Original Article

Impact of ventilator associated pneumonia on outcome in patients with chronic obstructive pulmonary disease exacerbation

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ABSTRACT

Background and Objective: There are sparse data regarding the impact of ventilator-associated pneumonia (VAP) on outcome among patients with chronic obstructive pulmonary disease (COPD) exacerbation. **Materials and Methods:** This retrospective study included patients with COPD exacerbation requiring endotracheal intubation for more than 48 h admitted in a single respiratory unit from January 2008 to December 2009. Records of these patients were checked for the occurrence of VAP. **Results:** One hundred and fifty-three patients required endotracheal intubation for COPD exacerbation during this period. The mean age of this cohort was 61.46 ± 11.3 years. The median duration of COPD was 6 years (range: 1-40). A total of 35 (22.8%) patients developed VAP (early: 9 and late: 26). The risk of mortality was comparable between two groups, that is, patients with and without VAP [odd's ratio (OR)–1.125; 95% confidence interval (CI), 0.622-2.035]. The duration of mechanical ventilation and hospital stay (median ± standard error, 95% CI) was 32 ± 10 (95% CI, 13-51) versus 10 ± 2 (95% CI, 6-14) days; $P \leq 0.001$ and 53 ± 26 (95% CI, 3-103) versus 18 ± 7 (95% CI, 5-31) days; $P = 0.031$, respectively was higher among patients with VAP. **Conclusions:** Our study has shown that VAP leads to increased duration of mechanical ventilation and hospital stay; however, the mortality is not affected.

KEY WORDS: Chronic obstructive pulmonary disease, endotracheal intubation, in-hospital mortality, ventilator-associated pneumonia

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is a common complication of endotracheal intubation leading to high morbidity and mortality.[1] However, the mortality attributable to VAP is debatable.[2-5] Recently, a meta-analysis by Muscedere *et al.*,[5] concluded that VAP is associated with increased mortality in intensive care unit (ICU); however, there was no increase in overall hospital mortality. Authors also reported the prolongation of stay in ICU and hospital attributed to VAP. In addition to the mortality, the extended hospital and ICU stay consume

significant hospital resources. The cost of care of such patients is significantly higher as compared with patients without this complication (US $104,983 ± 91,080 vs. 63,689 ± 75,030).[6] However, it should be noted that, these results denote impact of VAP among heterogeneous group of patients requiring mechanical ventilation due to different pulmonary and nonpulmonary diseases.

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality among smokers and some nonsmokers.[7,8] Its natural course is characterized by exacerbations of the disease leading to acute respiratory failure and hospitalization.[9] Although non-invasive mechanical ventilation (NIV) is "the standard of care" for management of acute exacerbation of COPD;[10] however, endotracheal intubation becomes essential in large proportion of cases either because of clinical condition or nonavailability of resources. Though endotracheal intubation is life-saving among these patients; however, it may be complicated by VAP. Furthermore, COPD itself is a risk factor for nosocomial lower respiratory

infections.[11,12] Various factors which may contribute to the increased risk of lower respiratory infections among these patients include presence of structural lung disease, need of repeated hospitalization and antibiotic use, and use of corticosteroids. Considering the risk profile of these patients, VAP is expected to have significant adverse effect on the clinical course among patients with COPD. However, data on impact of VAP in patients with COPD are sparse. To the best of our knowledge, this is limited to one study which showed that ICU mortality, duration of mechanical ventilation, and ICU stay were significantly higher among patients with VAP.[13]

Our hospital is a tertiary care center where exacerbation of COPD is among the common causes of respiratory failure requiring endotracheal intubation and admission to medical ICU. However, there are no published data in this settings regarding impact of VAP on various clinically important outcomes among these patients. Therefore, we conducted this study to find the impact of VAP on in-hospital mortality, time spent on mechanical ventilation, and duration of hospital stay among intubated patients with acute exacerbation of COPD.

MATERIALS AND METHODS

This retrospective study included patients with COPD exacerbation admitted under a single respiratory unit during January 2008 to December 2009, at a tertiary care medical center in India. Initially, hospital admission records of all patients admitted during the above-specified period were reviewed to find out the patients with diagnosis of acute exacerbation of COPD who required endotracheal intubation for at least 48 h. Patients with admitting diagnosis of community-acquired pneumonia were excluded. Records of remaining patients were checked for the occurrence of VAP during hospital stay. The diagnostic criteria of VAP included the radiographic features suggestive of pneumonia plus presence of any two of the following: Fever, leukocytosis, purulent or change in the character of endotracheal aspirate (ETA), isolation of the pathogen from of ETA, or other respiratory specimen and hypoxemia.[1] The detailed clinical, biochemical, and other relevant data of these patients were then recorded in an excel sheet. The data were analyzed using SPSS 11.5.0 (Standard version, copyright © SPSS Inc., 1989-2002). The results were expressed as mean ± standard deviation or median with interquartile range (for numerical variable) or standard error with 95% confidence intervals or proportions (categorical variables), wherever applicable. For comparisons Student's *t*-test, Mann-Whitney, Chi-square, or Fisher's exact test were used and $P < 0.05$ was considered significant.

RESULTS

Total 186 patients were admitted with acute exacerbation of COPD during the specified period. Among these 153 patients required endotracheal intubation and included for the analysis. The baseline characteristics of these patients are shown in Table 1.

Using clinical, radiological, and/or microbiological criteria, the overall incidence of VAP was 22.8% (35/153). Among these, 25.7% (9/35) patients developed early-VAP (development of VAP within 5 days of intubation), while late-VAP (development of VAP after ≥5 days of intubation) was observed among 74.3% (26/35) of patients. The comparison of various clinical characteristics of the patients with VAP and those without it are shown in Table 2. The mean duration of endotracheal intubation before development of VAP was 9.9 ± 5.5 days. The microbiological etiology could be established in 77.1% (27/35) patients. Various specimens used for microbiological diagnosis included tracheal aspirate (26), bronchoscopic or nonbronchoscopic bronchoalveolar lavage (7), and blood cultures (2). The pathogens isolated include *Acinetobacter baumannii*-65.4% (17/35), *Pseudomonas aeruginosa* − 26.9% (7/35), and *Staphylococcus aureus* and *Klebsiella pneumonia* in one each.

Impact of VAP on clinical outcome
The overall in-hospital morality among intubated patients with acute exacerbation of COPD was 51% (78/153). The risk of 28-day mortality among patients with VAP was comparable with patients without VAP [Odds ratio (OR)−1.125; 95% confidence interval (CI), 0.622-2.035]. Similarly, in-hospital mortality was also comparable between patients with VAP and without this (OR − 0.967; 95% CI, 0.815 − 1.147).

Table 1: Baseline characteristics of the study cohorts

Clinical parameters (*n*=153)	Observation
Age in years (mean±SD)	61.46±11.3
Gender [*n* (%) male]	102 (67)
Smoking status	
Smoker [*n* (%)]	110 (71.8)
Exposure to biomass fuel [*n* (%)]	15 (13.6)
Smoking index (mean±SD)	440±225
Duration of COPD [median (range) years]	6 (1-40)
Duration of exacerbation of symptoms before hospital admission [median (range) days]	6 (1-20)
APACHE II Score (mean±SD)	20.99±6.36
SAPS II (mean±SD)	46.66±13.62
Comorbidities [no. patients (%)]*	71 (46.4)
Hypertension [*n* (%)]	38 (24.8)
Diabetes mellitus [*n* (%)]	22 (14.4)
Cardiovascular diseases [*n* (%)]	21 (13.7)
Others [*n* (%)]¥	07 (7.1)
Arterial blood gas parameters (at the time of admission)	
pH (mean±SD)	7.26±0.13
PaO_2 (mean±SD mm of Hg)**	99.4±37.1
$PaCO_2$ (mean±SD mm of Hg)**	69.7±5.7
HCO_3 (mean±SD mm of Hg)	29.8±8.8
Oxygen saturation (%)	87.4±6.36%

*Many patients had more than one comorbidities. **Values are calculated after applying log transformation as the data was skewed. ¥Include -Chronic kidney disease (2), benign prostatomegaly (2), hypothyroidism (1), carcinoma lung (1), sleep apnea (1), dilated cardiomyopathy (1), osteoporosis (1), and carcinoma larynx (1). APACHE: Acute physiology and chronic health evaluation, COPD: Chronic obstructive pulmonary disease, SAPS: Simplified acute physiology score, SD: Standard deviation

The duration of mechanical ventilation and hospital stay (median ± standard error, 95% CI) was 32 ± 10 (95% CI, 13-51) versus 10 ± 2 (95% CI, 6-14) days; $P \le 0.001$ and 53 ± 26 (95% CI, 3-103) versus 18 ± 7 (95% CI, 5-31) days; $P = 0.031$, respectively was longer among patients with VAP. These differences were statistically significant even after adjusting for occurrence of VAP at different time during the clinical course as shown in Kaplan-Meier curves [Figures 1 and 2] and Table 3.

Table 2: The comparison of the baseline characteristics of patients with ventilator-associated pneumonia and without ventilator-associated pneumonia

Characteristics	Observations		*P* value
	With VAP (*n*=35)	**Without VAP (*n*=118)**	
Age (mean±SD, years)	61.09±10.73	61.15±12.16	0.978
Gender [*n* (%) male]	22 (64.7)	80 (67.2)	0.838
Smokers [*n* (%)]	25 (73.5)	119 (84.06)	0.203
Smoking index (mean±SD)	426.09±233.97	443.10±225.16	0.751
Duration of COPD (mean±SD, years)	9.00±6.578	7.61±6.41	0.271
Duration of exacerbation of symptoms [median (IQR), days]	7 (4-11)	6 (3-10)	0.821
APACHE II score	22.06±6.13	20.44±6.55	0.216
SAPS II score	48.94±12.00	45.99±14.586	0.307
Presence of comorbidity [n (%)]	16 (45.9)	55 (46.6)	0.746
Arterial blood gas analysis (at the time of admission)			
pH	7.27±0.12	7.26±0.13	0.502
PaCO$_2$ (mm of Hg)**	52.46±1.53	68.72±1.42	0.001
PaO$_2$ (mm of Hg)**	69.41±1.48	85.63±1.86	0.029
HCO$_3$- (mEq/dL)	27.51±8.64	30.53±8.81	0.079
Oxygen saturation (%)	84.75±15.89	88.16±13.85	0.222

*Values are calculated after applying log transformation as the data was skewed. APACHE: Acute physiology and chronic health evaluation, COPD: Chronic obstructive pulmonary disease, IQR: Interquartile range, SAPS: Simplified acute physiology score, SD: Standard deviation, VAP: Ventilator-associated pneumonia
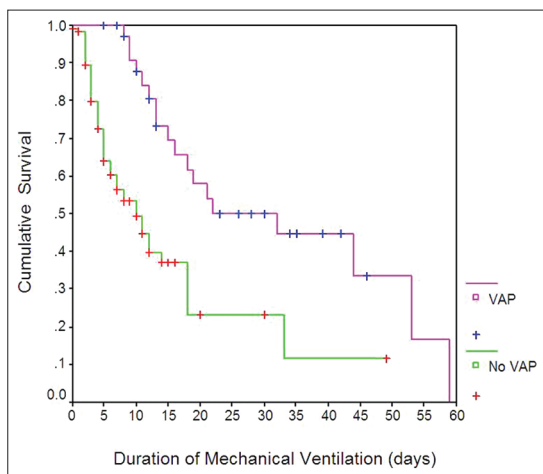
DISCUSSION

COPD is a chronic inflammatory disease of airways caused by an abnormal response to various inhalants, which include noxious gases and particles. Cigarette smoking is the most important culprit involved in the pathogenesis. Additionally, there is some contribution from various pathogens which include *Streptococcus pneumoniae*, *Hemophilus influenzeae*, *Morxella catarrhalis*, and *Pseudomonas aeroginosa* to the airway inflammation.[14-17] Persistent inflammation leads to defective innate defence mechanisms which allow the establishment and proliferation of the microbial pathogens which in turn further invoke the inflammatory response. The result of this whole process will be increased airway secretions, bronchospasm, and mucosal edema leading to clinical exacerbation of COPD. Many patients with exacerbation of disease land in ICU requiring endotracheal intubation. There is enough evidence which suggest that colonization by pathogenic microbes is quite common among patients with endotracheal tube.[18,19] This colonization may not result in VAP among patient without COPD. However, COPD patients are at disadvantage due to compromised immunity as a result of persistent lower airways inflammation and are at increased risk of development of VAP. This study has included such patients and demonstrated the impact of VAP in this subgroup.

Table 3: Impact of ventilator-associated pneumonia on various clinical outcome parameters

Clinical parameter	Patient population		*P* value
	With VAP	**Without VAP**	
In-hospital mortality (%)	51%	53.4	0.61
28-day mortality (%)	48.6	46.6	0.61
Duration of mechanical ventilation*	32±10 (13-51)	10±2 (6-14)	<0.031
Duration of hospital stay*	53±26 (3-103)	18±7 (5-31)	<0.001

*Values are calculated using Kaplan-Meier's survival analysis and expressed as median±standard error (95% confidence intervals). VAP: Ventilator-associated pneumonia

Figure 1: Kaplan-Meier survival curves comparing duration of mechanical ventilation between two groups
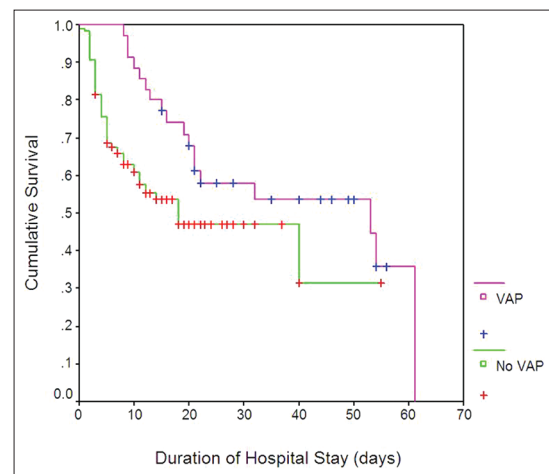
Figure 2: Kaplan-Meier survival curves comparing duration of hospital stay between two groups

Association between VAP and mortality remained debatable since long. Our study has shown comparable 28-day and in-hospital mortality among patients with VAP and without this complication. These results indicate that VAP is not a risk factor for death among these patients. This observation is consistent with prior studies which have shown that VAP is not an independent risk factor for death.[1,3,20-22] However, our study results are contradictory to other studies which showed significantly higher mortality among patients who developed VAP.[4,13,23-25] Among these, study by Nseir *et al.*,[13] has relatively homogeneous cohort of patients with COPD similar to our study. However, unlike our study, authors reported that development of VAP was associated with increased mortality among these patients.[13] The reason for these conflicting results may be due to differences in the potential risk factors, characteristics of study population, associated comorbidities, severity of illness, level of care, and so on. For example, in the study by Nseir *et al.*,[13] 26% patients had diagnoses other than COPD (pneumonia, heart failure, and others); our patients were more sick [simplified acute physiology score (SAPS) = 47 and 48 vs. 37 and 39]; and many were on systemic steroids. All these factors might have contributed to the differences in the mortality. Further, our study cohort was already very sick prior to development of VAP; therefore, the demonstration of additional contribution of VAP to overall mortality in such patient may be difficult. These results also explain that why many of the preventive strategies such as use of topical antibiotics/antiseptics, subglottic secretion drainage, chest physiotherapy, and so on successfully reduce the incidence of VAP but not the mortality caused by this.[26-28] Our study showed higher mortality rate (51%) than reported in the literature (2.5-30%).[29-32] There are various factors such as severity of the disease, presence of type-2 respiratory failure, high acute physiology and chronic health evaluation (APACHE) score, presence of hypoxemia or cor pulmonale, and so on which may affect the mortality among these patients.[33] Our study cohort had many of these risk factors such as type-2 respiratory failure (mean $PaCO_2$ = 69.42 ± 22.3 mm Hg), high APACHE II score (20.99 ± 6.36), and hypoxemia (SPO_2 = 87.4 ± 6.36%). Further, all these patients were intubated. We think all these factors have contributed to the excess mortality. In our study, the time spent on mechanical ventilation (more than 2 times) and duration of hospital stay (more than 2 times) was significantly higher in patients with VAP. These results are consistent with many previous studies.[1,13,20,21] This is not unexpected also as all these studies have shown that VAP leads to prolongation of requirement of mechanical ventilation. However, this information in our settings is important for the all of us who are involved in treating such critically-ill patients. This will help us to provide better information regarding the economic impact of this complication on the patient's family. Further, this information also helps us to identify the appropriate end points which may be used for the future preventive and therapeutics trials on these patients. These results suggest that all physicians involved in care of such patients should put every effort to reduce this complication. Use of NIV may be the best available therapeutic option to prevent these complications. Noteworthy majority of patients with acute exacerbation of COPD may be successfully managed with NIV.[10] It has been shown to improve various physiological parameters such as work of breathing, respiratory rate, severity of breathlessness, pH, $PaCO_2$, and so on. More importantly, it also reduces frequency of VAP, duration of stay in ICU, and hospital and mortality.[10] Therefore, each hospital should utilize its resources to make this facility available for each patient.

The strength of our study is good sample size and homogenous cohort of acute exacerbation of COPD. The majority of the studies described above have included patients with VAP suffering from variables diseases/conditions, admitted in surgical as well medical ICUs.[2,3,13] Our study has provided much needed data on the impact of VAP in relatively homogenous cohort of high-risk patients in Indian settings. This data may be useful in designing further studies involving any preventive or therapeutic intervention/s among such patients. The main limitation of our study is the retrospective study design. Therefore, it is difficult to establish cause and effect relationship. Second, these results are experience from a single center therefore may not be generalized to other centers with different setup and clinical practices. However, single center studies remove few of the confounders such as level of care, antimicrobial usage, and the pathogens responsible for VAP. Our results are comparable to prior studies involving patients with VAP; therefore, the results seem valid.

CONCLUSION

Our study has shown that VAP is common complication in patients intubated for exacerbation of COPD. VAP is associated with significantly longer duration of mechanical ventilation as well as hospital stay. However, it is not associated with increased risk of death.

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