Original Article

Incidence and risk factors of ventilator-associated pneumonia in the intensive care unit: a systematic review and meta-analysis

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Background: Ventilator-associated pneumonia (VAP) is a serious complication occurring in critically ill patients receiving mechanical ventilation in the intensive care unit (ICU). This study attempted to analyze VAP incidence in the ICU using a meta-analysis, investigate risk factors for VAP occurrence, and examine influence of VAP on outcomes.

Methods: A search was carried out in the Web of Science, PubMed, Embase, and The Cochrane Library databases to identify studies on incidence and risk factors of VAP in ICU patients. Study quality was tested by the Newcastle-Ottawa Scale. Data related to risk factors, incidence, and outcomes were utilized for meta-analysis. Meta-analysis was conducted using Stata 18 and Review Manager 5.4.

Results: Seventeen articles were included, comprising 6,222 patients, and incidence of VAP was 30% [95% confidence interval (CI): 24–37%]. Risk factor analysis showed that males [odds ratio (OR): 1.50; 95% CI: 1.29–1.75; P<0.001], smoking (OR: 1.30; 95% CI: 1.08–1.57; P=0.007) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score [weighted mean difference (WMD): 1.30; 95% CI: 0.31–2.30; P=0.01] were risk factors for VAP. Antibiotic prophylaxis (OR: 0.79; 95% CI: 0.63–0.99; P=0.04) was a protect factor for VAP. Compared with non-VAP patients, VAP patients had a prolonged duration of mechanical ventilation (WMD: 6.96; 95% CI: 5.42–8.50; P<0.001), ICU length of stay (WMD: 7.91; 95% CI: 5.43–10.39; P<0.001) and total length of hospital stay (WMD: 8.09; 95% CI: 3.70–12.48; P=0.0003). There was no significant difference in mortality rate between VAP and non-VAP patients (OR: 1.13; 95% CI: 0.79–1.63; P=0.50).

Conclusions: VAP incidence in the ICU was around 30%. Male, smoking, and high APACHE II score were risk factors for VAP, while antibiotic prophylaxis was a protective factor for VAP. VAP could lead to prolonged mechanical ventilation, ICU stay, and hospital stay, but it did not influence mortality.

Keywords: Ventilator-associated pneumonia (VAP); intensive care unit (ICU); incidence; risk factors; mortality

Submitted Jan 25, 2024. Accepted for publication Jul 12, 2024. Published online Sep 14, 2024.
doi: 10.21037/jtd-24-150
View this article at: https://dx.doi.org/10.21037/jtd-24-150

Introduction

A case of pneumonia that develops at least 48 hours following endotracheal intubation and mechanical ventilation is ventilator-associated pneumonia (VAP) (1). VAP is a usual complication in patients requiring invasive mechanical ventilation and is part of hospital-acquired pneumonia in the intensive care unit (ICU), which has a substantial impact on ICU patients (2). VAP is an infectious complication that results in the colonization of harmful

bacteria in the respiratory tract and pneumonia. It is linked to impaired host defense systems and insufficient infection management measures (3,4). VAP can be categorized into early-onset and late-onset forms based on onset time. Within the first 4 days (≤4 days) of mechanical ventilation, early-onset VAP affects patients and is typically brought on by bacteria susceptible to antibiotics. Multidrug-resistant bacteria are the cause of late-onset VAP, which manifests in patients on mechanical ventilation after 5 days (≥5 days) of ventilation (4). Clinical manifestations of VAP include fever, purulent sputum, and increased oxygen requirement of the ventilator (2,5).

It has been estimated that between 5% and 40% of individuals on mechanical ventilation still have VAP, despite advancements in the microbiology, epidemiology, and diagnostic criteria of the disease (6,7). Recent surgery, trauma, prior sepsis, reintubation, inter-hospital patient transfer, and other chronic illnesses are possible risk factors for VAP (8,9). VAP is linked to increased mortality and healthcare expenses (10-12). The death rate in VAP patients with pathogenic factors that are multidrug-resistant bacteria can reach 30–50% (13,14). A study in the United States estimated that the attributable cost of VAP is $40,144 [95% confidence interval (CI): $36,286–$44,220] (15). Delayed diagnosis of VAP may hinder therapy and lead to overuse of broad-spectrum antibiotics (16).

A thorough understanding of VAP incidence and risk factors is crucial for creating more effective prevention and control measures. However, earlier results have shown heterogeneity, incidence and risk factors of VAP in ICU patients and their impact on outcomes remain uncertain. This meta-analysis aimed to investigate VAP incidence in ICU patients, evaluate factors linked to its occurrence, and examine its effect on outcomes. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-150/rc).

Highlight box

Key findings

- A retrospective analysis of 17 articles involving 6,222 patients determined the incidence of ventilator-associated pneumonia (VAP) in intensive care unit (ICU) patients receiving mechanical ventilation to be 30%.
- Three risk factors for VAP were identified, including sex, smoking, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and one protective factor (antibiotic prophylaxis).
- VAP patients experienced significantly longer mechanical ventilation time, ICU length of stay, and total hospital stay compared to non-VAP patients. However, there was no significant difference in mortality rates between the two groups.

What is known and what is new?

- Previous literature has established the prevalence of VAP in ICU patients, but this study contributes by providing updated incidence rates and identifying significant risk factors.
- This study further confirms the high incidence of VAP in ICU patients. Additionally, the identified risk factors provide valuable insights for preventive strategies.

What is the implication, and what should change now?

- The results emphasize the ongoing challenge of VAP in ICU settings and underscore the need for preventive measures and rigorous management strategies.
- Clinicians should be aware of the identified risk factors for VAP and consider them in patient care and management protocols.
- Hospital administrators and policymakers should prioritize efforts to reduce the burden of VAP, including implementing infection control measures and promoting antimicrobial management programs.

Methods

Literature retrieval

A search was done in the Web of Science, PubMed, Embase, and The Cochrane Library databases to identify studies on the incidence and risk factors of VAP in ICU patients. The retrieval period was from the database inception through December 2023. The search keywords included ICU and VAP.

Literature screening

Inclusion criteria: (I) the study subjects were patients receiving mechanical ventilation in the ICU; (II) the study design was a cohort study or case-control study; (III) clear definition and diagnostic criteria for VAP were provided; (IV) one or more indicators of VAP incidence, risk factors, or clinical outcomes were reported.

Exclusion criteria: (I) duplicate publications; (II) publications classified as guidelines, reviews, or case analyses; (III) inability to extract data or contradictory data; (IV) non-English content.

Data extraction and quality assessment

Two investigators extracted data separately, while a third

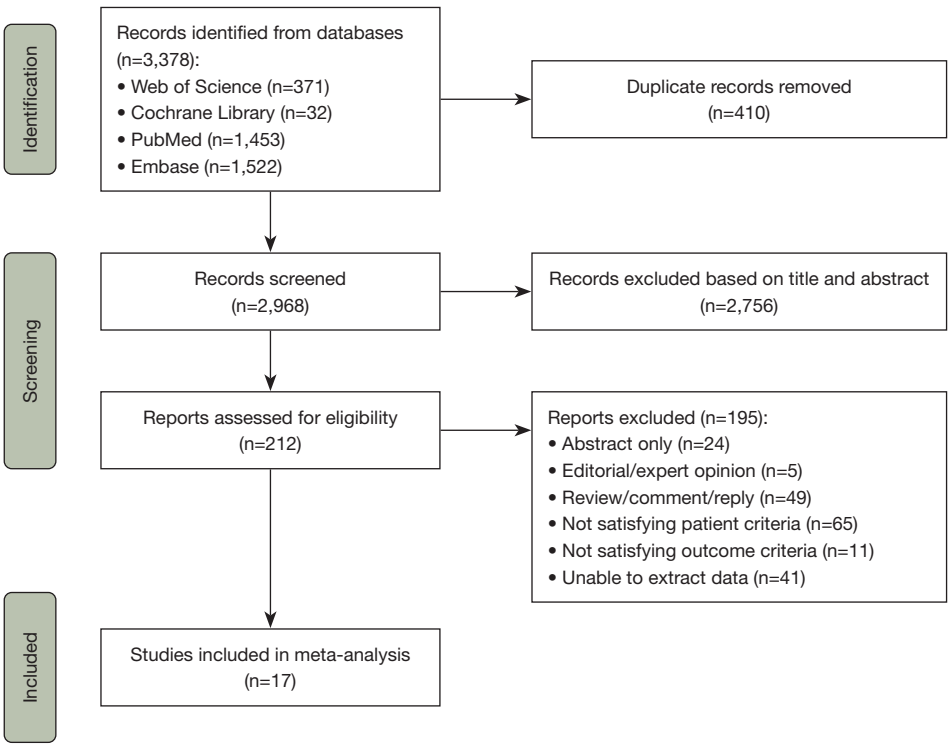

Figure 1 PRISMA flow chart for the included studies.

investigator reconciled any inconsistencies. The following data were extracted from the literature: authors, publication year, country, study type, number of patients, gender, age, type of ICU, disease distribution, VAP incidence, VAP risk factors, and clinical outcomes. Newcastle-Ottawa Scale (NOS) tested study quality. The study was deemed to be of high quality with NOS score ≥6; otherwise, it was deemed to be of low quality.

Statistical analysis

VAP incidence was computed by "metaprop" command in Stata18 (STATA Corporation, College Station, TX, USA). VAP risk factors and outcomes in ICU patients were assessed on Review Manager 5.4 (Cochrane Collaboration, UK). I^2 statistic was implemented to assess heterogeneity among study results. If $I^2 \leq 50\%$, there was no statistical heterogeneity among studies, and a fixed-effect model was applied. Conversely, there was statistical heterogeneity, and a random-effects model was utilized for meta-analysis. For continuous data, weighted mean difference (WMD) and 95% CI were computed. For categorical data, odds ratio (OR) and 95% CI were utilized. $P<0.05$ was deemed statistically significant. And publication bias was assessed using Egger's linear regression analysis.

Results

Literature retrieval results

As presented in *Figure 1*, 3,378 articles were retrieved from the database, and 410 duplicate documents were deleted. After excluding irrelevant literature by reading titles and abstracts, 212 articles were thoroughly read, 195 articles were excluded, and finally, 17 eligible articles were included (17-33).

Inclusion of study characteristics

The 17 articles involved 6,222 patients. Nine articles were retrospective studies, seven were prospective studies, and one study included prospective and retrospective cohorts (19). The maximum sample size included in the study was 1,285 subjects, and the minimum one was 89 subjects. The basic characteristics of literature included in this work are listed in *Table 1*. All studies had NOS

Table 1 Characteristics of studies included in this meta-analysis

Author	Year	Country	Study design	Sample size	Age, years (mean)	Male (%)
Battaglini	2023	Italy	Retrospective	1,285	54	65
Nisar	2023	Pakistan	Retrospective	589	NR	NR
Pawlik	2022	Poland	Mixed prospective and retrospective	371	66	67
Teng	2022	China	Retrospective	89	NR	55
Belay	2022	Ethiopia	Retrospective	312	35	59
Kaur	2022	India	Prospective	378	NR	76
Watson	2022	Australia	Retrospective	170	55.7	55
Suljevic	2020	Bosnia and Herzegovina	Retrospective	250	60.4	52
Robba	2020	European multicenter	Prospective	962	39.5	NR
Esnault	2017	France	Retrospective	175	36	79
Mathai	2015	India	Prospective	250	55.5	60
Jovanovic	2015	Serbia	Prospective	144	36.5	80
Song	2014	China	Retrospective	329	74	64
Lepelletier	2010	France	Retrospective	161	41	75
Gacouin	2009	France	Prospective	361	61.5	64
Hyllienmark	2007	Sweden	Prospective	221	56.5	NR
Apostolopoulou	2003	Greece	Prospective	175	52.5	70

NR, not reported.

scores greater than 6, representing high quality. Details of literature quality assessment are presented in Table S1. The types of ICUs and the distribution of diseases among the patients included in this study are detailed in Table S2.

VAP incidence rate

The random effects model concluded that VAP incidence in ICU patients receiving mechanical ventilation was 30% (95% CI: 24–37%), as illustrated in *Figure 2*. Egger's test showed no significant publication bias (P=0.77) (Figure S1). Subgroup analysis based on study design (prospective and retrospective) showed that VAP incidence rate in retrospective studies was 36% (95% CI: 29–44%), which was higher than that in prospective studies (25%, 95% CI: 16–35%), as presented in Figure S2.

Risk factors

We summarized 11 possible risk factors (reported in ≥3 studies). A significant relationship was observed between VAP and factors: sex (OR: 1.50; 95% CI: 1.29–1.75; P<0.001), smoking (OR: 1.30; 95% CI: 1.08–1.57; P=0.007), Acute Physiology and Chronic Health Evaluation II (APACHE II) score (WMD: 1.30; 95% CI: 0.31–2.30; P=0.01), and antibiotic prophylaxis (OR: 0.79; 95% CI: 0.63–0.99; P=0.04), as depicted in *Table 2* and Figures S3-S13.

Clinical results

Eight studies reported mechanical ventilation time. The random effects model summarized that time was significantly longer in VAP patients than in non-VAP patients (WMD: 6.96; 95% CI: 5.42–8.50; P<0.001). Eight studies involved ICU length of stay. Pooled results from random-effects model displayed a longer ICU length of stay for VAP patients than non-VAP patients (WMD: 7.91; 95% CI: 5.43–10.39; P<0.001). Four studies reported the total length of hospital stay. Summary results of random effects model illustrated a longer total length of hospital stay for VAP patients than non-VAP patients (WMD: 8.09; 95% CI: 3.70–12.48; P=0.0003).

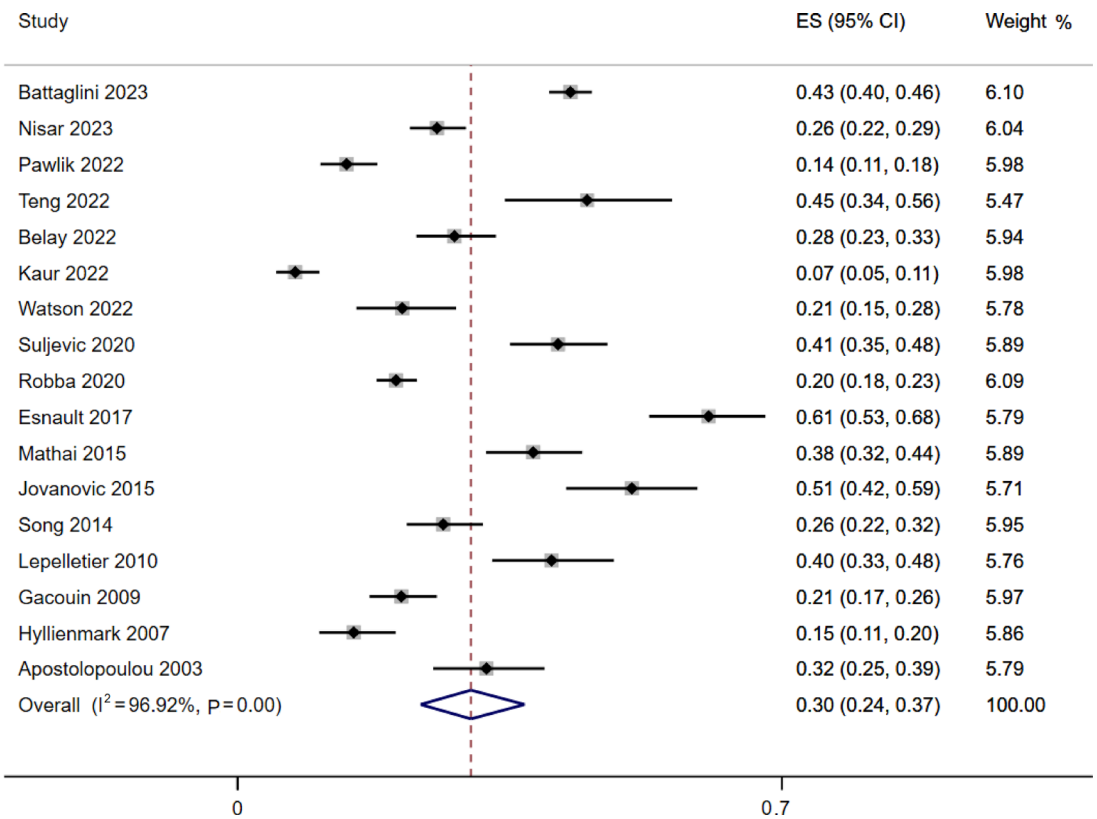

Figure 2 Incidence of VAP. ES, effect size; VAP, ventilator-associated pneumonia; CI, confidence interval.

Table 2 Risk factors of ventilator-associated pneumonia

Risk factors	Number of studies	Model	I^2, %	OR	WMD	95% CI	P
Male	11	Fixed	3	1.50	NA	1.29 to 1.75	<0.001
Age	4	Fixed	0	NA	2.41	−0.34 to 5.15	0.09
Hypertension	3	Fixed	5	0.99	NA	0.80 to 1.23	0.94
Diabetes	7	Random	82	1.13	NA	0.60 to 2.15	0.70
COPD	4	Fixed	0	1.39	NA	0.93 to 2.10	0.11
Smoking	5	Fixed	0	1.30	NA	1.08 to 1.57	0.007
APACHE II	4	Fixed	24	NA	1.30	0.31 to 2.30	0.01
Steroid use	6	Random	80	1.42	NA	0.65 to 3.08	0.38
Antibiotic prophylaxis	6	Fixed	21	0.79	NA	0.63 to 0.99	0.04
Barbiturates	3	Random	82	2.24	NA	0.92 to 5.48	0.08
Transfusion	4	Random	90	1.31	NA	0.56 to 3.04	0.53

OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; NA, not applicable; COPD, chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Seven studies reported mortality of patients. The random effects model summarized no significant difference in mortality rate between the two groups (OR: 1.13; 95% CI: 0.79–1.63; P=0.50), as shown in *Figure 3*.

Discussion

This work combined evidence from 17 studies, which involved 6,222 patients, to assess VAP incidence and risk factors in the ICU. VAP incidence in ICU patients receiving mechanical ventilation was approximately 30%. Male, smoking, and high APACHE II score were risk factors, while antibiotic prophylaxis was a protective factor for VAP. VAP patients had longer mechanical ventilation, ICU length of stay, and length of hospital stay than non-VAP patients. No difference was discernible in mortality rates between the two groups.

Literature reports VAP incidence in mechanically ventilated patients to be 10–40% (6,7), and our results fall within this range. VAP incidence was higher in retrospective studies than in prospective studies, which may be due to the inherent characteristics of these two types of studies. Retrospective study analyzes clinical data from a certain time period overall, and there may be biases in the data integrity and homogeneity. Retrospective studies typically have less accurate data than prospective studies do. Further prospective studies should be conducted, as we advise.

VAP is the most common pulmonary complication in trauma patients and a leading cause of hospital-acquired infection-related mortality (34,35). Previous studies have identified male gender as an independent risk factor for ICU-acquired pneumonia and VAP (36-40). A prospective cohort study of 521 ICU patients requiring mechanical ventilation for more than 12 hours confirmed that the male gender is an independent predictor of VAP (41). Rello *et al.* (42) investigated 842 patients who developed VAP, and their records indicated a significantly higher incidence in males (64.1% *vs.* 35.9%). Multivariate logistic regression analysis further confirmed the independent association between male gender and VAP development. Studies by Sharpe *et al.* (39) and Napolitano *et al.* (37) also found that the incidence of VAP was significantly higher in males than in females after trauma (3.8% *vs.* 2.6%, P=0.001). Increasing evidence suggests that the gender disparity in VAP incidence may be due to sex-specific responses to traumatic injury, indicating differences in immune function. This effect appears to be linked to the beneficial effects of estrogen and the detrimental effects of testosterone (37,43,44). Major sex hormones, estrogen and testosterone, have been shown to modulate immune responses by altering Th-1 and Th-2 cell-mediated immunity spectra and affecting the synthesis and release of cytokines such as interleukin (IL)-1 and IL-6 (45,46). Numerous animal studies have demonstrated that estrogen enhances the effector responses of immune cells (47,48), while male sex hormones exhibit immunosuppressive effects (43). In addition to improving immune responses, estrogen is believed to help maintain or improve the function of organs such as the heart, liver, lungs, and intestines following traumatic hemorrhage (49,50). Moreover, males often exhibit more behavior and social factors associated with VAP risk compared to females, such as smoking, alcohol consumption, and other unhealthy lifestyle habits (51). Smoking is a significant trigger for VAP as it damages the respiratory system, leading to shortened and irregular cilia and impaired ciliary movement, thereby reducing local respiratory defense mechanisms (52,53). Additionally, complications related to unhealthy habits, such as smoking-induced pneumonia (54), make males more susceptible, highlighting the importance of pre-existing comorbidities in lung injury susceptibility. Disease severity is frequently reported as a risk factor for VAP (25,28). The APACHE II score, based on initial values of 12 routine physiological measurements, age, and previous health status, is used to assess disease severity (55). The APACHE II score reflects the worst data within the first 24 hours of ICU admission, and many studies have confirmed its accuracy in reflecting disease severity and clinical outcomes in ICU patients (56,57).

Studies have reported an association between steroid therapy and the risk of developing VAP in ICU patients (58,59). However, a planned secondary analysis of a multicenter retrospective European cohort study involving 36 ICUs assessed the relationship between adjunctive corticosteroid use and VAP incidence, finding no significant correlation between the two (60). The results of our analysis also indicate no significant association between steroid use and the risk of VAP, consistent with the aforementioned study. Further research and data are needed to fully understand the relationship between COPD and VAP and to evaluate the role of COPD in the development of VAP. Our results also suggested that antibiotic prophylaxis was a protective factor for VAP. Although studies suggest that prophylactic antibiotic use can prevent early bacterial colonization of the upper respiratory tract, concerns exist that prophylactic antibiotic use may induce bacterial resistance and expose patients to late-onset VAP with hard-

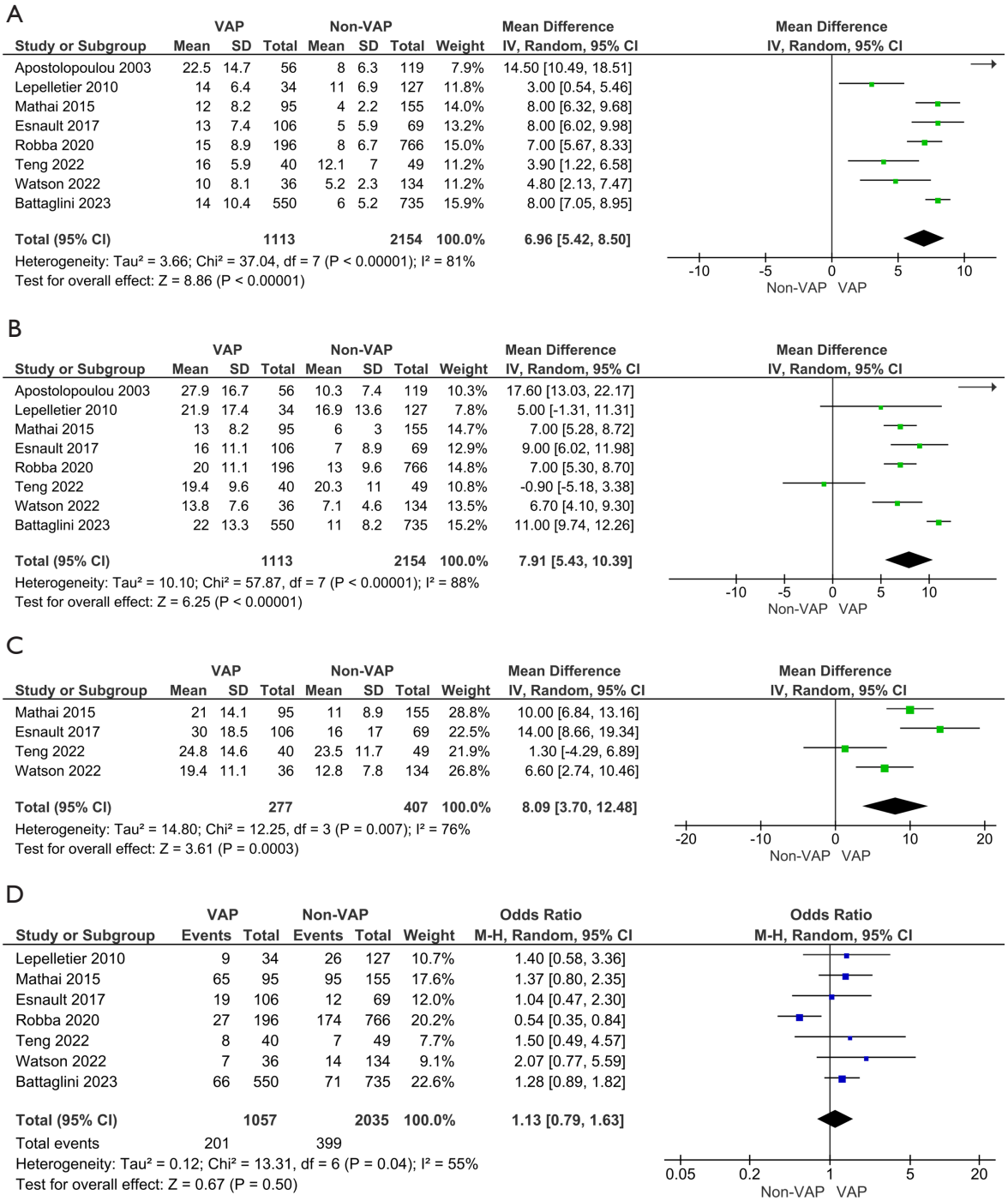

Figure 3 Clinical outcomes. (A) Duration of mechanical ventilation (day); (B) intensive care unit length of stay; (C) hospital length of stay; (D) mortality. VAP, ventilator-associated pneumonia; SD, standard deviation; CI, confidence interval; IV, inverse variance; M-H, Mantel-Haenszel.

to-treat pathogens (61-63). In surgical patients, preoperative prophylactic antibiotics use increases VAP risk by raising colonization of the oral cavity and detection rate of Gram-negative bacteria in tracheal aspirates (64). Meta-analysis reported that antibiotic treatment based on local prevention alone may reduce ventilator-associated tracheobronchitis (VAT) incidence in ICU patients receiving mechanical ventilation for more than 48 hours, but it does not reduce mortality (65). To establish sensible antibiotic regimens, such as local application, to accomplish successful treatment while reducing the risk of resistance, clinical anti-infection practices need to fully account for the likelihood of microbial resistance and have a greater understanding of pathogens for VAP in this group (66-68).

Our study did not observe a discernible association between VAP and mortality, congruous with earlier studies (30,69). This may be because VAP is merely a transient condition that can be treated with the right antibiotics if it is identified early in the ICU (70), it prolongs the acute phase of the disease but is unlikely to affect the mortality rate. Furthermore, advancements in antibiotic management have improved the progress of healthcare-associated infections, thereby affecting outcomes (71). ICU stay, mechanical ventilation, and hospital stay prolonged due to VAP are in line with previous investigations (72,73). This also indicates that VAP imposes a greater burden on patients and consumes more medical resources (12,23).

The study we conducted has several limitations. First, bias may be introduced because half of the included articles were retrospective studies. Second, we were unable to do subgroup analysis for various forms of VAP (early-onset versus late-onset) because of the limited number of studies. Third, due to a limited number of studies, we failed to analyze more outcomes including treatment costs.

In conclusion, VAP incidence in the ICU was around 30%. Male, smoking, and high APACHE II were risk factors for VAP, while antibiotic prophylaxis was a protective factor for VAP. VAP could lead to prolonged mechanical ventilation, ICU stay, and hospital stay, but it has no impact on the mortality rate. Further large-scale prospective investigations are warranted to verify these findings.

Conclusions

This study conducted a retrospective analysis of 17 articles on VAP in ICU patients, involving a total of 6,222 patients. The incidence rate of VAP among patients receiving mechanical ventilation in the ICU was determined to be 30%. Three potential risk factors were identified, including gender, smoking, and APACHE II score, along with one protective factor (antibiotic prophylaxis). VAP patients experienced significantly longer mechanical ventilation time, ICU length of stay, and total hospital stay compared to non-VAP patients. However, there was no significant difference in mortality rates between the two groups. These findings underscore the importance of reducing the burden of VAP in the ICU environment through preventive measures and vigilant management strategies.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-150/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-150/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-150/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Li W, Cai J, Ding L, Chen Y, Wang X, Xu H. Incidence and risk factors of ventilator-associated pneumonia in the intensive care unit: a systematic review and meta-analysis. J Thorac Dis 2024;16(9):5518-5528. doi: 10.21037/jtd-24-150