EJTAS ISSN 2786-7447
EUROPEAN JOURNAL OF THEORETICAL AND APPLIED SCIENCES
OPEN ACCESS
PEER REVIEWED

Risk Factors Predicting in Hospital Mortality Among Intubated Patients with Exacerbation of Chronic Obstructive Pulmonary Disease Associated with Ventilation-Associated Pneumonia

Alizamin Sadigov, Rauf Baylarov, Malahat Sultanova,
Nilufer Aghazade, Namazli Nigar
Pulmonary and Critical Care department, Therapeutic and Education Clinic, Medical University of Azerbaijan, Baku city, Azerbaijan

Suggested Citation
Sadigov, A., Baylarov, R., Sultanova, M., Aghazade, N. & Nigar, N. (2023). Risk Factors Predicting in Hospital Mortality Among Intubated Patients with Exacerbation of Chronic Obstructive Pulmonary Disease Associated with Ventilation-Associated Pneumonia. *European Journal of Theoretical and Applied Sciences, 1*(4), 525-534.
DOI: 10.59324/ejtas.2023.1(4).47

Abstract:

Approximately every fourth patients with acute exacerbation of chronic obstructive pulmonary disease (AE COPD) will require intensive care unit (ICV) admission with further mechanical ventilation (MV) and therefore with high risk of development ventilator- associated pneumonia (VAP). VAP is the commonest ICU infection and results in increased morbidity/ mortality. 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 reduction of mortality. This retrospective study involved patients with AE of COPD who required MV and admitted in respiratory care unit at a University teaching Hospital from January 2017 to December 2022 various baseline demographic and clinical features were compared between patients with VAP and without VAP. Although various baseline demographic and clinical features were compared between survivors and non-survivors with VAP. The study included 164 intubated patients with AE of COPD with age of 60.42+ 8.44 years, 48 patients developed VAP. Multivariable analysis showed that severe sepsis/septic shock, pulmonary complications such as bilateral and multi-lobar lung infiltrates, malnutrition, concomitnant bronchiectasis and history of previous hospitalization were independent predictors in-hospital mortality in intubated COPD patients associated with VAP with odds ratio (95%) confidence interval of 3.74(1.04-7.69; p= 0.004), 4.26 (0.48-9.24: p= 0.002), 2.89(1.01- 5.96: p=0.012), 2.48 (1.14-5.41; p= 0.019), 3.26 (1.46-7.52;p= 0.01, respectively). *Acinotebacter baumannii* was the most common causative organism (n= 21: 43.7%) and was frequent finding among non-survivors with VAP.(p=0.001). All infections releated to Acinotebacter baumannii were multidrug resistant (MDR). Our retrospective study provide to clinicans and especially to ICU department physicians a tool approach to identify the mortality rosk of VAP complicated the intubated COPD patients. We found a high burden of concominant bronchiectasis releated to in hospital mortality and several other predictors associated with fatal outcomes, which could help identife found a high burden of concominant bronchiectasis releated to in hospital mortality and several other predictors associated with fatal outcomes, which could help identify patients who might benefit from adequate, early amprical antibiotic treatment, as well as, determine prognosis. Although prevention of malnutrition and exacerbations leading to hospitalization of COPD patients may associated with decreased fatal outcomes. Our findings should be validated by studies with larger samples of patients.

Keywords: *Chronic obstructive pulmonary disease, predictor, ventilator-associated pneumonia, pathogens, in hospital mortality.*

Introduction

Ventilator-associated pneumonia (VAP) is te second most common infection after urinary tract, acquired during stay in the intensive care unit (ICU) (Kalil et al., 2016). Risk factors which are associated with VAP varies and some of them are patient-spesific factors such as age and pre-existing lung disease (chronic obstructive pulmonary disease, COPD) (Cook et al., 1998). Other factors are care-releated factors, such as head- of the –bed angle, emergency intubation, aspiration, previous antibiotic treatment and reintubation (Morehead & Pinto, 2000). 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 increased risk of development VAP and average hospital stays (Hugonnet, Uçkay & Pittet, 2007).

The early recognition of patients at a high risk of developing VAP and subsequent prevention of its progression (Tejerina et al., 2006). Its progression are highly valiable in critical care units. There is no clearly evident regarding the impact of VAP o COPD patients, however, the existing limited number of studies suggests that VAP development results in higher mortality and longer duration of mechanical ventilation and ICV stay (Chastre & Fagon, 2002; Kollef et al., 2006; American Thoracic Society, & Infectious Diseases Society of America, 2005). Majority of patients with respiratory failure due to exacerbation of CPD may be managed with application of non-invasive ventilation (NIV) (Esper et al., 2006). However, a significant proportion of such patients requires endotracheal intubation and mechanical ventilation due to various causes. 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 (Papazian et al., 1996; Bregeon et al., 2001; Vincent et al., 2009).

Common pathogens causing VAP include *Pseudomonas aeruginosa, Acinotebacter baumanii, Klebsiella pneumonia* and *Staphulococcus aureus*. However, these causative agents of VAP may vary according to the study population and ICU setting (Hunter, 2012).

We planned this study with the purpose to describe the predictors for poor patient outcomes in intubated COPD patients whom developed VAP and modifiable risk factors for prevention of VAP and reduction of mortality rate.

Materials and methods

Study Design, Patients and Setting

This retrospective study was conducted between January 2017 and December 2022 with a pulmonary and critical care department of university hospital. All patients admitted with exacerbation of COPD and requiring mechanical ventilation for > 48 h were eligible for participation in the study. Diagnosis, exacerbations, ICU admission and invasive mechanical ventilation of COPD were based on the existing GOLD guidelines. Clinical diagnosis of VAP was based on criteria new or progressive infiltrate on chest radiograph (with no other possible causes such as cardiogenic pulmonary edema, atelectasis, and pulmonary embolism and at least two of following variables-fever > 38 C, leukocytosis > 12000/dl) or leukopenia (< 4000/ dl). Purulent secretions, isolation of causative pathogenic organism, or increased oxygen requirement (Shah, D'Cruz & Murphy, 2018; Kalanuria, Ziai & Mirski, 2014; Dhawan et al., 2015). The patients with clinical diagnosis of VAP underwent flexible bronchoscopy and bronco alveolar lavage in case broncoscopy was contraindicated, a patient underwent endotracheal aspirate (ETA) (Gadre et al., 2018). Microorganism stain and culture on appropriate media with thresholds of > 10^6 CFU/ml in sputum and ETA, and > 10^4 CFU/ml in BAL, and >10^3 in bronchial brush, respectively (Hadda et al., 2014).

Data Collection

All baseline demographic and clinical data were analyzed and recorded. Furthermore, data

recording use of vasopressors at admission, use of systemic corticosteroids prior to admission, number of exacerbation episodes in the past year which a patient required hospitalization, the albumin level of admission, use of antibiotics in the past 90 days and history of contaminant bronchiectasis were recorded.

Statistical Analysis

Data were managed on Excel spread-sheet and analyzed using statistical sofwave stata version 14 (Stata Corp, Texas, USA). Quantitative variables were expressed as mean + standard devation and median for normal and skewed data, respectively. Univariable analysis was done for identification of potential risk factors for the in hospital mortality of patients with VAP. Independent t-test (for normal data) and Mann-Whitney Utest for skewed data) were used to compare mean median valves between the groups. Change in mean was compares using paired t-test (for normal data/and Wilcoxon signed-rank test for skewed data). Fishers's exact test and Chi-square test were used to check that statistical significance for categorical variables. Stepwise multivariate logistic regression analysis was carried out taking pr0bability o removal as 0.1 and entry as 0.05 to find the independently associated factors responsible for in-hospital mortality o VAP developed in intubated patient with COPD and adjusted odds ratio was calculated. All tests were two-tailed and $p< 0.05$ was considered statistically significant.

Results

During the study period, 101 of 56 patients of COPD with exacerbation admitted to ICV required up front intubation and mechanical ventilation. NIV was initiate in 176 patients: among these, 63 failed NIV and subsequently required intubation. Oxygen therapy with requiring medications for COPD exacerbations have received 291 patients and among these, 8 failed with oxygen therapy and subsequently required NIV. This, a total of 164 patients were available or study. Patient recruitment has been shown in figure 1.

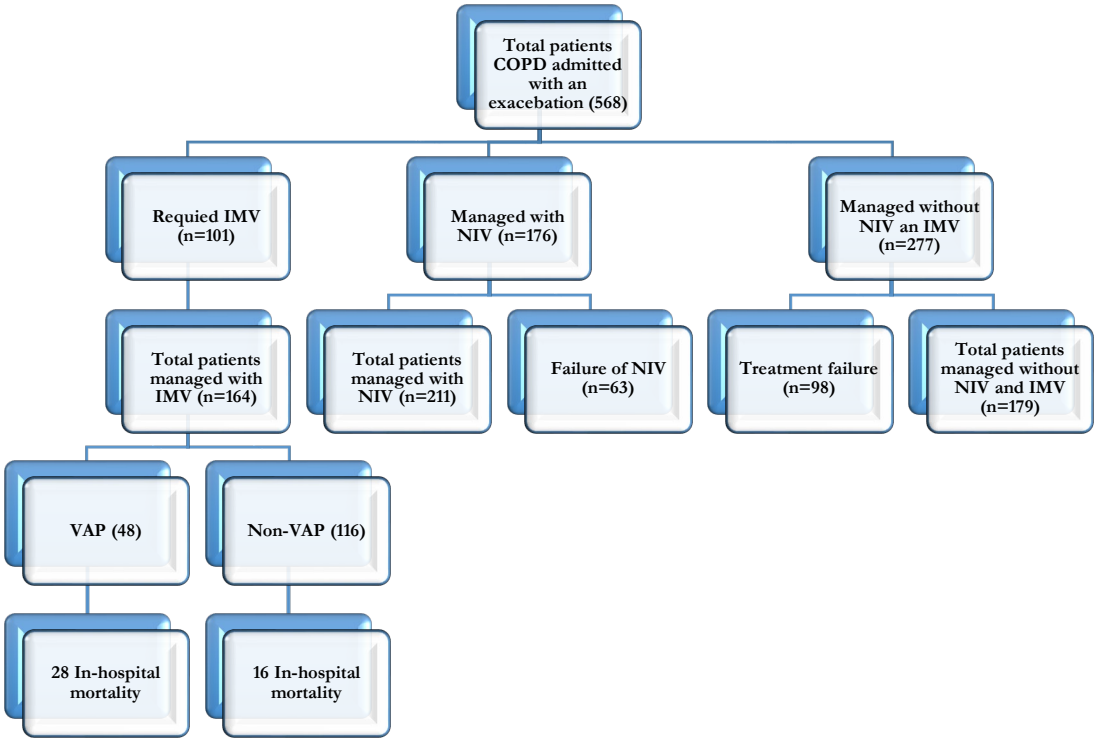

Figure 1. Flow Diagram Showing the Recruitment of the Patients

Median (IQR) duration of ICV stay was 10 (5.,4) days, and was higher in VAP group compared to non-VAP group (OR 2.14 [0.88-5.26]: p< 0/01). However, the median [IQR] time between hospitalization and intubation was not differ (p> 0.05). Among the study cohort, 48 patients developed VAP, and median [IQR] duration of endotracheal intubation before the development of VAP was 7 (4,11) days, however this time was longer among non-survivors (OR 1.90 [0.7-4.12]: p< 0.05). The overall in hospital mortality among intubated patients with acute exacerbation of COPD was 14% (n= 16/116), among patients with VAP who have died was 28 (58%) (Table 1)

Various clinical parameters were compared between patients having VAP and without VAP (Table 1).

Table 1. Baseline Clinical Characteristics Between Ventilator-Associated Pneumonia and Non Ventilator-Associated Pneumonia Developed in COPD Patients

Variables	COPD associated VAP (n=48)	COPD intubated without VAP (n=116)	P valve
Age, mean +/- SD years	61.12 +/- 8.19	60.9 +/- 8.46	0.270
Gender, n (%)			
Male	39 (81.2)	92 (79.3)	0.421
Female	9 (19.8)	24 (21.7)	0.379
BMI, at admission	20 +/-4	23 +/- 4	0.01
Smoking index, median (range)	380 (240-1300)	220 (180-700)	<0.001
Duration of COPD, median (range)	11 (5-17)	6 (2-14)	<0.001
Number of exacerbations in the past 1 year, median (range)	3 (1-5)	1 (0-3)	<0.001
Previous hospitalization for COPD ≥2, n (%)	40 (83)	38 (33)	<0.001
Indication of ET, n (%) NIV failure	29 (60.4)	34 (29.3)	0.01
Severe respiratory failure	19 (39.6)	82 (60.7)	<0.05
Coexisting bronchiectasis, n (%)	28 (58)	19 (16.4)	0.02
SOFA score at admission, mean +/- SD	8.16 +/-3.14	4.21 +/- 1.56	<0.001
Vasopressor use at admission, n (%)	29 (60)	16 (14)	0.003
Antibiotics use in the past 90 days, n (%)	35 (73)	37 (32)	0.02
Bilateral and multi-lobar pneumonia, n (%)	41 (85)	--	NA
In-hospital mortality, n (%)	28 (58)	16 (14)	0.002

Note: VAP: Ventilator-associated pneumonia; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; NIV: Non-invasive ventilation; ICU: Intensive care unit; SOFA: Sequental organ failure assessment; ET: Endotracheal.

Body mass index (BMI) was significantly lower in intubated but VAP developed COPD patients (p=0/01). Duration of COPD also significantly impact to the development of VAP in COPD patients (10[5-17]) vs 6 { 2-14}:p< 0.001) and long history with COPD with previous hospitalization rate >2 was predictable for development of VAP in case of intubation (p< 0.001). Indication for intubation also was differ between patients group and VAP group patients were intubated commonly related to NIV failure (p=0.01), However non –VAP group patients were intubated mostly related to severe respiratory failure with respiratory acidosis (arterial blood pH was < 7.25). Coexisting bronchiectasis(BE) was common presented finding among VAP patients-and has to be considerable as patient-specific risk factor for development of VAP in intubated COPD patients (p= 0.002}.

On univariate analysis, SOFA score at admission, use of vasopressor, concominant bronchiectasis, previous COPD exacerbations requiring hospitalization >2, antibiotis use in the

pat 90 days, use of systemic corticosteroids prior to current admission, low albumin level, and MDR pathogens associated with an increased risk or poor outcomes for patients (Table 2). ON multivariable analysis, use of vasopressors and septic shock at admission, coexisting BE, history of previous hospitalization >2 in the past year and low albumin level predicted the high risk of development VAP in COPD patients (Table 2).

Table 2. Predictors Associated with an Increased Risk of Development VAP in Intubated COPD Patients

Factor	OR (95%Y.Cl); P
Univariable analysis: SOFA score at admission	2.81 (1.10-5.21); <0.001
Vasopressor use at admission	4.96 (1.65-10.88); 0.005
Coexisting bronchiectasis	4.52 (1.26-10.26); <0.001
History of previous hospitalization ≥2 in the past year	5.21 (1.44-11.12); <0.001
Systemic corticosteroid use prior for admission	4.98 (1.68-10.32); <0.001
Antibiotic use in the past 90 days	3.21 (1.16-7.46); <0.04
Low Albumin level (<3.5 g/l)	3.94 (1.84-8.16); <0.001
Multivariable analysis: Septic shock and use of vasopressors	2.92 (1.19-6.24); 0.01
Coexisting bronchiectasis	3.98 (1.51-9.42); 0.02
History of previous hospitalization ≥2 in the past year	2.76 (1.12-6.41); <0.01
Malnutrition	2.16 (0.94-5.16); 0.01

Note: Odds ratio, Cl: Confidence interval.

Bronchoscopic (n=21) and non-bronchoscopic (endotracheal aspirate) (n=27) BAL were used for microbiological diagnosis of VAP. Microbiological etiology of VAP was established in 43/48 patients and all obtained microorganism were gram-negative. MDR pathogens were established in 38/43 (88.4%) cases (see Table 3).

A.baumanii was the most frequent organism (n=21: 43.7%) followed by ***Pseudomonas aeruginosa*** (n=16: 33.3%), ***K.pneumoniae*** (n=5: 10.4%) and ***Enterobacter spp.***(n=2: 4.2%).The prvelance of ***P.Aeruginesa*** causative agents was releated to high frequence of concurrent in bronchiectasis. ***Acinetobacter baumanii*** infection all causes was MDR and most frequent was among non-survival patients.

Table 3. Pathogens Isolation and its Impact to in Hospital Mortality Rate

MDR pathogen, n (%)	Survival VAP patients, n=20	No-survival VAP patients, n=28	P valve
Acinetobacter baumannii	3 (15%)	18 (64.3%)	0.001
Pseudomonas aeruginosa	7 (35%)	9 (32.1%)	0.21
Klebsiella pneumonia	2 (10%)	3 (10.7%)	0.44
Enterobacter spp.	2 (10%)	0	NA
No obtained	3	2	NA

The Cox regression model showed that the septic shock and use of vasoactive agents were associated with in hospital mortality (Table 4). Furthermore, the presence pulmonary complications of VAP such as plevral effusions, bilateral and multilobar lung infiltrates, Pa02/FiO2 < 200, age concomitant bronchiectasis and previous history of hospitalization >2 also were associated with in-hospital mortality.

We explored the comparison between PaO2/FiO2 <200 and bilateral and multi-lobar pneumonia pattern among patients and have found significant impact of pneumonia extension to the PaO2/FiO2 pattern in term on early recognition of acute respiratory distress syndrome (ARDS) in such patients (p= 0.01). Combination these two factors in VAP developed in COPD patients is strong predictor for in-hospital mortality.

Fiqure 2 shows Kaplan-Meier curves for the variables associated with in-hospital mortality.

Table 4. Multivariate Regression Analysis Predicting of in Hospital Mortality in VAP Developed in COPD Patients

Variables	OR	95% Cl	P
SOFA score at admission	3.74	1.04-7.69	0.004
History of previous hospitalizations ≥2	3.26	1.46-7.52	0.01
Use of vasopressors at admission	3.12	1.11-6.94	0.005
Coexisting bronchiectasis	2.48	1.14-5.41	0.019
Malnutrition	2.89	1.01-5.96	0.012
Bilateral and multi-lobar pneumonia	4.26	0.98-9.24	0.002
PaO2/FiO2 <200	3.74	1.15-8.16	0.001

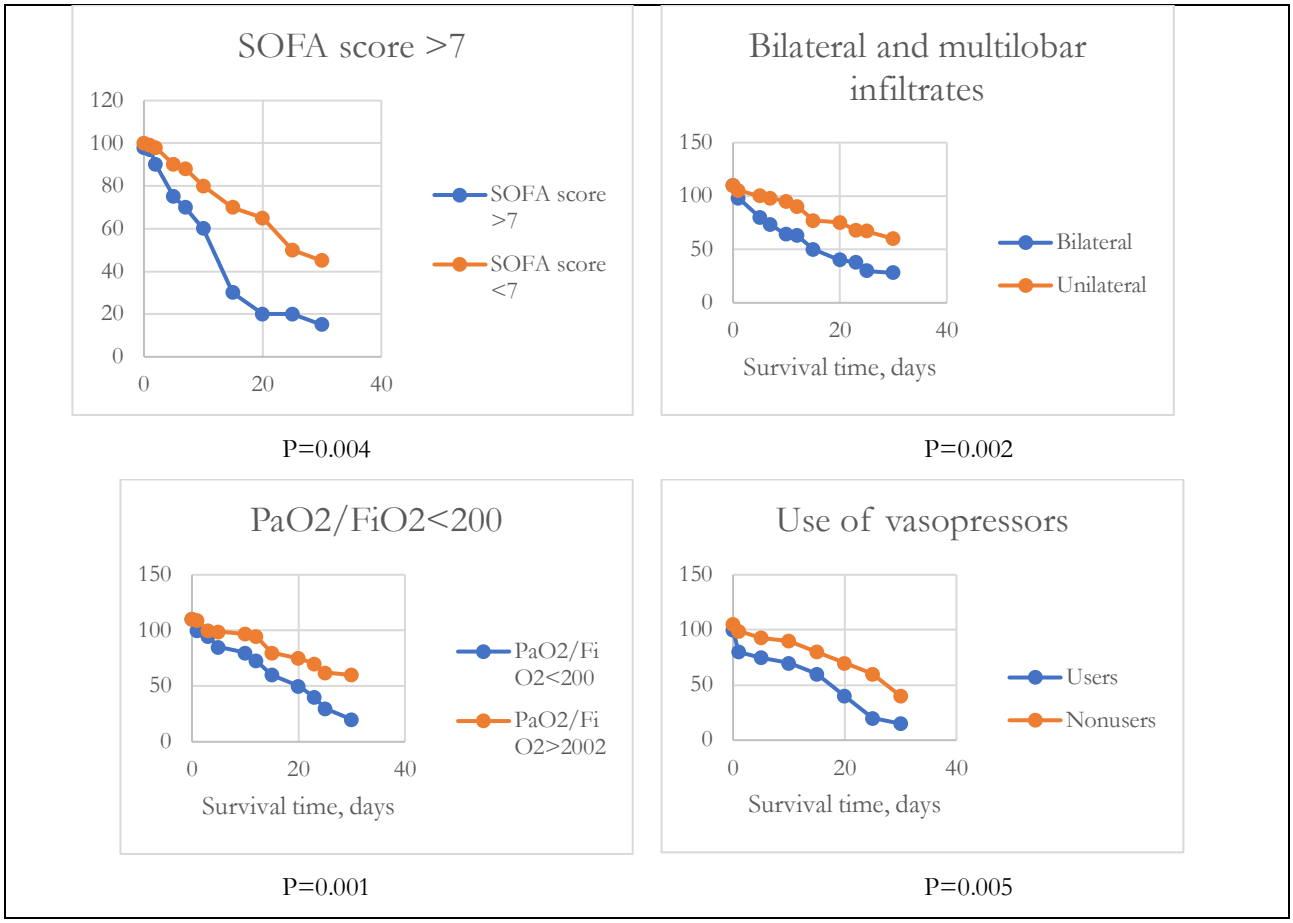

Figure2. Kaplan-Meier curves for Variables Associated with In-Hospital Mortality in Patients with Ventilator – Associated Pneumonia Developed in COPD Patients

Among patients who received vasoactive drugs, 22 (76%) had a bilateral and multilobar pneumonia and only 7 (24%) had a unilateral pneumonia (p<0.001). Among patients who had bilateral and multilobar pneumonia 27 (66%) had PaO2/FiO2 <200 and only 14 (34 %) had PaO2/FiO2>200 (p<0.002).

Discussion

We performed a retrospective analysis of VAP developed in intubated COPD patients.We found that,the SOFA score, the history of previous hospitalization >2 in the past year, use of vasopressor agents, concomitant bronchiectasis, malnutrition, bilateral and multi-lobar pneumonia and PaO2/FiO2 <200 were associated with an increased in hospital mortality.To our information,this is the study with one of cohorts of VAP developed in COPD patients on intubation,complicting of previously small studies and the first one to address medicators of in hospital mortality.The lack of information on this topic could be explain with lack of knowledges predictable risk factors for development the VAP in intubated COPD patients and misdiagnosis due to high frequency of other lung complications during MV in such patients.We decided to use mechanically ventilated COPD patients with developed VAP, because in a retrospective study it is easier to identify the predictors for responsible development of VAP and although to identify risk factors for in hospital mortality,in accordance with the definition of the National Association for Medical Direction of Respiratory Care (Wedzicha et al., 2017).

In our cohort, we found in intubated patients with COPD whom developed VAP a significant burden of coexisting BE. The high frequency of bronchiectasis probably explains the high number of MDR pathogens as causative agents of VAP in COPD patients and can be included as patient specific risk factor for development of VAP in COPD patients and as predictor for in-hospital mortality in such patients.

Regarding microbiological isolates all of the episodes of VAP in COPD patients in our study were caused by gram-negative pathogens, almost half of them being *Acinotebacter baumannii*, second common causative agent was *P.aeruginosa* corroborating one study on VAP intratracheostomized patients (Torres et al., 1990). In our study prior *P.aeruginesa* colonization of the airway was related to frequent coexisting BE, which was present in 28 (58%) patients with VAP. The high frequency of *A.baumannii* infection was related to colonization of this agent in ICU setting of hospital and it was independent risk factor for in hospital mortality in patients (p=0.001). The relationship between COPD and VAP has been studied to some extent: both conditions interact in number of levels: COPD patients on MV increased of VAP (Sadigov, Mamedova & Mammadov, 2019). COPD is an independent factor associated with increased mortality, longer length of MV, longer length of ICV stay, and higher rates of infection with pseudomonas aeruginosa in patients with VAP (Ahmed & Niederman, 2001; Kalil et al., 2016; Sadigov, 2020). However, we found association between coexisting bronchiectasis in COPD patients and in-hospital mortality (p=0.019). This is our new finding suggested the presence of bronchiectasis in intubated COPD patients may predict the development of VAP in such patients and may associated with in-hospital mortality.

The SOFA score is a useful tool for predicting mortality in critically ill patients and the initial SOFA score has been proven to have valve in predicting ICU mortality (Kobayashi et al., 2017). In our study SOFA score was associated with increased in-hospital mortality (p=0.004). However SOFA score may be more prognostic with complexity of use of vasopressor agents (Koulenti et al., 2019; Koulenti et al., 2015). In our cohort the interaction between SOFA score and use of vasopressor agents was higher in term on predicting of in-hospital mortality (p=0.002).

Conclusions

Our study has been shown that bilateral and multi-lobar extent of VAP in COPD patients was associated with increased risk of in-hospital mortality (p= 0.002) and this finding was first one to address predictors of in-hospital mortality. As known such patients with VAP are at high risk of development of ARDS (Sadigov, 2020) and assessment of another predictable risk factor PaO2\FiO2 ratio together with pneumonia extent significantly increased the predicting of in hospital mortality (Sadigov, Mamedova & Mammadov, 2019). In our study PaO2\FiO2 <200 was associated with significantly higher predicting of in hospital mortality and the correlation between bilateral multi-lobar lung infiltrates and PaO2\FiO2 <200 in term on predicting mortality risk was p< 0.002.

The present study has several limitations. First it is a study carried out in a single center. The settings of cares fore patients with intubated COPD may differ among other centers and have heteregenous populations second, the retrospective nature of the study may carry biases inherent to this type of design. Some variables and cofounders may not have been taken in to account given the difficulty of including them in a retrospective study. We have used Cox regression analysis, in which we cannot assess other variables such as antibiotic use prior to intubation or the presence of co infections, might have affected our results. Third, the definition used for VAP might have led to the inclussion of some patients with ventilator-associated tracheobronchitis in concominant pulmonary complications such as atelectasis and pulmonary oedema, which is a limitation inherent to the definition. Fourth, our sample size was somewhat small, and the results might not be fully generalizable for some of the findings. This highlights the need for multicenter studies that address the important aspects of VAP in COPD patients.

In conclusion, we found a high burden of concominant bronchiectasis in COPD patients, in our sample, in development of VAP and in-hospital mortality rates. We idenifired several factors associated with fatal outcomes, which could help identify patients who might benefit from nutritional support of appropriate, early empirical antibiotic treatment, as well as predict prognoses. These findings should be validated by studies with larger samples of patients.

References

Ahmed, Q. A., & Niederman, M. S. (2001). Respiratory infection in the chronically critically ill patient. Ventilator-associated pneumonia and tracheobronchitis. *Clinics in chest medicine, 22*(1), 71–85. https://doi.org/10.1016/s0272-5231(05)70026-5

American Thoracic Society, & Infectious Diseases Society of America (2005). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American journal of respiratory and critical care medicine*, *171*(4), 388–416. https://doi.org/10.1164/rccm.200405-644ST

Bregeon, F., Ciais, V., Carret, V., Gregoire, R., Saux, P., Gainnier, M., Thirion, X., Drancourt, M., Auffray, J. P., & Papazian, L. (2001). Is ventilator-associated pneumonia an independent risk factor for death?. *Anesthesiology, 94*(4), 554–560. https://doi.org/10.1097/00000542-200104000-00005

Chastre, J., & Fagon, J. Y. (2002). Ventilator-associated pneumonia. *American journal of respiratory and critical care medicine*, *165*(7), 867–903. https://doi.org/10.1164/ajrccm.165.7.2105078

Cook, D. J., Walter, S. D., Cook, R. J., Griffith, L. E., Guyatt, G. H., Leasa, D., Jaeschke, R. Z., & Brun-Buisson, C. (1998). Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Annals of internal medicine*, *129*(6), 433–440. https://doi.org/10.7326/0003-4819-129-6-199809150-00002

Dhawan, N., Pandya, N., Khalili, M., Bautista, M., Duggal, A., Bahl, J., & Gupta, V. (2015). Predictors of mortality for nursing home-acquired pneumonia: a systematic review. *BioMed research international, 2015*, 285983. https://doi.org/10.1155/2015/285983

Esper, A. M., Moss, M., Lewis, C. A., Nisbet, R., Mannino, D. M., & Martin, G. S. (2006). The role of infection and comorbidity: Factors that influence disparities in sepsis. *Critical care medicine*, *34*(10), 2576–2582. https://doi.org/10.1097/01.CCM.0000239114.50519.0E

Gadre, S. K., Duggal, A., Mireles-Cabodevila, E., Krishnan, S., Wang, X. F., Zell, K., & Guzman, J. (2018). Acute respiratory failure requiring mechanical ventilation in severe chronic obstructive pulmonary disease (COPD). *Medicine*, *97*(17), e0487. https://doi.org/10.1097/MD.0000000000010487

Hadda, V., Khilnani, G. C., Dubey, G., Nallan, R., Kumar, G., & Guleria, R. (2014). Impact of ventilator associated pneumonia on outcome in patients with chronic obstructive pulmonary disease exacerbation. *Lung India: official organ of Indian Chest Society*, *31*(1), 4–8. https://doi.org/10.4103/0970-2113.125886

Hugonnet, S., Uçkay, I., & Pittet, D. (2007). Staffing level: a determinant of late-onset ventilator-associated pneumonia. *Critical care (London, England)*, *11*(4), R80. https://doi.org/10.1186/cc5974

Hunter, J. D. (2012). Ventilator associated pneumonia. *BMJ (Clinical research ed.)*, *344*, e3325. https://doi.org/10.1136/bmj.e3325

Kalanuria, A. A., Ziai, W., & Mirski, M. (2014). Ventilator-associated pneumonia in the ICU. *Critical care (London, England)*, *18*(2), 208. https://doi.org/10.1186/cc13775

Kalil, A. C., Metersky, M. L., Klompas, M., Muscedere, J., Sweeney, D. A., Palmer, L. B., Napolitano, L. M., O'Grady, N. P., Bartlett, J. G., Carratalà, J., El Solh, A. A., Ewig, S., Fey, P. D., File, T. M., Jr, Restrepo, M. I., Roberts, J. A., Waterer, G. W., Cruse, P., Knight, S. L., & Brozek, J. L. (2016). Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *63*(5), e61–e111. https://doi.org/10.1093/cid/ciw353

Kalil, A., Klompas, M., Muscedere, J., Sweeney, D., Palmer, L., Napolitano, L., O'Grady, N., Bartlett, J., Carratalá, J., El Solh, A., Ewig, S., Fey, P., File, T., Restrepo, M., Roberts, J., Waterer, G., Cruse, P., Knight, S. & Brozek, J. (2016). Executive Summary: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia. *2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clinical Infectious Diseases*, *63*, 575-582. https://doi.org/10.1093/cid/ciw504

Kobayashi, H., Uchino, S., Takinami, M., & Uezono, S. (2017). The Impact of Ventilator-Associated Events in Critically Ill Subjects With Prolonged Mechanical Ventilation. *Respiratory care*, *62*(11), 1379–1386. https://doi.org/10.4187/respcare.05073

Kollef, M. H., Morrow, L. E., Niederman, M. S., Leeper, K. V., Anzueto, A., Benz-Scott, L., & Rodino, F. J. (2006). Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. *Chest*, *129*(5), 1210–1218. https://doi.org/10.1378/chest.129.5.1210

Koulenti, D., Blot, S., Dulhunty, J. M., Papazian, L., Martin-Loeches, I., Dimopoulos, G., Brun-Buisson, C., Nauwynck, M., Putensen, C., Sole-Violan, J., Armaganidis, A., Rello, J., & EU-VAP/CAP Study Group (2015). COPD patients with ventilator-associated pneumonia: implications for management. *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology*, *34*(12), 2403–2411. https://doi.org/10.1007/s10096-015-2495-6

Koulenti, D., Parisella, F. R., Xu, E., Lipman, J., & Rello, J. (2019). The relationship between ventilator-associated pneumonia and chronic obstructive pulmonary disease: what is the current evidence? *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology*, *38*(4), 637–647. https://doi.org/10.1007/s10096-019-03486-2

Morehead, R. S., & Pinto, S. J. (2000). Ventilator-associated pneumonia. *Archives of internal medicine*, *160*(13), 1926–1936. https://doi.org/10.1001/archinte.160.13.1926

Papazian, L., Bregeon, F., Thirion, X., Gregoire, R., Saux, P., Denis, J. P., Perin, G., Charrel, J., Dumon, J. F., Affray, J. P., & Gouin, F. (1996). Effect of ventilator-associated pneumonia on mortality and morbidity. *American journal of respiratory and critical care medicine, 154*(1), 91–97. https://doi.org/10.1164/ajrccm.154.1.8680705

Sadigov, A, Mamedova, I. & Mammadov, K. (2019). Ventilator-associated pneumonia and in-hospital mortality: Which risk factors may predict in-hospital mortality in such patients? *Journal of Lung Health and Diseases, 3*(4), 8-12. https://doi.org/10.29245/2689-999X/2019/4.1157

Sadigov, A. (2020). Predictors of in-hospital Mortality in patients with ventilator-associated pneumonia: Who is at risk for in-hospital mortality? *Chest Journal, 157*(6), A52. https://doi.org/10.1016/j.chest.2020.05.060

Shah, N. M., D'Cruz, R. F., & Murphy, P. B. (2018). Update: non-invasive ventilation in chronic obstructive pulmonary disease. *Journal of thoracic disease, 10*(Suppl 1), S71–S79. https://doi.org/10.21037/jtd.2017.10.44

Tejerina, E., Frutos-Vivar, F., Restrepo, M. I., Anzueto, A., Abroug, F., Palizas, F., González, M., D'Empaire, G., Apezteguía, C., Esteban, A., & Internacional Mechanical Ventilation Study Group (2006). Incidence, risk factors, and outcome of ventilator-associated pneumonia. *Journal of critical care*, *21*(1), 56–65. https://doi.org/10.1016/j.jcrc.2005.08.005

Torres, A., Aznar, R., Gatell, J. M., Jiménez, P., González, J., Ferrer, A., Celis, R., & Rodriguez-Roisin, R. (1990). Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *The American review of respiratory disease, 142*(3), 523–528. https://doi.org/10.1164/ajrccm/142.3.523

Vincent, J. L., Rello, J., Marshall, J., Silva, E., Anzueto, A., Martin, C. D., Moreno, R., Lipman, J., Gomersall, C., Sakr, Y., Reinhart, K., & EPIC II Group of Investigators (2009). International study of the prevalence and outcomes of infection in intensive care units. *JAMA, 302*(21), 2323–2329. https://doi.org/10.1001/jama.2009.1754

Wedzicha, J. A., Ers Co-Chair, Miravitlles, M., Hurst, J. R., Calverley, P. M., Albert, R. K., Anzueto, A., Criner, G. J., Papi, A., Rabe, K. F., Rigau, D., Sliwinski, P., Tonia, T., Vestbo, J., Wilson, K. C., & Krishnan, J. A., Ats Co-Chair (2017). Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *The European respiratory journal, 49*(3), 1600791. https://doi.org/10.1183/13993003.00791-2016