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Risk factors of ventilator-associated pneumonia in intensive care patients at tertiary referral hospital

Ayu Permatasari Tribuana Tungga Dewi[1], Ni Made Mertaniasih[2*], Bambang Pujo Semedi[3], Lindawati Alimsardjono[2], Pepy Dwi Endraswari[2]

[1]Clinical Microbiology Specialist Program, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia
[2]Departement of Medical Microbiology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia
[3]Departement of Anesthesiology and Reanimation, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia

*Corresponding to:
Ni Made Mertaniasih; Departement of Medical Microbiology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia; nmademertaniasih@gmail.com

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) occurs after endotracheal intubation and ventilator for more than 48 hours therefore it is an emerging threat to patient safety. The aim of this study is to determine the incidence and compare the risk factors of ventilator patients diagnosed with ventilator-associated pneumonia and patients with ventilators who are not diagnosed with ventilator-associated pneumonia.

Methods: This study used a retrospective observational with a case-control approach. Data was collected from January 2019 to December 2021. The risk factors to be analysed were comorbidities, antibiotic therapy, length of stay in the intensive care unit, duration of ventilator use, and history of surgery.

Results: There were 18 patients in the VAP and the control groups met the inclusion and exclusion criteria. The incidence of incidents in 2019 was 3.2 per 1000 ventilator days; in 2020, it was 1.2 per 1000 ventilator days; and in 2021, it was 1.2 per 1000 ventilator days. Comparison test results using Mann-Whitney showed a difference with a $p<0.05$. Patients with prolonged use of ventilators ($p<0.05$) and prolonged hospitalization ($p<0.05$) have a higher risk of developing ventilator-associated pneumonia. The average VAP occurs on the fourth day on a ventilator. Gram-negative bacteria, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Klebsiella pneumoniae* cause most bacterial infections

Conclusion: There is a high risk of developing VAP in patients with prolonged use of ventilators and extended stays in the intensive care unit of the tertiary referral hospital.

Keywords: ventilator-associated pneumonia, intensive care unit
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INTRODUCTION

Pneumonia is an infection caused by pathogenic microorganisms in the lower respiratory tract.[1] This infection can be acquired in the community or a hospital setting. ventilator-associated pneumonia (VAP) occurs in the hospital after endotracheal intubation and ventilator for more than 48 hours. Symptoms of infection appear after more than 48 hours. Previously the patient had no infection.[2] VAP is a healthcare-associated infection often occurring in the intensive care unit (ICU). The incidence of VAP in North American hospitals is 1-2.5 cases per 1000 ventilator-days. Meanwhile, Europe reports much higher rates. The EU-VAP/CAP study reported an incidence of VAP of 18.3 per 1000 ventilator-days. The incidence of VAP in Asian countries is reportedly 3.5–46.0 per 1000 days of mechanical ventilation.[4] The multicentre study conducted in India in 2014 showed that the VAP rate in India was 6.74 per 1000 mechanical ventilation. The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) in 2016 reported that the death rate for VAP in the United States reached 13%. In Europe, a multi-center prospective study reported a 30-day VAP mortality rate of 29.9%.[5]

The World Health Organization (WHO) declared a COVID-19 pandemic on March 11, 2020. In 2020. National Healthcare Safety Network (NHSN) of The Centers for Disease Control and Prevention (CDC) study stated that there had been an increase in nosocomial HAI, including infection by prolonged use of ventilators. VAP remains one of the most common causes of nosocomial infection and death in critically ill patients hospitalized in ICU.[5-7] VAP can cause patients to have difficulty getting off the ventilator and to stay in the hospital longer, thus causing a financial burden on the patient.[15] Therefore, it is essential to clarify VAP risk factors to know more and get better prevention and VAP control.[5-9] This study aimed to determine the incidence of VAP in the intensive care unit and determine the risk factors for the cause of VAP in patients treated in the intensive care unit of a tertiary referral hospital.

METHODS

A retrospective observational study with a case-control approach was conducted at the Clinical Microbiology Department, ICU, and Medical Records Unit at Dr. Soetomo Hospital. The inclusion criteria were patients over 18 years of age and on

a ventilator for more than two calendar days in the Surgical Intensive Care Unit. Age, gender, comorbidity, and length of stay were the risk factors to be analysed. Secondary data of patients in the intensive care unit of the tertiary referral hospital, taken from January 2019 to December 2021 were collected from the medical records of the intensive care unit both digitally and manually. The research data were analyzed descriptively. The comparison test was performed using the Mann-Whitney test. Statistical analysis was done using Statistical Package for Social Science (SPSS) software version 25. The result is considered significant if $p \leq 0.05$.

RESULTS

In this study, 8295 patients were treated in the intensive observation room and 2259 patients in the ICU during 2019-2021. There were 18 patients diagnosed with VAP according to inclusion criteria in the case group and 18 patients on ventilators without pneumonia as controls. VAP patients in this study were found in the intensive observation room of the intensive care unit as many as nine patients and in the ICU as many as nine patients. Patients in the control group were 13 patients from the intensive observation room and five patients from ICU. The youngest age was found in the control group, which was 20 years old, and the oldest was 80. The youngest case group is 21 years old, and the oldest is 77 years old. The comparison test results using the Mann-Whitney test in the two groups showed no difference in the age factor in the case and control groups.

Male patients had the same number in both groups, with the same proportion of 9 (50%) of the case and control groups. Female patients have the same percentage of 50%. The comparison test results using the Mann-Whitney in the two groups showed no difference with a p-value > 0.05. The incidence rate of ventilator-associated pneumonia was calculated based on the Regulation of the Minister of Health of the Republic of Indonesia concerning guidelines for infection control in health service facilities. In this guideline, the incidence of VAP was calculated by dividing the number of patients diagnosed with VAP by the number of days the patient on a ventilator who does not have pneumonia multiplied by 1000 ventilator days. The incidence in 2019 was 3.2 per 1000 ventilator days; in 2020, it was 1.2 per 1000 ventilator days; and in 2021, it was 1.2 per 1000 ventilator days.

Comorbidities were found in 4 (22.2%) patients out of 18 case groups, with comorbid hypertension in 3 (16.7%) and comorbid diabetes found in 1 (5.6%) patients. In the control group, 2 (11.1%) patients had comorbidities. However, more than one comorbidity was often found in the control group. The Mann-Whitney test for both groups showed no difference in comorbid risk factors with a p>0.05 (Table 1). Antibiotics used

Table 1. Characteristics of variables in the case and control groups

Variable	VAP N (%)	Non VAP N (%)	p-value
Age			0.184
Minimal	21	21	
Maximal	77	80	
Mean	44.78	51.1	
Gender			1.000
Male	9 (50)	9 (50)	
Female	9 (50)	9 (50)	
Intensive care			0.18
ICU	9 (50)	13 (72.2)	
Intensive observation room	9 (50)	5 (27.8)	
Comorbid			0.39
Hypertension	3 (16.7)	0 (0)	
Diabetic mellitus	1 (5.6)	0 (0)	
Renal failure	0 (0)	0 (0)	
Comorbid more than one			
DM + HT	0 (0)	1 (5.6)	0.33
DM + renal failure	0 (0)	1 (5.6)	
No Comorbid	14 (77.8)	16 (88.9)	
Duration ventilator use			0.000
Minimal	6	2	
Maximal	62	6	
Mean	15.36	2.86	
Duration of intensive care unit stay			0.000
Minimal	6	2	
Maximal	62	9	
Mean	15.53	3.47	
Surgery			0.08
Yes	11(61.1)	16 (88.9)	
No	7 (38.9)	2 (11.1)	
Antibiotic pre-VAP			0.15
Yes	16 (88.9)	18 (100)	
No	2 (11.1)	0 (0,0)	
Antibiotic			0.15
Cephalosporin generation I	7 (38.9)	14 (77.8)	
Cephalosporin generation III	7 (38.9)	4 (22.2)	
Beta-lactam	2 (11.1)	0 (0,0)	
No antibiotics	2 (11.1)	0 (0.0)	

DM: diabetic mellitus; HT: hypertension

Table 2. Characteristics of bacteria in the case group

Bacteria	N (%)
Acinetobacter baumanii	4 (22,2)
Cronobacter sakazuki	1 (5.6)
Klebsiella pneumoniae	5 (27,8)
Klebsiella pneumoniae ESBL	2 (11.1)
Providencia rustigiani	1 (5.6)
Pseudomonas aeruginosa	3 (16.7)
Pseudomonas aeruginosa MDRO	1 (5.6)
Staphylococcus aureus	1 (5.6)

ESBL: extended-spectrum beta-lactamases; MDRO: multidrug-resistant organism

before VAP were found in both groups. Based on the comparative test using the Mann-Whitney on the use of antibiotics in the group with VAP and the control group, there was no difference between the two groups with a p>0.05 (Table 1). Administration of antibiotics was found in 16 (88.9%) of the case group, 18 (100%) of the control group. Antibiotics often used were third-generation cephalosporin, namely 7 (38.9%), and first-generation cephalosporin is 7 (38.9%) in the group with VAP. In the control group, first-generation cephalosporins were used more frequently, namely 14 (77.8%).

The length of stay in the intensive care unit differed in the case and control groups. In the case group, patients were treated for a minimum of 6 days, a maximum of 62 days. The control group has a minimum of two days and a maximum of nine days. The average diagnosis of VAP occurred on day 4 in the case group. The results of the comparison test using the Mann-Whitney for the two groups showed that there was a difference (p<0.05). Surgery was present in both the case group and the control group. Surgery was obtained in 11 (61.1%) in the case group and 16 (88.9%) in the control group. Surgery in the case group occurred because the cases of patients with trauma were found to be the most in the case group, namely 12 (33.3%). Surgery in the control group occurred because of the large number of cases of patients with malignancy, namely 20 (55.9%) patients. Comparative test results using Mann-Whitney for the two groups showed no differences in surgical risk factors (p=0.08) (Table 1).

Gram-negative bacteria caused most bacterial infections in the case group. The control group did not get the sputum culture examination results because the clinical examination and supporting examinations found no signs of infection due to ventilator-associated pneumonia (VAP). The most bacteria found in the case group were *Klebsiella pneumoniae* (27.8%), *Acinetobacter baumanii* (22.2%), and Pseudomonas aeruginosa (16.7%) (Table 2).

DISCUSSION

Ventilator-associated pneumonia (VAP) is an infection in intensive care patients on ventilators. In this study, the incidence of VAP in 2019 was 3.2 per 1000 ventilator days, 1.2 per 1000 ventilator days in 2020, and 1.2 per 1000 ventilator days in 2021. It can be seen that there is a decrease in the incidence of VAP from year to year. Over time, a decrease in VAP incidence has also been observed in studies on VAP in Europe, namely in Italy and Germany.[6,7] A reduction in the incidence of ventilator-associated pneumonia was found in the VAP study in the United States, which was 1-2.5 per 1000 ventilator days.[8]

The lower incidence in our study could be due to the small number of cases compared to other studies which show a lower incidence. Incidence varies greatly depending on the population studied, such as the incidence in trauma patients of 17.8% in the VAP study conducted by Aguiar-Alves et al, 2022.[3] A decrease in the incidence of VAP can also occur with an increase in the compliance rate of the ventilator bundle for more than one year, which efficiently reduces the incidence of VAP. Reducing the duration of intubation and the length of stay in the ICU can also lead to a decrease in the incidence of VAP.[8-15]

Khilnani et al. 2019 examined the characteristics of ventilator-associated pneumonia patients in India in stating that there was no difference in age in both the VAP and non-VAP groups.[15] Male VAP patients were found to be higher than female patients. Research conducted by Yao et al, 2020 also found that the male sex was dominant in VAP and non-VAP patients.[10] In our study, men also predominated in VAP and non-VAP patients. The common comorbidities in VAP patients are hypertension, heart disease, diabetes mellitus, and renal failure. Hypertension (8.3%) and renal failure (5.6%) were seen in most patients with VAP.[11] This comorbidity was also found in a study conducted by Arayasukawat et al, 2021 in Northeastern Thailand. The most comorbid was diabetes mellitus with 85.7% in the VAP group and 80.7% in the non-VAP group, followed by hypertension with 82.9% in the VAP group and 75.4% in the non-VAP group. In chronic renal disease, 51.4% were found in VAP and 40.4% in non-VAP. This study aligns with our study, where hypertension, heart disease, diabetes mellitus, and renal failure were frequently encountered comorbidities, and no differences were found in comorbid factors.[15-17]

Antibiotic resistance has increased in recent decades. In study by Sun et al, 2022 found that antibiotics and hospitalization for more than five days were risk factors for antibiotic resistance in VAP pathogens.[13] In a study of 397 VAP patients conducted by Fan et al, 2016 showed unnecessary use of antibiotics was a risk of developing antibiotic resistance.[17] Longer use of prophylactic antibiotics also increases the risk of developing resistance to VAP pathogens.[15] Hurley et al study in 2016 found that about 20% of *Escherichia coli* and *Klebsiella pneumoniae* bacteria in VAP patients had resistance to the cephalosporin class. In the VAP group, the most frequently used antibiotic was the third-generation cephalosporin 61.1% whereas in the control group, the most frequently used antibiotic was the first-generation cephalosporin 22.2%.[9]

Our research has shown differences in the duration of ventilator use and

stays in the intensive care unit in the case and control groups. In the case group, the duration of ventilator use and duration of stay were significantly higher. The duration of mechanical ventilation significantly increases the incidence of VAP. Our research is in line with a study conducted by Le Pape et al, 2022 which confirmed that the incidence of VAP increased from 5% for patients receiving mechanical ventilation for one day to 69% for those receiving mechanical ventilation for more than one day than 30 day.[18]

There was no difference in surgery in our study. This study is in line with the research by Hellyer et al, 2020 which biomarker-guided antibiotic stewardship in suspected ventilator-associated pneumonia.[4] This study showed no significant differences between VAP and non-VAP patients. However, what distinguished VAP and non-VAP patients was the length of time they used the ventilator and the length of stay in the intensive care unit. In our study, surgical VAP patients spent an average of more than six days on a ventilator. Non-VAP patients with surgery are on a ventilator for an average of 2 days. The length of stay in the intensive care unit is also two days whereas patients who experienced VAP spent an average of 4 days on a ventilator.[18,19]

More prolonged treatment in the intensive care unit can cause the microorganisms in the VAP group to vary. This study is in line with research conducted by Aguiar-Alves et al, 2022 which found that the organisms associated with VAP varied according to many factors, including duration of mechanical ventilation, length of intensive hospitalization before VAP occurred, time, and cumulative exposure to antimicrobials.[3] The longer a person is treated in the intensive care unit, the higher the risk of the patient experiencing contact with medical staff, contact with invasive medical devices, exposure to germs that colonize the intensive care unit, and drugs that can indirectly reduce the body's immune response and immunity.[19-21]

Gram-negative bacteria are the most common bacteria found in our study. The same results were obtained in a study conducted by Mustikaningtyas et al in 2022 at Dr. Soetomo Hospital, which also found that gram-negative bacteria were the most common.[19] Research by Emonet et al, 2019 also explained that >50% of the bacteria grown in VAP patients are gram-negative. Common gram-negative bacteria are *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Klebsiella pneumoniae*.[21] Research by Arthur et al in 2016 shows that the main bacteria growing in VAP are gram-negative bacteria *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* sp., *Escherichia coli*, along with the gram-positive bacteria S. aureus and Enterococcus faecium.[20] Even though there are variations in microorganisms in each study, these three bacteria are still commonly found in VAP patients.[3,19-21] *Pseudomonas aeruginosa* is one of the most common bacteria that cause VAP, with a prevalence of approximately 4.2% and the resulting mortality reaching 13.5%, even with adequate antibiotic treatment.[22] A study by Luyt et al, 2020 showed that the mortality of VAP patients with Pseudomonas aeruginosa has increased to 41.9%. Pseudomonas aeruginosa MDR can also be found in patients with early VAP who have no risk factors.[23]

CONCLUSION

In this study, the incidence of VAP in 2019 was 3.2 per 1000 ventilator days, 1.2 per 1000 ventilator days in 2020, and 1.2 per 1000 ventilator days in 2021. Patients with prolonged use of ventilators and longer stays in the intensive care unit are at high risk of developing VAP. Surgery, comorbidities, and antibiotic therapy are not significant risk factors for VAP. *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* are most common causative bacteria.

CONFLICT OF INTEREST

The authors affirmed that there were no conflicts of interest in this study.

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ETHICAL CLEARANCE

This study has obtained ethical clearance from the Research Ethics Committee of Dr. Soetomo Hospital Surabaya with reference letter number 0954/LOE/301.4.2/VII/2022.

AUTHOR CONTRIBUTION

All authors contributed equally in this research and publication of this manuscript.

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