CHAPTER 2

INTUBATED PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: WHAT IS COMMON RISK FACTOR FOR POOR PATIENT OUTCOME?

Acceptance date: 02/09/2024

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ABSTRACT: Background: Approximately every fourth patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) will require intensive care unit (ICU) admission with further mechanical ventilation (MV) and therefore with high risk for development ventilator- associated pneumonia (VAP). Aim: The study was aimed to learn risk factors predicting in-hospital mortality among patients with AE COPD associated with VAP and to evaluate the modifiable risk factors in term on improvement of patient outcomes. Methods: This study included patients with AE of COPD who required MV and admitted in respiratory and critical care medicine unit at university teaching hospital from January 2017 to December 2022 and the various baseline demographic and clinical features were compared between patients with- and without VAP. Results: The study included 164 intubated patients with AE of COPD with age of 60.4+_8.4 years, in 48 patients have developed VAP. Multivariable analysis showed severe sepsis/septick shock at admission, pulmonary complication as ARDS with PaO2/FIO2 <200, malnutrition, concominant bronchiectasis and history of previous hospitalization were independent predictors in-hospital mortality .OD for septic shock was 3.74(1.04- 7.69) .p=0.004; for ARDS with PaO2/FiO2<200 was 1.26(0.48-9.24).r =0.002;for malnutrition 2.89(1.01-5.96), p=0.012 for concominant BE 2.48(1.14-5.41),p=0.019; and for previously frequent hospitalization was 3.26(1.46-7.52).p=0.01, respectively. *Acinotebacter baumannii* (n=21/43.7\%) was frequent finding among non-survivors with VAP(p=0.001) and all infections related to this pathogens were multi-drug-resistant (MDR). *Pseudomonas*

aeruginosa was common in patients with concominant BE (p=0.001). Conclusions: We found several predictors associated with fatal outcomes, which could be help identify patients who might benefit from adequate early empirical antibiotic treatment, as well as determine prognosis. Prevention of malnutrition and severe exacerbations leading hospitalization of COPD patients may associated with decreased fatal outcomes.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the second most common infection acquired during stay in the intensive care unit (ICD).The incidence of VAP may be as high as 40% among patients on mechanical ventilation. Mortality rates among patients with VAP differ in different settings; however, it may be as high as 78%. VAP led to increased duration of hospital and ICU stay, antibiotic usage, and cost of care. Early recognition of risk Factors with development of VAP and its causative pathogens maybe be one of the important steps toward achieving this goal. The presence of chronic obstructive pulmonary disease (COPD), organ failure, coma and re- intubation are risk factors which have been associated with development of VAP. Common causative pathogens of VAP, include *Pseudomonas aeruginosa, Acinotebacter baumanni, Klebsiella pneumoniae*,and *Staphylococcus aureus*. However, these risk factors and microbiology of VAP may vary according to the study population and ICU settings. The natural course of COPD is characterized by exacerbations leading of acute respiratory failure and hospitalization.

Majority of these patients may be managed with application of noninvasive ventilation (NIV) or by using of high-flow nasal cannula (HFNC) oxygenation in the ward setting. However, a significant proportion of such patients requires endotracheal intubation and mechanical ventilation and so admission to ICU setting. Data suggest that in up to 6%-12% of patients in ICU receiving mechanical ventilation, the underlying reason for intubation was an exacerbation of COPD. For COPD patients the endotracheal intubation is lifesaving, it can be complicated by the development of VAP and >50%. of patients of COPD who developed VAP succumb to it. It is, therefore, important to understand the risk factors and pathogens causing VAD and although the risk factors predicting in hospital mortality among intubated COPD patients for appropriate risk stratification, development of preventive strategies, selection of appropriate antimicrobial agents, and modifying risk factors which are responsible for in hospital mortality.

We planned this study with the aim to describe the predictors for in hospital mortality and possibility to modify risk factors in term on reduction mortality rate.

MATERIALS AND METHODS

Study design, patients, and setting

This retrospective study was conducted between January 2017 and December 2022 at a critical care department teaching hospital medical university of Baku Azerbaijan. All patients admitted with exacerbation of COPD and requiring mechanical ventilation for >48h were eligible for enrolling in the study. Exacerbation of COPD was defined clinically as an episode of worsening of respiratory symptoms, particularly dyspnea, cough, sputum production, and sputum purulence .

All patients were given a standard of care for the management of the exacerbation of COPD.

For prevention of VAP, a standard of care was used: elevation of the head end of the bed by 30°-45° peptic ulcer prophylaxis, daily sedation, free time, daily assessment for readiness for extubation endotracheal cuff pressure checked at least three times per day and kept 20-30 mmHg, and chlorhexidine mouthwash twice daily.

DEFINITIONS

Diagnosis of COPD was based on the existing GOLD guidelines. Clinical diagnosis of VAP was based on criteria new or progressive infiltrates on chest radiograph (with no suggestions causes such as atelectasis, embolism, and heart failure) and at least two of the following variables - fever > 38°C, leukocytosis (>12000/dl),or leukopenia (<4000/dl) purulent secretions, isolation of pathogenic organism, or increased oxygen requirement. Those patients with clinical diagnosis of VAP underwent flexible bronchoscoply and bronchoalveolar lavage (BAL) for microbiological diagnosis. In case bronchoscopy was contraindicated, a patient underwent endotracheal aspirate (ETA). Microbiological diagnosis was achieved by gram stein and culture on appropriate culture media with thresholds of ≥ 104 CFU/ml and >10 5 CFU/ml in BAL an ETA, respectively.

DATA COLLECTION

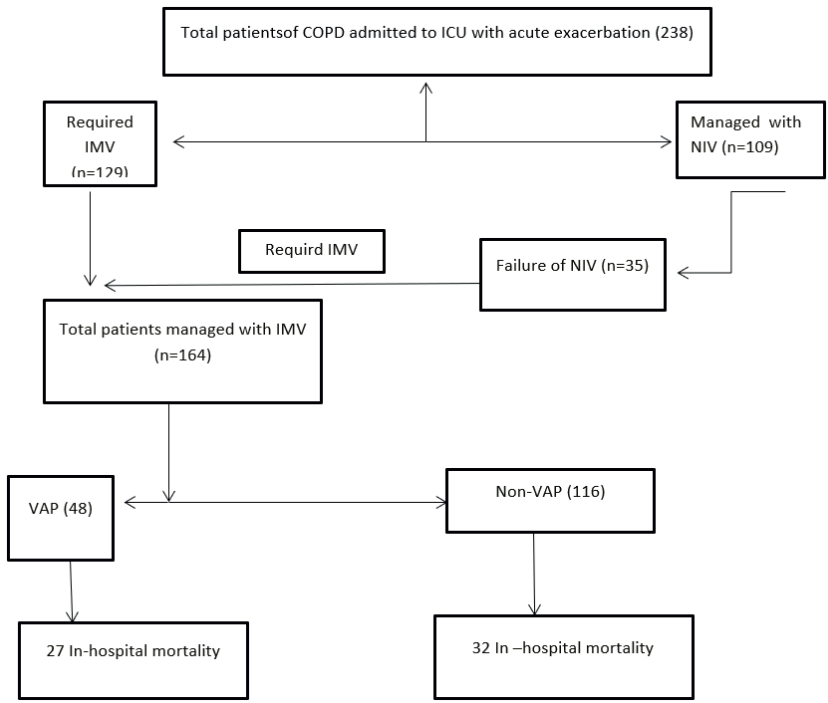
All baseline demographic and clinical data were recorded. Furthermore, data regarding size of endotracheal tube at admission, use of vasopressor at admission, use of systemic corticosteroids prior to admission, smoking history, use of antibiotics in the past 90 days, number of exacerbation episodes in the past year requiring hospitalization of patient, history of pulmonary tuberculosis (TB), presence of any comorbidities such as bronchiectasis, diabetes, chronic liver, or kidney disease, and need of re-intubations were required during the current admission were recorded

STATISTICAL AND ANALYSIS

Data were managed on Excel spread sheet and analyzed using statistical Software Stata version 14. Quantitative variables were expressed as mean standard deviation and median for normal and skewed data respectively. Univariate analysis was done for identification of potential risk factor for the development of VAP. Independent t-test (for normal data) and Mann-Whitney U-test (for skewed data)were used to compare mean/ median values between the groups. Change in mean was compared using paired t-test (for normal data)and Wilcoxon signed-game test (for skewed data). Fisher's exact test and Chi-square test were used to check the statistical significance for categorical variable. Stepwise multivariate logistic regression analysis was carried out taking probability of reversal as 0.1 and entry as 0.05 to find the independently associated factor of in-hospital mortality of VAP and adjusted odds ratio was calculated. All tests were two-tailed, and P<0.05 was considered statistically significant

RESULTS

During the study period, 164 of 238 patients of COPD with exacerbation 'admitted under pulmonary medicines services required upfront intubation and mechanical ventilation. Non-invasive ventilation (NIV) was used in 109 patients, among these, 35 failed NIV and subsequently required intubation. Thus, a total of 164 patients were available for study. Patient recruitment has been shown in Figure 1.



Fiqure1: Flow diagram showing the recruitment of the patients

Study cohort (n=169) consisted predominantly of male, heavy smokers, with median duration of COPD of 7 years in Non- VAP, 10 years in VAP Group (p<0.001). The baseline patient's characteristics are shown in Table 1.

BASELINE CHARACTERISTICS OF PATIENTS ENROLLED TO STUDY

Parameters	*Intubated patients with AE COPD without VAP (n=116)*	*Intubated patients with AE COPD with VAP (n=48)*	*P value*
Age,mean +SD years	**61,4±8,9**	**60,9**	0,841
Gender,Male n(%)	41(85)	102(87,9)	0,695
Smoking index pak-years	72±29	56±26	<0,001
Duration of COPD,median range	11(5-16)	7(3-17)	<0,001
Number of severe exacerbation in the past 1 year,median range	3(1-4)	1(0-3)	<0,001
Median of ICU stay,mean+-SD days	12(5-18)	8(4-13)	<0.001
Comorbidities n(%)			
DM	21(77)	14(12)	0,001
Hypertension	21(44)	40(32)	0,09
Old tuberoculosis	25(52)	26(22)	0,003
Bronchiectasis	28(58)	27(23)	0,002
SOFA score on admission,mean +SD	7,81±4,12	4,10±1,48	0,003
Vasopressor use at admission,n(%)	23(48)	15(13)	<0,002
Antibiotics used in the past 90 days,n(%)	37(77)	42(36)	<0,002
Hospital mortality n(%)	27(56)	32(27)	<0,01

Median (interquartile range [IQR]) duration of ICU stay was differ (p<0.001) and was significantly higher among VAP patients. Re-intubation required in 27 (16%) patients and was markedly higher among VAP patients (OR 22.16 [5.84-64.25]; p<0.001) Univariate analysis has showed the predictors associated with development of VAP in study cohorts, and highs SOFA score at admission (p<0.001), septic shock required vasopressor use at admission (OR 4.92 [1.52-16.24]):p=0.005, antibiotic use in the past 90 days (OR 4.34 [1.09-12.12]; p=0.032), number of severe exacerbation of COPD required hospitalization in the past year (OR 20.01[2.80-58.41); P=0.004), the presence of bronchiectasis and history of pulmonary tuberculosis (P=0.007 and p=0.02; respectively), and malnutrition (OR 5.29[1.84-10,26]; P<0,006) were associated with an increased risk of VAP in intubated COPD patients

PREDICTORS ASSOCIATED WITH THE DEVELOPMENT OF VENTILATOR-ASSOCIATED PNEUMONIA

Factor	OR(95%IC);	P
Univariate analysis:		
Sofa score at admission	2.78 (160-4.54);	<0.001
Vasopressor use at admission	4.92(1.52-16.24);-	0.005
Antibiotics in the past go days	4.34(1.09-12.12);-	0.032
Number of severe exacerbation of COPD in the past year	20.01(2.80-58.41);	-0.004
Presence of Bronchiectasis	4.28(1.04-9.28);	-0.007
History of pulmonary tuberculosis	3.27(1.12-7.58);	-0.02
Re-intubation during content admission	22.16(5.84-64.25);	<0.001
Malnutrition	2.70(1.29-5.63):	-0.01
Multivariate analysis:		
SOFA score at admission	5.29(1.84-10.26):	<0.006
Vasopressor use at admission	2.66(1.14-5.17);	0.04
Re- intubation	14.21(3.46-38.11);	-0.005
History of previous hospitalization	6.74(1.86-12.17);	-0.004
Presence of Bronchiectasis	2.48 (1.08-6.29);	-0.019
History of pulmonary tuberculosis	2.21(1.01-5.13);	-0049
Malnutrition	2.89 (1.36-6.43);	-0.012

The overall in hospital mortality among intubated patients with acute exacerbation of COPD was 35.9%. (n=59/164) Among patients with VAP, 27/56%.) died.

On multivariable analysis , only SOFA Score at admission, re-intubation, history Of previous hospitalization, history of bronchiectasis and previously pulmonary TB malnutrition and vasopressor use at admission significantly predicted the development of VAP (Table 2).

Bronchoscopic (n=22) BAL, and endotracheal aspirate (ETA) (n=26) were used for microbiological diagnosis of VAP. Microbiological etiology of VAP could be established in 44/48(91.6%) patients Gram-negative organisms in 41(93.2%) BAL specimens and ETA obtained by bronchoscopic and non-bronchoscopic technique.

Acinotebacter baumannii was the most Frequent isolated organism (n=21/43.7%), followed by *Pseudomonas aeruginosa* (n=11; 22,9%), *K. pneumonia* (n=5;10.4%) and *Eschericha coli* (n=4; 8.3%). In 3(6.2%) patients, only Gram staining was positive while cultures showed growth by *Staphylococcus aureus.*

Multivariate analysis showed malnutrition, severe sepsis/septic shock at admission, pulmonary complication as ARDS with PaO2 FiO2<200, Concominant bronchiectasis and history of previous hospitalization were independent predictors in-hospital mortality (Table 3).

MULTIVARIATE ANALYSIS OF IN HOSPITAL MORTALITY IN PATIENTS ENROLLED TO STUDY

Variables	**OR**	**95%CI**	**P**
Malnutrition	2.89	1.01-5.96	-0.012
Septic shock at admission	3.74	1.04-7.69	-0.004
ARDS with P/F<200	4.26	0.48-9.24	-0.002
History of previous hospitalization	3.26	1.46-7.52	-0.01
Presence of bronchiectasis	2.48	1.14-5.41	-0.019
MDR ***Actinobacter boumannii*** infection	3.4	1.2-7.6	- 0.01

OR for septic shock was 3.74([1.04- 7.69]; P=0.004); For ARDS with PaO2/FiO2<200 was 4.26 ([0.48-9.24]; P=0.002) for malnutrition 2.89 ([1.01-5.96],P=0012 for concominant BE 2.48 ([1.14-5.41];P= 0.019); an for previous frequent hospitalization was 3.26 ([1.46-7.52];p= 0.01) respectively. *Acinotebacter baumannii* infection was frequent among non-survivors with VAP (P=0.001 and all isolations related to this pathogen were multi-drug resistant (MBR). *Pseudomonas aeruginosa* was common. in patients with Concominant BE(p=0.001).

DISCUSSIONS

This single center retrospective study has shown that intubated COPD patients with VAP have specific risk factors associated with disease development and in-hospital mortality. By this study during five years period we identified baseline variables that are independently associated with death.

The development of VAP is a serious event during the ICU course in intubated patients and it may be associated with an increased risk of Fatal outcome. The development of VAP in intubated COPD patients is crucial because significance of anatomical and functional changes and to microbial colonization in airways. There has been established guidelines proposed by various scientific organizations for the prevention of the de development of VAP. However, despite these efforts, a large number of patients develop this complication. Finding the risk factors which may help in the Stratification of these patients with Further modification of their management strategy. Our study has demonstrated that malnutrition, SOFA Score at admission, vasopressor use at admission re-intubation, history of previous hospitalization, presence of bronchiectasis and history of pulmonary tuberculosis are predictors for the development of VAP in intubated COPD patients. The association of re-intubation and VAP has also been observed by other authers.There have been few other studies which hease reported an association between history of pulmonary TB and VAP. However, we have not found the studies which Suggested about association of bronchiectasis and VAD in intubated COPD patients, and it was Finding in our study. The possible explanation for the association of past TB and bronchiectasis and VAP seems underlying structural lung disease with microbial colonization which increases the propensity for the development of VAP. We have used bronchoscopic BAL, and endotracheal aspirate For microbiological identification of VAP in COPD patients.*Aciontebacter baumannii* was the most common isolate among patients with VAP in our study. Compared to other studies the gravity of this in our study pathogen as causative agent was higher

We have identified the predictors for fatal outcome in intubated COPD patients with VAP.

Malnutrition, septic shock at admission, ARDS with PaO2/FiO2<200, history of previous hospitalization, presence of concominant bronchiectasis in COPD patients, and

MDR *Acinotebacter baumannii* infection are strongly associated with an increased in hospital mortality in such patients and in a few studies we have found the similarity with our study. We Found their in this population, factors such as severe sepsis/ septic shock and PaO2/FiO2 <200 may play major role in predicting the risk of death.

Our study has also some limitations. First it has been performed in patients on based retrospective analysis, and we could not include specific predictors which can be more clearly explain the development of VAP and Fatal outcome in intubated COPD patients.

Second in our study the high. Frequency of MDR pathogens, particularly *Acinotebacter baumannii* in patients with etiological diagnosis may not be generalized to other ICU department with low prevalence of MDR pathogens.

Third we could not collect data baseline Functional capacity of VAP in COPD patients just due to it was retrospective study and even despite this we thought that these data would be useful to predict risk of death.

Our retrospective study provides to clinicians, especially to ICU department physicians a tool to approach to identify the in mortality risk in intubated COPD patients with VAP. Our study suggests that ARDS with P/F< 200, Septic shock and multi-drug resistant *Acinotebacter baumannii* infection in such patients are associated with poor patient outcomes and death risk. This, only the identification of patients with COPD who have intubated and are at high risk for develop of VAP with highest probability to die may help İCU clinicians and pulmonologists, to decide on the best management of VAP

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