Risk Factors for Multi-Drug Resistance (MDR) Infections in COVID-19 Patients with Secondary Bacterial Infections

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ABSTRACT

***Background**: The COVID-19 pandemic has significantly affected global health, contributing to an increase in secondary bacterial infections caused by multidrug-resistant (MDR) pathogens, thereby increasing morbidity and mortality. This study aims to evaluate the risk factors of MDR bacterial infections in affected COVID-19 patients.* ***Methods**: This retrospective cohort study analyzed medical records, as well as clinical and epidemiological data of COVID-19 patients with secondary bacterial infections hospitalized in Cipto Mangunkusumo General Hospital during 2020 – 2021. During the procedures, only patients with positive microbial culture results were included. Bivariate and multivariate analyses were carried out to evaluate risk factors of MDR bacterial infections.* ***Results**: A total of 3203 medical records of COVID-19 patients were assessed, and 192 subjects were enrolled. The results showed that the most common secondary infection and pathogen were pneumonia and Acinetobacter baumanii, respectively. In addition, the most common MDR pathogen was A.baumanii. In the multivariate log-binomial analysis, the risk factors associated with MDR bacterial infections in COVID-19 were female gender (RR 1,194;CI95% 1,024 – 1,393 p 0,020), comorbidity (RR 1,181;CI95% 1,006 – 1,385, p 0,041), prior antibiotic use (RR 1.718;CI95% 1,127 – 2,620 p 0,012), and history of invasive procedure (RR 1,979;CI95% 1,423 – 2.753 p <0,001).* ***Conclusion**: Comorbidities, female gender, prior antibiotic use, and a history of invasive procedures were risk factors for secondary bacterial infections with an MDR pathogen in hospitalized COVID-19 patients.*

***Keywords**: COVID-19, secondary bacterial infection, MDR bacterial infection.*

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic has significantly affected global health since its emergence in Wuhan in December 2019. As of November 2023, approximately 772 million cases and 6.9 million deaths have been reported worldwide, including 6.81 million cases and 161,918 deaths in Indonesia.[1,2] Although case numbers have substantially decreased, the pandemic has shown several important challenges in infectious disease management, particularly the role of co-infections and secondary bacterial infections.

In severe COVID-19, secondary bacterial infections occur in approximately 6.9–8.1% of cases and represent a significant clinical concern, as viral infection predisposes patients to bacterial superinfection.[3] This phenomenon is associated with various conditions wherein a viral infection renders patients more susceptible to secondary bacterial infections. Given the substantial number of COVID-19 cases, the occurrence of secondary bacterial infections has become a significant concern. Several studies have shown that the reported prevalence varies widely across literature and settings. De Bruyn et al. found secondary infections in approximately 68% of hospitalized patients,[4] while Indonesian data from Lie KC in Cipto Mangunkusumo Hospital reported a lower incidence of 14.5%, predominantly involving *Acinetobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp.[5] This study also found that secondary infections were associated with markedly increased mortality (56.8% vs. 11% without infection).

A substantial proportion of these infections is caused by multidrug-resistant (MDR) organisms, particularly in intensive care settings, where rates range from 30% to 50%.[6] Sinto et al. reported MDR pathogens in 50% of bacterial infection cases, while Santoso et al. showed a strong association between MDR infections and mortality (AOR 5.63; p = 0.001).[7,8] The COVID-19 pandemic has also been associated with an increase in antimicrobial resistance, with Polly et al. documenting a 23% increase in MDR incidence density, including higher rates of carbapenem-resistant *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus*.[9] Similarly, de Carvalho et al. observed an increase in carbapenem-resistant Gram-negative bacteria along with the COVID-19 burden. These results show the growing impact of MDR pathogens as a critical complication of COVID-19.[10]

Considering the clinical impact of secondary bacterial infections with MDR organisms, evaluating the factors contributing to such infections is essential. Previous studies showed risk factors related to MDR bacterial infections in COVID-19, including intensive care admission, invasive mechanical ventilation, steroid administration, healthcare facility treatment, high Body Mass Index (BMI), and multiple comorbidities.[3,6,11,12,13]

Despite the existing literature, most results were obtained from ICU populations, limiting their generalizability to broader hospitalized patients. Data from Indonesia are also limited, further showing the need for context-specific evaluation. Therefore, this study aims to assess risk factors for MDR bacterial infections among hospitalized COVID-19 patients. The procedures were carried out across ICU/HCU and non-ICU settings, with variable selection informed by previously identified determinants of secondary bacterial infections.[2]

METHODS

This was a retrospective cohort study using secondary data from medical records. Consecutive sampling was carried out in COVID-19 patients with secondary bacterial infections who were hospitalized at Cipto Mangunkusumo General Hospital from 2020 to 2021. Inclusion criteria were adult patients aged ≥18 years, confirmed COVID-19 patients proven by the results of Polymerase Chain Reaction (PCR) obtained from nasopharyngeal swabs. Exclusion criteria were incomplete data from medical records. Secondary bacterial infections were defined as patients with an infection that occurred > 48 hours after admission or worsening of pneumonia, as well as clinical signs, laboratory, or radiological results, with proven microbiological results. Microbiological results were taken from sputum, blood, and urine samples. MDR

infections were caused by bacterial isolates found to be non-susceptible to at least 1 agent in ≥3 antimicrobial categories. Subgroups of MDR organisms include extensively drug-resistant (XDR) and pandrug-resistant (PDR) isolates. XDR organisms are resistant to almost all antimicrobial categories, but remain susceptible to only 1 or 2. Meanwhile, PDR organisms are resistant to all available antimicrobial agents across all categories. These classifications vary by microorganism, as species with intrinsic resistance require the exclusion of those categories before applying the definitions. Magiorakos et al. was examined for a comprehensive list and standardized criteria.[14]

The parametric data were shown as frequency, percentage, mean, and standard deviation, while the nonparametric data were reported as frequency and percentage. Bivariate analysis and log-binomial for multivariate analysis were performed and reported as the p-value and risk ratio (RR). Multicollinearity Assessment was carried out using the variance inflation factor (VIF) and model performance metric using Hosmer–Lemeshow test. The accepted level of significance was $p<0.05$. Statistical analysis was performed using IBM SPSS v.26 and Stata v.17.

This study has been approved by the FKUI Medical Study Ethics Committee, and the RSCM Research Department has granted permission with letter number: KET-1135/UN2.F1/ETIK/PPM. 00.02/2023

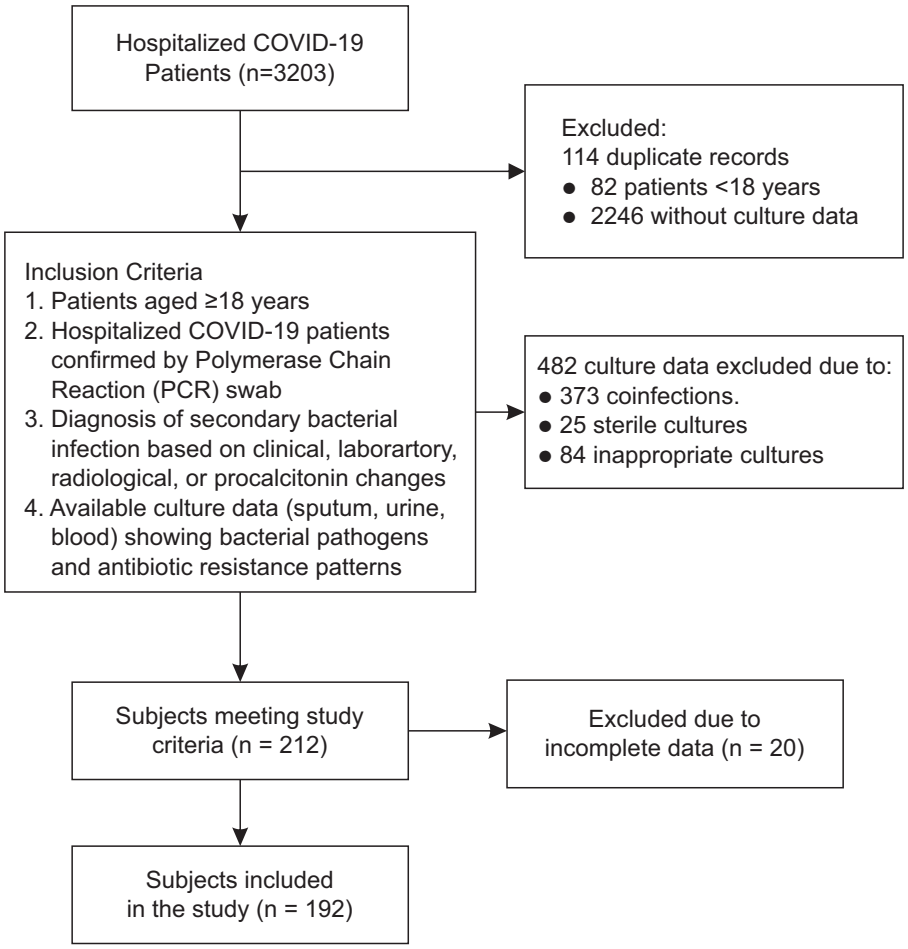

Figure 1. Flow Diagram.

RESULTS

Data were retrospectively collected from the medical records of hospitalized COVID-19 patients at Cipto Mangunkusumo General Hospital between 2020 and 2021. Of 3,203 patients, records were screened according to inclusion and exclusion criteria. A total of 114 duplicate records, 82 patients aged <18 years, and 2,246 records without culture results were excluded. Among the remaining 373 records with positive culture data, 25 yielded sterile results, and 84 were excluded due to non-eligible specimen sources (i.e., not sputum, urine, or blood). Ultimately, 192 patients were included in the final analysis.

The baseline characteristics of the study population are in **Table 1**. The majority of patients were male (57.8%), obese (50.5%), and had a Charlson Comorbidity Index (CCI) <2 (50.5%). The majority presented with severe or critical COVID-19 (60.9%), had received antibiotics before the diagnosis of secondary bacterial infection (83.8%), and had undergone invasive procedures beforehand (71.3%). Most patients were managed in intensive care settings (ICU/HCU) at the time of secondary infection (79.6%) and had poor performance status (ECOG 3–4) (70.8%). Pneumonia was the most common type of secondary infection (85.4%), and *Acinetobacter* spp. was the predominant pathogen (35.3%). The most frequent comorbidity was diabetes mellitus (34.9%), followed by malignancy (12.5%) and chronic kidney disease (11.9%).

Bivariate analysis was performed to identify factors associated with MDR bacterial infection among COVID-19 patients with secondary infections. Significant associations were observed for disease severity at admission, previous antibiotic use, history of invasive procedures, and intensive care unit (ICU) treatment. **Table 2** presents the statistical significance and relative risk estimates for each variable.

Variables with $p < 0.25$ in the bivariate analysis were included in the multivariate model. These comprised gender, comorbidity (CCI), COVID-19 severity at admission, antibiotic use, history of invasive procedures, and site of care during secondary infection (ICU vs. non-ICU). Multivariate analysis was performed using a log-binomial regression model, with stepwise elimination of variables with $p > 0.05$. The final model identified gender, comorbidities, antibiotic use, history of invasive procedures, and site of care as independent risk factors for MDR secondary infections. A history of invasive procedures conferred the highest risk (RR 1.979; 95% CI 1.423–2.753; $p < 0.001$), followed by antibiotic use (RR 1.718; 95% CI 1.127–2.620; $p = 0.012$).

Table 1. Characteristics of Study Participants

Variable	Total subjects (n=192)
Age (th), median (IQR)	54 (42-62,5)
Age Category n (%)	
<60 th	127 (66,1)
≥60 th	65 (33,8)
Gender, n (%)	
Female	81 (42,2)
Male	111 (57,8)
Obesity, n (%)	
No	95 (49,4)
Yes	97 (50,5)
Commorbidity, n (%)	
CCI <2	97 (50,5)
CCI ≥ 2	95 (49,4)
Type of Commorbidty	
DM	67 (34,9)
Solid cancer	24 (12,5)
CKD	23 (11,9)
CVD	21 (10,9)
COVID-19 Degree, n (%)	
Mild-moderate	75 (39,0)
Severe- critical	117 (60,9)
Antibiotic history, n (%)	
No	31 (16,1)
yes	161 (83,8)
Time of secondary	
≥14 Days	46 (24)
<14 days	146(76)
Invasive procedure history, n (%)	
No	55 (28,6)
Yes	137 (71,3)
Intensive care when secondary infections, n (%)	
No	76 (39,6)
Yes	116 (60,4)
Survival	
Alive	85 (44,3)
Death	107 (55,7)
Secondary infections	
Worsening of pneumonia/ Hospital Acquired Pneumonia	164 (85,4)
Urinary Tract Infection	14 (7,3)
Blood stream infection	14 (7,3)
Pathogen	N = 281
Acinetobacter baumanii	99 (35,3)
Klebsiela pneumonia	77(27,4)
Pseudomonas aeruginosa	25(8,89)
Escherichia coli	19 6,77)
Staphyococcus epidermidis	19 (6,77)
Pathogen MDR	N=107
Acinetobacter baumanii	52 (48,6)
Klebsiela pneumonia	23 (21,5)
Pseudomonas aeruginosa	8 (7,47

Table 2 Bivariate Analysis of Variable

Variable	MDR Bacterial Infection		RR (IK 95%)	p value
	Ya (%)	Tidak (%)		
Age				
≥ 60 th	49 (75,4)	16 (24,6)	1,113 (0,926 – 1,337)	0,252
< 60 th	86 (67,7)	41 (32,3)		
Gender				
Female	62 (76,5	19 (23,5)	1,164 (0,972-1,394)	0,099
Male	73 (65,8)	38 (34,2)		
Obesity				
No	67 (70,5)	28 (29,5)	0,994 (0,827 – 1,194)	0,949
Yes	68 (70,1)	29 (29,9)		
Commorbidity				
CCI ≥ 2	72(75,8)	23 (24,2)	1,167 (0,969 – 1,404)	0,102
CCI < 2	63 (64,9)	34 (35,1)		
COVID-19				
Severe-Critical	95 (81,2)	22 (18,8)	1,522 (1,211 – 1,914)	<0,0001
Mild-Moderate	40 (53,3)	35 (46,7)		
Antibiotic history				
Yes	123 (76,4)	38 (23,6)	1,973 (1,257 – 3,099)	0,003
No	12 (38,7)	19 (61,3)		
Invasive procedure history				
Yes	114 (83,2)	23 (16,8)	2,179 (1,544 – 3,075)	< 0,0001
No	21 (38,2)	34 (61,8)		
Intensive care when secondary infections	99 (85,3)	17 (14,7)	1,802 (1,405 – 2,310)	< 0,001
Yes	36 (47,4)	40 (52,6)		
No				
Time of secondary infection				
≥ 14 hari	34 (73,9)	12(26,1)	1,182 (0,686-2,035)	0,54
< 14 hari	101 (69,2)	45(30,8)		

Table 3 Multivariate Analysis with Log-Binomial

Variable	β	RR (IK 95%)	p
Step 1			
Female	-0,181	1,198 (1,028-1,396)	0,021
Commorbidity	0,177	1,194 (1,020 – 1,397)	0,027
Severity of COVID-19	0,142	1,152 (0,914 – 1,453)	0,231
Antibiotic History	0,480	1,616 (1,033 – 2,529)	0,036
Previous Invasive procedure	0,520	1,683 (1,146 – 2,474)	0,008
Intensive care when secondary infection	0,187	1,205 (0,877 – 1,658)	0,250
Step 2			
Female	-0,185	1,194 (1,024-1,393)	0,020
Commorbidity	0,166	1,181 (1,006 – 1,385)	0,041
Antibiotic History	0,541	1,718 (1,127 – 2,620)	0,012
Previous Invasive procedure	0,682	1,979 (1,423 – 2.753)	<0,0001

The regression model was evaluated with a multicollinearity assessment, as well as the AUC and Hosmer–Lemeshow test. Multicollinearity assessment was performed using pairwise correlation analysis and the VIF. The pairwise correlations among independent variables were generally low, with no correlation coefficients exceeding 0.7, with a mean VIF of 1.33.

The Hosmer–Lemeshow test showed that there was no significant difference between the observed and predicted outcomes with AUC 0.793 with AUC 0,793 (95% IK 0,719 – 0,867).

Table 4. Multicollinearity assessment

Variable	VIF
ICU admission	1.77
Previous Invasive procedure	1.47
Comorbidity	1.40
Severity of COVID-19	1.39
Age > 60	1.31
Antibiotic History	1.13
Obese	1.12
Female	1.03

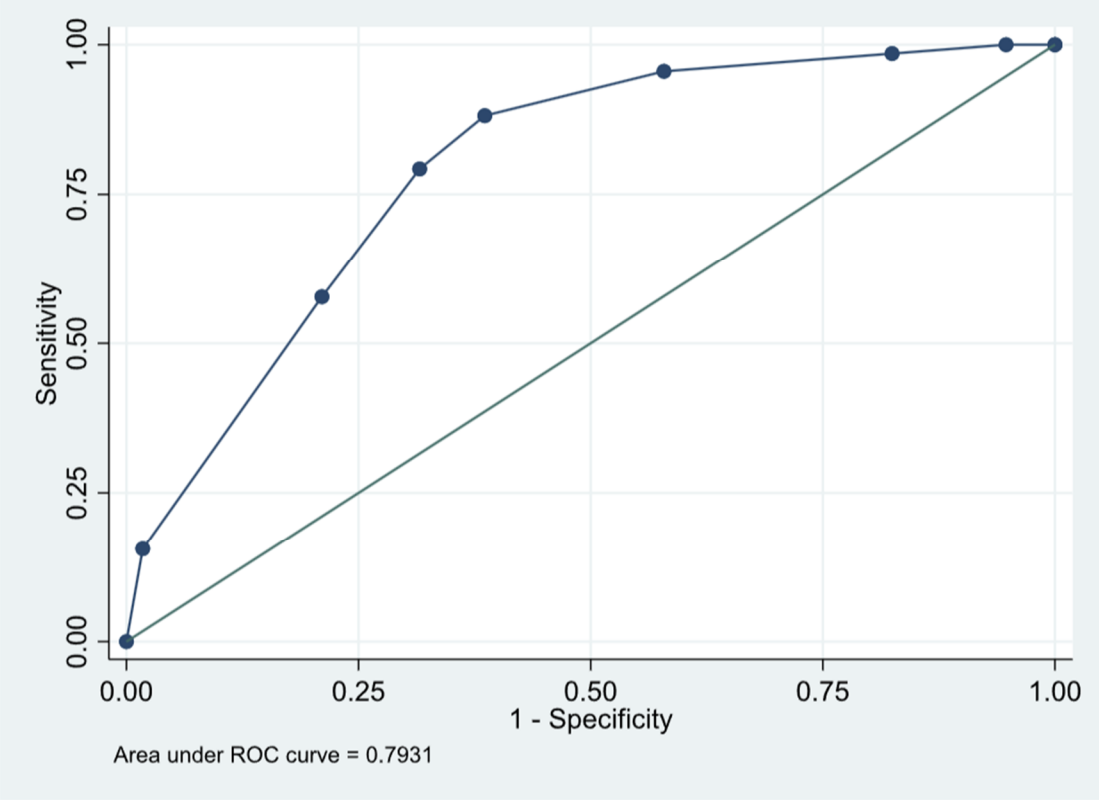

Figure 2. Hosmer–Lemeshow test.

DISCUSSION

A total of 192 participants were included in this study. Pneumonia was the most common secondary infection, accounting for 85.4% of cases, including worsening pneumonia and hospital-acquired pneumonia (HAP). Urinary tract infections (UTIs) and bloodstream infections (BSIs) each accounted for 7.29% of cases. These results are consistent with previous studies by De Macedo et al., Caiazzo et al., and Grasselli et al., which similarly reported pneumonia, catheter-associated UTIs, and BSIs as the most frequent secondary infections in COVID-19 patients.[11,12,15,16]

The most frequently isolated pathogen was *Acinetobacter baumannii* (35.2%), followed by *Klebsiella pneumoniae* (27.4%) and *Pseudomonas aeruginosa* (8.9%). Among MDR isolates, *A. baumannii* remained the predominant organism (48.6%), followed by *K. pneumoniae* (21.5%). Carbapenem-resistant *A. baumannii* (CRAB) was the most common MDR phenotype (18.5% of all isolates), followed by extended-spectrum beta-lactamase (ESBL)-producing organisms (5.69%). These results are consistent with previous studies, which also identified Gram-negative bacteria, particularly *A. baumannii* and *K. pneumoniae*, as the dominant pathogens in secondary infections among COVID-19 patients.[11,12]

This study identified comorbidity burden, antibiotic use, and history of invasive procedures as independent risk factors for MDR bacterial infections. A higher CCI was associated with increased MDR risk, consistent with Caiazzo et al., who reported that CCI ≥2 was significantly associated with MDR infection (OR 3.451; 95% CI 1.113–10.700).[12] Similarly, De Souza et al. showed that kidney disease is a risk factor for Gram-negative MDR infections (OR 2.84).[17] Patients with multiple comorbidities appear more susceptible to MDR secondary infections.

Antibiotic exposure was also significantly associated with MDR infections. This result was consistent with De Souza et al., who reported carbapenems and beta-lactams as independent

risk factors, while other antibiotic classes showed significance only in bivariate analysis.[17] The biological plausibility lies in selective pressure from antibiotic exposure, which promoted the emergence and dominance of resistant organisms over time.

In this study, invasive procedures were strongly associated with MDR infection. Mechanical ventilation and central venous catheter (CVC) use have been consistently identified as risk factors in previous studies.[3,11,17] De Macedo et al. reported that invasive interventions, including mechanical ventilation and CVC insertion, were associated with Gram-negative MDR infections.[11] Similarly, De Souza et al. observed that mechanical ventilation and CVC use were more frequent in COVID-19 patients with MDR infections compared to non-MDR cases.[17] A review by Pasero et al. identified invasive mechanical ventilation as the most consistent risk factor for MDR secondary infections across multiple studies.[3] Although Son et al. observed similar trends, the association did not reach statistical significance in multivariate analysis.[6] Disruption of epithelial barriers and increased exposure to healthcare-associated pathogens likely contribute to this association. Mechanical ventilation impairs respiratory mucosal defences, facilitating bacterial colonization and infection, while procedures such as CVC insertion and surgery bypass the skin barrier, providing direct access for pathogens.

Female sex was associated with a higher risk of MDR infections, which was inconsistent with previous reports. However, this result must be interpreted with caution. De Macedo et al. identified male sex as a risk factor (aOR 2.11)[11], and studies in non-COVID populations have similarly shown male predominance in MDR Enterobacteriaceae infections. This discrepancy could be explained by characteristics specific to the study population. A subgroup of female patients (8.85%) presented with severe COVID-19 during pregnancy, all of whom had low comorbidity burden (CCI <2) and underwent invasive procedures, predominantly caesarean section. A substantial proportion of these patients (13 cases) developed secondary MDR infections. This subgroup influenced the observed association between female sex and MDR risk. Importantly, sex was not significant in the bivariate analysis but became significant after multivariate adjustment, suggesting potential confounding or interaction with other variables such as comorbidity burden and invasive procedures. Due to the relatively small sample size, subgroup or sensitivity analyses were not performed, as these could not provide reliable estimates. Therefore, the observed association between female sex and MDR infection must be considered hypothesis-generating rather than conclusive. Further studies with larger and more balanced populations were needed to clarify this relationship.[3]

COVID-19 severity and location of secondary infections were significant in bivariate analysis but not in multivariate analysis, suggesting that their effects were mediated by other variables. Patients with more severe disease are more likely to receive antibiotics, undergo invasive procedures, and have a higher burden of comorbidities, which account for the loss of significance after adjustment. Consistent with this, De Macedo et al. did not directly assess disease severity but identified hypoxemia (SpO_2 <92%), a marker of severe disease, as a significant factor (OR 2.70; 95% CI 1.27–5.74; p = 0.0009).[11] Similarly, Son et al. reported an association between corticosteroid use and MDR infections (aOR 15.07), reflecting treatment intensity rather than severity per se.[6] In this study, ICU/HCU care was also associated with MDR infection in bivariate analysis but not after adjustment. Comparison with previous studies is challenging, as many were conducted exclusively in ICU populations. However, evidence from non-COVID-19 settings has consistently identified ICU admission as a risk factor for MDR infections, including nosocomial pneumonia and BSIs. This association is related to the critical care environment, where patients have more severe disease, greater exposure to invasive devices (such as mechanical ventilation, CVC), higher antibiotic use, and increased contact with healthcare personnel. These factors contribute to a higher risk of MDR bacterial infections in critically ill patients. [18,19,20]

The model from the log-binomial test was tested. The pairwise correlations among independent variables were generally low, with no correlation coefficients exceeding 0.7, showing the absence of strong linear relationships between predictors. The highest observed correlations were moderate, including between geriatric status and comorbidities (r = 0.4807), and between COVID-19 severity and secondary infection location (r = 0.5089), but these remained below the threshold of concern. These results showed that multicollinearity was not a significant issue in the model, and all variables were retained for subsequent multivariable analysis.

The Hosmer–Lemeshow test shows no significant difference between the observed and predicted outcomes with AUC 0.793 with AUC 0,793 (95% IK 0,719 – 0,867). The model showed good discriminatory ability, showing an adequate capacity to distinguish between patients with and without MDR bacterial infection. In addition, the Hosmer–Lemeshow test showed no significant difference between observed and predicted outcomes, suggesting good model calibration. In practical terms, the model correctly ranks patients according to their risk with reasonable accuracy, with a nearly 80% probability that a randomly selected patient with MDR infection will have a higher predicted risk than a patient without MDR infection. These results support the utility of the model as a tool for risk stratification in hospitalized COVID-19 patients, although further validation in external populations is warranted to confirm its generalizability.[5]

Strengths and Limitations of the Study

Few studies have investigated the risk factors for MDR infections in COVID-19 patients with secondary infections in Indonesia. This study adds to the limited data on this topic and setting, including non-critical populations (patients in regular inpatient care), a rarity in international study. When compared to studies with similar topics, this study delves deeper into the comparison between patients with secondary MDR bacterial infections and those without MDR. This is distinct from other studies that primarily compare with critical COVID-19 cases. Therefore, this study is relatively novel and is anticipated to contribute valuable insights to the existing body of knowledge, comprising a substantial number of COVID-19 patients, with a total of 3203 individuals screened for inclusion, covering the entire span of patients in 2021 and a portion from 2020.

However, this study has its limitations. It adopts a retrospective cohort design based on medical record data, which introduces information bias. Efforts to mitigate this bias have been made through operational limitations. In addition, being a single-centre study, the data presented here differ from those in other locations. The inclusion of only patients with available culture data may introduce selection bias. Not all patients with suspected secondary bacterial infections underwent microbiological testing, particularly those with mild to moderate disease, those treated empirically without cultures, or those who died before cultures could be obtained. As a result, the study population could be skewed toward more severe cases or those with higher clinical suspicion of infection, which are also more likely to involve hospital-acquired and MDR pathogens. This led to an overestimation of MDR prevalence and limited the generalizability of our results to the broader population of hospitalized COVID-19 patients. Although this limitation is inherent to retrospective studies conducted during an emergency outbreak setting, it must be considered when interpreting the results. Future prospective studies with systematic microbiological sampling were needed.[4]

CONCLUSION

In conclusion, comorbidities, a history of invasive procedures, and a history of antibiotic use are identified as risk factors for the occurrence of MDR infections in cases of COVID-19 patients with secondary infections. A history of invasive procedures poses the highest risk, followed by a history of antibiotic use and comorbidities.

CONFLICT OF INTERESTS

All the authors declare that there are no conflicts of interest.

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