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ORIGINAL RESEARCH NTENSIVE CARE

Mortality risk factors and the ventilator-associated pneumonia (VAP) in the ICU of a tertiary hospital in Indonesia

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ABSTRACT

Background & Objective: Mortality of patients with ventilator-associated pneumonia (VAP) in the ICU is influenced by several risk factors, including comorbidities, SOFA scores, malnutrition, and sepsis with multi-drug resistant (MDR) pathogens. We aimed to determine the risk factors for VAP patient mortality in the ICU of a tertiary hospital in Indonesia over a period of time.

Methodology: This descriptive observational study was conducted retrospectively in the ICU of Dr. Hasan Sadikin Hospital, Bandung, Indonesia, during 2021-2022. The hospital records of all patients diagnosed with VAP during this period were retrieved and the records of the deceased patients were analysed for various risk factors, which may have led to mortality.

Results: The results of this study showed that 64 patients experienced VAP, with 49 (76.6%) patients expired. The VAP patients who died were mostly male (63.3%), the median age was 61 years, median BMI of 22.2 kg/m^2, with hospital length of stay (LOS) of 13 days, ICU LOS of 10 days, and ventilator LOS of 8 days. The majority had SOFA scores between 10-12 (46.9%), the PF ratio was 195.1 ± 77.5, albumin value was 2.11 ± 0.64. The most common comorbidity was hypertension (40.8%) with a high neutrophil-lymphocyte ratio (NLR) value (69.4%), the most common pathogen found was Acinetobacter baumannii (18.4%), and in the most of the patients experiencing MDR (53.3%), the cause of ICU admission was respiratory system disorders (40.8%). Bivariate analysis showed hospital LOS, ICU, ventilator, PF ratio, comorbidities, NLR, SOFA score, nutritional status, and MDR pathogens were associated with VAP mortality with $P < 0.05$.

Conclusion: This study concludes that the risk factors for mortality of VAP patients in the ICU of Dr. Hasan Sadikin Hospital, Bandung in 2021-2022 are comorbidities, a high neutrophil-lymphocyte ratio, SOFA score, poor nutritional status, and sepsis with multi-drug resistant pathogens. Identifying risk factors is essential for preventing and managing VAP in the ICU to reduce mortality.

Abbreviations: LOS - Length of Stay; MDR - Multi-Drug Resistant; NLR - Neutrophil-Lymphocyte Ratio; VAP - Ventilator-Associated Pneumonia

Keywords: Mortality, risk factors, ventilator-associated pneumonia (VAP)

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1. INTRODUCTION

Ventilator-associated pneumonia (VAP) is a hospital-acquired infection that occurs most frequently in the ICU, being a significant cause of morbidity and mortality in critically ill patients in the ICU undergoing invasive mechanical ventilation via endotracheal tube (ETT) or tracheostomy.[3,4] VAP is

estimated to occur at a rate of 3% per day on the first five days, 2% per day on days 6 to 10, and 1% per day after day 10. The diagnostic clinical triad for VAP consists of signs of infection, including fever, purulent discharge, and leukocytosis, along with bacteriological evidence of lung infection and radiological findings suggestive of lung infection.[5,6]

Research in 2019 showed that 145 patients experienced VAP, a mortality rate of 42.8%. The high mortality rate is influenced by several risk factors, including age over 70, male gender, smoking history, and previous comorbid diseases such as diabetes mellitus, heart failure, stroke, and chronic obstructive pulmonary disease. A picture of increased mortality is also seen in VAP patients who experience an increased neutrophil-lymphocyte ratio (NLR), infection with multidrug-resistant (MDR) microorganisms, and a high Sequential Organ Failure Assessment (SOFA) score. These risk factors are associated with mortality in VAP patients.[1]

Another study in 2019 showed a picture of the mortality of VAP patients in several conditions. In male patients, 44.2% experienced mortality, and COPD comorbid disease was the highest risk factor at 51.9% causing mortality in VAP patients. Other comorbidities such as neurological disease (42.3%), congestive heart failure (36.5%), and kidney failure (28.8) play a role in causing mortality in VAP patients. This research shows that the profile of VAP patients who experience mortality has several risk factors. Other factors assessed include pleural effusion, increased C-reactive protein (CRP) values, acute respiratory distress syndrome (ARDS).[1,2]

There are various causes of mortality of VAP patients in the ICU, including advanced age and comorbidities such as heart, kidney, and cerebrovascular disease.

Analysis of risk factors for mortality in VAP patients can provide a focus in carrying out therapy. Identified risk factors that cause high mortality can be used as a focus for prevention and management. The combination of several risk factors significantly increases the mortality rate of VAP patients. The high mortality rate in VAP patients undergoing treatment in the ICU shows that preventive measures are essential to reduce patient mortality.[1,13] However, the risk factors for VAP patient mortality in the ICU of a Tertiary Hospital in Indonesia is still unknown.

We aimed to determine the risk factors for VAP patient mortality in the ICU of a Tertiary Hospital in Indonesia.

2. METHODOLOGY

The research method used in this research is descriptive observational. The data collection method was carried out retrospectively, taken from document searches of medical records of patients with Ventilator-Associated Pneumonia (VAP) in the ICU of RSUP Dr. Hasan Sadikin Bandung in 2021-2022. The inclusion criteria in this study were medical records of patients diagnosed with VAP in the ICU of RSUP Dr. Hasan Sadikin Bandung from January 2021 to December 2022. The exclusion criteria in this study were patients with community-acquired pneumonia (CAP) and pediatric patients (age ≤ 17 years). The exclusion criteria in this study were incomplete patient medical records.

Determining the sample in this study used a total sampling method where all patients who met the inclusion and exclusion criteria were used as the research sample. The research sample will then be divided into two groups: the group of VAP patients who are alive and the group of VAP patients who died.

After obtaining approval from the Research Ethics Committee at the Faculty of Medicine, Padjadjaran University/RSUP Dr. Hasan Sadikin Bandung and receiving permission from the Medical Education and Research Section of RSUP Dr. Hasan Sadikin Bandung, a retrospective assessment was carried out on the medical data of VAP patients who experienced

Table 1: Characteristics of VAP patients based on age, BMI, LOS, PF ratio, and albumin value

Variables	VAP Patients		p-value
	Alive (n = 15)	Deceased (n = 49)	
Age (y)	54 (29-73)	61 (18-80)	0.349
Body mass index (kg/m^2)	23.2 (17.6-31.22)	22.2 (15.6-36.7)	0.968
Hospital length of stay (days)	23 (10-68)	13 (2-110)	0.057
ICU length of stay (days)	15 (3-67)	10 (0-76)	0.122
Length of ventilation (LOV) (days)	10 (1-49)	8 (0-76)	0.949
P/F ratio	271.6 ± 103.5 (74.75-432.8)	195.1 ± 77.5 (77.4-351.2)	0.003
Albumin	2.24 ± 0.33 (1.78-3.0)	2.11 ± 0.64 (0.42-3.4)	0.461

***Notes**: Numerical data are presented with mean, median, standard deviation and range. The results of normality testing on the variables of age, BMI, Hospital LOS, ICU LOS, ventilator LOS showed an abnormal distribution so that the presentation of data used the median, while the variables of PF ratio and albumin were normally distributed so that the presentation of data used the mean and standard deviation.*

Table 2. Characteristics of VAP Patients based on gender, surgery, comorbidities, NLR value, SOFA, germ type, nutritional status, MDR, and base diagnosis (N = 64)

Characteristics		VAP Patients		P-value
		Alive (n = 15)	Deceased (n = 49)	
Gender	Male	12 (80)	31 (63.3)	0,242
	Female	3 (20)	18 (36.7)	
Surgical Patients	Yes	6 (40)	22 (44.9)	0,231
Comorbidities	Hypertension	9 (60)	20 (40.8)	0,334
	Smoking	2 (13.3)	5 (10.2)	
	Cardiomegaly	2 (13.3)	5 (10.2)	
	Other cardiac issues	0 (0)	9 (18.4)	
	Heart failure	1 (6.7)	7 (14.3)	
	Diabetes mellitus	2 (13.3)	14 (28.6)	
	Renal disease	3 (20)	20 (40.8)	
	Pulmonary edema	0 (0)	5 (10.2)	
	COPD	2 (13.3)	1 (2)	
	CNS	4 (26.7)	12 (24.5)	
	Hemato-oncology	4 (26.7)	12 (24.5)	
	Sepsis	5 (33.3)	17 (34.7)	
	Covid-19	3 (20)	7 (14.3)	
NLR	High (≥ 11,0)	6 (40)	34 (69.4)	0,634
	Normal (< 11,0)	9 (60)	15 (30.6)	
SOFA Score	0-6	4 (26.7)	3 (6.1)	0,303
	7-9	7 (46.7)	5 (10.2)	
	10-12	3 (20)	23 (46.9)	
	13-14	1 (6.7)	11 (22.4)	
	15-24	0 (0)	7 (14.3)	
Nutrition Status	Malnourished	2 (13.3)	20 (40.8)	0,367
	Not malnourished	13 (86.7)	29 (59.2)	
Bacterial Specimens	Candida tropocalis	0 (0)	2 (4.1)	0,538
	Acinetobacter baumannii	6 (40)	9 (18.4)	
	Staphylococcus aureus	0 (0)	3 (6.1)	
	Candida albicans	1 (6.7)	3 (6.1)	
	Pseudomonas aeruginosa	2 (13.3)	2 (4.1)	
	Staphylococcus haemolyticus	0 (0)	1 (2)	
	Klebsiella pneumoniae	2 (13.3)	4 (8.2)	
	Enterobacter cloacae	0 (0)	2 (4.1)	
	Escherichia coli	0 (0)	2 (4.1)	
	Candida parapsilosis	0 (0)	1 (2)	
	Stenotrophomonas maltophilia	0 (0)	2 (4.1)	
MDR	Yes	7 (46.7)	8 (53.3)	0,015
	No	8 (16.3)	41 (83.7)	
Underlying Diagnosis	Respiratory disease	7 (46.7)	20 (40.8)	0,926
	Nervous system disease	6 (40)	16 (32.7)	
	Urology system disease	0 (0)	2 (4.1)	
	Digestive system disease	1 (6.7)	3 (6.1)	
	Cardiology system disease	0 (0)	1 (2)	
	Others	1 (6.7)	7 (14.1)	

Note: Categorical data are presented as frequency and percentage

mortality in the ICU of RSUP Dr. Hasan Sadikin Bandung 2020-2021. Patients with a diagnosis of VAP were obtained from ICU patient register data and patient flowcharts from January 2021 to December 2022, then analyzed again according to the VAP diagnosis criteria based on CPIS criteria, which included examination of body temperature, leukocytes, chest x-ray examination results, culture examination results, and the results of checking the PaO_2:FiO_2 ratio. A CPIS score of more than six is categorized as VAP.

After that, research data was collected from the patient's medical records, including age, gender, length of ventilation (LOV), length of stay (LOS), SOFA score, neutrophil-lymphocyte value (NLR), results of patient culture examination, patient nutritional status, underlying disease or indication for admission to the ICU and mortality rates in the ICU. Data was taken from flowchart medical records and ICU patient status. The SOFA score is taken from the flowchart and is based on the patient's laboratory examination. NLR data and culture examination results were taken from the RSHS laboratory website, which contains complete laboratory examination data for each patient. The data processing method in this research includes several stages, namely data that has been edited and, coded and processed using the SPSS version 25.0 for Windows program.

3. RESULTS

The results of research on patients treated at Hasan Sadikin Hospital in 2021-2022 showed that 64 patients experienced VAP (VAP) with 15 patients (23.4%) experiencing an improvement in their condition and 49

Table 3: Relationship between characteristics and VAP mortality

Variables		VAP Patients		OR (95% CI)	P-value
		Alive n (15)	Deceased n (49)		
Gender	Male	12 (27.9)	31 (72.1)		0.187
	Female	3 (14.3)	18 (85.7)		
Surgery	Yes	6 (21.4)	22 (78.6)		0.738
Comorbidities	Yes	9 (16.7)	45 (83.3)	7.5 (1.753-32.087)	0.008
NLR	High NLR	6 (15)	34 (85)	3.4 (1.026-11.270)	0.040
	Normal NLR	9 (37.5)	15 (62.5)		
SOFA Score	0 – 6	4 (57.1)	3 (42.9)		0.001
	7 – 9	7 (58.3)	5 (41.7)		
	10 – 12	3 (11.5)	23 (88.5)		
	13 – 14	1 (1)	11 (91.7)		
	15 – 24	0 (0)	7 (100)		
Malnutrition	Malnourished	2 (9.1)	20 (90.9)	4.483 (0.911-22.07)	0.045
	Not malnourished	13 (31)	29 (69)		
Bacterial pathogens	Tidak ditemukan	4 (18.2)	18 (81,8)		0.666
	Candida tropocalis	0 (0)	2 (100)		
	Acinetobacter baumannii	6 (40)	9 (60)		
	Staphylococcus aureus	0 (0)	3 (100)		
	Candida albicans	1 (25)	3 (75)		
	Pseudomonas aeruginosa	2 (50)	2 (50)		
	Staphylococcus haemolyticus	0 (0)	1 (100)		
	Klebsiella pneumoniae	2 (33.3)	4 (66,7)		
	Enterobacter cloacae	0 (0)	2 (100)		
	Escherichia coli	0 (0)	2 (100)		
	Candida parapsilosis	0 (0)	1 (100)		
	Stenotrophomonas maltophilia	0 (0)	2 (100)		
MDR Microorganism	MDR	7 (46.7)	8 (53.3)	0.223 (0.063-0.791)	0.015
	Non MDR	8 (16.3)	41 (83.7)		
Underlying Diagnosis	Respiratory disease	7 (25.9)	20 (74.1)		0.885
	Nervous system disease	6 (27.3)	16 (72.7)		
	Urology system disease	0 (0)	2 (100)		
	GIT disease	1 (12.5)	7 (87.5)		
	Cardiology disease	1 (25)	3 (75)		
	Others	0 (0)	1 (100)		

Note: Chi square/ Fischer exact tests' P-value < 0.05 considered as significant

patients (76.6%) dying. The characteristics of the subjects in this study can be seen in Tables 1 and 2.

Many previous studies have shown that several factors significantly cause mortality in VAP patients. Research conducted by Feng et al. in 2017 showed that four risk factors for VAP experienced mortality: previous use of antibiotics for a long time, NLR value, MDR pathogens, and SOFA score. [1] Research by Sadigov et al. in 2019 showed the patient mortality rate of VAP increases with risk factors of malnutrition, severe sepsis or septic shock, ARDS, Acinetobacter baumannii infection with antibiotic resistance, and COPD comorbidities.[2] In this study, statistical bivariate analysis tests were carried out to identify the relationship between several variables and mortality in VAP patients.

4. DISCUSSION

The research results show that the VAP mortality rate in the ICU at Dr. Hasan Sadikin in 2021-2022 is relatively high, namely 76.6%. A high mortality rate was also found in research conducted in China in 2019, in which out of 145 patients diagnosed with VAP, 60% succumbed. Research in Surabaya in 2018 showed that 18 patients were diagnosed with VAP with as much as 50% mortality.[6,10] Several risk factors were identified related to mortality in VAP patients treated in the ICU at Hasan Sadikin Hospital during 2021-2022.

This study found that VAP patients with the youngeer than 18 y and those older than 80 y suffered from mortality. Most VAP patients who expired were male (63.3%). In a research in Qatar, of 106 VAP patients, around 80.2% were male. Gender and age are related to the function of the body's immune system. Gender is also related to differences in hormonal regulation, which plays a role in immune system regulation, namely estrogen and testosterone. During puberty in women, immune dimorphism can occur, which causes women's immunoglobulins to be higher than men's, making them more resistant to infection.[6,28] In our study, men had a mortality of 63.3% and women 36.7% (Table 2). This study shows that the characteristics of VAP mortality are following other researches where men have a higher mortality risk than women. Statistical analysis, however, showed no relationship between gender and mortality, with a P = 0.187 (Table 3).

Other studies show that the incidence of VAP is high in older adults aged 65-74 years. Age is related to the body's physiological function, immunological response, and comorbid conditions, which often cause mortality in VAP patients in the ICU. The results of this study show that VAP patients who died had an age range of 18-80 y, with a median of 61 y (Table 1). Age influences mortality risk following previous research that the physiological function of body organs decreases in old age. In geriatric patients with comorbidities, especially heart disease, the patient's risk of mortality will increase.[20,21] The statistical analysis results show no relationship between age and VAP mortality in this study, with a P = 0.354 (Table 3). This result shows that other risk factors can influence the mortality of VAP patients.

The length of stay affects the mortality rate of VAP patients in the ICU. Longer treatment times indicate higher mortality. VAP patients who survive have a shorter treatment time (Table 1). Statistical analysis showed that Hospital LOS, ICU LOS, and LOV had a relationship with VAP mortality in the RSHS ICU with a p-value < 0.05 (Table 3). This means that the long time spent in the ICU and intubation time cause a high incidence and mortality rate of VAP. The length of time a patient is treated in the ICU makes the patient vulnerable to exposure to infection in the hospital, worsening the patient's condition and causing mortality. Previous research in 2019 showed that patients who experienced VAP found it difficult to wean the ventilator, the treatment time was long, and the risk was life-threatening.[2] Research in 2015 showed that using a ventilator for more than nine days caused more mortality than using a ventilator for less than nine days. These two factors put patients at greater risk of experiencing infections in the hospital, thus worsening the patient's clinical condition.[36,37]

The decrease in PF ratio in this study showed a significant relationship to VAP mortality with a p-value of 0.003 (Table 3). Patients in the ICU have varying degrees of ARDS, from mild to severe. This situation shows the degree of lung damage and oxygenation function, which can increase mortality risk. Damage to the lung parenchyma causes oxygenation and ventilation functions to be disrupted. This can affect the length of use of the ventilator and will increase the risk of exposure to infection in patients. The 2019 study showed similar results where there were 121 patients with VAP, 32 of them had a low PF ratio below 250, and 46.2% of patients died.[1,2]

The study results showed that comorbid factors were associated with the incidence of mortality in VAP patients in the Hasan Sadikin Hospital ICU with a p-value of 0.008 (p-value <0.05). There were 45 patients (83.3%) who had comorbidities who experienced mortality (Table 3). The comorbidities found in this study were varied. This study does not explicitly link one comorbidity to mortality but includes whether there is a comorbidity.

Respiratory system disorders were the most common factor causing 27 patients to be admitted to the ICU. A total of 20 patients (40.8%) developed VAP and experienced mortality (Table 2). Research in Turkey in 2015 showed the characteristics of the causes of patients being treated in the ICU.[15] This situation developed into VAP during ICU treatment and caused patient mortality. Another characteristic is seen in comorbid VAP patients who experience mortality. Immunosuppressive conditions in patients who have

comorbidities are an essential factor in mortality in VAP.[15]

This study shows that an SOFA score of 10-12 has a mortality rate of 88.5%, while an SOFA score of 15-24 shows a mortality rate of 100%. The analysis results show that the higher the SOFA score, the higher the mortality rate. Statistical analysis showed that patients with a high SOFA score were associated with the incidence of VAP mortality in the RSHS ICU with a p-value of 0.001 (Table 3). The SOFA scoring kit can evaluate physiological, respiratory, coagulation, hepatic, central nervous system, and renal function. Multiorgan failure shows a high mortality rate as well.[1,15]

The results of research regarding the NLR ratio showed that of the 49 VAP patients who died, around 34 patients (85%) had a high NLR rate in VAP patients in the ICU at RSUP Dr. Hasan Sadikin Bandung. The NLR value is classified as high if it is above 11.0. The analysis results show that a high NLR is associated with VAP mortality in the ICU with a p-value of 0.004 (Table 3) and that VAP patients with a high NLR value are 3.4 times more likely to experience mortality. Approximately 85% of VAP patients who died had an NLR value above 11.0. The physiological immune response of leukocytes to infection is characterized by an increase in neutrophils and a decrease in lymphocytes. A higher NLR value indicates that a severe inflammatory process is occurring.[1,15] Research in 2021 showed that 54 VAP patients who died in the ICU had high NLR values with a mean value of 11.43. Another study in 2017 showed that an increase in the NLR value, namely 11.0 to 13.4, had a mortality rate of 30% in 13 VAP patients. This shows that NLR is a better prognostic marker than conventional infection markers such as CRP, white blood cell count, and procalcitonin, which are relatively expensive.[2,14]

This study shows the results of several pathogens found in VAP patients. Statistical analysis shows that the type of germ that causes VAP has no relationship with mortality, with a p-value of 0.666 (Table 3). This characteristic indicates that infection with just one type of germ does not cause mortality. In some cases, there are patients whose condition improves and survives. Some germs that cause infections develop into MDR pathogens.

A total of 27 patients had MDR pathogens, and 18 patients (66.7%) experienced mortality. This study showed 15 VAP patients with MDR, eight of whom underwent mortality (53.3%). Analysis results showed significant results with a p-value of 0.015 ($p<0.05$) (Table 3), which means there is a relationship between MDR pathogens and the mortality of VAP patients in the ICU. MDR pathogens have more substantial virulence, and MDR infections have limited drug options, making them one of the risk factors that cause death in VAP patients. Research in 2019 showed that 66 patients were diagnosed with VAP, Pseudomonas aeruginosa, and 35 VAP patients caused 31 VAP patients were caused by other bacteria such as Enterobacteriaceae and Acinetobacter spp. Around 47.8% of patients experienced mortality.[1,2]

The research results showed that 22 VAP patients experienced malnutrition. There were 20 patients (90.9) of whom experienced mortality. The results of this analysis show that there is a relationship between malnutrition and VAP mortality in the ICU at RSUP Dr. Hasan Sadikin Bandung with a p-value of 0.045 (p-value <0.05) (Table 3). Diagnosis of malnutrition is based on the criteria of a body mass index (BMI) below 21 kg/m2 and serum albumin below 3.5 gr/L.[2,13] All VAP patients experienced malnutrition with an average albumin value of 2.11 ± 0.64. Based on statistical analysis, malnutrition is related to VAP mortality with a p-value of 0.045 (Table 3). These results are also relatively similar to previous research by Scislo et al. in 2017, showing that 45 (37.2%) VAP patients in the ICU experienced malnutrition with albumin values below 2.5 g/dL. Malnutrition causes immunodeficiency, which causes susceptibility to infections.[35,36]

The study results show a picture of the factors seen in VAP patients during treatment in the ICU who experience mortality. Based on the analysis, there is also a relationship between these risk factors and the occurrence of VAP mortality in the ICU. Hospital length of stay (LOS), ICU LOS, and length of ventilator (LOV) are risk factors associated with VAP mortality in the ICU. The longer the hospitalization time, the higher the risk of mortality. Data on PF ratio, comorbidities, NLR, SOFA score, malnutrition, and MDR pathogens are also factors related to mortality. These results are similar to previous research in that these risk factors were seen in VAP patients undergoing treatment in the ICU who died. VAP patients with high SOFA scores are the most dominant factor causing mortality.

5. LIMITATIONS

This research has a weakness; it was carried out retrospectively and relied on documentation and reports in patients' medical records. The reporting of existing mortality case data is not uniform, so that many other risk factors can be listed in this study.

6. CONCLUSION

The incidence of ventilator-associated pneumonia (VAP) in the ICU at Hasan Sadikin Hospital Bandung in 2021-2022 was 64 people, with 15 patients (23.4%) experiencing an improvement in their condition and 49 patients (76.6%) dying. In this study, risk factors were associated with VAP patients' mortality in the ICU, namely comorbidities, high neutrophil-lymphocyte ratio, SOFA score, malnutrition, and multi-drug resistant pathogens. The results of this study can be a reference for further research, especially in a

prospective cohort, to determine the risk factors that influence the outcome of VAP patients in the ICU.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

All authors took equal part in the requisition od the data, statistical analysis, literature search and manuscript preparation.

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