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Critical priority Multidrug-Resistant Organisms (MDROs) secondary infection among COVID-19 patients: hidden threat during a pandemic? A retrospective study

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ABSTRACT

Background: The global Coronavirus Disease 2019 (COVID-19) pandemic is superimposed on the ongoing Multidrug-Resistant Organisms (MDROs) pandemic. Bacterial co-infection, particularly those caused by MDROs, is one of the risk factors linked to higher morbidity and mortality rates in COVID-19 patients. This study aims to compare critical priority MDROs profile causing bacteremia in COVID-19 and non-COVID-19 patients during a pandemic.

Methods: A hospital-based retrospective cross-sectional study was conducted at Dr. Soetomo General Academic Hospital from April 2020 to December 2021. This study used a consecutive sampling technique, which included and analyzed all identified microorganism isolates from blood specimens that met the inclusion criteria. The Mann-Whitney test was used to compare MDRO profiles between COVID-19 and non-COVID-19 patients, which is significant if $p < 0.05$.

Results: The total proportion of critical priority MDRO isolates in COVID-19 patients was 90/390 (23.08%), while in non-COVID-19 patients were 377/1446 (26.07%) isolates (p=0.228). Carbapenem-resistant *Acinetobacter baumannii* (CRAB) had a higher proportion of events in COVID-19 patients (12.05% vs. 7.05%, $p \leq 0.001$). In contrast, extended-spectrum *β*-lactamases (ESBL)-producing *Klebsiella pneumoniae* (ESBL-KP) had a higher proportion of events in non-COVID patients (7.54% vs. 2.82%, $p \leq 0.001$). *Acinetobacter baumannii* exhibited a high level of resistance, with 149/223 (66.82%) of the isolates being CRAB, with the COVID-19 group accounting for 47/59 (79.66%) and the non-COVID-19 group accounting for 102/164 (62.19%; $z = 2.438$; $p = 0.015$).

Conclusion: The high proportion and resistance rate of critical priority MDROs, CRAB particularly, among COVID-19 patients, highlights the importance of effective AMR control practices and prevention strategies during the pandemic.

Keywords: Bacteremia, COVID-19, CRAB, Critical Priority MDROs.
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INTRODUCTION

As the world faces COVID-19, an even more serious hidden threat emerges: antimicrobial resistance (AMR), which is not only still present but has worsened.[1] More than 29,400 people died from AMR infections commonly associated with healthcare during the first year of the pandemic. Nearly 40% of these people contracted the infection while in the hospital. According to the Centers for Disease Control and Prevention (CDC) 2019 threats report, AMR caused more than 2.8 million infections and more than 35,000 deaths annually in the United States between 2012 and 2017.[1] AMR has served as one of the enormous threats to global health and the economy in the past few years. Besides, the current COVID-19 pandemic is expected to accelerate the global rate of AMR growth.[2]

During the COVID-19 pandemic, the number of hospitalized patients increased the number of healthcare-associated infections (HAIs) and the risk of transmission of multidrug-resistant organisms (MDROs).[3] The COVID-19 pandemic emerges as a two-edged sword in terms of controlling AMR and limiting the spread of MDROs, as it has both positive and negative consequences. The pandemic serves as a stark reminder of the importance of basic infection prevention measures in Infection Control and Prevention (IPC) programs, including hand washing, cleaning of hospital equipment and environment and the use of personal protective equipment (PPE) when providing patient care to prevent the spread of MDROs in hospitals. However, the pandemic created various problems in terms of the use of antibiotics both at the community level and in hospitals.[4,5] The increase in COVID-19 patients being hospitalized was consistent with the increase in the administration of antibiotic therapy aimed at preventing secondary infections, which were feared to occur in patients, contrary to data which stated that out of 70% of COVID-19 patients

receiving antibiotic therapy, only 10 only % of them suffer from secondary infections due to bacteria.[6] Increased consumption of antibiotics to treat or prevent secondary bacterial infections in COVID-19 patients or as a potential therapy for COVID -19, such as teicoplanin, azithromycin and hydroxychloroquine, are thought to have contributed to the increase in AMR.[7-9] The increased use of antibiotics and biocidal agents such as disinfectants increases the concentration of antimicrobial agents in waste, which facilitates selective pressure and contributes to the resistance mechanism.[7,8]

The COVID-19 pandemic has emphasized the need to consider bacterial co-infection and secondary infection in viral infections especially hospitalized patients. Secondary infection in terms of bacteremia, particularly that caused by MDROs, is a risk factor associated with increased morbidity and mortality rates during viral infections and has also been linked to COVID-19.[2,10,11] Between 1997 and 2013, the percentage of bacteremia cases caused by Gram-negative bacteria increased significantly, from 33% to 43%. Various studies have consistently identified members of the order *Enterobacterales*, particularly *Escherichia coli* and *Klebsiella pneumoniae*, as the most prevalent, and non-*Enterobacterales* species, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[12] This is consistent with the WHO's list of pathogen priority groups, in which these four species have critical priority based on urgency and clinical significance.[13] Despite being the fifth most common pathogen of Gram-negative bacteremia, *Acinetobacter baumannii* has a very high resistance rate of up to 71%. Hence, it is critical to discuss these four problematic Gram-negative species in the context of bacteremia.[12] This study aims to compare critical priority MDRO profiles causing bacteremia in COVID-19 and non-COVID-19 patients during a pandemic.

METHOD

Study design

A hospital-based retrospective cross-sectional study was conducted from April 2020 to December 2021. The study was performed at Dr. Soetomo General Academic Hospital in Surabaya, East Java, Indonesia. All hospitalized patients with positive blood cultures were included and analyzed in this study. Confirmed COVID-19 patients were compared to non-COVID-19 patients during the same period.

Study population

Patients were considered to have COVID-19 if they were positive for SARS-CoV-2 RNA by reverse transcriptase PCR (RT-PCR) from respiratory secretions. Blood culture results from the COVID-19 patients registered between 1 April 2020 to 31 December 2021 were included and referred to as the "COVID-19 group" hereinafter. Non-COVID-19 patients are defined as patients with positive blood culture results registered between 1 April 2020 to 31 December 2021 with no confirmed PCR positivity for SARS-CoV-2.

Laboratory methods

This study utilized three distinctive blood culture bottles: BD Bactec Plus Aerobic, BD Bactec Plus Pediatric, and BD Bactec Plus Anaerobic. The Bactec Incubator's blood culture system was employed to incubate those bottles until a positive signal was attained, or the maximum length was five days. Specimens from the positive bottles were then subcultured onto the main agar plates, that is, blood agar plate (BAP), chocolate agar plate (CAP) and Mac Conkey agar plate. Direct Gram-staining is performed on positive blood culture specimens. Identification was performed using Gram-positive and Gram-negative panels from the BD Phoenix™ automated identification and susceptibility testing system and VITEX-2 based on gram staining and the characteristics of the colonies growing on agar media. Antibiotic susceptibility testing (AST) was carried out using the micro-dilution method by BD Phoenix™ and VITEK-2 systems in accordance with the manufacturer's recommendations and added with the manual disk diffusion method.

SARS-CoV-2 RT-PCR. Testing for SARS-CoV-2 was performed by RT-PCR assays: Cobas SARS-CoV-2 (Roche Molecular Systems, Inc., Branchburg, NJ).

Data analysis

This study used a consecutive sampling technique, which included and analyzed all identified microorganism isolates from blood specimens that met the inclusion criteria during the research period. This study concentrated on critical priority MDROs based on WHO criteria, comprising Carbapenem-resistant *Acinetobacter baumannii* (CRAB), Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), Carbapenem-resistant Enterobacteriaceae (CRE) including Carbapenem-resistant *Escherichia coli* (CREC), Carbapenem-resistant *Klebsiella pneumoniae* (CRKP), extended-spectrum *β*-lactamases (ESBL) -producing *Escherichia coli* and *Klebsiella pneumoniae* (ESBL-EC, ESBL-KP).

Isolation of the same microorganism from blood specimens within 14 days was not considered a new episode and was excluded from the analysis. The following isolates were considered contaminants if grown in less than two bottles of blood culture and were excluded from analysis: *Bacillus* spp., *Corynebacterium* spp., *Cutibacterium* spp., coagulase-negative *staphylococci* (CoNS), *Micrococcus* spp., *Cellulomonas* spp., *Lactobacillus* spp., *Dermabacter* spp., *Facklamia* spp., *Rothia* spp., *Exiguobacterium* spp., *Brevibacterium* spp., and *Trueperella* spp.

Statistical analysis

The incidence rate of critical priority MDROs were compared in both groups using the Chi-square statistic. Differences in MDROs profile between groups were analyzed by Mann-Whitney statistical analysis. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Characteristic of subject

The total number of isolates derived from blood specimens and suspected as pathogens causing bacteremia in hospitalized patients from April 2020 to December 2021 was 1836 isolates. Of 1836 isolates, there were 390 isolates (21.24%) from patients with confirmed COVID-19 and 1446 isolates (78.76%) from non-COVID-19 patients. Table 1 shows the characteristics of the subjects in this study. In the two groups, it was indicated that

Table 1. Characteristics of subjects.

Characteristic	COVID-19	non-COVID-19	p
Gender			
Male	234 (60)	812 (56.15)	0.174
Female	156 (40)	634 (43.85)	
Age			
0-5 years	17 (4.36)	450 (31.12)	<0.001**
6-18 years	9 (2.31)	177 (12.24)	
19-30 years	25 (6.41)	108 (7.47)	
31-45 years	87 (22.31)	171 (11.83)	
46-59 years	149 (38.21)	315 (21.78)	
>60 years	103 (26.41)	225 (15.56)	
Room			
Emergency department	40 (10.26)	213 (14.73)	0.487
High care unit	169 (43.33)	557 (38.52)	
Low care unit	181 (46.41)	676 (46.75)	
Etiology			
Gram-positive	168 (43.08)	441 (30.50)	<0.001**
Gram-negative	203 (52.05)	876 (60.58)	
Fungal	19 (4.87)	129 (8.92)	

Note: *significant <0.05; **significant <0.001.

there was no distinction in gender and room distribution. The difference which was considered significant was pointed out in the distribution of age and the etiology of bacteremia. Most patients who experienced bacteremia in the COVID-19 group were 46–59 years old (38.21%), and the non-COVID-19 group was 0–5 years old (31.12%) ($p < 0.001$). The etiology of bacteremia in COVID-19 and non-COVID-19 patients is significantly different, in which the majority were Gram-negative (52.05% vs. 60.58%), followed by Gram-positive (43.08% vs. 30.50%) and fungal (43.08% vs. 30.50%) ($p < 0.001$).

Bacteremia Microorganism Profile in COVID-19 and non-COVID-19 Patients

The most isolated species of microorganisms were *Klebsiella pneumoniae* 239/1836 (13.02%) isolates, *Acinetobacter baumannii* 223/1836 (12.15%) isolates, *Staphylococcus aureus* 211/1836 (11.49%) isolates, *Escherichia coli* 177/1836 (9.64%) isolates, *Candida* spp 124/1836 (6.75%) isolates, *Pseudomonas aeruginosa* 115/1836 (6.26%) isolates, *Enterococcus faecalis* 100/1836 (5.45%) isolates, *Enterobacter cloacae* 69/1836 (3.76%) isolates, *Staphylococcus haemolyticus* 62/1836 (3.38%) isolates, and *Staphylococcus epidermidis* 61/1836 (3.32%) isolates. The comparison of microorganism distribution in COVID-19 and non-COVID-19 is displayed in Table 2.

Microorganisms detected from blood cultures differed significantly between the two groups studied ($p = 0.017$). *Acinetobacter baumannii* was the pathogen with the highest proportion in the COVID-19 patient group, with 59/390 (15.13%) isolates, while *Klebsiella pneumoniae* had the highest proportion in the non-COVID-19 patient group, with 195/1446 (13.49%) isolates. The proportion of *Escherichia coli* and *Pseudomonas aeruginosa* isolates in the non-COVID-19 patient group was higher, with 177/1446 (9.64%) and 97/390 (6.71%) isolates compared to 29/1446 (7.44%), and 18/390 (4.62%) isolates in the COVID-19 patient group.

Critical Priority MDROs Profile in COVID-19 and non-COVID-19 Patients

The total proportion of critical priority MDRO isolates in COVID-19 patients was 90/390 (23.08%), while it was 377/1446 (26.07%) in non-COVID-19 patients ($p = 0.228$). CRAB had a higher proportion of events in COVID-19 patients (12.05% vs. 7.05%, p 0.001). ESBL-KP, on the other hand, had a higher proportion of events in non-COVID patients (7.54% vs. 2.82%, p 0.001). There are no differences in the proportion of other critical priority MDRO events between COVID-19 and non-COVID-19 patients, as shown in Table 3.

Acinetobacter baumannii exhibited high resistance, with 149/223 (66.82%) of the isolates being CRABs, with the COVID-19 group accounting for 47/59 (79.66%) and the non-COVID-19 group accounting for 102/164 (62.2%; $z = 2.438$; $p = 0.015$). *Pseudomonas aeruginosa* exhibited moderate resistance, with 33/115 (28.70%) of the isolates being CRPA, with the COVID-19 group accounting for 6/18 (33.33%) and the non-COVID-19 group accounting for 27/97 (27.84%; $z = 0.472$; $p = 0.637$). In total *Escherichia coli* isolates, 104/177 (58.76%) ESBL-EC and 14/177 (7.91%) CREC were found. In the COVID-19 patient group, the proportion of ESBL-EC was 17/29 (58.62%) with 1/29 (3.45%) CREC, and in the non-COVID-19 group, the proportion of ESBL-EC was 87/148 (58.78%) with 13/148 (8.78%) CREC ($z = 0.841$; $p = 0.400$). In total *Klebsiella pneumoniae* isolates, there were 120/239 (50.21%) ESBL-KP and 47/239 (19.67%) CRKP. In the COVID-19 group, the proportion of ESBL-KP was 11/44 (25%) with 8/44 (18.18%) CRKP, and in the non-COVID-19 group, it was 109/195 (55.89%) ESBL-KP with 39/195 (20 %) CRKP ($z = 3.118$; $p = 0.002$). Figure 1 displays the resistance rate of critical priority pathogens causing bacteremia in COVID-19 and non-COVID-19 patients.

DISCUSSION

The high proportion of male patients in the COVID-19 patient group is consistent with the findings of a study, which stated that there was an increased risk of hospitalization and the severity of the COVID-19 consequences in male patients compared to females so that male dominates the frequency of COVID-19 hospitalizations.[14] Furthermore, the male gender was associated with higher hospital mortality rates, the risk of respiratory intubation, and a longer length of stay in COVID-19 patients.[15] Increased hospitalization rates in older age groups are associated with pre-existing age-related immunity as well as the presence of comorbidities such as cardiovascular disease and metabolic disorders that commonly accompany older patients, resulting in more severe disease severity.[16] The rates of hospitalization and COVID-

Table 2. List of microorganisms causing bacteremia in COVID-19 and non-COVID-19 patients.

Microorganism species	COVID-19 n (%)	non-COVID-19
Klebsiella pneumoniae	44 (11.28)	195 (13.49)
Acinetobacter baumannii	59 (15.13)	164 (11.34)
Staphylococcus aureus	46 (11.79)	165 (11.41)
Escherichia coli	29 (7.44)	148 (10.24)
Other Gram-negative rod[a]	22 (5.64)	127 (8.78)
Pseudomonas aeruginosa	18 (4.62)	97 (6.71)
Enterococcus faecalis	25 (6.41)	75 (5.19)
Enterobacter cloacae	14 (3.59)	55 (3.80)
Candida spp.	10 (2.56)	53 (3.67)
Staphylococcus haemolyticus	14 (3.59)	48 (3.32)
Staphylococcus epidermidis	26 (6.67)	35 (2.42)
Streptococcus spp.	13 (3.33)	31 (2.14)
Other Gram-positive coccus	14 (3.59)	30 (2.07)
Staphylococcus hominis	19 (4.87)	17 (1.18)
Candida tropicalis	4 (1.03)	28 (1.94)
Candida albicans	1 (0.26)	28 (1.94)
Enterobacteriaceae spp.	4 (1.03)	24 (1.66)
Pseudomonas spp.	5 (1.28)	21 (1.45)
Salmonella spp.	1 (0.26)	24 (1.66)
Other Fungus	4 (1.03)	21 (1.45)
Enterococcus faecium	6 (1.54)	15 (1.04)
Other Gram-positive rod	3 (0.77)	15 (1.04)
Streptococcus pyogenus	3 (0.77)	10 (0.69)
Acinetobacter spp.	2 (0.51)	9 (0.62)
Burkholderia cepacia	2 (0.51)	8 (0.55)
Streptococcus faecalis	2 (0.51)	3 (0.21)

Note: [a]*Moraxella* spp., *Neisseria* spp., *Kocuria* spp., *Proteus* spp., *Achromobacter* spp., *Providencia* spp., *Sphingomonas* spp., *Kluyvera* spp., *Serratia* spp., *Stenotrophomonas* spp., *Aeromonas* spp., *Pantoea* spp., *Morganella* spp., *Citrobacter* spp.
[b]*Enterococcus* spp., *Abiotrophia* spp., *Leuconostoc* spp., *Globicatella* spp., *Granulicatella* spp.
[c]*ryptococcus* spp., *Tricosphorum asahii*, *Millerozyma farinose*, *Kodamaea ohmeri*
[d]*Clostridium* spp., *Bacillus* spp., *Corynebacterium* spp., *Gemella* spp.

19-related deaths vary significantly by country. This variation could be due to differences in healthcare facilities and/or patient epidemiological characteristics. However, there is a consistent and distinct pattern of exponential increase in age-related mortality regardless of geographic region.[17] Elderly patients are a significant risk factor for COVID-19 death among COVID-19 patients. Additionally, age is also affecting the time from hospitalization to death and viral clearance.[18]

The most isolated species of microorganisms that cause bacteremia in the COVID-19 and non-COVID-19 patient groups include *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Enterobacter cloacae*, *Staphylococcus haemolyticus* and *Staphylococcus epidermidis* These results were consistent with the previous study indicating that the top 10 species isolated from patients with bacteremia between 1997 and 2016 encompassed *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Enterobacter cloacae*, *Streptococcus pneumoniae*, *Enterococcus faecium*, and *Acinetobacter baumannii*.[12] Secondary transmission of SARS-CoV-2 infection by *Acinetobacter baumannii* has been widely reported in the literature during the COVID-19 pandemic, including research from Wuhan (China), France, Spain, Iran, Egypt, New York (USA), Italy, and Brazil.[11,16,19–23] Apart from *Acinetobacter baumannii*, other critical priority MDROs, namely *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*, were also reported as co-infected pathogens in COVID-19 patients in these various studies. In a meta-analysis study on the incidence of co-infection in COVID-19 patients, there were 1,959 isolates identified, 569 (29%) of which were MDROs, with the highest proportion of isolates being *Klebsiella pneumoniae* (n = 169), *Acinetobacter baumannii* (n = 148), *Pseudomonas aeruginosa* (n = 65), and *Escherichia coli* (n = 43). Another study also identified *Acinetobacter baumanni* as the responsible agent in COVID-19 patients with secondary ventilator-associated pneumonia (VAP) infections.[24] A study in Spain showed that 16% of patients with COVID-19 had fungal or bacterial co-infection/superinfection, and MDR *Acinetobacter baumannii* is the leading cause of respiratory tract infections in the form of VAP, which develops into bacteremia with outbreaks contributing to this.[21] Based on previous studies, evaluating data from 212 patients with severe COVID-19 found that *Acinetobacter baumannii* was the second most common pathogen isolate with positive bacterial cultures and was responsible for the third highest mortality rate in co-infected COVID-19 patients.[25] A study in Iran reported co-infection with MDR *Acinetobacter baumanni* in 17 of 19 COVID-19 patients with high resistance to all antimicrobials tested, except colistin, which showed a resistance rate of 52%, with all patients dying.[19] Among 1,495 COVID-19 patients who were hospitalized in Wuhan, 102 (6.8%) patients had secondary bacterial infections, mainly due to *Acinetobacter baumanni* (35.8%) with a high resistance rate (91.2%), and almost half (49.0%, 50/102) died during hospitalization. *Klebsiella pneumoniae* was identified as the second most common cause (30.8%), with a resistance rate of 75.5%.[16]

An Italian study's retrospective analysis of 32 COVID-19 ICU patients revealed that

Table 3. The proportion of critical priority MDRO events as a cause of bacteremia in COVID-19 and non-COVID-19 patients.

Pathogen	COVID-19			non-COVID-19			p
	CR	ESBL	non-MDR	CR	ESBL	non-MDR	
Acinetobacter baumannii	47 (12.05)	-	12 (3.08)	102 (7.05)	-	62 (4.29)	0.001**
Pseudomonas aeruginosa	6 (1.54)	-	12 (3.08)	27 (1.87)	-	70 (4.84)	0.665
Escherichia coli	1 (0.26)	17 (4.36)	11 (2.82)	13 (0.90)	87 (6.02)	48 (3.32)	0.100
Klebsiella pneumoniae	8 (2.05)	11 (2.82)	25 (6.41)	39 (2.70)	109 (7.54)	47 (3.25)	0.001**

Note: CR = Carbapenem-resistant; ESBL = extended spectrum β-lactamases; non-MDR = non-Multi Drug Resistance. *significant <0.05; **significant <0.001.

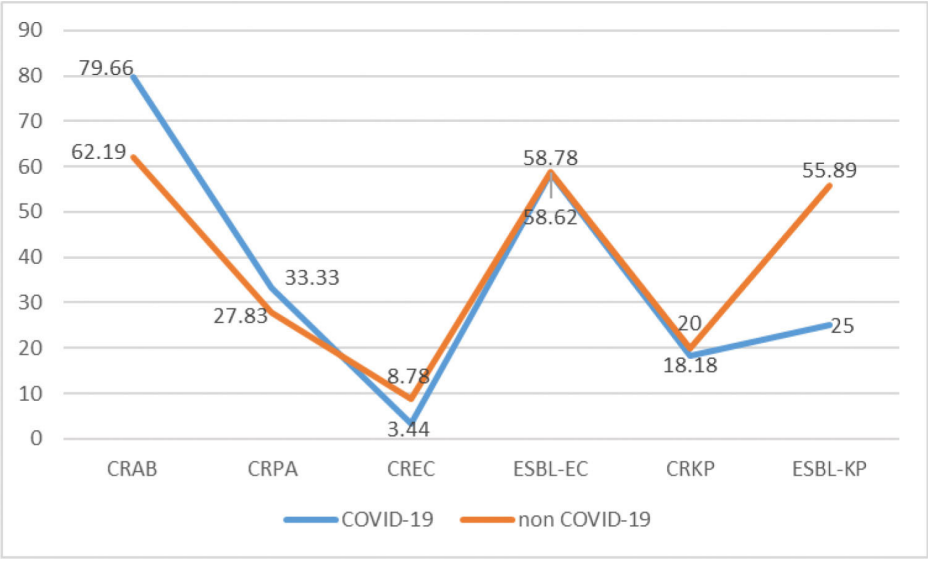

Figure 1. Resistance rate of critical priority MDROs causing bacteremia in COVID-19 and non-COVID-19 patients.

50% of patients developed MDR infections during their ICU stay. Overall, >80% of isolated MDR bacteria are Gram-negative bacilli, and the second most commonly isolated pathogen is CRAB.[26] *Acinetobacter baumannii* was detected in 20% of samples obtained from COVID-19 patients in the ICU in Beijing, China.[27] The highest incidence of CRAB co-infection was documented in an Egyptian study of 2.7% of patients hospitalized with COVID-19.[22] The Spanish study demonstrated co-infection with *Acinetobacter baumanni* to occur in 2.4% of hospitalized patients (17 of 712; 16 of 17 were in the ICU); as a predictor of mortality.[21] The mortality rate of *Acinetobacter baumannii* infection is 20-60%; significance across a wide clinical spectrum, such as bacteremia, pulmonary infection, meningitis, and diarrhea, has been widely reported.[28] Various factors contribute to the pathogenicity of *Acinetobacter baumannii*, including cell-surface hydrophobicity, which increases the adhesion ability of bacteria, the production of slime polysaccharides, which are toxic to neutrophils, the production of verotoxins, and the presence of siderophores and outer membrane proteins, which induce apoptosis of epithelial cells. In addition to the various virulence factors possessed by *Acinetobacter* spp., this organism poses major clinical problems due to its resistance to antibiotics, which causes treatment failure with available antibiotics. CRAB is one of the pathogens with a high incidence in the ICU and often causes outbreaks; this is due to the ability of *Acinetobacter baumannii* to survive for a long time on wet or dry surfaces, which is facilitated by its virulence factor, namely cell surface hydrophobicity.[29]

Patients with COVID-19 are at increased risk of bacterial co-infection, especially by MDROs, besides other factors that increase the risk of severe infection. Treatment management with the use of steroids in most patients with COVID-19, in addition to other immunomodulators, and the use of broad-spectrum empiric antimicrobials also contributes to the increased incidence of co-infection of patients with COVID-19 by MDROs. Overusing empirical antimicrobials in COVID-19 patients during the pandemic supports a significant increase in MDROs of carbapenemase-producing Gram-negative rods.[30] Surveillance data allows early detection of MDRO outbreaks, thereby enabling faster treatment to limit the rate of spread to other patients. Implementing cohort or isolation of patients with MDRO infections, decolonization with chlorhexidine, general environmental cleaning, and investigations of transmission sources from both environmental sources around patients and health workers are some crucial steps that can be taken to suppress further transmission of critical priority MDROs in the ICU.[31-33]

This study looks at secondary infections, specifically bacteremia, in COVID-19 patients caused by MDRO and how they differ from non-COVID-19 patients. In the hospital, both COVID-19 and non-COVID-19 patients face a new health risk: antimicrobial resistance. Identifying MDRO pathogens as a cause of co-infection or secondary infection in hospitalized patients, particularly with COVID-19, highlights the importance of appropriate control practices and prevention strategies. There are several limitations to this study as well. First, we could not obtain baseline clinical data such as comorbidity, disease duration, length of hospital stays, and patient treatment. As a result, we could not assess the impact of

differences in patient characteristics on blood culture results. Second, because the current study was limited to bacteremia, data on other culture results were not analyzed, excluding the analysis of other secondary infections such as pneumonia. Further research is needed to investigate the clinical characteristics of COVID-19 patients with secondary infection, either bacteremia or other secondary infections such as pneumonia, as well as to assess the relationship between COVID-19 and AMR, the effect of AMR on the severity of COVID-19, and whether COVID-19 patients are more susceptible to infection by MDROs.

CONCLUSION

The proportion of critical priority MDRO events does not differ significantly between COVID-19 and non-COVID-19 patients, but the distribution of critical priority MDRO isolates does. The findings of this study highlight that *Acinetobacter baumannii* exhibited a high level of resistance, and even more, CRABs had a higher proportion of events in COVID-19 patients. The high proportion and resistance rate of critical priority MDROs, CRAB particularly, among COVID-19 patients, highlights the importance of effective AMR control practices and prevention strategies during the pandemic.

CONFLICTS OF INTEREST

None to declare.

ETHICAL CLEARANCE

This study was approved by the Dr. Soetomo General Academic Hospital Research Ethics Committee, Surabaya, Indonesia (approval number: 0923/LOE/301.4.2/VI/2022).

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AUTHORS' CONTRIBUTIONS

All authors contributed equally to this manuscript. The final manuscript was read and approved by all authors.

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