk factors, a forest plot of subgroup analyses, a funnel plot of outcomes, meta-regression tables, the PRISMA checklist, the quality appraisal of the included studies, and the GRADE evidence quality assessment.

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**Authors' contributions**
PO, HMPG, DM, and JRM were the main contributors regarding conceptualisation, methodology, analysis and interpretation of the data, as well as writing and editing the manuscript. HMPG, AR and DM critically revised the statistical methods. PO, HMPG, DM, JRM and AR, made substantial contributions to the editing and revision of the manuscript. All authors read and approved the final manuscript.

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**Data availability**
Data is provided within the manuscript or supplementary information files.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]Centro de atención e investigación médica (CAIMED), Chia, Colombia
[2]Universidad El Bosque, Bogotá, Colombia
[3]Postgraduate division, Epidemiology master's degree coordinator, Universidad El Bosque, Bogotá, Colombia
[4]Intensive Care Unit Los Cobos Medical Center- Hospital San José. Research Group Gribos, Bogotá, Colombia
[5]Critical Care Department, Hospital del Mar Barcelona, Spain. Critical Care Illness Research Group (GREPAC), Hospital Del Mar Research Institute (IMIM). Department of Medicine and Life Sciences (MELIS), Universitat Pompeu Fabra (UPF), Barcelona, Spain
[6]Unidad de cuidado intensivo Clínica Reina Sofia, Clínica Colsanitas. Grupo de Investigación en Nutricion Clínica y Rehabilitación, grupo Keralty, Bogotá, Colombia

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