Incidence Rates, Risk Factors, and Mortality Rates of Ventilator-Associated Pneumonia: A meta-analysis.

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Abstract

Background: Ventilator-associated pneumonia (VAP) is the second most common nosocomial infection in Intensive care units (ICUs) and is associated with the significant utilization of health-care resources. However, the incidence rates, risk factors and mortality rates of VAP are controversial.

Methods: The Web of Science, EMBASE, PubMed and Cochrane Library databases through May 2020 were independently searched by two researchers to collect all relevant studies. Data including incidence rates, risk factors and mortality rates of VAP were extracted for the meta-analysis.

Results: 24 studies, including 10 retrospective studies and 14 prospective studies on VAP were included in our analysis. In the meta-analysis, we found that the VAP rate was 20/1000 ventilator-days (95% confidence interval (CI) 17–22%). The data demonstrated that trauma (odds ratio (OR) 1.51; 95% CI 1.21-1.88), steroids use (OR 1.51; 95% CI 1.25-1.82), enteral feeding (OR 3.40; 95% CI 2.56-4.52), nasogastric tube placement (OR 2.96; 95% CI 1.75-5.00), tracheostomy (OR 3.65; 95% CI 1.93-6.90), reintubation (OR 6.08; 95% CI 4.62-8.00), central vascular catheter (CVC) placement (OR 3.83; 95% CI 2.55-5.77), blood transfusion (OR 1.75; 95% CI 1.16-2.64), H₂ blockers use (OR 2.28; 95% CI 1.27-4.07) and Chronic obstructive pulmonary disease (COPD) (OR 1.24; 95% CI 1.07-1.44) were risk factors of VAP. When patients developed VAP, duration of ICU stay (OR 11.09; 95% CI 7.50-14.68) and duration of mechanical ventilation (MV) (OR 12.96; 95% CI 10.42-15.51) were significantly increased. What's more, VAP was associated with an increased risk of mortality (OR 1.38; 95% CI 1.04-1.83).

Conclusions

This study may contribute to the development of improved infection control strategies for high-risk patients. Additional studies are needed in the future to clarify the incidence rates, risk factors and mortality rates of VAP.

Background

Critically ill patients admitted to ICUs often require MV to maintain gas exchange until the underlying disorder is corrected. However, prolonged MV has many complications [1, 2]. VAP is the first most common infection in ICUs [3]. VAP is defined as nosocomial pneumonia that arises at least 48 hours after the initiation of MV [4, 5]; it has long been recognized as a worldwide problem, and there has been a substantial increase in the incidence and mortality rates of and economic burden associated with VAP [6, 7].

The increasing prevalence of VAP in recent years has made VAP - related health risks a global concern. The incidence rates of VAP in the United States, Europe, Latin America, and Asia Pacific were 13.50%, 19.40%, 13.80%, and 16.00% respectively in a prospective observational study (P = 0.04) [6]. The mortality rate of VAP is high, ranging from 14.00% to 44.40%, and can reach 78.00% in specific settings [8-12]. VAP was shown to prolong the ICU length of stay and increase the risk of death in critically ill patients [13]. A recent meta-analysis showed that patients with VAP had significantly longer ICU lengths of stay (mean =

6.10 days; 95% CI, 5.32-6.87)[14]; A study showed that patients who developed VAP incurred $\geq$ \$10,019 in additional hospital costs. Methods to effectively prevent and treat VAP remain a medical challenge[15].

In recent years, there has been an increasing amount of literature on the risk factors of VAP[16-19]. Moreover, the risk factors have been further confirmed in several meta-analyses. However, some studies focused on risk factors of VAP in neonates, while others focused on the incidence rates, risk factors and outcomes of VAP in special ICUs, which may have excluded some data from general ICUs and mixed ICUs[5, 20]. As such, we systematically reviewed the incidence rates, risk factors and mortality rates of VAP patients in general and mixed ICUs to provide evidence for the clinical prevention of VAP.

Methods

Data source collection and screening strategy

The Web of Science, EMBASE, PubMed and Cochrane Library databases were searched through May 2020 by two researchers independently to collect all relevant studies. The search terms were (Ventilator-Associated Pneumonia OR Pneumonia, Ventilator Associated OR Ventilator Associated Pneumonia OR VAP) AND Risk factors OR risk factor OR Factor, Risk OR Factors, Risk) NOT (PICU OR Pediatrics OR Pediatric OR Newborn OR Neonates OR Neonate OR children). We also manually searched the references of the initially identified articles, including relevant review papers.

Inclusion and exclusion criteria

Eligible studies had to meet the following criteria: (1) Patients come from the general and mixed ICUs; (2) studies with a cohort or case-control study design; (3) studies that included the risk factors of VAP as outcomes; (4) studies including critical patients under MV for 48 hours or more; (5) studies that clearly stated the definition and diagnosis of VAP; and (6) studies published in English. Studies were excluded if (1) the subjects of the study are elderly patients, cancer patients, stroke patient or other special patients; (2) studies were duplicates; (3) studies were editorials, comments or literature reviews; (4) studies reported overlapping data; or (5) studies contained incomplete data that were still unavailable after contacting the author.

The titles and abstracts of the retrieved studies were independently screened according to the above criteria by two researchers. The full texts of the potentially relevant studies were then obtained and strictly assessed. Disagreements were resolved by discussion with a third researcher.

Data extraction

Two reviewers separately extracted the relevant data from the literature. The extracted data include the following: 1) first authors and published year; 2) country and study design; 3) number of cases and control patients, the sample size and the incidence rates of VAP; and 4) a definition of VAP, a description of the setting and the ages of the patients. Disagreements were resolved by discussion with a third researcher.

Quality assessment

The Newcastle–Ottawa Scale (NOS)[21] was used to assess the quality of included studies. The NOS was applied considering three broad perspectives: 1) the selection of the study groups; 2) the comparability of the groups; 3) the ascertainment of either the exposure or outcome of interest. Quality assessments were independently performed by two researchers. Disagreements on ratings were resolved by discussion with a third researcher.

Statistical analysis

Heterogeneity was determined by the I^2 test. If $I^2 \leq 50\%$, fixed-effect models were used. Otherwise, heterogeneity was considered to be present if $I^2 > 50\%$ and random effects models were used. Combined statistical analyses were performed on the data of each study to calculate the combined OR and 95% CI. The Z test was performed. The results were considered statistically significant when $P < 0.05$. Subgroup analyses according to study design, region, diagnostic criteria, sitting and sample size were further performed. All statistical analyses were performed using Review Manager 5.3. The Preferred Reporting Items for meta-analysis statement (PRISMA) was used as a guide in this paper[22].

Results

Literature selection

Through searching the Cochrane Library, EMBASE, PubMed and Web of Science, 743 potentially relevant articles were retrieved. After the removal of duplicates, the titles and abstracts of the remaining 327 studies were screened for eligibility. The full texts of 71 potentially eligible studies were then strictly assessed. Finally, 24 studies[23-46]were included in the present meta-analysis (Fig. 1)

Characteristics of the included studies

All 24 studies included in the meta-analysis were published in English. The time of publication was from 1998 to 2020. Of these, 10 were retrospective studies and 14 were prospective studies. The number of patients with VAP was 2699, and the number of patients without VAP was 9511. According to the NOS, two articles received eight scores, seven articles received seven scores, thirteen articles received six scores, and two articles received five scores. The main characteristics of the included studies are shown in Table 1a,b.

Incidence rates of VAP

The pooled incidence of VAP was 20/1000 ventilator-days (95% CI 17–22%), as shown in Fig. 2a. Stratified analysis based on variation in the study design was applied because of its potential effect on the incidence of VAP (Fig. 2b). The forest plot illustrated that the incidence of VAP in retrospective studies (18%) was relatively lower than their counterparts in prospective studies (21%); We performed a subgroup analysis by region to explore its impact on VAP incidence (Fig. 2c), and the results showed that the

incidence of VAP in Europe (25%) was relatively higher than North America (16%), Asia (20%) and other region(12%); We also performed a subgroup analysis by definition of VAP (Fig. 2d), and the forest plot illustrated that the incidence of VAP were 16% in CDC criteria and 25% in non-CDC criteria respectively; Additionally, considering that the 13 studies had different types of study design, we conducted a subgroup analysis based on the sample size(<100, 100-200, 200-300, 300-1000, >1000), and we found that as the sample size increased, the incidence of VAP decreased (31%, 27%, 22%, 17%, 15%)(Fig. 2e); In addition, we performed a subgroup analysis according to different settings (medical and surgical ICUs, mixed ICUs, general ICUs)(Fig. 2f). The forest plot indicated that the incidence of VAP in medical and surgical ICUs (26%) was relatively higher than their counterparts in mixed ICUs and general ICUs (23% and 15%).

Risk factors for VAP

Considering the various risk factors included in these studies, we chose 19 risk factors for the meta-analysis. These factors included tracheotomy, H₂ blocker use, nasogastric tube placement, impaired consciousness, prior antibiotic treatment, steroids use, enteral feeding, parental nutrition, blood transfusion, CVC placement, previous surgery, reintubation ,diabetes, COPD, trauma, acute respiratory distress syndrome (ARDS), sedation, sucralfate, respiratory failure (Table 2).

There were 10 potential risk factors (reported in at least two studies) summarized in this meta-analysis. We found a significant relationship between VAP and the following risk factors: trauma (OR 1.51; 95% CI 1.21-1.88), steroids use (OR 1.51; 95% CI 1.25-1.82), enteral feeding (OR 3.40; 95% CI 2.56-4.52), nasogastric tube placement (OR 2.96; 95% CI 1.75-5.00), tracheostomy (OR 3.65; 95% CI 1.93-6.90), reintubation (OR 6.08; 95% CI 4.62-8.00), CVC placement (OR 3.83; 95% CI 2.55-5.77), blood transfusion (OR 1.75; 95% CI 1.16-2.64), H₂ blockers use (OR 2.28; 95% CI 1.27-4.07) and COPD (OR 1.24; 95% CI 1.07-1.44) were risk factors of VAP as noted in Table 3 ($P < 0.05$). No significant differences were detected for impaired consciousness, prior antibiotic treatment, previous surgery, ARDS, sedation, sucralfate and respiratory failure ($P > 0.05$). Therefore, these factors were determined not to be risk factors for VAP. The forest plots of the risk factors were described in Fig. 3a,b,c,d,e,f,g,h,i,j. Among these risk factors, we found significant heterogeneity in tracheotomy ($I^2 = 84\%$) and blood transfusion($I^2 = 54\%$), and we conducted a subgroup analysis based on sample size(<300, 300-600, >600; ≤ 100 , >100). As a result, I^2 in each subgroup drops below 50%, which may indicate that the sample size was the cause of heterogeneity (Fig. 3k,l.)

Clinical Outcomes

After data integration of 15 studies, pooled results showed that VAP was associated with mortality (OR 1.38; 95% CI 1.04–1.83), as shown in Fig. 4a. However, considering that $I^2 = 77\%$, a subgroup analysis was performed based on the sample size (<100, 100-200, 200-500, 500-1000, 1000-2000,> 2000), we found that heterogeneity was reduced (57%, 59%, 0%, 0%,18%), but in subgroups with sample sizes of 100-500 and> 2000, there was no correlation between VAP and mortality(Fig. 4b); In addition, our pooled

results also showed that duration of ICU stay and MV were increased significantly in patients infected with VAP (OR 11.09; 95% CI 7.50-14.68; OR 12.96; 95% CI 10.42-15.51), as shown in Fig. 4c,d. Considering the existence of obvious heterogeneity ($I^2=85\%$, $I^2=79\%$), we performed subgroup analyses based on CDC criteria (CDC criteria, non-CDC criteria) and sample size (<1000, >1000) respectively. Interestingly, the heterogeneity was reduced separately in each subgroup, as shown in Fig. 4e, f. However, we did not find this association in the two variables (age and APACHE II scores).

Discussion

This meta-analysis showed that the incidence of VAP was 20/1000 ventilator-days (95% CI 17–22%) according to the pooled data of the included studies. Previous studies have shown that the incidence of VAP was between 9.00%-53.00%, and the result of our meta-analysis was within this range[3, 12, 47, 48]. Differences in study design, region, diagnostic criteria, sittings and sample size may explain this wide range; The result demonstrated that the incidence of VAP in prospective studies was significantly higher than retrospective studies (21% vs.18%), which was consistent with the study of Li et al[16]. Information obtained retrospectively from the abstraction of medical records is measurably less accurate than information obtained prospectively from research subjects[49]. We recommend conducting more prospective research in the future to obtain more rigorous results; In addition, We found that the incidence of VAP in Europe was significantly higher than in other regions, which may be related to the fact that European countries have established the VAP surveillance system to more accurately diagnose VAP[50]; Additionally, in a subgroup based on whether CDC diagnostic criteria were used, the incidence of VAP in studies using CDC criteria was lower than not using CDC criteria(25% vs.16%). There is currently no gold standard for diagnosing VAP, and a study has shown the 2013 CDC criteria failed to detect 55.9 percent of confirmed VAP cases[51]. We also look forward to determining the gold standard for the diagnosis of VAP in the future, so as to more accurately confirm the diagnosis of VAP; We conducted a subgroup analysis based on the size of the sample size. We found that the larger the sample size, the lower the incidence of VAP, and the heterogeneity of the results were reduced accordingly, which also showed that the sample size may be the cause of heterogeneity. We recommend that additional large-sample studies be carried out in the future to obtain more rigorous results regarding VAP; Considering different ICUs, the subgroup analysis was performed and the results showed that the incidence of VAP in general ICUs was lower than in mixed ICUs and medical and surgical ICUs. What is more, through the subgroup analysis, heterogeneity also decreased accordingly, which indicating that different ICUs may be the cause of heterogeneity.

VAP was associated with invasive operations which included re-intubation, tracheostomy, nasogastric tube placement, enteral feeding, blood transfusion, CVC placement. Appropriate reduction of invasive operations may reduce the occurrence of VAP. Tracheotomy is one of the most common surgical procedures in ICUs and is used to prevent complications due to prolonged MV. Studies have shown that the incidence of VAP was related to the time of tracheotomy. and tracheotomy increased ICU stay and mortality[52]; Enteral feeding is administered in critically ill patients requiring intensive care to provide

nutritional support, correct hypoproteinemia, maintain the balances of water and electrolytes and reduce the incidence of infection[53, 54]. Gastric emptying is an important indicator of enteral feeding intervention. Delayed gastric emptying leads to nutritional intolerance and gastric reflux, increasing the risk of VAP[55, 56]; An indwelling gastric tube can impair cardiac sphincter function and increase the chance of gastric fluid reflux, leading to aspiration. Bacteria in the stomach may colonize the pharynx through the antiperistaltic action of the stomach and along the gastric tube and enter the lower respiratory tract, resulting in infection[57]; Furthermore, we found a significant association between re-intubation and development of VAP, which is in accordance with previous study[58]. Re-intubation is associated with transfer of organisms from upper respiratory to lower respiratory tract, which could explain the higher incidence of VAP among such cases[58, 59]; Interestingly, CVC placement was also found to be a risk factor for VAP in this meta-analysis. A survey of device-associated infection rates in adult ICUs in Catalonia showed that CVC placement ranged from 18% to 98%[60]. This may be an alternative marker to severe illness or prolonged stay in the ICU indicating an increased risk of VAP; Furthermore, blood transfusion was independently correlated with infection rates, and increased the risk of VAP[61, 62]. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day Mortality in general surgery patients [63]. Therefore, we should try to reduce blood product transfusion if condition permits[64].

H₂ blockers are commonly administered in ICU patients, but these can lead to an acid and base imbalance in the stomach and increase the incidence rates of VAP due to gastric content reflux. In the study conducted by Herzig et al, H₂ blocker use increased the risk of VAP by altering the upper gastrointestinal flora[65]; Patients receiving steroids are more prone to develop VAP, which was consistent with the result of previous studies, which is attributable to the suppressive effects of steroids on innate and acquired immunity[66, 67]; Blunt trauma increased risk of development of pneumonia. Patients who sustain blunt trauma can experience cardiopulmonary dysfunction and weakness of expiratory muscles, which cause ineffective cough and aspiration. In addition, aspiration can increase the risk of VAP[68]. It has been suggested that, especially in the patients with traumatic brain injury (TBI), VAP may not be preventable, because of these nonmodifiable risk factors[69]. The only variable that significantly increased the odds ratio for VAP was trauma[70].

The main finding of this study was that VAP increased the mortality. This was consistent with the results of previous study, which ultimately showed that VAP seem to be an independent risk factor for death[8, 71]. Additionally, VAP increased the MV time and prolonged the ICU length of stay. This is in agreement with the findings of many studies, indicating that VAP imposed a great burden on patients[11, 72, 73].

This meta-analysis had some limitations. First, the diagnostic criteria for VAP included were inconsistent. Seven studies used the CDC criteria [25,26,29,31,32,42,43], two used the American Thoracic Society criteria [27,46]. Many methods have been used for the clinical diagnosis, epidemiological analysis and hospital surveillance of VAP, but there are currently no unified diagnostic criteria for VAP, which may lead to clinical heterogeneity. We look forward to a clear and uniform VAP diagnostic standard in the future. Second, we enrolled patients from different ICUs. In this meta-analysis, the recruited patients were from

different types of ICUs; The number of meta-analyses of the risk factors of VAP has been gradually increasing. Some meta-analyses of VAP included patients who underwent heart surgery, neonates or patients with traumatic brain injury[74]. To some extent, some mixed ICUs and general ICUs were omitted, and not included in the meta-analysis. Thirdly, the including studies were published in a quite long period 1998-2020, and clinical practice might have several changes and the results might not represent well the presence.

Our study also had some advantages. First, previous meta-analysis only focused on the risk factors of VAP. In this meta-analysis, we focused on the incidence rates, risk factors and mortality rates of VAP, resulting in a comprehensive understanding of VAP. Second, the quality of the literature we included was generally high, which increased the credibility of our results. Third, in terms of retrieval strategy formulation, literature screening, data entry, data analysis and other aspects, our research team carried out the research in strict accordance with regulations, which ensured the authenticity of the meta-analysis results.

Conclusions

In this study, we integrated all eligible VAP studies and demonstrated that the risk of developing VAP in ICU patients was high, with a combined incidence of 20%. We also found that VAP was associated with an increase in mortality in ICU patients, and we identified 10 risk factors for VAP. This review will help physicians understand the importance of VAP, identify risk factors for VAP as early as possible and develop methods for the clinical treatment and prevention of VAP. Additional studies are needed in the future to clarify the incidence rate, risk factors, and mortality rate of VAP in ICU patients.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HW and OC were the designers of this work. HW, and MY performed the process of study selection, data extraction, as well as study quality assessment. HW and CB conducted data analysis. DJ and OC provided methodological advice. HW wrote the original manuscript. YJ and OC polished and revised the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Abbreviations

OR: odds ratio; CI: confidence interval;CVC: central vascular catheter; VAP: Ventilator-associated pneumonia; ICUs: intensive care units;MV: mechanical ventilation; NOS: Newcastle–Ottawa Scale; CDC: Centers for Disease Control and Prevention; PRISMA : Preferred Reporting Items for Systematic reviews and Meta-Analyses; COPD: Chronic obstructive pulmonary disease ; ARDS: acute respiratory distress syndrome; ECDC: European Centre for Disease Prevention and Control; MICU: Medicine Intensive Care Unit; CCU: Critical Care Unit.

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Tables

Table 1a The main characteristics of the included studies

First author(year)	Period	Country	Study design	Case/ controls	Incidence (%)	Sample
Apostolopoulou (2003) [23]	March 2000 to August 2000	Greece	Prospective cohort study	56/119	/	175
Charles (2013) [24]	November 2009 to July 2011	India	Prospective cohort study	18/58	53.25	76
Cook (1998) [25]	October 1992 to May 1996	Canada	Prospective cohort study	177/837	14.80	1014
Erbay (2004) [26]	January 2000 to December 2002	Turkey	retrospective case control study	37/60	8.90	97
Ibrahim (2001) [27]	March 1998 to December 1999	USA	Prospective Cohort Study	132/748	/	880
Joseph (2009) [28]	October 2006 to December 2007	India	Prospective Cohort Study	36/164	22.94	200
Karatas (2016) [29]	January 2011 to December 2013	Turkey	retrospective cohort study	178/974	15.7	1152
Lahoorpour (2013) [30]	September 2007 to June 2008	Iran	retrospective case control study	48/135	/	183
Maria(2020) [31]	July 2014 to February 2017	Poland	retrospective case control study	431/1441	/	1872
Murphy(2014)[32]	December 2010 to November 2011	Cannada	retrospective case control study	47/188	18.20	235
Myny (2005) [33]	1996 to 1998	Belgium	Prospective Cohort Study	89/296	/	385
Nseir (2007) [34]	January 1996 to January 2001	France	retrospective case control study	124/230	18.00	354
Papakrivou[2018][35]	February2013 to December 2015	Greece	Prospective Cohort Study	45/78	/	123
Ranjan (2014) [36]	June 2009 to May 2010	India	Prospective cohort study	60/45	31.70	105
Ranjit (2011) [37]	January 2008 to July 2010	USA	Prospective cohort study	22/47	/	69
Rocha (2008) [38]	March 2005 to March 2006	Brazil	retrospective case control study	84/191	24.59	275
Saravu (2013) [39]	October 2009 to May 2011	India	retrospective case control study	52/52	/	104
Six (2016) [40]	18month	France	retrospective case control study	141/362	14.70	503
Sofianou (2000) [41]	12 months	Greece	Prospective cohort study	67/131	/	198
Tejerina (2006) [42]	March 1 1998 to March 31 1998	20 countries	Prospective Cohort Study	439/2458	15.00	2897
Tsakiridou (2014) [43]	2010 to 2012	Greece	Prospective Cohort Study	46/147	23.83	193

Tsakiridou (2018) [44]	2015 to 2016	Greece	Prospective cohort study	36/64	/	100
Turković (2017) [45]	September 2009 to March 2013	Croatia	retrospective case control study	60/82	/	142
Jaillette 2011 [46]	December 2006 to December 2007	France	Prospective Cohort Study	137/302	20.00	439

Table 1a The main characteristics of the included studies

First author(year)	Definition of VAP	Setting	Age	Quality assessment
Apostolopoulou (2003) [23]	Clinical, radiographical, microbiological criteria	Multidisciplinary ICUs	52.00±20.00 (16 to 92)	6
Charles (2013) [24]	Clinical, microbiological criteria	ICUs	48.11±18.20(14 to 82)	6
Cook (1998) [25]	the modified CDC and Prevention criteria Clinical, radiographical, microbiological criteria	ICUs	Adult	8
Erbay (2004) [26]	Clinical, radiographical, microbiological criteria, CDC criteria	Medical and surgical ICUs	20 to 74	6
Ibrahim (2001) [27]	Clinical, radiographical, American thoracic society	Medical and surgical ICUs	69.30±13.20 (17 to 98)	8
Joseph (2009) [28]	Clinical, microbiological criteria	MICU and CCU	37.60±16.10 (14 to 80)	7
Karatas (2016) [29]	CDC criteria	Anesthesia and Reanimation, Surgical, Medical and Neurology ICUs	67.80±21.10 >18	5
Lahoorpour (2013) [30]	Clinical, radiographical, microbiological criteria	ICUs	15-80	6
Maria (2020) [31]	CDC and ECDC criteria, microbiological	ICUs	>16	6
Murphy (2014) [32]	Clinical, microbiological criteria, CDC criteria	mixed, medical and surgical ICUs	53 to 73	6
Myny(2005)[33]	Clinical criteria	Surgical and medical ICUs	60 (44-70)	6
Nseir(2007)[34]	Clinical, radiographical, microbiological criteria	ICUs	60.00±16.00	7
Papakrivou(2018) [35]	Clinical, radiographical, microbiological criteria	ICUs	58.2 ± 1.6 >18	7
Ranjan (2014) [36]	Clinical and microbiological criteria	Multidisciplinary ICUs	>15	6
Ranjit (2011) [37]	Clinical, radiographical	ICUs	33.66±18.84	7
Rocha (2008) [38]	Clinical, radiographical	Medical and surgical ICUs	47.80±17.40 (> 15)	5
Saravu (2013) [39]	Clinical, radiographical, microbiological criteria	medical, surgical and trauma ICUs	≥18	6
Six (2016) [40]	Clinical, microbiological criteria	30-bed mixed ICUs	46 to 74	6
Sofianou (2000) [41]	Clinical, radiological and microbiological criteria.	Multidisciplinary ICUs	Adult	6
Tejerina (2006) [42]	the modified CDC and Prevention criteria	ICUs	Adult	7

Tsakiridou (2014) [43]	Clinical, radiographical, microbiological criteria, CDC criteria	ICUs	66.00±17.00	7
Tsakiridou (2018) [44]	Clinical, radiographical, microbiological criteria	Medical and surgical ICUs	Adult	6
Turković (2017) [45]	Clinical, radiographical, microbiological criteria	Surgical and Neurosurgical ICUs	49-76	6
Jaillette 2011 [46]	American Thoracic Society and the Infectious Diseases Society of America	Medical and surgical ICUs	Adult	7

CDC: Centers for Disease Control;

ECDC: European Centre for Disease Prevention and Control

MICU: Medicine Intensive Care Unit;

CCU; Critical Care Unit.

Table 2 Risk factors of VAP in patients in the meta-analysis

Risk factors	Combined studies	Analysis model	Heterogeneity of studies(I^2) (%)	Pooled OR (95% CI)	Z	P
Prior antibiotic treatment	14	random	88	1.16 [0.72, 1.87]	0.63	0.530
COPD	14	fixed	19	1.22 [1.01, 1.47]	2.09	0.040*
Trauma	8	fixed	0	1.51 [1.21, 1.88]	3.62	0.000*
Previous surgery	19	fixed	48	0.88 [0.79, 0.99]	2.08	0.060
Diabetes	10	random	55	0.97 [0.75, 1.25]	0.25	0.800
Steroids	13	fixed	46	1.51 [1.25, 1.82]	4.33	0.000*
Parental nutrition	4	random	71	1.63 [0.82, 3.24]	1.40	0.160
Enteral feeding	6	fixed	49	3.40 [2.56, 4.52]	8.40	0.000*
Nasogastric tube	4	fixed	37	2.96 [1.75, 5.00]	4.05	0.000*
Tracheostomy	10	random	84	3.15 [1.67, 5.95]	3.53	0.000*
Reintubation	6	random	43	6.08 [4.62, 8.00]	12.90	0.000*
CVC placement	3	fixed	0	3.83 [2.55, 5.77]	6.44	0.000*
Blood transfusion	5	random	52	1.89 [1.18, 3.04]	2.63	0.009*
ARDS	5	fixed	0	1.18 [0.88, 1.59]	1.10	0.270
Sedation	3	fixed	14	1.31 [0.91, 1.89]	1.45	0.150
H ₂ blockers	4	fixed	23	2.28 [1.27, 4.07]	2.78	0.005*
Sucralfate	3	random	90	1.62 [0.64, 4.11]	1.01	0.310
Respiratory failure	8	random	86	1.64 [0.87, 3.11]	1.53	0.130
Impaired consciousness	5	random	87	2.01 [0.77, 5.25]	1.43	0.150

* $P < 0.05$

Figures

Figure 1

Flow diagram of literature selection

Fig. 2b Incidence rates of VAP by subgroup analysis of study design

Figure 2

Fig. 2a Incidence rates of VAP in patients. Fig. 2b Incidence rates of VAP by subgroup analysis of study design. Fig. 2c Incidence rates of VAP by subgroup analysis of region. Fig. 2d Incidence rates of VAP by subgroup analysis of CDC criteria. Fig. 2e Incidence rates of VAP by subgroup analysis of sample size. Fig. 2f Incidence rates of VAP by subgroup analysis of sitting.

Fig. 2d Incidence rates of VAP by subgroup analysis of CDC criteria

Fig. 2e Incidence rates of VAP by subgroup analysis of sample size

Fig. 2f Incidence rates of VAP by subgroup analysis of sitting

Fig. 3a The forest plot analysis of tracheotomy

Ersoy (2004)	30	37	14	60	3.4%	14.08 (5.09, 30.88)
Karadas (2016)	146	178	611	974	57.5%	2.71 (1.01, 6.85)
Buoniciuti et al. (2011)	18	33	39	47	4.3%	4.30 (0.11, 17.11)

Study or Subgroup	VAP		NON VAP		Weight	Odds Ratio M-H,Fixed,95%CI
	Events	Total	Events	Total		

Site 1 (2016)	24	141	47	362	11.0%
Subtotal (95% CI)		278		664	22.0%
Total events	51		95		

Fig. 3b **The forest plot analysis of H₂ blockers**

Study or Subgroup	Events	Total	Events	Total	Weight	M-H,Fixed,95%
Enay(2004)	32	37	41	60	14.8%	2.97 (1.00, 8.11)
Shahmoradian(2006)	108	435	407	740	73.0%	2.67 (2.34, 3.07)

Turkoptel (2017)	78	60	20	82	7.2%	1.53 (0.5)
Total (2015-18)	885		3072	500 (0%)		5.55 (5.2)

Test for overall effect: $Z = 3.99$ ($P = 0.0001$)
 Test for subgroup differences: $Chi^2 = 43.05$, $df = 2$ ($P = 0.00001$), $I^2 = 95.9\%$

Study or Subgroup	VAP		Non VAP		Weight	M-H, Random, 95% CI
	Events	Total	Events	Total		
Edwards 2004	14	37	25	60	13.0%	1.13 [0.48,

Study or Subgroup	VAP		Non-VAP		Weight	M-H,Fixed,IV,Random,IV
	Events	Total	Events	Total		
Acute Inflammation (COPD)	2	56	17	116	5.1%	0.04, 0.21

Heterogeneity: $\chi^2 = 0.31$, $df = 1$ ($P = 0.58$), $I^2 = 0\%$.
Test for overall effect: $Z = 0.14$ ($P = 0.89$).

State or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%
Aggravated assault (CIC03)	25	56	27	119	10.7%	1.79 [1.02, 3.12]

Total (95% CI)	634	4025	6659	0.24 [0.19, 0.29]
Total events	244	991		
Heterogeneity: $\chi^2 = 16.04$, $df = 13$ ($P = 0.25$); $I^2 = 19\%$				

Test for subgroup differences: Chi² = 5.37, df = 1 (P = 0.02); I² = 81.4%

Fig. 3a The forest plot analysis of trauma

Figure 3

Fig. 3a The forest plot analysis of tracheotomy. Fig. 3b The forest plot analysis of H2 blockers. Fig. 3c The forest plot analysis of nasogastric tube. Fig. 3d The forest plot analysis of enteral feeding. Fig. 3e The forest plot analysis of CVC placement. Fig. 3f The forest plot analysis of blood transfusion. Fig. 3g The forest plot analysis of trauma. Fig. 3h The forest plot analysis of reintubation. Fig. 3i The forest plot analysis of steroids use. Fig. 3j The forest plot analysis of COPD. Fig. 3k tracheotomy by subgroup analysis of sample size. Fig. 3k blood transfusion by subgroup analysis of sample size.

Fig.4a The forest plot analysis of mortality

Figure 4

Fig.4a The forest plot analysis of mortality. Fig.4b Mortality of VAP by subgroup analysis of sample size. Fig.4c The forest plot analysis of duration of ICU stay. Fig.4d The forest plot analysis of duration of MV. Fig. 4e duration of ICU stay by subgroup analysis of CDC criteria. Fig. 4f duration of MV by subgroup analysis of sample size.

Fig.4b Mortality of VAP by subgroup analysis of sample size

Fig.4c The forest plot analysis of duration of ICU stay

Fig.4d The forest plot analysis of duration of MV

Fig. 4e duration of ICU stay by subgroup analysis of CDC criteria

Fig. 4f duration of MV by subgroup analysis of sample size