



# Correlation between Multidrug Resistance Infection with Clinical Outcomes of Critically ill Patients with COVID-19 Admitted to an Intensive Care at RSUP Dr. M. Djamil in Indonesia

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## Abstract

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**BACKGROUND:** Approximately 14–50% of severe COVID-19 patients are admitted to the Intensive Care Unit (ICU) that acquires a multidrug-resistant bacterial infection (MDR) and worsens clinical outcomes of patients.

**AIM:** We aim to determine the increased risk of MDR infection in the ICU including large-spectrum antibiotic administration, invasive procedure performance (mechanical ventilation), and clinical outcomes of patient.

**METHODS:** We analyzed 227 patients with a primary diagnosis of COVID-19 on mechanical ventilation who were admitted to ICU COVID-19 RSUP Dr. M. Djamil from 2020 to 2021. Demographic information, sputum culture results, intubation, and clinical outcomes were all collected in the medical records for this retrospective cohort study. Patients who were hospitalized for <48 h in the ICU were excluded from the study. An independent t-test and a Chi-square test were used to analyze the data.

**RESULTS:** In sixty patients (26.4%), bacteria were found in the sputum culture, 40 patients (66.7%) of them were MDR. The most common bacteria found was *Acinetobacter baumannii* (35%) followed by *Klebsiella pneumoniae* (21.7%). There is a significant relationship between MDR (p-value 0.000) and intubation (p-value, 000) to clinical outcomes of patients (improvement or death). There is a significant relationship between intubation and MDR (p-value 0.009).

**CONCLUSION:** MDR patient status affected the outcomes of COVID-19 patients in the ICU. Patients with MDR were more likely to have a poor clinical outcome.

## Introduction

The World Health Organization (WHO) declared COVID-19 as a public health emergency. To the date of writing this study, there have been more than 113 million confirmed cases of COVID-19, including about 2.5 million deaths, according to the WHO reports. COVID-19 infection in Indonesia showed a rapid increase in incidence over a short period and the mortality rate of critically ill patients remains high [1], [2].

Ever since, the virus has been spreading worldwide claiming thousands of lives. Due to serious respiratory disease in humans, some patients with severe cases need to be hospitalized in intensive care with mechanical ventilation support [3], [4].

The diagnosis of COVID-19 using laboratory panels was recommended. These panels include complete blood count and coagulation tests such as D-dimer, prothrombin time, or partial thromboplastin time. Other biochemical tests are recommended, such as C-reactive protein (CRP), Interleukin, ferritin, liver, renal tests, and cardiac troponin reflecting the

development of viral sepsis, systemic inflammatory response syndrome, and/or multiple organ failure [2].

Various studies of hospitalized patients with COVID-19 note the empiric use of antibiotics in a majority of patients; however, there is evidence that the inflammatory serological markers that are usually associated with bacterial infection, such as raised procalcitonin and CRP [5].

Study Baskaran *et al.*, the overall median length of stay in Intensive Care Unit (ICU) was 9 days. Thus, a significant proportion of critically ill COVID-19 patients may be exposed to ICU acquisition of multidrug-resistant (MDR) bacterial infections. In general, MDR infection rates in ICU patients range from 14% to nearly 50%. Determinants of increased MDR infection risk in ICU include large-spectrum antibiotic administration, invasive procedure performance (mechanical ventilation, central venous access, etc.), and prolonged bed stay. In addition, ICU patients often present with sepsis-related immune system downregulation [6], [7].

Antimicrobial resistance is a growing crisis that affects global health and demands urgent action. Ramadan *et al.* discovered that patients with COVID-19 who had severe cases had a multidrug-resistant

pattern. Among the isolated gram-positive strains, all *Staphylococcus aureus* were MRSA and 100% carried the *mecA* gene. Methicillin resistance is a growing problem in coagulated positive and negative staphylococci [2].

During influenza viral pneumonitis epidemics and pandemics, increased secondary bacterial, and fungal infections were reported, poor patient outcomes were noticed with *S. pneumoniae*, *H. influenzae*, *S. aureus*, and *Aspergillus* spp. As the COVID-19 pandemic continues, a considerable increase in antimicrobial resistance is foreseen through the heavy use of antibiotics in COVID-19 patients. Multidrug-resistant bacteria are leading to increased morbidity and mortality. Therefore, the need for antibiotic treatment should be promptly evaluated and discontinued when not appropriate [2], [8].

This study aims to determine the increased risk of MDR infection in the ICU including large-spectrum antibiotic administration, invasive procedure performance (mechanical ventilation, central venous access, etc.), and patient outcome.

## Methods

### Study population

In this retrospective cohort study, we analyzed 227 patients with a primary diagnosis of COVID-19 on mechanical ventilation who were admitted to ICU COVID-19 RSUP Dr. M. Djamil from 2020 to 2021. Patients who were hospitalized for <48 h in the ICU and those with incomplete data were excluded from this study. Collecting data at Dr. RSUP. M. Djamil Padang is the national referral hospital for COVID-19 in West Sumatera.

We created two sets of models, the first employing patient characteristics and physiology on admission to the ICU, and the second using physiology, treatment, and complications during ICU admission. We noted each patient's most extreme physiological variables on days 1 and 5 of ICU admission.

This research involves humans as research subjects. The ethical implications of this research follow the provisions of the Declaration of Helsinki and have passed the ethical test of the ethics committee of RSUP dr. M. Djamil in Padang with number LB.02.02/5.7/505/2021. All medical matters relating to this research are confidential. Research subjects have the right to refuse to participate in the study if they do not agree. All research costs and other costs incurred as a result of this research are borne by the researcher.

### Clinical data collection and outcome

We reviewed the electronic medical records

system in the hospital and collected the clinical information of all participants, including demographic data such as age, sex, and results of laboratory findings including sputum culture results, intubation, and clinical outcomes of patients when they were admitted and on the 5<sup>th</sup> day of therapy.

The sampling method used was total sampling. The primary endpoint of our study was clinical outcome of patients (whether they died or improved). We hypothesized that there is a correlation between multidrug resistance and clinical outcomes of patients, the correlation between intubation and multidrug resistance, and the correlation between intubation and clinical outcomes of MDR patients.

### Statistical analysis

All the authors had unrestricted access to the raw data. Missing data were not imputed. Numerical data were summarized using the mean, standard deviation, minimum, and maximum with comparisons between groups using the independent t-test. Categorical data were presented as numbers and percentages, with group comparisons using the Chi-square or Fisher's test at a 5% significance level. Data processing was done using an application statistical package for the social science version 18 (SPSS Ver. 18).

## Results

Sixty patients (26.4%), bacteria were found in the sputum culture, 40 (66.7%) of them were MDR patients. Patients with multidrug resistance are more common in men, adults, and patients with comorbid diabetes mellitus and hypertension (Table 1).

**Table 1: Characteristics of patients with multidrug resistance bacteria in critically ill patients with COVID-19 treated in the ICU at RSUP Dr. M. Djamil, Padang**

Variable	No. Growth		MDR		Non-MDR		Total	
	f (n = 167)	%	f (n = 40)	%	f (n = 20)	%	f (n = 227)	%
Gender								
Men	89	71.8	22	17.7	13	10.5	124	100
Women	78	75.7	18	17.5	7	6.8	103	100
Age								
Adult (18–64)	106	73.6	27	18.8	11	7.6	144	100
Elder (> 65)	61	73.5	13	15.7	9	10.8	83	100
Comorbid								
Diabetes mellitus	23	92.0	1	4.0	1	4.0	25	100
Hypertension	9	81.8	1	9.1	1	9.1	11	100
CKD	3	100	0	0	0	0	3	100
AKI	2	100	0	0	0	0	2	100
CVD	4	100	0	0	0	0	4	100

MDR: Multidrug resistance.

Based on Table 2, the most common bacteria found in sputum patient were *Acinetobacter baumannii* (35%) followed by *Klebsiella pneumonia* (21.7%), and *Escherichia coli* (11.5%).

Figure 1 illustrates antibiotic sensitivity pattern

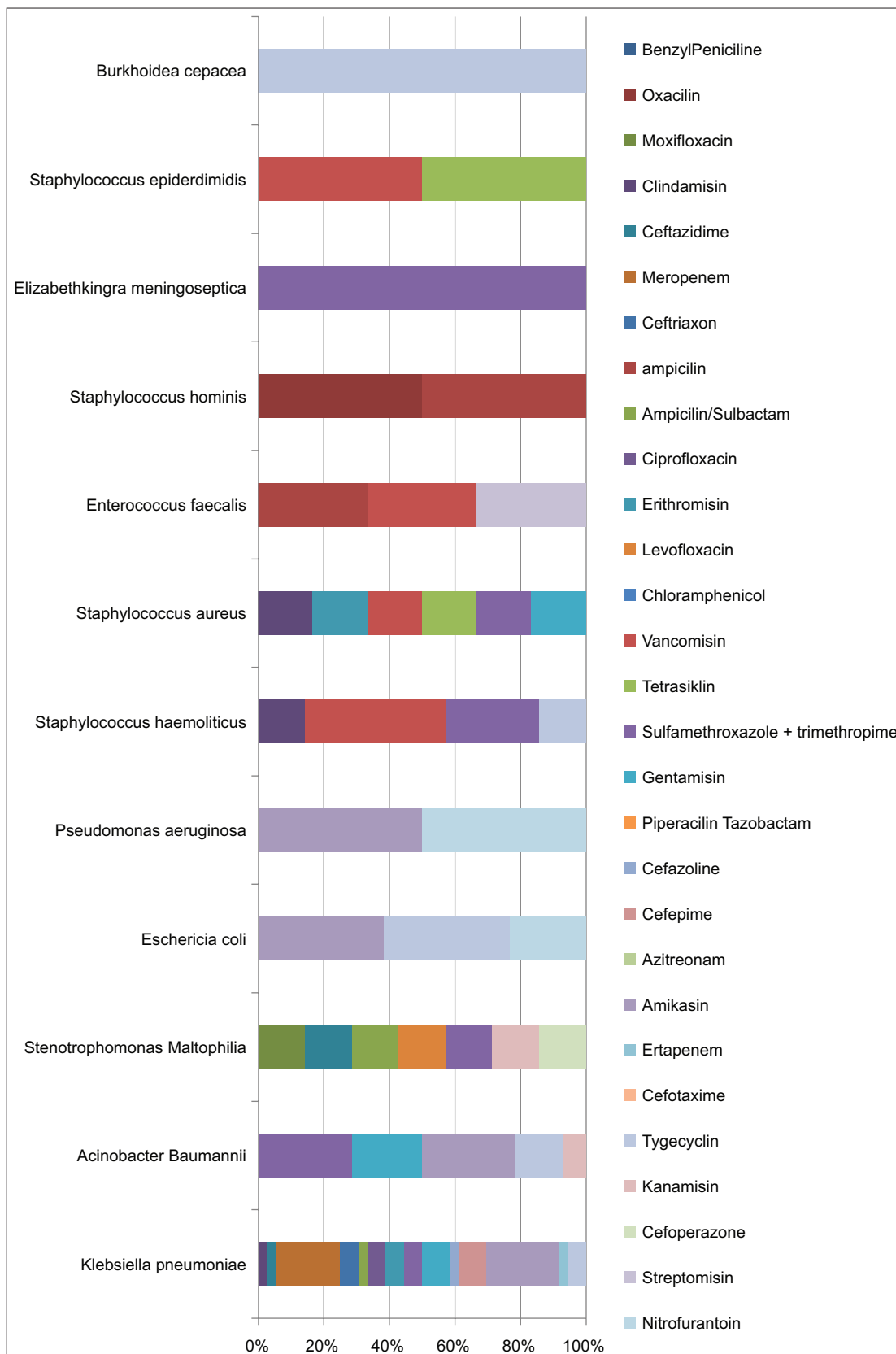


Figure 1: Antibiotic sensitivity pattern in multidrug resistance bacteria in critical ill patients with COVID-19 treated in the ICU Dr. M. Djamil, Padang

in multidrug resistance in critical ill patients with COVID-19. Klebsiella pneumonia bacteria are still very sensitive to various kinds of antibiotics.

Based on Table 3, there is a significant

relationship between multidrug resistance and clinical outcomes of patients (improvement/death) with  $p = 0.000$ . There is a significant relationship between intubation and clinical outcomes of MDR patients

**Table 2: Multidrug-resistant bacteria in critical patients with COVID-19 treated in the ICU at RSUP Dr. M. Djamil, Padang**

Variable	MDR		Non-MDR		Total	
	f (n = 40)	%	f (n = 20)	%	f (n = 60)	%
Types of germs						
<i>Klebsiella pneumonia</i>	9	69.2	4		30.8	13
<i>Acinetobacter baumannii</i>	11	52.4	10		47.6	21
<i>Stenotrophomonas maltophilia</i>	3	75.0	1		25.0	4
Escherichia coli						
<i>Pseudomonas aeruginosa</i>	6	85.7	0		0	7
<i>Staphylococcus hemolyticus</i>	2	25.0	3		75.0	4
<i>Staphylococcus aureus</i>	4	100	0		0	4
MRSA						
<i>Pantosa sp</i>	1	100	0		0	1
<i>Enterococcus Faecalis</i>	0	0	1		100	1
<i>Staphylococcus hominis</i>	0	0	1		100	1
<i>Elizabethkingra meningoseptica</i>	1	100	0		0	1
<i>Staphylococcus epidermidis</i>	1	100	0		0	1
<i>Burkholderia cepacea</i>	1	100	0		0	1

MDR: Multidrug-resistant, MRSA: methicillin-resistant *Staphylococcus aureus*.**Table 3: The relationship between resistance and intubation/HFNC to clinical outcomes of multidrug resistance patients with COVID-19 treated in the ICU of RSUP Dr. M. Djamil, Padang**

Variable	Outcome		p-value
	Death	Recovery	
Resistance			
No growth	56	111	0.000
Non-MDR	12	8	
MDR	32	8	
Oxygen demand intubate	98	64	0.000
HFNC	2	63	

MDR: Multidrug-resistant, HFNC: High-flow nasal cannula.

(p-value 0.000).

Based on Table 4, there is a significant relationship between intubation and multidrug resistance (p-value 0.009).

**Table 4: The relationship between resistance and intubation/HFNC to multidrug resistance patients with COVID-19 treated in the ICU at RSUP Dr. M. Djamil, Padang**

Variable	Intubasi	HFNC	p-value
Resistance			
No growth	110	57	0.009
Non-MDR	17	3	
MDR	35	5	

MDR: Multidrug-resistant, HFNC: High-flow nasal cannula.

## Discussion

Based on Table 1, 66.7% of the results of the sputum culture examination are MDR. Patients with multidrug resistance are more common in men, older people, and patients with comorbid diabetes mellitus and hypertension. There is a relationship between age, gender, and comorbidity to clinical outcomes of severe COVID-19 patients. In general, MDR infection rates in ICU patients range from 14% to nearly 50%, and the overall rate of suspected or proven infection was 54%, which was higher than in the ICU. During the pandemic, other respiratory coronavirus infections, such as MERS-CoV and SARS-CoV, co-infected with secondary infections.

Age, long duration of mechanical ventilation, comorbid diabetes mellitus, and hypertension were

independent high-risk factors for secondary infection in severe and critical COVID-19 patients. Old people was also associated with slow recovery and delayed response to therapeutic measures. Increased hyperinflammation in severe COVID-19 and the independent use of glucocorticoids and antibiotics are associated with secondary infection.

In a meta-analysis study conducted by Pasero *et al.* (2020), it was stated that 32–50% of critically ill COVID-19 patients developed an MDR infection during the ICU stay [9]. In line with the study of Li *et al.*, as many as 69 cases developed an MDR infection in critically ill COVID-19 patients during the ICU stay [10]. A retrospective study conducted by Palanisamy *et al.* (2021) stated that as many as 21–68% of 750 patients developed an MDR infection, and diabetes and hypertension contributed to critical COVID-19 deaths in patients who developed an MDR infection with male patients aged 54–70 years. However, in this study, there was no relationship between age, gender, and the incidence of MDR [11]. Alfonso-Sanchez *et al.* (2021) stated that 55% of the 364 patients admitted to the COVID ICU were men with an average age of 66.7 years with comorbid diabetes and hypertension. According to this study, there is a link between comorbidity and age and bacterial colonization and mortality in critically ill COVID-19 patients [12].

Based on Table 2, it was found that *Acinetobacter baumannii* (35%), *Klebsiella pneumonia* (21.7%), and *Escherichia coli* (11.5%). In early to mid-2021, we found that *Acinetobacter baumannii* (35%) was the most dominant in sputum culture, but after mid-year, there was a change in the pattern of bacteria, with *Klebsiella pneumonia* (21.7%) being the most dominant. This happened in the early to mid-week when we routinely administered intravenous carbapenem and meropenem antibiotic therapy, and in the middle of the year, there was a change in therapeutic guidelines for giving routine intravenous cefoperazone antibiotic therapy, resulting in a change in the bacterial pattern.

A meta-analysis study conducted by Pasero *et al.* (2020) mentions that *Staphylococcus aureus*, *Enterococcus spp.*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter spp.* bacteria most often experience MDR, cause death, and cause resistance to carbapenem antibiotics [9]. In the study, Palanisamy *et al.* (2021) stated that gram-negative pathogens such as *Acinetobacter baumannii* were the most common organism isolated, followed by *Klebsiella pneumonia* (32.8% and 21.9%) [11].

Based on Figure 1, in this study, we found that *Klebsiella pneumonia* was still sensitive to the antibiotics clindamycin, ceftazidime, meropenem, ceftriaxone, ampicillin-sulbactam, ciprofloxacin, erythromycin, sulfamethoxazole + trimethoprim, gentamicin, cefazolin, cefepime, amikacin, ertapenem, cefotaxime, and tigecycline, while *A. Baumannii* was only sensitive to the antibiotics sulfamethoxazole +

trimethoprim, gentamicin, amikacin, tigecycline, and kanamycin. *Klebsiella pneumoniae* bacteria are the most sensitive to antibiotics. We also found that the antibiotics sulfamethoxazole + trimethoprim, gentamicin, amikacin, tigecycline, and kanamycin were the most sensitive to bacterial patterns in severe COVID-19.

This is in contrast to the research of Medrzycka-D-Abrowska *et al.* (2021) who stated that *Klebsiella* caused resistance and was less sensitive, especially to the carbapenem class of antibiotics [13]. In line with the research of Palanisamy *et al.* (2021), which stated that, the gram-negative bacteria *Klebsiella pneumoniae* and *Enterococcus* sp. cause more antibiotic resistance, especially in the carbapenem group. In the study, the carbapenem resistance rates for *A. baumannii* and *K. pneumoniae* were 91.2% and 75.5%, respectively. A retrospective study in a French ICU found that 26 COVID-19 patients who were admitted to the ICU for acute respiratory failure were considered to be co-infected with a pathogenic bacterium, and two or five isolates were resistant to third-generation cephalosporins and amoxicillin/clavulanate [11]. In contrast to Buehler *et al.* (2021), who stated that the third-line class of antibiotics, tigecycline, ceftazidime/avibactam, or ceftolozane/tazobactam were sensitive to MDR and became the treatment of choice for secondary infections in COVID-19 [14].

Based on Tables 3 and 4, it is found that the relationship between MDR and intubation to clinical outcomes of patients (improvement/death) then the relationship between MDR and intubation is on the MDR. Prolonged use of ventilation and intubation in patients will increase nosocomial infections and VAP/HAP. This is following the study by Buehler *et al.* (2021), which stated that the use of mechanical ventilation, especially intubation, caused super infection in critical COVID-19 patients and gave a poor outcome. Research also says super infection in COVID-19 patients which critically leads to higher mortality. Research conducted by Alfonso-Sanchez *et al.* (2021) who also stated that secondary colonization of COVID-19 patients in the ICU gave a poor outcome and prognosis [12]. Research by Palanisamy *et al.* (2021) stated that endotracheal tubes cause secondary infection in COVID-19 patients treated in ICU and that there is a relationship between MDR and endotracheal tubes [11].

The potential for excessive use of antibiotics in the era of the COVID-19 pandemic is a global threat to the increasing incidence of multiresistant bacteria. To address the facts and available data, antibiotics are recommended for severe cases of COVID-19 and we do not recommend routine antibiotics for mild cases of COVID-19. If there is a sepsis condition that is strongly suspected to be due to bacterial co-infection, the selection of antibiotics is adjusted to the clinical condition, the focus of infection, and risk factors present in the patient. Blood cultures should be performed and sputum

cultures (with special care) should be considered. We suggest that the administration of antibiotics must be rational in the era of the COVID-19 pandemic using the Antimicrobial Stewardship principle: (1) taking culture material before giving antibiotics. Samples were adjusted according to the focus of infection and the patient's condition; (2) empiric antibiotic choice for VAP/HAP follows the microbiological pattern and local resistance pattern in each hospital; (3) evaluation of the rational use of antibiotics in the era of the COVID-19 pandemic; (4) the principles of prevention of nosocomial infections must continue to be observed; and (5) stop antibiotics if clinical and supporting examination results have improved (leukocyte parameters, type count, CRP, procalcitonin, imaging, and culture results) so that multiresistant bacteria can be prevented.

The study has several limitations. First, no timing of infection onset, duration of intubation, or information about the resolution of infection, appropriateness of treatment choice, or effectiveness of antibiotic choice were collected. In addition, point prevalence studies are also biased by the LOS, potentially resulting in oversampling of patients with longer ICU stays and influencing mortality risk assessment. Second, this was a single-center study that was performed at an Indonesian national referral hospital in Padang. Therefore, the patients may have had more complex conditions or comorbidities than those in the general population. Furthermore, additional studies are needed in a wider population. We suggest collecting data from other national referral hospitals in Indonesia in future studies.

## Conclusion

MDR patient status affected the outcome of COVID-19 patients in ICU. Patients with MDR were more likely to have a poor outcome.

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