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Evaluation of Ventilator-Associated Pneumonia Risk Factors and Pathogens in COVID-19 Patients: A Retrospective Study

COVID-19 Hastalarında Ventilatör İlişkili Pnömoni Risk Faktörleri ve Patojenlerin Değerlendirilmesi: Retrospektif Bir Çalışma

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ABSTRACT

AIM: Many patients followed in intensive care units during the COVID-19 pandemic required mechanical ventilation. In the present study, the purpose was to examine the risk factors, frequency, and causative pathogens of ventilator-associated pneumonia in COVID-19 patients in intensive care units.

MATERIAL AND METHOD: The study had a retrospective study design and was conducted among COVID-19 patients followed in the tertiary intensive care units of a training and research hospital. COVID-19 patients, who were older than eighteen years, and intubated in the tertiary intensive care units between March 2020 and January 1, 2021, were included in the present study. Microbiological data such as positive endotracheal aspirate cultures, infectious microorganisms, and antibiotic susceptibility were collected from the patient files. Univariate and Multivariate Binary Logistic Regression analysis were used to determine the risk factors effective in ventilator-associated pneumonia.

RESULTS: Ventilator-associated pneumonia was observed in 52.9% (108) of patients, which was confirmed by growth in endotracheal aspirate cultures. The length of hospital stay (17.56±14.09) and mechanical ventilation (14.55±11.66) (day) of the patients who had culture growth were significantly longer than the length of hospital stay (9.74±6.01) and mechanical ventilation (7.12±4.32) (day) of the patients without growth (P<0.001, P<0.001, respectively).

CONCLUSION: In conclusion, as the ventilator-associated pneumonia was evaluated in intensive care patients who were intubated during the COVID-19 pandemic, it was found that the most important predictive factor for ventilator-associated pneumonia was the duration of mechanical ventilation. Acinetobacter baumannii was detected to be the most common causative pathogen in the study.

Keywords: COVID-19, SARS-CoV-2, Nosocomial infections, Ventilator-associated pneumonia, Critical care

ÖZET

AMAÇ: COVID-19 pandemisi esnasında yoğun bakımlarda takip edilen hastaların çoğunda mekanik ventilasyon gerekliliği ortaya çıkmıştır. Bu çalışmada yoğun bakım ünitelerindeki COVID-19 hastalarında ventilatör ilişkili pnömonilerin risk faktörlerinin, sıklığının ve etkenlerinin incelenmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Bu çalışma retrospektif bir tasarıma sahiptir ve bir eğitim araştırma hastanesinin 3. Basamak yoğun bakımlarında takip edilen COVID-19 hastaları arasında yapılmıştır. Çalışmaya Mart 2020 ile 1 Ocak 2021 arasında 3. Basamak yoğun bakımlarda entübe olarak takip edilen on sekiz yaşından büyük COVID-19 hastaları dahil edildi. Hasta dosyalarından endotrakeal aspirat kültürlerindeki üremeler, enfeksiyöz mikroorganizmalar ve antibiyotik duyarlılıkları gibi mikrobiyolojik veriler toplandı. Ventilatör ilişkili pnömonide etkili olan risk faktörlerini belirlemek için tek değişkenli ve çok değişkenli ikili Lojistik Regresyon analizi kullanıldı.

BULGULAR: Hastaların %52.9 (108)'unda ventilatör ilişkili pnömoni görüldü ve endotrakeal aspirat kültürlerindeki üreme ile doğrulandı. Kültürde üreme görülen hastaların hastane yatış (17.56±14.09)(gün) ve entübe takip süreleri (14.55±11.66) (gün) üreme görülmeyen hastaların hastane yatış (9.74±6.01) ve entübe takip (7.12±4.32) sürelerinden anlamlı yüksek bulundu (sırasıyla, P<0.001, P<0.001).
Sonuç: Sonuç olarak, COVID-19 pandemisinde entübe yoğun bakım hastalarında ventilatör ilişkili pnömonilerin irdelendiği bu çalışmada en önemli prediktif faktörün mekanik ventilasyon süresi olduğu saptandı. Çalışmada en sık etkenin Acinetobacter baumannii olduğu tespit edildi.

Anahtar Kelimeler: COVID-19, SARS-CoV-2, hastane enfeksiyonları, ventilatör ilişkili pnömoni, yoğun bakım.

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INTRODUCTION

The COVID-19 pandemic, which started in China in 2019 and spread to the entire world, affected the lives of millions of people. There was an unexpected and unavoidable increase in hospital and intensive care hospitalizations all over the world during the COVID-19 pandemic. Many patients followed up in intensive care units (ICU) required mechanical ventilation.[1] Prolonged mechanical ventilation periods because of respiratory failure cause an increased risk of ventilator-associated pneumonia in intensive care patients[2]. The most common hospital-acquired infection in mechanically ventilated patients is ventilator-associated pneumonia (VAP)[3]. With the increased hospital and intensive care hospitalizations, increases were inevitable in secondary bacterial infections and antibiotic use during the COVID-19 pandemic. The use of broad-spectrum empirical antibiotics in these patients is considered to increase the incidence of infections with agents with multiple antibiotic resistance[4]. It is also considered that steroids and other anti-cytokine treatments used to suppress cytokine storm in these patients may predispose them to secondary infections[5], [6]. Based on these considerations, in this study, the purpose was to examine the frequency, predictive factors, and causative pathogens of ventilator-associated pneumonia in COVID-19 patients who were diagnosed as PCR positive in our hospital and were observed intubated in the ICU.

MATERIAL AND METHOD

The study had a retrospective cohort study design and was conducted among COVID-19 patients followed in the tertiary intensive care units of a training and research hospital. The Karamanoglu Mehmetbey University Faculty of Medicine Ethics Committee approved this study (28.03.2022, 02-2022/14). Since the study was retrospective, informed consent was waived. The study included COVID-19 patients, who were older than 18 years, and intubated in the tertiary intensive care units between March 2020 and January 1st, 2021. Patients with positive SARS-CoV-2 nasal swab PCR test results were enrolled in the study, patient records were reviewed, and demographics such as age, sex, and comorbidities were collected. Microbiological data such as growths in endotracheal aspirate (ETA) cultures, infectious microorganisms, and antibiotic susceptibility were collected from the patient files. The diagnosis of pneumonia was made based on radiological and microbiological data in the presence of at least two of the following criteria; body temperature above 38.5°C or below 36.5°C, leukocyte count greater than 12000 cells per µL or less than 4000 cells per µL, and purulent tracheal secretions7. The diagnosis of VAP was considered as pneumonia developing at least 48 hours after the intubation in a patient who did not have pneumonia during intubation and was supported by invasive mechanical ventilation8. Gram staining, quantitative microbiological culture and susceptibility tests of the pathogens, and direct microscopic examinations of endotracheal aspirate samples were made in the microbiology laboratory. The presence of growth was diagnosed in the samples that had at least 105 colony-forming units (CFU) isolation per milliliter (mL) in ETA culture[7], [8].

The steroid and anti-cytokine treatments taken by the patients for the treatment of COVID-19 were also recorded. Those who were intubated in the intensive care unit for at least three days were enrolled in the study, and patients who had shorter intensive care stays were not enrolled. Infection findings and culture growths occurring at least 48 hours after admission to the ICU were considered infections that originated from the ICU. The APACHE II prognostic score was calculated for all patients at the time of admission to the ICU. All patients were evaluated for VAP by the same consultant infection specialist. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analysis of the data was performed using the SPSS (Version 22, SPSS Inc., Chicago, IL, USA) software. The normal distribution of the data was evaluated with the Shapiro-Wilk test. Means and standard deviations were used to provide descriptive statistics for numerical data. Categorical variables were presented as numbers (n) and percentages (%). Comparisons of proportion between categorical variables were performed using the Pearson Chi-square test or Fisher`s exact test, depending on sample sizes in the cross-tab cells. Two independent groups' normally distributed data were compared using the Student's t-test, and non-normally distributed data were compared using the Mann-Whitney U-Test. The risk factors effective in VAP were identified using univariate and multivariate binary logistic regression analysis. For each parameter identified in the Binary Logistic Regression study as statistically significant, Odds Ratios (OR) with 95% Confidence Intervals were generated. Limits of statistical significance were defined as P <0.05.

RESULTS

The data obtained from a total of 204 patients were analyzed. The descriptive statistics on the sociodemographic and clinical characteristics of the patients are given in Table 1.

Table 1. Descriptive statistics for the demographic and clinical characteristics of the patients (n=204)

Variables	(n=204)	Percentages (%)
Gender		
Male	116	56.9%
Female	88	43.1%
Chronic Disease		
Yes	172	84.3%
No	32	15.7%
DM		
Yes	71	34.8%
No	133	65.2%
HT		
Yes	111	54.4%
No	93	45.6%
CAD		
Yes	46	22.5%
No	158	77.5%
CHF		
Yes	21	10.3%
No	183	89.7%
COPD		
Yes	26	12.7%
No	178	87.3%
CKD		
Yes	13	6.4%
No	191	93.6%
Alzheimer's Disease		
Yes	9	4.4%
No	195	95.6%
CVD		
Yes	11	5.4%
No	193	94.6%
Dexamethasone		
Yes	39	19.1%
No	165	80.9%
Lowdose Methyl Prednisolone		
Yes	19	9.3%
No	185	90.7%
HighdoseMethyl Prednisolone		
Yes	30	14.7%
No	174	85.3%
Tocilizumab		
Yes	20	9.8%
No	184	90.2%
Growth in ETA cultures		
Yes	108	52.9%
No	66	32.4%
Failed to obtain	30	14.7%
Variables	**Mean Values**	**±standard deviation (min-max)**
Age	73.55	±11.36 (39-96)
APACHE score	23.34	±8.25 (10-51)
Length of hospital stay (days)	13.44	±11.71 (4-90)
Intubated follow-up time (days)	10.82	±9.69 (3-83)
Growth date in culture (which day of intubation) (n=108)	7.66	±4.81 (3-27)
Total	**204**	**(%100)**

Categorical data are presented as the frequency (percentage)

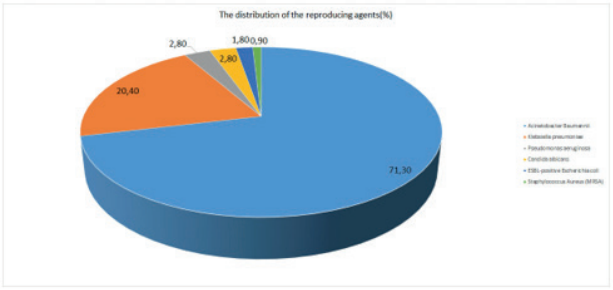
Numerical data are presented as the mean±standard deviation (min-max

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, CVD: Cerebrovascular Disease, ETA: Endotracheal aspirate

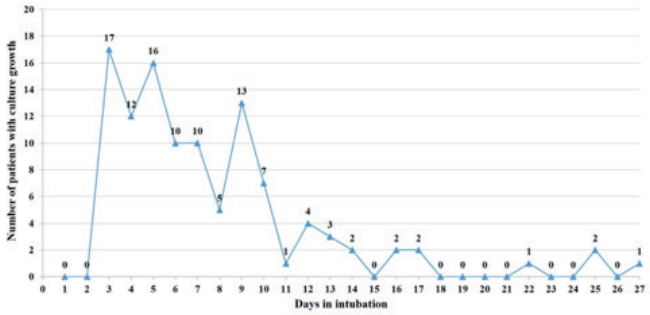
Endotracheal aspirate (ETA) cultures reproduced in 52.9% (108) of the patients, no growth was detected in 32.4% (n=66) of the patients, and culture was not obtained from 30 patients. The mean age and APACHE Scores of the patients with VAP and those without VAP were not significantly different (P=0.147, P=0.973, respectively). The time of hospitalization (17.56 ± 14.09)(days) and intubation period (14.55 ± 11.66) of the patients with VAP were significantly longer than thetime of hospitalization (9.74 ± 6.01) and intubation period (7.12 ± 4.32)(days) of the patients without VAP (P<0.001, P<0.001, respectively). The intubation period of the patients with chronic di-

sease (10.34 ± 9.76) were significantly lower than those without the chronic disease (13.44 ± 9.04) (P=0.002).

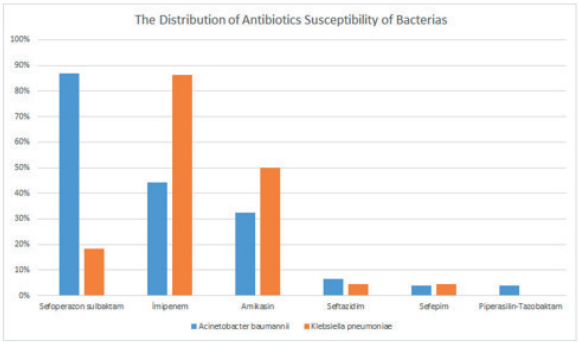
The distribution of the microorganisms in patients with growth in culture is given in



Graphic 1. The distribution of the microbial agents grown in the cultures of the patients
Graphic 1
on a pie chart. The number of culture growths in all patients according to days of intubation is shown in



Graphic 2. The number of patients who had culture growth on the day of intubation
Graphic 2
with a line graph. Culture growth was detected at the most on the third day in 17 patients. ETA culture growth was detected in 52.9% (n=108) of the patients. The mean growth time in culture (the day of intubated follow-up) was 7.66 ± 4.81 days (3-27). The most common pathogen in ETA cultures was Acinetobacter baumannii (n=77, 71.3%). The sensitivity rates of pathogens grown in cultures to antibiotics are given in



Graphic 3. The distribution of antibiotic susceptibility of bacteria
Graphic 3.
Among the pathogens, 87% (67) of Acinetobacter baumannii were sensitive to Cefoperazone sulbactam, and among the Klebsiella pneumoniae, 86.4% (19) were susceptible to Imipenem. The pathogens were resistant to the other antibiotics (i.e., Amoxicillin-Clavulanate, Ceftriaxone, Cefuroxime-Axetil, Ciprofloxacin, Trimethoprim-Sulfametaxazole, and Cefoxitin) whose sensitivity was evaluated in our hospital.

Statistical results about the relationship between sociodemographic and clinical characteristics of the patients and culture growth are given in Table 2. The incidence of VAP in patients with at least one chronic disease (58%) was significantly lower than patients without chronic conditions (80.6%) (P=0.019). The incidence of VAP in patients with CHF (35%) was found to be significantly lower than patients without CHF (65.6%) (P=0.008). The incidence of VAP was similar in the other disease groups in this study, except for CHF (Table 2).
Table 2. Statistical results of the relationship between socio-demographic and clinical characteristics and ventilator-associated pneumonia

Variables		Ventilator-associated pneumonia			*P* values
		Yes (%)	No (%)	Total (100%)	
Gender	Male	67 (65)	36 (35)	103	0.329[a]
	Female	41 (57.7)	30 (42.3)	71	
Chronic Disease	Yes	83 (58)	60 (42)	143	**0.019[a]**
	No	25 (80.6)	6 (19.4)	31	
DM	Yes	33 (61.1)	21 (38.9)	54	0.861[a]
	No	75 (62.5)	45 (37.5)	120	
HT	Yes	54 (58.7)	38 (41.3)	92	0.331[a]
	No	54 (65.9)	28 (34.1)	82	
CAD	Yes	24 (58.5)	17 (41.5)	41	0.594[a]
	No	84 (63.2)	49 (36.8)	133	
CHF	Yes	7 (35)	13 (65)	20	**0.008[a]**
	No	101 (65.6)	53 (34.4)	154	
COPD	Yes	14 (63.6)	8 (36.4)	22	0.871[a]
	No	94 (61.8)	58 (38.2)	152	
CKD	Yes	2 (25)	6 (75)	8	0.055[b]
	No	106 (63.9)	60 (36.1)	166	
Alzeihmer	Yes	5 (83.3)	1 (16.7)	6	0.410[b]
	No	103 (61.3)	65 (38.7)	168	
CVD	Yes	7 (70)	3 (30)	10	0.744[b]
	No	101 (61.6)	63 (38.4)	164	
Dexamethasone	Yes	29 (78.4)	8 (21.6)	37	**0.021[a]**
	No	79 (57.7)	58 (42.3)	137	
Low dose Methyl Prednisolone	Yes	12 (70.6)	5 (29.4)	17	0.446[a]
	No	96 (61.1)	61 (38.9)	157	
High dose Methyl Prednisolone	Yes	15 (51.7)	14 (48.3)	29	0.208[a]
	No	93 (64.1)	52 (35.9)	145	
Tocilizumab	Yes	15 (75)	5 (25)	20	0.205[a]
	No	93 (60.4)	61 (39.6)	154	
Total		108	66	174	

[a]Chi-Square test

[b]Fisher exact test

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, CVD: Cerebrovascular Disease

The incidence of VAP in patients who received dexamethasone treatment (78.4%) was found to be significantly higher than the rate of VAP (57.7%) in patients who were not treated with dexamethasone (P=0.021). The incidence of VAP was statistically similar in patients who received and did not receive low-dose methylprednisolone, high-dose methylprednisolone, and tocilizumab treatment (P=0.446, P=0.208, P=0.205, respectively; Table 2).

Results of univariate and multivariate logistic regression analysis performed to determine the effects of intubation period, presence of chronic disease, and dexamethasone treatment, which were statistically and significantly associated with ventilator-associated pneumonia, are given in Table 3.

Table 3. Results of univariate and multivariate logistic regression analysis performed to determine the risk factors effective in the occurrence of ventilator-associated pneumonia

	Univariate		Multivariate	
	P values	OR (CI 95%)	*P* values	OR (CI 95%)
Intubation period	<0.001	1.21 (1.12 – 1.32)	<0.001	1.19 (1.1 – 1.29)
Chronic Disease no / yes	0.023	3.01 (1.16 – 7.79)	0.178	-
Dexamethasone yes / no	0.024	2.66 (1.13 – 6.24)	0.173	-
Nagelkerke R Square: 0.303, Classification success of multivariate model: 72.4%				

OR: Odds Ratio, CI: Confidence Interval,

Intubation period, presence of chronic disease, and dexamethasone treatment were significant in the univariate model. Only intubation period was found to be important in the multivariate model. Chronic disease status and the effect of dexamethasone treatment were insignificant according to the results of the multivariate model (P=0.178, P=0.173), and the impact of intubation period was significant (P< 0.001: OR: 1.19 (1.1 - 1.29)). One-day increase in the intubated follow-up period increased the probability of VAP by 1.19 times (19%).

DISCUSSION

In the present study, in which ventilator-associated pneumonia was examined in intensive care patients who were intubated during the COVID-19 pandemic, the most important risk factor was found to be the duration of mechanical ventilation. A 1-day increase in the intubated follow-up period caused a 1.19-fold (19%) increase in the incidence of VAP. Ventilator-associated pneumonia was detected in 52.9% (108) of the patients clinically and microbiologically, and Acinetobacter baumannii was found to be the most common causative agent. When the antibiotic sensitivity of this pathogen was examined, it was found that the highest sensitivity rate (87%) was in Cefoperazone sulbactam.

Ventilator-associated pneumonia (VAP) was detected in 52.9% (108) of the patients in the present study. Considering that the incidence of VAP seen in the normal population was 9-27%, the rate in the present study was quite high3. In previous studies conducted on COVID-19 patients, VAP was detected at rates ranging from 48-86% 9-13. The frequency of VAP in this study was similar to the rate reported in the study of Llitjos et al.(52%) 11. In another study, the rate of VAP was found to be 64% in COVID-19 patients12. Also, in a study that investigated the frequency of VAP in COVID-19 patients undergoing extracorporeal membrane oxygenation (ECMO), it was shown that this rate could be as high as 86%13. The differences in these results between hospitals and countries; may depend on different local factors such as antibiotic regimens used, quality of healthcare, diagnostic criteria, and antimicrobial resistance patterns.

A significant relationship was found in the study of Blonz et al. between the male gender and the incidence of VAP. However, gender had no effect on the occurrence of VAP in the present study9. Although it is expected that the incidence of VAP is higher in patients with chronic disease, it was found that the rate of VAP development was lower in patients with at least one chronic disease in our study. It was considered that the reason for this was that COVID-19 patients who had chronic diseases lost their lives in a shorter time because of the high mortality in patients who had chronic diseases. It was considered that the shorter intubation follow-up period in COVID-19 patients who had chronic diseases compared to COVID-19 patients without chronic diseases was effective in this outcome.

The prolonged mechanical ventilation time, steroid therapy, and anti-cytokine treatments may be responsible for these high rates[14, 15]. As seen in this study, the prolongation of mechanical ventilation in patients increases the occurrence of VAP. Also, it was considered that following the patients in the prone position on a mechanical ventilator during the treatment also increases the occurrence of VAP15. On the other hand, the suppression of the immune system caused by COVID-19 might also have been effective in these results. Previous studies showed that COVID-19 suppresses the immune system, especially with its effects on lymphocytes[16, 17]. Culture growth was detected most on the third day in our study. It was thought that such early occurrence of ventilator-associated pneumonia may be due to the suppression of the immune system and damage to the lung tissue due to COVID-19[18].

Although many benefits of using steroids were seen in the treatment of COVID-19 in previous studies[19-21], there is an opinion that it may also predispose to infection[14, 22]. In the present study, VAP development was found to be higher in patients receiving dexamethasone treatment when compared to the group that was not treated with dexamethasone (78.4% vs 57.7%). However, as seen in the multivariate logistic regression analysis results in our study, it was found that dexamethasone treatment had no effects on the occurrence of VAP. Dexamethasone treatment for COVID-19 in a recent study did not result in an increase in ICU acquired infections[23]. The results found in our study are similar to the results of this study.

Although Pseudomonas aeruginosa and Klebsiella pneumoniae were prominent as causative pathogens in ventilator-associated pneumonia in the pre-COVID-19 period3, Acinetobacter baumannii became prominent during the COVID-19 pandemic[14, 22, 24, 25, 26]. The most common pathogens were found to be Acinetobacter baumannii (n=77, 71.3%), Klebsiella pneumoniae (n=22, 20.4%), and Pseudomonas aeruginosa (n=3, 2.8%), respectively in the present study. The results in our study were similar to the previous studies in the literature.

In a previous study, the rate of lower respiratory tract infections because of Acinetobacter baumannii was reported to be as high as 1% of all the patients who should stay in an Italian hospital due to COVID-1927. Acinetobacter baumannii can be colonized, especially in the hands of healthcare professionals in intensive care units[28]. Healthcare staff had to use protective equipment such as gloves, masks, and overalls for a long time to protect themselves during the pandemic. Also, to reduce the contamination to the personnel in wards and ICU, the shifts were divided into long periods and it was aimed to benefit from the protective equipment for a maximum period. Again, drugs and infusions were not prepared at the bedside but were prepared in the collective areas of the ICU to stay behind the patient less. When all these are considered together, multi-drug-resistant microorganisms that can colonize in the hands of healthcare staff may have found the opportunity to be transmitted more frequently. These reasons may be the explanation for the high rates in the present study. The rate of transmission from healthcare staff can be reduced if the right practices are carried out to reduce healthcare-associated infections.

When the antibiotic susceptibilities in the data were examined, it was found that the majority of Acinetobacter baumannii that reproduced in cultures were sensitive to at least one or two of the Cefoperazone sulbactam, Imipenem and Amikacin triads. Among these, Cefoperazone sulbactam had the highest sensitivity rate. Also, it was found that the agent was resistant to most of the other antibiotics (Amoxicillin-Clavulanate, Ceftriaxone, Cefuroxime-Axetil, Ciprofloxacin, Trimethoprim-Sulfametaxazole, Cefoxitin).

In this study, with the data at the beginning of the COVID-19 Pandemic, the frequency, causative agents, and antibiotic susceptibilities of VAP in ICUs of our hospital were determined. According to these results, our empirical antibiotic choices were reviewed in our hospital for VAP patients and an attempt was made to increase the effectiveness of antibiotic treatment. Although we know that these data cannot be generalized to all hospitals; these data can provide an idea for our colleagues regarding both pathogens and antibiotic sensitivity.

This study had some limitations. The results of the study include the data of the COVID-19 intensive care unit patients of only one hospital in our country. For this reason, since the results obtained depend on the local conditions of our hospital, they cannot be generalized for other hospitals in our country and the world. Also, the results may change in further studies to be conducted after vaccination because the present study was performed before the administration of COVID-19 vaccines.

CONCLUSION

In conclusion, it was found that the most important risk factor was the duration of mechanical ventilation for ventilator-associated pneumonia, which was examined in intensive care patients intubated during the COVID-19 pandemic. Also, Acinetobacter baumannii was found to be the most common causative microorganism in the study.

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REFERENCES

1.Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574-81.

2.Vincent JL, Sakr Y, Singer M, et al. Prevalence and Outcomes of Infection Among Patients in Intensive Care Units in 2017. JAMA. 2020;323(15):1478-87.

3.Hunter JD. Ventilator associated pneumonia. BMJ. 2012;344:e3325.

4.Lima WG, Brito JCM, da Cruz Nizer WS. Ventilator-associated pneumonia (VAP) caused by carbapenem-resistant Acinetobacter baumannii in patients with COVID-19: Two problems, one solution? Med Hypotheses. 2020;144:110139.

5.Bartoletti M, Pascale R, Cricca M, et al. Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study. Clin Infect Dis. 2021;73(11):e3606-e3614.

6.Gregoire E, Pirotte BF, Moerman F, et al. Incidence and Risk Factors of COVID-19-Associated Pulmonary Aspergillosis in Intensive Care Unit-A Monocentric Retrospective Observational Study. Pathogens. 2021;10(11):1370.

7.Martin-Loeches I, Povoa P, Rodríguez A, et al. Incidence and prognosis of ventilator-associated tracheobronchitis (TAVeM): a multicentre, prospective, observational study. Lancet Respir Med. 2015;3(11):859-68.

8.Kalil AC, Metersky ML, Klompas M, et al. 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. Clin Infect Dis. 2016;63(5):e61-e111.

9.Blonz G, Kouatchet A, Chudeau N, et al. Epidemiology and microbiology of ventilator-associated pneumonia in COVID-19 patients: a multicenter retrospective study in 188 patients in an un-inundated French region. Crit Care. 2021;25(1):72.

10.Maes M, Higginson E, Pereira-Dias J, et al. Ventilator-associated pneumonia in critically ill patients with COVID-19. Crit Care. 2021;25(1):25.

11.Llitjos JF, Bredin S, Lascarrou JB, et al. Increased susceptibility to intensive care unit-acquired pneumonia in severe COVID-19 patients: a multicentre retrospective cohort study. Ann Intensive Care. 2021;11(1):20.

12.Razazi K, Arrestier R, Haudebourg AF, et al. Risks of ventilator-associated pneumonia and invasive pulmonary aspergillosis in patients with viral acute respiratory distress syndrome related or not to Coronavirus 19 disease. Crit Care. 2020;24(1):699.

13.Luyt CE, Sahnoun T, Gautier M, et al. Ventilator-associated pneumonia in patients with SARS-CoV-2-associated acute respiratory distress syndrome requiring ECMO: a retrospective cohort study. Ann Intensive Care. 2020;10(1):158.

14.Giacobbe DR, Battaglini D, Enrile EM, et al. Incidence and Prognosis of Ventilator-Associated Pneumonia in Critically Ill Patients with COVID-19: A Multicenter Study. J Clin Med. 2021;10(4):555.

15.Ippolito M, Misseri G, Catalisano G, et al. Ventilator-Associated Pneumonia in Patients with COVID-19: A Systematic Review and Meta-Analysis. Antibiotics (Basel). 2021;10(5):545.

16.Jamilloux Y, Henry T, Belot A, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev. 2020;19(7):102567.

17.Wang F, Nie J, Wang H, et al. Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia. J Infect Dis. 2020;221(11):1762-9.

18.Rendeiro AF, Ravichandran H, Bram Y, et al. The spatial landscape of lung pathology during COVID-19 progression. Nature. 2021;593(7860):564-9.

19.Fadel R, Morrison AR, Vahia A, et al. Early Short-Course Corticosteroids in Hospitalized Patients With COVID-19. Clin Infect Dis. 2020;71(16):2114-20.

20.Mikulska M, Nicolini LA, Signori A, et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLoS One. 2020;15(8):e0237831

21.RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(8):693-704.

22.Russo A, Gavaruzzi F, Ceccarelli G, et al. Multidrug-resistant Acinetobacter baumannii infections in COVID-19 patients hospitalized in intensive care unit. Infection. 2022;50(1):83-92.

23 Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020;8(3):267-76.

24.Rollas K, Ersan G, Emgin O, et al. Evaluation of Microorganisms Isolated from Endotracheal Aspirate Cultures in Patients with and without COVID-19 in the Intensive Care Unit: Single-Centre Retrospective Analysis. J Crit Intensive Care 2022;13:66–72.

25.Rouzé A, Martin-Loeches I, Povoa P, et al. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. Intensive Care Med. 2021;47(2):188-98.

26.Rangel K, Chagas TPG, De-Simone SG. Acinetobacter baumannii Infections in Times of COVID-19 Pandemic. Pathogens. 2021;10(8):1006.

27.Ripa M, Galli L, Poli A, et al. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. Clin Microbiol Infect. 2021 Mar;27(3):451-7.

28.Montoya A, Schildhouse R, Goyal A, et al. How often are health care personnel hands colonized with multidrug- resistant organisms? A systematic review and meta-analysis. Am J Infect Control. 2019 Jun;47(6):693-703.