REVIEW

The relationship between ventilator-associated pneumonia and chronic obstructive pulmonary disease: what is the current evidence?

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Abstract
Chronic obstructive pulmonary disease (COPD) affects approximately 65 million people from which > 25% will require intensive care unit (ICU) admission. Ventilator-associated pneumonia (VAP) is the commonest ICU infection and results in increased morbidity/mortality and costs. The literature on the interaction between COPD and VAP is scarce and controversial. The project aimed to search the literature in order to address the following: (i) Is COPD a risk factor for VAP development? (ii) Does COPD impact the outcome of patients with VAP? (iii) Does VAP development impact the outcome of COPD patients? (iv) Does COPD impact the aetiology of VAP? Current evidence on the topic is controversial. Regarding the impact of VAP on COPD patients, the majority of the existing limited number of studies suggests that VAP development results in higher mortality and longer duration of mechanical ventilation and ICU stay. Also, the majority of the studies exploring the impact of COPD on VAP outcomes suggest that COPD is independently associated with a decrease in survival, although the number of such studies is limited. Regarding the aetiology, *Pseudomonas aeruginosa* is the most frequent pathogen in VAP patients with COPD. Noteworthy, one study suggests that *P. aeruginosa* is higher in COPD patients even in the early-onset VAP subgroup. This manuscript provides a comprehensive overview of the available literature on the interaction between COPD and VAP, highlighting the differences and limitations that may have led to controversial results, and it may act as a platform for further research with important clinical implications.

Keywords Respiratory infections · Critically ill patient · Intubation · Chronic bronchitis · Epidemiology · Hospital-acquired pneumonia · Mechanical ventilation · COPD · ICU · VAP

Introduction

Ventilator-associated pneumonia (VAP) is a common complication of endotracheal intubation; it is defined as pneumonia occurring at least 48 h after initiating mechanical ventilation (MV) [1, 2]. VAP is the second most common nosocomial infection and the leading cause of death from nosocomial infections in the intensive care unit (ICU) [1]. The prevalence of VAP ranges broadly from 9 to 27%; this variability might

be attributed, at least partially, to the lack of a "gold standard" for diagnosis, differences in infection control practices, different case-mix and variable underlying diseases [1, 3, 4]. Overall, VAP is associated with increased mortality and, in survivors, VAP is associated with an increase in MV duration, ICU and hospital stay [3, 5–7]. VAP is also one of the causes of the increase in the cost of healthcare, with estimated mean attributable costs ranging from around $11,000 [7] to 40,000 USD [8]. Reported all-cause mortality ranges widely from 20

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to 50% [2]. Regarding VAP attributable mortality a meta-analysis has reported it as 13% [9]; however, it remains a controversial issue with a significant number of studies tending to ignore confounding factors, such as severity-of-illness measures over time, underlying diseases and comorbidities [10].

Chronic obstructive pulmonary disease (COPD) is characterised by an airflow limitation associated with an abnormal inflammatory response of the lungs to noxious gas particles, such as cigarette smoke or pollutants [11, 12]. According to the World Health Organization (WHO) estimates, 65 million people have moderate to severe COPD [13]. More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally [13]. COPD causes lung tissue destruction, and it impairs the normal repair and defence mechanism of the lungs [11, 14, 15]. COPD leads to a chronic structural damage to the lungs, which along with decreased mucosal clearance and microbiome imbalances, makes them more vulnerable to invading pathogens and to developing lower respiratory tract infections [11, 16]. During the course of COPD, it is estimated that > 25% of the patients will require ICU admission for acute exacerbations and 26–74% of these patients will receive mechanical ventilator support, resulting in increased average hospital stays and healthcare costs [17, 18]. Moreover, COPD is a common comorbidity of ICU patients admitted for other medical reasons [19].

COPD is a well-recognised risk factor for community-acquired pneumonia (CAP) development [12, 16, 20–23]; however, the relationship between COPD and VAP remains controversial and underexplored. In this manuscript, the recent findings in the literature will be analysed, while also highlighting the differences and limitations which may have influenced the results. The relationship between COPD and VAP will be discussed by following the order of four research questions, formulated in Table 1.

Methods

A narrative review methodology was conducted to provide a broad overview of the current evidence on the relationship between COPD and VAP. The database search was the first step used to review the literature. The databases used were EMBASE and PubMed. The second element of the search

Table 1 Research questions

I	Is COPD a risk factor for VAP development?
II	Does COPD impact the outcome of patients with VAP?
III	Does VAP development impact the outcome of COPD patients?
IV	Does COPD impact the aetiology of VAP?

was through internet sites, particularly the WHO site. The third element was to identify relevant articles from all the literature obtained.

The database search was conducted using a combination of the following Mesh Terms and keywords: chronic obstructive pulmonary disease, chronic obstructive airway disease, obstructive lung disease, chronic bronchitis; ventilator associated pneumonia; intensive care. Keywords were combined using the Boolean operators (AND, OR).

The articles which met the criteria for inclusion needed to be for adult population (≥ 18 years) and published in English between January 2005 and October 2018, plus prior references in the selected articles. Current recommendations from the Cochrane Foundation to conduct the literature search were followed. Review articles were not included. Further breakdowns of the search strategy are summarised in Fig. 1.

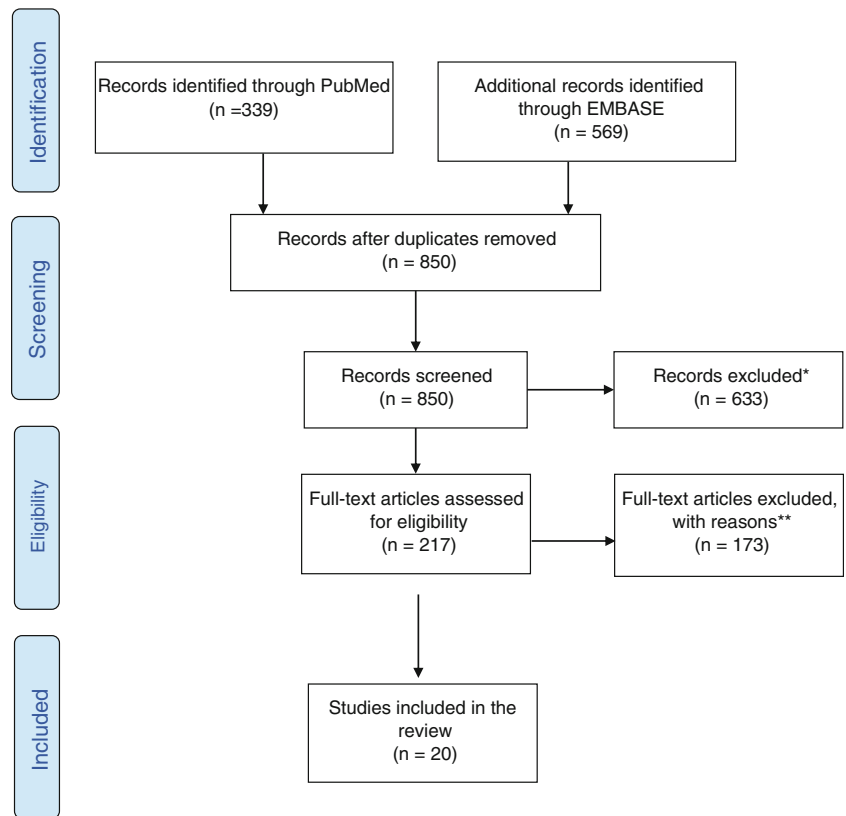## Is COPD a risk factor for VAP development?

The current literature on whether COPD is a risk factor for VAP development is controversial.

Data from the EU-VAP project demonstrated that VAP prevalence and incidence did not differ between patients with and without COPD [5]. The EU-VAP project was a prospective, observational cohort study developed in 27 ICUs from 9 different countries in Europe; it is the largest study examining the relationship of COPD and VAP from multiple European centres [5]. Excluding trauma patients, 397 out of 2082 patients had COPD (19.1%) [5]. Baseline characteristics and severity of illness at ICU admission did not differ between COPD patients with and without VAP development, and there was no significant difference in the median onset of VAP between the two groups [5]. The reported prevalence of VAP did not differ significantly between COPD and non-COPD ICU patients (18.6% vs. 18.2%, respectively, ns). Similarly, VAP incidence was not significantly different between patients with and without COPD, even when those with neurological major organ failure and CAP on admission were excluded (15.5 vs 17.5 per 1000 ventilation days at risk, ns) [5]. Therefore, the above study did not identify COPD as a risk factor for VAP development [5].

Similar results were obtained by Rodríguez et al. [24] in a prospective, observational, case-control study of 235 patients receiving MV in two multidisciplinary ICUs. Of these patients, 60 (25.5%) had a non-exacerbated COPD, while the remaining 175 (74.5%) were not diagnosed with COPD, representing the control group [24]. When premorbid pulmonary function tests were not available, clinical criteria, along with medical records with compatible physical findings and evidence of hyperinflation on chest radiograph, were used for COPD diagnosis [24]. The unadjusted analysis showed that the incidence of VAP in patients with COPD was 16.6% (10 patients), versus 36.0% (63 patients) in patients without

Fig. 1 PRISMA chart; 806 articles excluded

Identification

Records identified through PubMed (n = 339)

Additional records identified through EMBASE (n = 569)

Screening

Records after duplicates removed (n = 850)

Records screened (n = 850)

Records excluded* (n = 633)

Eligibility

Full-text articles assessed for eligibility (n = 217)

Full-text articles excluded, with reasons** (n = 173)

Included

Studies included in the review (n = 20)

*Reasons for excluding records:
- Language limitation: not in English language
- Not original articles
- Irrelevant population
- Irrelevant study type

** Reasons for excluding records
- Not relevant to the main subject
- Full text not available
- Not VAP (eg community acquired-pneumonia)

COPD [24]. However, after adjustment of VAP episodes per 1000 MV days, no significant difference was noticed between those with COPD and those without (11.9/1000 vs 16.0/1000) [24]. Therefore, the study concluded that intubated patients with non-exacerbated COPD were not exposed to a higher risk of VAP, suggesting that VAP development was associated with extra days of mechanical ventilation rather than with COPD as a comorbidity [24]. Furthermore, the median VAP development in COPD patients was 7.5 days, and 4 days in patients without COPD [24]. No significant difference was seen in the development of VAP between survivors (13.2%) and non-survivors (22.7%) [24]. Patients with exacerbated COPD were not included in the study. Limitations of this study include imbalances in comorbidities and admission types between the cases and control patients as well as a lack of information regarding the cause of death [24]. In addition, spirometry data prior to ICU admission were only available

for less than 20% of COPD patients, while the remaining cases were defined as COPD without using an objective criteria [24].

Contrary to the above, Tejerina et al. [25] conducted a retrospective analysis of a database from a prospective, multicentre international cohort from 20 countries of 2897 patients who received mechanical ventilation for > 12 h [25]. VAP developed in 439 (15%) patients and, in the multivariate analysis, COPD was identified as a risk factor for VAP development (OR 95% CI 3.9 (2.2–6.9), $p < 0.001$).

Along the same lines as the above studies were the results of a meta-analysis related to VAP in populations undergoing cardiac surgery, of which five studies [26–30] yielded similar results to the above [31]. The analysis of the 6416 patients recruited in these five studies shows that VAP occurred more frequently in patients with COPD (fixed effect model, 95% CI, 1.18, 2.01, $p < 0.01$). Chang et al. [32], Karatas et al. [33],

Liu et al. [34] and Al-Dorzi et al. [35] also identified COPD as a risk factor for VAP development. Interestingly, Saied et al. [36] reported that the risk factors for VAP differ based on the time of onset, with COPD being associated with increased risk for developing late onset pneumonia.

On the other hand, Rinaudo et al. [37], in a prospective observational case-control study, analysed the role of COPD in 279 patients with ICU-acquired pneumonia (ICUAP), both with VAP (156) and with non-ventilator associated pneumonia (NV-ICUAP: 123). In contrast to other studies, subjects with absence of pulmonary function testing (PFT) were not included in the study [37]. Current and former smokers (≥ 10 pack-years) without a clinical diagnosis of COPD and without PFT were excluded to avoid misclassification of undiagnosed COPD in the non-COPD group, while those with forced spirometry without obstructive ventilator pattern were included in the non-COPD group [37]. COPD severity was assessed with the GOLD criteria [12]: 9 patients were stage I (13%), 24 stage II (34%), 30 stage III (42%) and 8 stage IV (11%) [37]. Interestingly, the prevalence of VAP development was lower in patients with COPD than those without COPD (42% [30/71] vs. 61% [126/208], respectively, $p = 0.011$) [37]. In this study, patients with COPD had a lower incidence of VAP, but a higher incidence of non-ventilator ICU-acquired pneumonia [37]. A strength of the study is the well-defined population of patients with and without COPD, whereas the lack of microbiological documentation in 41% of ICUAP cases represents one of the study's limitations [37].

Finally, Gursel et al. [38], in a retrospective analysis of a prospective computerised database of a Turkish ICU, explored the role of co-existence of bronchiectasis with COPD and reported that VAP development was significantly higher in patients with COPD plus bronchiectasis vs. COPD alone (60% vs. 45%, $p = 0.034$).

Does COPD impact the outcome of patients with VAP?

COPD has an adverse impact on respiratory muscle function, which can be amplified during critical illness. Other factors such as older age and frequent use of corticosteroids may also be accountable for the high mortality rate reported in COPD patients developing VAP [11].

In the study of Rinaudo et al., patients' outcome was monitored up to 90 days after pneumonia onset, and COPD was found to be independently associated with a decrease in survival in patients who had VAP [37]. The 90-day mortality rate was significantly higher in COPD patients with VAP (18 (62%) vs 45 (37%); $p = 0.015$) [37]. Consistent with the latter findings, a cumulative survival curve at 90 days was significantly different in VAP patients with COPD, with difference in mortality increasing even after discharge, suggesting delayed effects possibly due to hyperinflammation after pneumonia resolution. The authors did not analyse the impact that

the severity of lung obstruction according to GOLD staging had on outcomes [37]. Notably, the association between COPD and worse survival was seen only in VAP patients, and COPD was not associated with worse survival in patients who developed non-ventilator ICUAP [37]. Additionally, the sequential organ failure assessment (SOFA score), previous use of corticosteroids and serum levels of IL-6 and IL-8 were found to be lower in COPD patients who had a non-ventilator ICUAP [37]. This might explain why COPD was associated with a higher mortality in VAP patients only, as these factors may have counterbalanced the results [37]. The multivariate analysis showed that COPD was independently associated with worse survival in VAP patients [37].

Similarly, Makris et al. [39] identified COPD as an independent risk factor for ICU mortality in patients with VAP. This single-centre, prospective, observational study included 215 patients with VAP; 65 (30%) of them had COPD (GOLD stage I 4 (7.8%), stage II 18 (35.2%), stage III 14 (27.4%), stage IV 15 (29.5%) [39]. Patients were classified as having COPD based on spirometry or prior diagnosis; for 21% of COPD patients, in which baseline spirometry could not be performed, the severity of COPD was assessed based on previous official medical records [39]. Only microbiologically confirmed cases of COPD were included in the study cohort [39]. COPD patients were found to have a mortality rate significantly higher than non-COPD patients (60% vs. 43%, $p = 0.027$) [39]. The mortality rate differed based on GOLD stages of severity and were 25%, 82%, 77.5%, and 66% for stages I, II, III, and IV, respectively [39]. In the multivariate analysis, after adjusting for potential confounding factors, such as comorbidities, advanced age, severity of VAP and severity of critical illness, COPD remained one of the risk factors for mortality (OR 2.58, 95% CI 1.33–5.02, $p = 0.005$), along with a higher simplified acute physiology score (SAPS II) at ICU admission and presence of shock on the day of VAP diagnosis [39]. No significant association was found between ICU stay and mechanical ventilation in less severe COPD patients (GOLD stage I–III); however, patients with advanced COPD (GOLD stage IV) were found to have significantly longer ICU stay and duration of mechanical ventilation compared to non-COPD patients [39]. In the sub-group of survivors, stage IV COPD patients had marginally longer mechanical ventilation duration (69 (24–103) vs. 26 (15–41), $p = 0.005$) and ICU stay (74 (37–113) vs. 34 (28–58), $p = 0.07$) compared to non-COPD patients [39]. Limitations of this study include the significant differences between COPD and non-COPD subgroups, although these were partially accounted for by the multivariate analysis adjustments, and the potential underestimation of COPD prevalence [39]. Prior COPD diagnosis or spirometry was compulsory for COPD definition; however, not all patients with COPD had been previously diagnosed [39]. Indeed, it is not uncommon for COPD to be firstly diagnosed during ICU admission based on clinical and

radiological findings [39]. Therefore, current or former smokers with COPD might have been misclassified as non-COPD due to the absence of prior clinical diagnosis or PFTs [39].

Similarly, Lisboa et al. [40] conducted a prospective, observational cohort study in 3 Spanish ICUs on 441 patients with VAP in which COPD resulted being more common in VAP non-survivors than in survivors (27.6% vs. 16.9%, $p < 0.05$).

Lastly, a prospective study by Rello et al. recruited 129 consecutive episodes of VAP over 35 months [41]. Antecedent COPD was diagnosed using the standard criteria recommended by the American Thoracic Society [42]. In the univariate analysis, antecedent COPD was found to be significantly associated with attributable mortality in VAP patients [41]. However, when a step-forward logistic regression analysis was applied, the effects of antecedent COPD on VAP mortality were not statistically significant [41].

Does VAP development impact the outcome of COPD patients?

Most studies conclude that VAP development impacts the outcome of COPD patients in the ICU; however, some studies did not identify a correlation between VAP and worse outcomes.

According to a secondary analysis on the EU-VAP project, VAP leads to a longer duration of mechanical ventilation and hospital stay and is an independent risk factor for mortality in the ICU [5]. The development of VAP in COPD patients resulted in an increase of 17% in mortality rate compared to COPD patients that did not develop VAP (48.1% vs 31.1%, $p = 0.005$) [5]. Furthermore, the median duration of mechanical ventilation was reported to be 12 days longer (18 vs 6 days, $p < 0.001$), as well as the median length of ICU stay (23 vs 9 days, $p < 0.001$) [5]. VAP, along with SAPS II, were identified as independent predictors of mortality in ICU patients [5]. McCabe chronic disease status was assessed, but the severity of COPD based on GOLD staging was not recorded; therefore, we could not conclude whether there is a relationship between COPD severity and VAP or ICU outcome [5].

Similar results were obtained by Nseir et al. [43] in a single-centre, prospective, observational, case-control study conducted on a total of 1241 patients diagnosed with COPD, of which 77 (6%) developed VAP, with the vast majority being late-onset (71%). Length of ICU stay (26 ± 17 vs 15 ± 13, $p < 0.001$), duration of mechanical ventilation (24 ± 15 vs 13 ± 11, $p < 0.001$) and mortality rate (50 vs 22, $p < 0.001$) were all higher in COPD patients who developed VAP compared to control patients; VAP was identified as an independent risk factor for mortality in COPD patients in the ICU (64% vs 28%, $p < 0.001$) [43]. However, mortality rate, length of ICU stay and length of MV were all significantly lower in

VAP patients receiving corticosteroids [43]. Limitations of this study include the fact that COPD severity was not recorded [43].

In agreement with the above findings are the results of a single-centre, prospective, observational, clinical study conducted by Badawy et al. [44]. Patients with an acute exacerbation of COPD and in need for MV for ≥ 48 h were included in the study. From 152 included patients, 92 developed VAP [44]. VAP was identified as a risk factor for morbidity and mortality in COPD patients: the risk of death in COPD patients with VAP was as high as 47.8%, compared to 30% in COPD patients without VAP [44]. VAP caused by multidrug-resistant organisms was particularly associated with an increased risk for mortality in ICU COPD patients, due to a higher risk of receiving the wrong antibiotic treatment [44]. COPD patients who developed VAP were also seen to have an ICU stay of 18.2 ± 8.8 (vs 7.4 ± 2.9 in COPD without VAP, $P = 0.0001$), a MV duration of 15 ± 8.07 (vs 4.23 ± 1.5 in COPD without VAP), and a clinical pulmonary infection score (CPIS) of 8.8 ± 1.7 (vs 4.21 ± 1.5 in COPD without VAP) [44]. Older age, late-onset VAP, re-intubation and prolonged use of antibiotics were identified as predictors of mortality in COPD patients who developed VAP [44].

In addition, in another retrospective single-centre study by Gursel [17] which included 86 COPD patients, a logistic regression analysis showed that VAP was an independent predictor for ICU stay > 10 days in patients with COPD. VAP was also identified as an independent predictor for MV > 7 days (OR 6; 95% CI 2–23, $p = 0.011$) and MV > 15 days (OR 14, 95% CI 3–66, $p = 0.001$), but it was not a risk factor for MV > 21 days [17].

Contrary to the results of the abovementioned studies, in the study by Rodriguez et al. [24], although COPD was overall an independent risk factor for mortality (HR 2.1, 95% CI 1.10–3.94), the mortality rate was not significantly different between patients with non-exacerbated COPD who developed VAP compared to those without VAP (50% vs. 34%, respectively).

Along the same lines as above were also the results of the study by Hadda et al. [45], conducted in patient with exacerbated COPD. This retrospective, single-centre study was conducted in an Indian hospital and included 186 ICU patients with an exacerbation of COPD; 82% (153) required intubation and mechanical ventilation, and of these, 23% (35) developed VAP (¾ were late-onset VAP) [45]. Neither in-hospital nor 28-day mortality rate of intubated COPD patients was significantly different between patients who developed VAP and those who did not (51% vs 53.4% and 48.6% vs 46.6%, respectively) [45]. Duration of mechanical ventilation (32 ± 10 vs 10 ± 2, $p < 0.031$) and ICU stay (53 ± 26 vs 18 ± 7, $p < 0.001$) were both longer in COPD patients with VAP [45]. The main strength of the study is that it is a homogenous

Table 2 Summary of the main studies that have explored aspects of the interaction between COPD and VAP in adult patients (≥18 years) since 2005

Publication	Type of study	VAP definition	COPD definition	Main findings
Chang L et al., *Can Respir J*, 2017 [32]	Retrospective, single-centre study in China; analysis of 197 ICU patients with acute cerebral haemorrhage; 82 developed VAP (64% LOP)	VAP diagnosis according to the guidelines of the Chinese Society of Respiratory Diseases for the diagnosis and treatment of HAP (% of microbiological confirmation not provided)	COPD definition not provided	-COPD was independent risk factors for VAP development in ICU patients with acute cerebral haemorrhage (OR 1.942, 95% CI 1.258–2.843, $p = 0.012$)
Saied et al., *PlosOne* 2017 [36]	Retrospective analysis of the prospective French multicentre OUTCOMEREA database; 7784 patients with ≥48 h MV; 1234 developed VAP (64% LOP)	Clinical definition* and microbiological confirmation (required) by QT cultures of TA, BAL or plugged telescopic catheter; LOP defined as VAP ≥ 7 days after intubation	COPD definition not provided	-COPD exacerbation was higher in LOP vs. non-LOP (9.3 vs 6.9%, $p = 0.05$)
Liu Y et al., *Front Med*, 2017 [34]	Retrospective, single-centre, case control study in a China; 465 patients undergone major oncological surgery for head and neck cancer (SHNC); 95 developed VAP	Clinical diagnosis according to ATS/IDSA criteria [1] and microbiological confirmation (required) by BAL of PSB samples cultures (QT)	COPD definition not provided	-COPD was independent risk factors for VAP development in ICU patients with SHNC (OR 1.70, 95% CI 1.00–2.86)
Karatas et al., *Pak J Med Sci*, 2016 [33]	Retrospective, single-centre study in a Turkish ICU; 1152 patients with >48 ICU stay and MV; VAP developed in 15.4%	VAP defined according to CDC/NHSN criteria [48]	COPD defined as per Charlson score	-Presence of COPD was an significant risk factor for VAP development (OR 4.19, 95% CI 2.56–6.62, $p = 0.035$)
Koulenti et al., *Eur J Clin Microbiol Infect Dis.*, 2015 [5]	Secondary analysis of a prospective, European multi-centre observational cohort study, conducted in Europe, in 2082 non-trauma ICU patients	Clinical diagnosis according to ATS/IDSA criteria [1]; various types of specimens (TA, BAL, PBS, quantitative, semi-quantitative or qualitative cultures); microbiologic confirmation (not required for the diagnosis) in 76% of VAP cases; LOP defined as VAP ≥ 7 days after intubation	Pulmonary function tests or clinical criteria, medical history and evidence of hyper-inflation on chest radiograph; PTFs not necessary for defining COPD; GOLD staging not used for severity	-COPD did not affect VAP incidence and prevalence -COPD was not a risk factor for VAP development -COPD did not affect the median onset of VAP -VAP increased ICU-LOS and MV-duration of COPD patients -VAP development in COPD patients was independent predictor of ICU mortality (OR 2.28, 95% CI 1.35–3.87) -*P. aeruginosa* was significantly more frequently isolated in COPD patients with VAP vs. without VAP; the difference was significant even in early-onset VAP
Rinaudo et al., *Chest*, 2015 [37]	Prospective, single-centre, observational, case-control study, conducted in Spain, in 279 patients with ICUAP (156 VAP)	Clinical diagnosis according to ATS/IDSA criteria [1]; microbiological confirmation (not required for diagnosis) in 59% of ICUAP cases	-Definition of COPD according to ATS/ERS criteria [49]; confirmed by PFTs -COPD severity assessed using GOLD criteria	-90-day mortality was significantly higher in COPD patients with VAP vs. without VAP (18 (62%) vs. 45 (37%), $p = 0.15$) -Higher rate of Aspergillus and lower of Enterobacteriaciae in COPD patients with ICUAP vs. without COPD

Table 2 (continued)

Publication	Type of study	VAP definition	COPD definition	Main findings
Badawy et al., Egypt J Chest Dis Tuberc, 2015 [44]	Prospective, single-centre, observational study, conducted in Egypt, in 152 patients with COPD exacerbation (AECOPD) with ≥ 48 h MV; 92 (60%) developed VAP	Clinical diagnosis according to ATS/IDSA 2005 criteria [1] and microbiological confirmation (required) with QT cultures ($\geq 10^5$) of TA		-AECOPD patients with VAP vs. without had increased MV duration (15 vs. 5 days, $p = 0.0001$), ICU-LOS (18.2 vs. 7.4, $p = 0.0001$) and mortality (47.8% vs. 30%, p = 0.03) -Klebsiella spp. was the most frequent pathogen followed by E. coli
Hadda et al., Lung India, 2014 [45]	Retrospective, single-centre study, conducted in India, in 186 ICU patients admitted to ICU with COPD exacerbation and153 required ≥ 48 h intubation (patients admitted with CAP were excluded); 35 (28%) developed VAP	Clinical diagnosis [50];various types of specimens (TA, bronchoscopic and non-bronchoscopic BAL); microbiological confirmation in 77.1%	COPD definition not provided	-VAP development did not affect neither 28-day mortality nor in-hospital mortality -VAP increased significantly MV duration and ICU-LOS vs. those that did not develop VAP -A. baumannii (65.4%) the most frequently isolated pathogen, followed by P. aeruginosa (26.9%)
Al-Dorzi et al., Am J Infect Control, 2012 [35]	Prospective, single-centre, observational, cohort study conducted in Saudi Arabia during a 6-year period; 2812 patients with ≥ 48 h of MV, 433 patients with VAP	Clinical diagnosis according to CDC 2003 criteria [51]	COPD definition not provided	-There was no difference in underlying COPD between patients with vs. without COPD (8.2 vs. 9.9, ns)
Makris et al., Respiratory medicine, 2011 [39]	Prospective, single-centre, observational study, conducted in France, 215 patients with VAP; 65 had underlying VAP	Clinical diagnosis according to ATS/IDSA criteria [1] and microbiological confirmation (required) by quantitative cultures of TA or BAL	-COPD defined according to ATS-ERS criteria [49] -COPD severity assessed using GOLD criteria- available in 18.3% of COPD patients	-COPD was a risk factor for ICU mortality of patients with VAP (OR 2.58, 95% CI 1.34–5.00) -Higher MV duration and ICU stay of patients with severe COPD and non-COPD
Rodriguez et al., Chest, 2011 [24]	Prospective, observational, case-control study, conducted in Spain, in 235 patients with COPD	Clinical diagnosis#; QT TA cultures; microbiological confirmation was not required for VAP diagnosis (% with microbiological diagnosis not provided)	-Premorbid pulmonary function testing otherwise clinical criteria, medical records and radiograph; only non-exacerbated COPD include in the cohort -COPD severity assessed using GOLD criteria	-VAP incidence did not differ between patients with non-exacerbated COPD vs. without COPD -VAP development did not affect the mortality rate of patients with non-exacerbated COPD
Lisboa et al., Chest, 2008 [40]	Prospective, observational cohort in 3 Spanish ICUs, 441 patients with VAP	Clinical diagnosis [1]; collection of respiratory (PSB or BAL or QT TA) and blood cultures; microbiological confirmation (not required for the diagnosis) in 74.4% of VAP	-COPD was defined as a disease state characterised by the presence of airflow limitation due to chronic bronchitis or emphysema -GOLD stage severity not provided	-COPD was more common in VAP non-survivors vs. survivors (27.6% vs. 16.9%, $p < 0.05$)
Gursel, et al., Heart & Lung, 2006 [38]	Retrospective analysis of a prospective, single-centre, computerised database of Turkish ICU; in 93 ICU patients with exacerbated COPD needing MV; in 29 bronchiectasis coexisted; 49 patients developed VAP	Clinical diagnosis based on CPIS [52] and microbiological diagnosis using endotracheal aspirate	-Post-bronchodilator or best-recorded forced expiratory volume in 1 s (FEV1) less than 70% predicted with FEV1/FVC less than 70% accepted for diagnosis; clinical criteria, medical history and evidence of hyper-inflation on chest radiograph	-VAP development was significantly higher in patients with COPD plus bronchiectasis vs. COPD only (60% vs. 45%, $p = 0.034$) -P. aeruginosa was the most frequent pathogen of VAP; PA was more

Table 2 (continued)

Publication	Type of study	VAP definition	COPD definition	Main findings
			considered supportive. 68% had PFTs; severity assessed according to ATS/ERS 2004 criteria [49] -Bronchiectasis defined based on clinical and radiological findings (1/2 had chest CT)	frequent in COPD+ bronchiectasis vs. COPD only
Tejerina et al., *J Crit Care*, 2006 [25]	Retrospective analysis of a prospective, multi-centre, cohort study conducted in 361 ICUs of 20 countries and included 5183 adults patients with >12 h of MV; 2897 patients had ≥48 h of mechanical ventilation; 439 patients developed VAP	Clinical diagnosis according to CDC 1989 definition [53]	Not provided	-COPD is an independent risk factor for VAP development (OR 3.9 95%CI 2.2–6.9, p < 0.001)
Gursel et al., *Respiration* 2005 [17]	Retrospective analysis of a prospective, single-centre observational study conducted in a Turkish ICU; 86 patients with COPD requiring MV; 56% developed VAP	VAP according to CDC 1989 criteria [53] and microbiological confirmation (required) by quantitative cultures of TA	-COPD severity was classified according to GOLD criteria	-VAP was independent predictors for MV > 7 days (VAP; odds ratio, OR 6; 95% CI 2–23, p = 0.011) and for MV >15 days (OR 14, 95% CI 3–66, p = 0.001) but not for >21 days -Most frequent VAP pathogen was P. aeruginosa
Nseir et al., *Chest*, 2005 [43]	Prospective, single-centre, observational case-control study, conducted in France, in 1241 patients with COPD	Clinical diagnosis* and microbiological diagnosis (required) using tracheal aspirate culture (≥10⁶ CFU/mL)	-COPD defined according to ATS criteria [54] -Information on severity of COPD unavailable	-VAP increases length of ICU stay and MV-duration of COPD patients -VAP is an independent risk factor for mortality of COPD patients (OR 7.7, 95% CI 3.2–18.6, p < 0.001) -P. aeruginosa (31%) was the most frequently isolated pathogen, followed by A. baumannii (19%)

TA tracheal aspirate, *MV* mechanical ventilation, *LOS* length of stay, *EOP* early-onset VAP, *LOP* late-onset VAP, *BAL* bronchoalveolar lavage, *PSB* protected specimen brushing, *HAP* hospital-acquired pneumonia, *LRTI* lower respiratory tract infections

*Clinical diagnosis of VAP used: intubated and mechanically ventilated patients for >48 h with new and/or progressive and persistent pulmonary infiltrates on a chest radiograph plus 2 or more of the following criteria fever (≥38.5 °C) or hypothermia (<36.5 °C), leukocytosis (>10 × 10⁹/L), leukopenia (<1.5 × 10⁹/L), purulent tracheobronchial secretions

Clinical diagnosis of VAP used: new, persistent pulmonary infiltrates not otherwise explained on chest X-ray plus the presence of local purulent respiratory secretions) and systematic signs of inflammatory response (WBC >10 × 10⁹/L, rise in WBC >20% or fever)

cohort, while the main limitation is the retrospective study design, which makes it difficult to establish a cause–effect relationship [45].

Does COPD impact the aetiology of VAP?

COPD leads to physiological changes which predispose patients to infections. The loss of epithelium integrity and impairment of mucosal clearance lead to an increased risk for infection in patients with COPD, particularly from Gram-negative bacilli [46]. Whether antipseudomonal therapy should be part of empiric therapy, even in early onset pneumonia, is an important issue.

Koulenti et al. [5] observed that the prevalence of *Pseudomonas aeruginosa* VAP was 26.4% in COPD patients, vs 15.8% in patients without COPD. The prevalence of non-fermenting Gram-negative bacilli VAP was noticed to be 49.9% in COPD and 18.5% in non-COPD patients ($p = 0.020$), and it was even higher in COPD patients with an early onset-VAP (54.1% vs 20%, $p < 0.001$), which is particularly significant for the selection of empirical antibiotic therapy [5]. Similar results were obtained by Nseir et al. [43], who observed that *P. aeruginosa* (31%), *A. baumannii* (19%) and *S. aureus* (14%) were the most frequently isolated microorganisms in VAP patients with COPD. The prevalence of multidrug-resistant (MDR) bacteria in these patients was found to be 41% [43]. The most frequently isolated microorganisms by Makris et al. [39] were again *P. aeruginosa* (39%) and *S. aureus* (17%); a total of 136 MDR bacteria were isolated in 57% of the patients. In the same line were the results of the retrospective study by Gursel [17], who reported *P. aeruginosa* as the most commonly isolated pathogen. Moreover, in another study from the same author [38], the impact of co-existence of bronchiectasis with COPD was explored and *P. aeruginosa* was reported as being more frequent in COPD in the presence of bronchiectasis versus COPD alone [38]. However, the study was small and a larger study is needed to shed light on the impact of bronchiectasis/COPD combination on VAP aetiology [38].

Contrary to the above, a study by Badawy et al. [44] on microbiologically confirmed VAP in patients with exacerbated COPD, Gram-negatives (56%) were still the most frequent pathogens, but the most frequent isolate was *Klebsiella* spp. followed by *E. coli*, while MRSA was the most frequent Gram-positive pathogen.

Finally, Rello et al. [47], in a prospective, observational single-centre study that included 72 cases with microbiologically confirmed VAP out of 568 mechanically ventilated patients, reported that COPD was an independent risk factor for *P. aeruginosa* VAP (RR 29.9, 95% CI 4.86–184.53).

The summary of the main studies included in this review (since 2005) are presented in Table 2, with depicted differences in settings and definitions.

Conclusions

This manuscript critically and comprehensively reviews the current literature on the interaction between VAP and COPD, a topic that has important clinical implications for the decision making of ICU physicians. In subjects undergoing mechanical ventilation, there were studies that identified COPD as a risk factor for VAP development, as opposed to other studies where COPD was not observed to cause a higher incidence of VAP. The literature on whether antecedent COPD is a risk factor for worse outcomes in patients who develop VAP is also controversial. However, most studies agree that VAP development increases morbidity and mortality of ICU patients with COPD. Regarding VAP aetiology, the most common causative agents of VAP in COPD patients were Gram-negative bacilli, with *Pseudomonas aeruginosa* being the most prevalent.

The identified controversy on the findings may be a result of heterogeneity in definitions used for VAP and COPD diagnosis, i.e. for VAP, the need or not of microbiological confirmation, sampling/culture methods (e.g. bronchoscopic vs. non-bronchoscopic, qualitative vs. quantitative cultures); for COPD, the need for pulmonary function tests vs. diagnosis based on history/clinical findings/imaging. Moreover, differences in the cohorts, such as case-mix, demographics, comorbidities, severity of illness and management practices might have contributed to the controversial findings as well.

Methodological aspects that need improvement have been detected and priorities for further research in the field have been elucidated. Unfortunately, only a few references for each research question used logistic regression models, i.e. COPD impact on VAP incidence [25, 32, 34] and outcomes [37, 39–41], and VAP impact on COPD outcomes [5, 17, 38, 43, 44]. Identification of COPD subgroups that would benefit the most from more stringent VAP prevention measures could lead to a decrease in VAP development and related healthcare costs. On the other hand, the elucidation of COPD's impact on the aetiology of early-onset VAP could lead to a change in the current guidelines for the empirical management of VAP for patient with underlying COPD or for specific subgroup of COPD patients. Further studies with stratification of severity based on the GOLD staging are warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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