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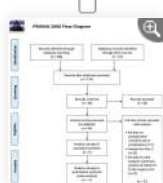
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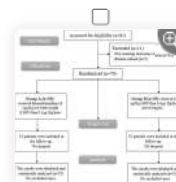
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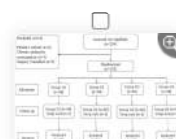
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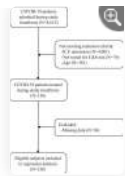
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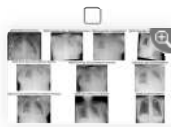
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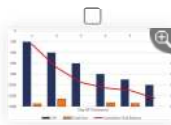


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# Multidrug-Resistant Organism Infections Correlate with Increased Mortality in COVID-19 Patients: A Retrospective, Observational Cohort Study

I Wayan Sumardika, Frederick Cokro<sup>1</sup>, I Wayan Suranadi<sup>1</sup>, Komang Januartha Putra Pinatih<sup>2</sup>

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## Abstract

**Background:** The uncontrolled use of antibiotics is a big problem that will lead to antibiotic resistance. One of the recommendations for Corona Virus Disease 2019 (COVID-19) therapy is antibiotics. This study aimed to present the incidence of multidrug-resistant organism (MDRO) infections in COVID-19 patients and the risk of mortality in COVID-19 patients in the Indonesian population. **Materials and Methods:** A retrospective cohort study was conducted at a tertiary medical center in Indonesia. A total of 120 subjects were included in this study and divided equally into group M (COVID-19 patients with MDRO infections) and group N (without MDRO). The culture was conducted between the 17th and 10th days of treatment. A  $2 \times 2$  table and chi-square test calculated the relative risk (RR) of MDRO causing mortality in COVID-19 patients. **Results:** The median age was 52 and 51 years old in groups M and N, respectively ( $P = 0.599$ ). Based on the documented data related to microbiological culture to detect the types of microorganisms, carbapenem-resistant *Acinetobacter baumannii* was found to be the most MDRO isolated (30%), followed by extended-spectrum beta-lactamase (26.6%). Bivariate analysis showed that MDRO infection strongly correlates with the incidence of death with a RR of 4.167 ( $P < 0.001$ ). **Conclusion:** MDRO infection is significantly correlated with mortality in COVID-19 patients. MDRO infections pose a four-fold chance of mortality compared to those without MDRO infections.

**Keywords:** Bacterial, COVID-19, drug resistance, incidence, multiple

## INTRODUCTION

The uncontrolled use of antibiotics is a big problem that will impact the future of humanity. Nowadays, especially in the era of the global Corona Virus Disease 2019 (COVID-19) pandemic, one of the main therapeutic recommendations is antibiotics. This has become a dilemma, where the threat of a crisis is directly caused by the COVID-19 infection and a more significant threat for the future, namely antibiotic resistance.

COVID-19 infection caused by severe acute respiratory syndrome coronavirus 2 was designated a global pandemic in 2020.<sup>[1]</sup> The prevalence of COVID-19 has reached 362 million cases, with a mortality rate of 5.68 million.<sup>[2]</sup> Apart from the nature of COVID-19, its morbidity and mortality rates are also caused by secondary bacterial or fungal infections.<sup>[3]</sup> Several studies have found that the prevalence

of COVID-19 patients with secondary infection reaches 14%–44%, where the secondary infection is associated with a poor clinical picture, a prolonged duration of hospitalization, and a high mortality rate.<sup>[4]</sup>

Extended hospitalization, prolonged use of mechanical ventilation, and infections acquired in health facilities have led to increased cases of infection by multidrug-resistant pathogens.<sup>[5]</sup> Multidrug-resistant organisms or

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MDROs are pathogens resistant to one or more classes of antibiotics and the most commercial antibiotics. Patients with COVID-19 and MDRO infection risk septic shock, worsening the clinical situation and increasing mortality.<sup>[5]</sup>

Studies on the incidence of COVID-19 with MDRO and identifying risk factors for MDRO are essential to control antibiotic resistance and prevent an increase in morbidity, mortality, length of stay, and cost of care in COVID-19 patients. The goal of this study was to present the characteristics, the rate of MDRO infections in COVID-19 patients, and the risk of mortality in COVID-19 patients in the Indonesian population.

## MATERIALS AND METHODS

This observational, retrospective cohort study was conducted from April to June 2022 at a tertiary medical center in Indonesia. The study was approved by the institutional ethical committee on March 30, 2022 (registry number: 1519/UN14.2.2.VII.14/LT/2022). The inclusion criteria were patients aged 18–60 years treated in the intensive care unit for COVID-19 from April to December 2020 and who had been tested for swab culture and antibiotic resistance. All subjects with incomplete medical records for the variables in this study were excluded. All subjects who were tested outside the mentioned period were also excluded. The study flow diagram is presented in Figure 1.

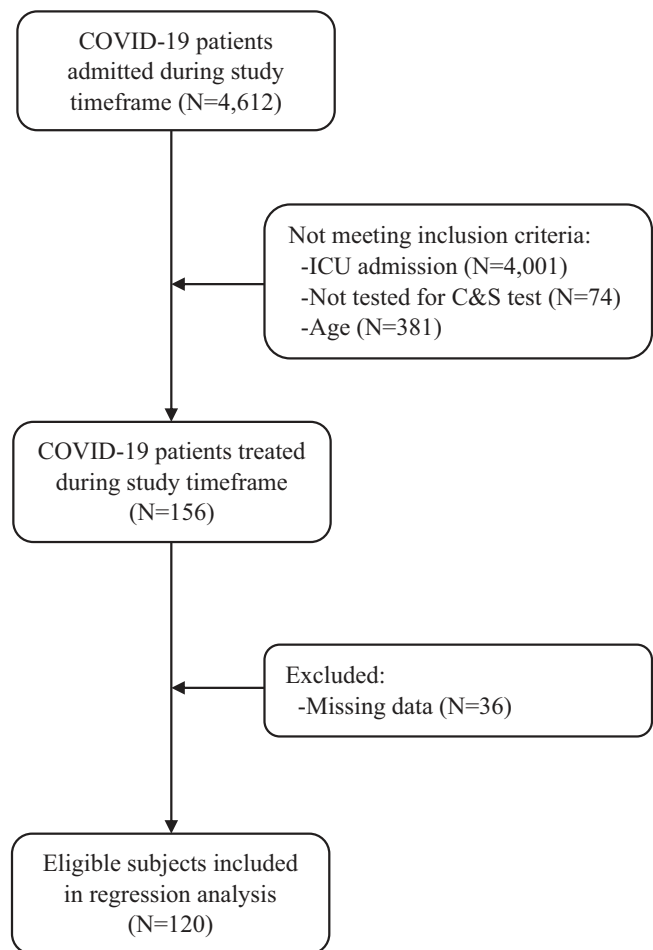
By all-inclusive sampling, we classify the subjects into the M group (MDRO infection) and the N group (non-MDRO infection). The minimum sample size in this study used the sample size formula for cohort studies.<sup>[6]</sup> Based on the formula, the minimal number of samples for the study was 30 samples for each group.

Demographic data were presented descriptively. We employed the Shapiro–Wilk test to test for normality. We then used a  $2 \times 2$  table to calculate the relative risk (RR) of MDRO causing mortality in COVID-19 patients. We used SPSS 28.0 software (IBM Corp., released 2021, IBM SPSS Statistics for Windows, Version 28.0; Armonk, NY: IBM Corp) as an analysis tool in this study. A  $P$  value of  $<0.05$  was considered significant.

## RESULTS

A total of equally assigned 120 subjects [Table 1] were enrolled in this study, with a median age of 52 and 51 years old in groups M and N, respectively ( $P = 0.599$ ). The most common comorbidity found in our study was diabetes mellitus. As per medical records, all subjects in the group M received at least one antibiotic compared with 54 (90%) in the group N.

Based on the documented data related to microbiological culture to detect the types of microorganisms [Table 2], carbapenem-resistant *Acinetobacter baumannii* (CRAB) was found to be the most MDROs isolated (30%),



**Figure 1:** Study flow diagram

followed by extended-spectrum beta-lactamase (ESBL). Meanwhile, we found that *Klebsiella pneumoniae* was the most common bacterial infection in the group N. The mortality rate was 83.3% in the group M compared with 20% in the group N. Bivariate analysis was carried out by comparing proportion comparisons to compare mortality in the two study groups with the Chi-square test [Table 3]. The test showed that MDRO infection strongly correlates with the incidence of death with a RR of 4.167 ( $P < 0.001$ ).

## DISCUSSION

Antibiotic therapy in the early days of the pandemic is one of the primary therapies used in managing COVID-19 and is also often used as a part of empiric therapy of infection according to diagnostic suspicion. In this study, more than 90% of all subjects received antibiotic therapy. This result is comparable to the previous studies.<sup>[7–9]</sup> The incidence of MDRO infection in this study was 23%. This figure is smaller than in previous studies by Bogossian *et al.*<sup>[10]</sup> and Giacobbe *et al.*<sup>[11]</sup>

The types of MDRO infections documented in this study were CRAB, ESBL, methicillin-resistant *Staphylococcus*

**Table 1: Subject characteristics**

Variables	Group M (N = 60)	Group N (N = 60)	P*
Age (years), median (IQR)	52 (9)	51 (9)	0.599
Sex, n (%)			0.754
Man	48 (80.0%)	52 (86%)	
Woman	12 (20.0%)	8 (14%)	
Diagnosis and comorbid, n (%)			-
Type II diabetes mellitus	10 (16.67)	12 (20)	
Chronic kidney disease	10 (16.67)	10 (16.67)	
Dyspepsia	6 (10)	10 (16.67)	
Hypertension	10 (16.67)	10 (16.67)	
Pleural effusion	4 (6.67)	2 (3.33)	
Coronary heart disease	8 (13.3)	2 (3.33)	
Empirical antibiotics, n (%)			0.076
Yes	60 (100)	54 (90)	
No	0 (0)	6 (10)	
All-cause mortality, n (%)			0.208
Yes	25 (83.3)	6 (20)	
No	5 (16.7)	24 (80)	

IQR = interquartile range

\*Shapiro-Wilk test

**Table 2: List of MDROs isolated from this study (group M)**

MDROs	N (%)
CRAB	18 (30)
ESBL	16 (26.67)
MRSA	2 (3.33)
MRSE	2 (3.33)

**Table 3: Correlation between MRDOs and mortality**

Variables	Mortality, n (%)		RR	95% CI	P*
	Yes	No			
MDRO	25 (83.3)	5 (16.7)	4.167	2.001–8.675	<0.001
Non-MDRO	4 (43.6)	26 (86.7)			

CI = confidence interval

\*Chi-square

*aureus* (MRSA), and methicillin-resistant *Staphylococcus epidermidis* (MRSE). A previous study also found that CRAB was the most common cause of MDRO infection.<sup>[12]</sup> Both *A. baumannii* and *K. pneumoniae* have been correlated significantly with mortality.<sup>[13-15]</sup>

A recently published review<sup>[16]</sup> reported that some causes of MDRO spread were empirical antibiotics use and the migration of MDRO bacteria from other patients. In COVID-19 settings, this migration may happen from personal protective equipment due to a lack of personnel.

Respiratory or multiple organ failure is the direct cause of death in COVID-19 cases, where secondary bacterial infections, especially MDRO, play an essential role in this process. This study's mortality rate was higher than in the previous reports.<sup>[4,12]</sup> Furthermore, we found

that COVID-19 patients with MDRO infections had a four-fold chance of mortality compared to those without MDRO.

The study had several design-related limitations. First, the sample size was small due to the limited time scope of this study. More extended and multicenter observations may provide a better understanding of this problem. Second, because of the institution's limited resources, especially in the COVID-19 setting, not all patients treated at our hospital were tested for culture swabs. The clinicians decided which patients were tested based on clinical judgment and personal experience. Third, we assessed the all-cause mortality rate instead of the COVID-19-specific mortality rate. Some subjects were admitted due to severe non-COVID-related issues, such as stage V renal failure, chronic obstructive pulmonary diseases, and heart failure. Although it is impossible to differentiate the cause of mortality in some patients, we believe that by doing so, we can specifically generalize the result of this study to the proper population.

## CONCLUSION

MDRO infection is significantly correlated with mortality in COVID-19 patients. MDRO infections pose a four-fold chance of mortality compared to those without MDRO infections. The presence of MDRO infection can cause patients to fall into worse conditions such as sepsis and multiple organ failure, leading to mortality.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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