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Risk Factors for Multidrug-Resistant Bacterial Infections in Hospital-Acquired Pneumonia at Cipto Mangunkusumo Hospital

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A B S T R A C T

Multidrug-resistant (MDR) hospital-acquired pneumonia (HAP) is linked to high mortality, extended hospital stays, and increased healthcare costs. Identifying risk factors for MDR HAP is essential to formulate effective management strategies. This study analyzed the proportion of risk factors associated with MDR bacterial infections in HAP patients treated at Cipto Mangunkusumo General Hospital. Using a retrospective cohort design, data were collected from medical records of HAP patients hospitalized between 2015 and 2016. A total of 68 patients met the inclusion criteria, while 10 were excluded due to fungal or non-pathogenic bacterial growth in sputum cultures. Patients were categorized as infected with MDR or non-MDR bacteria based on the resistance profile of their initial sputum cultures. Descriptive analysis was conducted using Microsoft Excel to calculate proportions of risk factors, without applying inferential statistical tests due to the limited sample size. The incidence of HAP was 6.12 per 1000 admissions in 2015 and 6.15 in 2016. MDR bacterial infections were observed in 95% of cases in 2015 and 82.1% in 2016. Key risk factors for MDR infections included prior antibiotic use within 90 days (100%), albumin levels <2.5 g/dL (100%), Charlson Comorbidity Index ≥3 (95.9%), age >60 years (95.2%), hospitalization >5 days (92.5%), nasogastric tube (NGT) insertion (92.1%), prior ICU/HCU admission within 90 days (81.8%), and steroid use >10 mg/day for >14 days (28.6%). These results emphasize that most HAP cases were caused by MDR bacteria, with prior antibiotic use and low albumin as predominant risk factors, necessitating targeted interventions for at-risk populations.

1. Introduction

Hospital-acquired pneumonia (HAP) is a leading cause of morbidity and mortality among hospitalized patients, with incidence rates in Asia ranging from 1 to 21 per 1,000 hospital admissions [1]. In Indonesia, HAP incidence is reported to be 538 cases per 100,000 hospital admissions, encompassing both adult and pediatric populations [2]. The condition is associated with significant mortality, with all-cause rates ranging from 13.1% to 27.7%, while multidrug-resistant (MDR) infections are particularly concerning, contributing to mortality rates as high as 25% to 60% [3].

MDR infections, particularly those caused by Gram-negative pathogens like Pseudomonas aeruginosa and Acinetobacter baumannii, impose considerable economic and clinical burdens [4]. For instance, patients

infected with MDR Pseudomonas aeruginosa incur a mean economic cost of €15,265 per admission compared to €4,933 for those infected with non-resistant strains [3]. In addition, the length of hospital stays is significantly longer in MDR infections than in infections caused by antibiotic-susceptible bacteria [3].

The prevalence of MDR bacteria varies significantly across regions. According to the Asian Network for Surveillance of Resistant Pathogens (ANSORP) study conducted in 73 hospitals across 10 Asian countries from 2008 to 2009, the prevalence of MDR pathogens was alarmingly high, with Klebsiella pneumoniae at 44.7%, Acinetobacter at 82%, and Pseudomonas aeruginosa at 42.8% . These patterns differ from those in Western countries, where Staphylococcus aureus is more predominant [5] .

In Southeast Asia, the burden of MDR infections in HAP has grown, as highlighted by recent studies. For example, Gandra et al. (2020) reported that Southeast Asia has one of the highest rates of antimicrobial resistance globally, driven by the overuse of antibiotics in healthcare settings [4]. Furthermore, there has been a consistent rise in MDR rates in HAP cases, with Acinetobacter baumannii and Klebsiella pneumoniae emerging as dominant pathogens in the region [6], [7].

Despite extensive global research, data on the risk factors for MDR bacterial infections in HAP patients in Indonesian hospitals remain sparse. Most existing studies focus on Western populations or broader Asian regions, which may not reflect the unique patterns in Indonesia [2], [4], [5]. The lack of local data hinders the development of effective, context-specific strategies to prevent and manage MDR HAP.

This study aims to address this gap by describing the proportion of risk factors associated with MDR bacterial infections in HAP patients at Cipto Mangunkusumo General Hospital, Jakarta. By identifying high-risk patient groups, the findings can inform institution-based empirical antibiotic treatment and targeted infection control measures to improve clinical outcomes.

2. Research Method

2.1. Study Design

This retrospective cohort study was conducted on patients diagnosed with hospital-acquired pneumonia (HAP) who were hospitalized at Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, during 2015–2016. The study included patients aged 18 years or older with positive sputum cultures. Data on demographic, clinical, and laboratory variables were extracted from both paper-based medical records and electronic health records (EHRs). To ensure consistency and accuracy, a two-step data validation process was implemented: independent double-checking by two reviewers and verification of key variables (such as diagnosis, lab results, and antibiotic use) against the hospital's electronic laboratory and pharmacy systems to minimize transcription errors.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria were patients diagnosed with HAP based on positive sputum cultures. Exclusion criteria included:

a. Patients with active pulmonary tuberculosis,

b. Sputum cultures showing fungal organisms without bacterial growth,

c. Sputum cultures showing only Streptococcus viridans,

d. Diagnoses of Community-acquired Pneumonia (CAP), Healthcare-associated Pneumonia (HCAP), or Ventilator-associated Pneumonia (VAP).

2.3. Patient Selection Process

The study employed total sampling, as the HAP population within the hospital during the study period was relatively small. This approach ensured that all eligible cases were included, minimizing sampling bias. A flowchart detailing the screening process for patient inclusion and exclusion is shown in Figure 1.

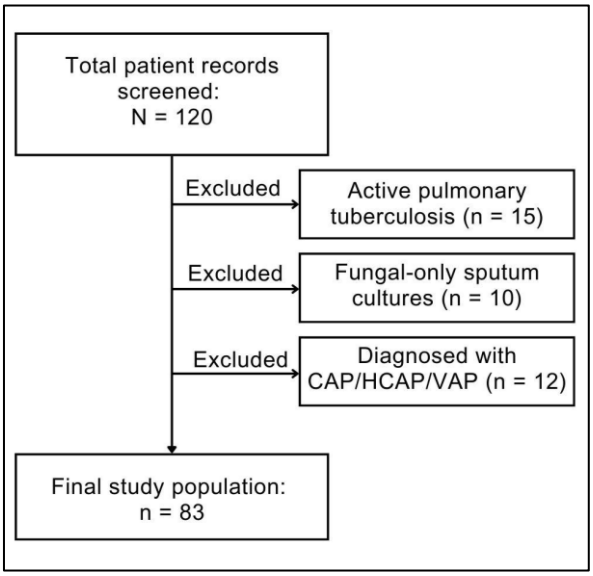

Figure 1. Patient Selection Flowchart

2.4. Data Collection

The data collected for this study included demographic information (age, gender), clinical data (comorbidities, prior antibiotic use, prior ICU/HCU hospitalization, and length of hospitalization), and laboratory data (albumin levels). Sputum culture results were analyzed and categorized according to Magiorakos et al., which classifies bacteria into sensitive, non-MDR, MDR, Extensively Drug-resistant (XDR), and Pandrug-resistant (PDR) categories [10].

2.5. Risk Factors Analyzed

Eight variables were specifically analyzed in this study as potential risk factors for MDR bacterial infections:

a. Prior ICU/HCU hospitalization in the last 90 days
b. Prior antibiotic use within 90 days
c. Proportion of patients with hospitalization >5 days
d. Nasogastric tube (NGT) insertion
e. Charlson Comorbidity Index ≥3
f. Prior steroid use (prednisone >10 mg/day or equivalent for >14 days)
g. Albumin level <2.5 g/dL
h. Age >60 years

2.6. Statistical Analysis

To investigate the relationship between risk factors and MDR infections, odds ratios (OR) were calculated to assess the association between various risk factors and multidrug-resistant (MDR) bacterial infections in hospital-acquired pneumonia (HAP). The odds ratio quantifies the strength of association between a specific risk factor and the likelihood of MDR infections. An OR greater than 1 suggests a positive association, indicating the factor increases the risk of MDR infections, while an OR less than 1 indicates a protective effect. The strength of the association can be categorized as follows: (a) OR between 1–2: weak association; (b) OR between 2–5: moderate association; (c) OR greater than 5: strong association.

2.7. Bacterial Classification

Sputum evaluations were conducted for all subjects. Patients were classified based on their sputum culture results as follows:

a. Infected with non-MDR bacterial infections if the sputum culture revealed sensitive or non-MDR bacteria.
b. Infected with MDR, XDR, or PDR if the sputum culture revealed resistant bacteria as per the categorization by Magiorakos et al. [10].

2.8. Data Analysis

The data were analyzed descriptively. Proportions and percentages were calculated for all variables to identify the distribution of risk factors associated with MDR bacterial infections. Microsoft Excel was used for data analysis.

2.9. Research Ethics

This study adhered to the principles of the Declaration of Helsinki and was approved by the Medical Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (Ethics Approval Number: 123/UN2.F1/ETIK/2017). All data were anonymized to protect patient confidentiality. Informed consent was waived due to the retrospective nature of the study.

3. Result and Discussion

3.1. HAP Incidence and Exclusion Criteria

The incidence of Hospital-acquired Pneumonia (HAP) in Cipto Mangunkusumo General Hospital during the years 2015 and 2016 was 6.12 per 1000 admissions and 6.15 per 1000 admissions, respectively. From the total of 68 HAP patients with positive sputum cultures, 10 patients were excluded from the analysis. The exclusions were as follows: 4 patients whose sputum cultures showed only fungal organisms without bacterial growth, and 6 patients whose sputum cultures showed only Streptococcus viridans (non-pathogenic in this context).

The proportion of HAP patients infected with MDR bacteria in 2015 and 2016 were 95% and 82.1%, respectively. This indicates a slight decrease in the proportion of MDR infections over the two years, although MDR bacteria remained a significant cause of HAP in the hospital. Table 1 shows the baseline characteristics of HAP patients compared to those with a positive culture. This table highlights age, sex, comorbidities, and other factors. For example, patients with a Charlson Comorbidity Index (CCI) ≥3 had an MDR prevalence of 95.9%, which suggests a strong relationship between high comorbidity and MDR infection risk.

Table 1. Baseline Characteristics of HAP Patients (n=280) Compared to HAP Patients with Positive Culture (n=68)

Baseline Characteristic	HAP (n=280)	HAP Patients with Positive Culture (n=68)
Age (years), median (min-max)	57 (18-95)	55 (19-80)
Sex, n (%)		
- Male	145 (51.8)	34 (50.0)
- Female	135 (48.2)	34 (50.0)
Smoking, n (%)	54 (19.3)	10 (14.7)
Comorbidities, n (%)		
- Cardiovascular diseasea	125 (44.6)	31 (45.6)
- Malignancy	114 (40.7)	35 (51.5)
- Diabetes Mellitus	81 (28.9)	16 (23.5)
- Chronic Lung Diseaseb	7 (2.5)	1 (1.5)
- Change in consciousness	76 (27.1)	11 (16.2)
- Sepsis	37 (13.2)	8 (11.8)
- Septic Shock	12 (4.3)	2 (2.9)
Ratio PaO2:FiO2 ≤200, n (%)	38 (13.6)	13 (19.1)
Pleural effusion, n (%)	36 (12.9)	8 (11.8)
Bilateral patch, n (%)	78 (27.9)	21 (30.9)

Note:

a. Includes hypertension, coronary artery disease, and chronic heart failure.
b. Includes chronic obstructive pulmonary disease (COPD) and asthma bronchial.

3.2. Risk Factors for MDR Infections

Table 2 shows the distribution of risk factors for MDR bacterial infections among HAP patients with positive cultures. Bar charts (Figure 2) have been added to visualize key proportions, such as the distribution of MDR pathogens and the relationship between ICU/HCU hospitalization and the prevalence of MDR infections. Table 3 depicted the odd ratio of each risk factors. The analysis identified several key risk factors significantly associated with MDR bacterial infections in HAP:

a. ICU/HCU hospitalization within 90 days prior to diagnosis was strongly associated with MDR infections (OR = 18.0). Patients who had been hospitalized in high-dependency care units were much more likely to have MDR infections compared to those who had not.

b. Antibiotic use within 90 days prior to diagnosis showed a perfect association with MDR infections. All MDR-infected patients had a history of recent antibiotic use, underscoring the critical role of antibiotic exposure in the development of resistance.

c. Hospitalization >5 days prior to diagnosis had a moderate association with MDR infections (OR = 3.1). Prolonged hospital stays likely increase the risk of exposure to resistant pathogens, although the association is weaker than some other factors.

d. Nasogastric feeding tube use was another strongly associated factor (OR = 11.7). This invasive device may facilitate colonization or infection by MDR bacteria, highlighting the need for careful monitoring of patients requiring tube feeding.

e. Charlson Comorbidity Index ≥3 was one of the strongest predictors of MDR infections, with an OR of 35.3. Patients with higher comorbidity scores were significantly more likely to develop MDR infections, likely due to weakened immune systems and frequent healthcare exposure.

f. Steroid use (prednisone >10 mg/day or equivalent for >14 days) was inversely associated with MDR infections (OR = 0.017). Patients receiving prolonged steroid therapy were less likely to have MDR infections, which may be attributed to unmeasured confounding factors or patient selection bias.

g. Albumin <2.5 g/dL also had a perfect association with MDR infections. All patients with low albumin levels (an indicator of poor nutritional and physiological status) were infected with MDR bacteria, suggesting that malnutrition or severe illness plays a critical role in susceptibility to resistant pathogens.

h. Age >60 years old showed a moderate association with MDR infections (OR = 5.0). Older patients were more likely to have MDR infections, potentially due to age-related declines in immunity and greater healthcare exposure.

In summary, factors such as ICU hospitalization, recent antibiotic use, prolonged hospital stays, nasogastric feeding tube use, and a Charlson Comorbidity Index ≥3 are significantly associated with increased risk of MDR bacterial infections. Notably, certain factors like recent antibiotic use and low albumin levels exhibit perfect associations, further emphasizing their importance in identifying high-risk patients. Conversely, steroid use was inversely associated, warranting further investigation to clarify this relationship. These findings underscore the need for careful management of modifiable risk factors, especially in high-risk patient populations, to mitigate the development and spread of MDR bacterial infections.

Table 2. Risk Factors Distribution of MDR Bacterial Infections in HAP (n=68)

Risk Factor	Infected by MDR Bacteria (n=63)	Infected by Non-MDR Bacteria (n=5)
ICU/HCU hospitalization within 90 days prior to diagnosis, n (%)	9 (81.8)	2 (18.2)
Antibiotic use within 90 days prior to diagnosis, n (%)	36 (100.0)	0 (0.0)
Hospitalization >5 days prior to diagnosis, n (%)	49 (92.5)	14 (93.3)
Nasogastric feeding tube use, n (%)	35 (92.1)	28 (93.3)
Charlson Comorbidity index ≥3, n (%)	47 (95.9)	16 (84.2)
Steroid (prednisone >10 mg/day or equivalent for >14 days), n (%)	2 (28.6)	61 (100.0)
Albumin <2.5 g/dL, n (%)	19 (100.0)	39 (90.7)
Age >60 years old, n (%)	20 (95.2)	43 (91.5)

Table 3. Odds Ratios for Risk Factors Associated with MDR Bacterial Infections

Risk Factor	Odds Ratio (OR)	Interpretation
ICU/HCU hospitalization within 90 days	18	Strong association: Patients with ICU/HCU hospitalization were significantly more likely to have MDR infections.
Antibiotic use within 90 days	Undefined	Perfect association: All patients with recent antibiotic use were infected by MDR bacteria.
Hospitalization >5 days prior to diagnosis	3.1	Moderate association: Prolonged hospitalization increases the risk of MDR infections.
Nasogastric feeding tube use	11.7	Strong association: Patients with feeding tubes were much more likely to have MDR infections.
Charlson Comorbidity Index ≥3	35.3	Very strong association: Higher comorbidity index strongly predicts MDR infections.

Risk Factor	Odds Ratio (OR)	Interpretation
Steroid use (prednisone >10 mg/day for >14 days)	0.017	Inverse association: Steroid use was associated with a lower likelihood of MDR infections.
Albumin <2.5 g/dL	Undefined	Perfect association: All patients with low albumin levels were infected by MDR bacteria.
Age >60 years old	5	Moderate association: Older patients were significantly more likely to have MDR infections.

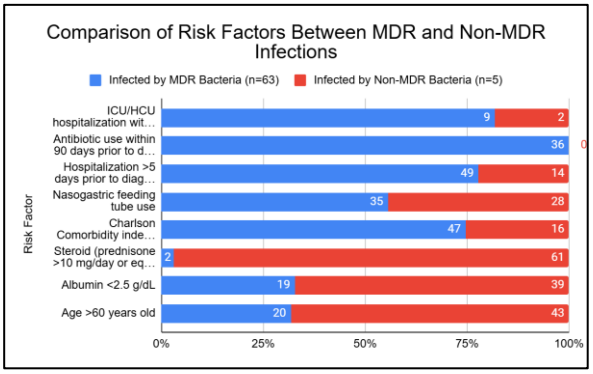

Figure 2. Comparison of Risk Factors Between MDR and Non-MDR Infections

3.3. Identification of Bacteria in MDR Infections

Table 4 provides details on the identification of bacteria found in sputum cultures of patients diagnosed with MDR infections. The most common pathogen identified was *Klebsiella pneumoniae*, followed by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Most of the isolates were Gram-negative bacteria. Figure 3 demonstrates pathogen distributions in sputum diagnosed with MDR infections.

Table 4. Identification of Bacteria Found in Sputum Diagnosed with Multidrug-Resistant Infections (n=81 Isolates)

Isolates	Patients Infected with MDR Bacteria (n=81)	n (%)
Klebsiella pneumoniae	22 (27.1)	
Acinetobacter baumannii	19 (23.4)	
Pseudomonas aeruginosa	5 (6.1)	
Acinetobacter Iwoffii	6 (7.4)	
Escherichia coli	2 (2.4)	
Enterobacter cloacae	3 (3.7)	
Klebsiella sp	3 (3.7)	
Staphylococcus epidermidis (MRSE)	4 (4.9)	
Staphylococcus saprophyticus (MRSS)	5 (6.1)	
Others	12 (14.8)	*Streptococcus dysgalactiae, Enterococcus faecalis, Enterobacter aerogenes, Streptococcus alpha-hemolyticus, Klebsiella oxytoca, Sphingomonas thalpophilum, Enterococcus sp, Proteus mirabilis, Stenotrophomonas maltophilia, Enterobacter sp, Acinetobacter sp*

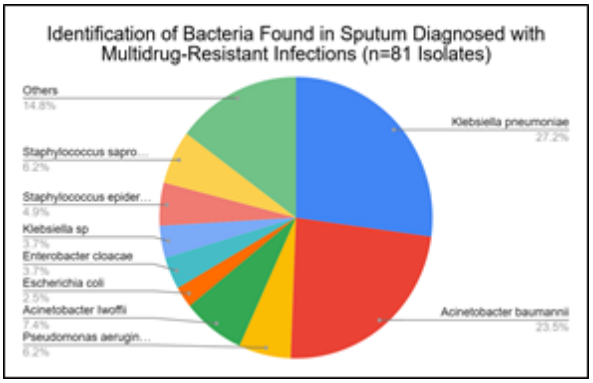

Figure 3. Bacteria Found in Sputum Diagnosed with MDR Infections

3.4. Further Evaluation

The most frequently used antibiotics prior to HAP diagnosis were:

a. Meropenem (15.9%)

b. Metronidazole (12.7%)

c. Ceftriaxone (11.1%)

d. Amikacin (11.1%)

e. Ampicillin sulbactam (11.1%)

Eight patients received antibiotic combinations prior to diagnosis.

3.5. Discussion

The present study identifies significant risk factors associated with multidrug-resistant (MDR) bacterial infections in patients with hospital-acquired pneumonia (HAP). These findings have important clinical implications for improving patient outcomes, especially in resource-constrained settings. Identifying high-risk patients can enable targeted interventions, such as stricter infection control measures, tailored antibiotic stewardship programs, and early initiation of appropriate therapy, ultimately reducing the incidence and adverse outcomes of MDR infections.

Among the significant risk factors identified, ICU or high-care unit (HCU) hospitalization within 90 days, recent antibiotic use, nasogastric tube feeding, and a Charlson Comorbidity Index ≥3 were the strongest predictors of MDR infections. Notably, recent antibiotic use and hypoalbuminemia (albumin <2.5 g/dL) showed perfect associations with MDR infections in this study

population. These findings underscore the importance of judicious antibiotic use to minimize the development of resistance and reinforce the need for careful nutritional assessment and support in hospitalized patients.

3.5.1. Risk Factors and Their Associations

ICU/HCU Hospitalization within 90 Days
Patients with a history of ICU or high-care unit (HCU) hospitalization within 90 days prior to diagnosis were significantly more likely to develop MDR infections. ICU settings increase the likelihood of invasive procedures, prolonged antibiotic exposure, and transmission of resistant pathogens. Compromised immunity in these settings may facilitate colonization progressing to infection, particularly by Klebsiella pneumoniae, which can act as a reservoir for MDR infections and increase cross-transmission risks [8].

Antibiotic Use within 90 Days (Odds Ratio: Undefined)
All patients with recent antibiotic use were infected by MDR bacteria, indicating a perfect association. Prior antibiotic use is a well-established risk factor for MDR infections, altering patient microbiota and selecting for resistant strains. Exposure to more than two antibiotic classes significantly increased the likelihood of MDR infections [3], [9].

Hospitalization >5 Days Prior to Diagnosis (Odds Ratio: 3.1)
Prolonged hospitalization increases the risk of MDR infections (Sfeir 2021). Longer stays often lead to colonization shifts from community-acquired pathogens (Streptococcus pneumoniae, Haemophilus influenzae) to hospital-acquired pathogens (Pseudomonas aeruginosa, MRSA). Late-onset HAP is frequently linked to MDR Gram-negative bacteria [7], [11].

Nasogastric Feeding Tube Use (Odds Ratio: 11.7)
Patients with nasogastric tubes (NGT) were much more likely to have MDR infections [1]. NGTs facilitate aspiration of gastric contents, leading to Gram-negative bacterial colonization. Biofilms, which form as early as the first day of insertion, further exacerbate infection risks and antibiotic resistance [1].

Charlson Comorbidity Index ≥3 (Odds Ratio: 35.3)
A high Charlson Comorbidity Index (CCI ≥3) strongly predicts MDR infections. Comorbidities such as cardiovascular disease and malignancies may weaken immunity, making patients more susceptible to MDR colonization and infection [12].

Steroid Use (Prednisone >10 mg/day for >14 Days) (Odds Ratio: 0.017)
Steroid use was associated with a lower likelihood of MDR infections. Corticosteroids impair immune defenses and have been associated with MDR Gram-negative infections, such as those caused by Pseudomonas aeruginosa and ESBL-producing Klebsiella pneumoniae. In ventilator-associated pneumonia (VAP), corticosteroids increased the risk of MDR infections [12].

Albumin <2.5 g/dL (Odds Ratio: Undefined)
All patients with hypoalbuminemia (albumin <2.5 g/dL) had MDR infections, indicating a perfect association. Malnutrition, reflected by hypoalbuminemia, impairs humoral immunity and macrophage function, weakening respiratory defenses [13]. Although no direct studies link albumin levels to MDR infections in HAP, similar findings have been reported in tuberculosis patients.

Age >60 Years (Odds Ratio: 5.0)
Older patients were significantly more likely to have MDR infections. Aging is associated with impaired B- and T-cell function, weakened mucosal barriers, and reduced lung capacity. Recent hospitalizations further increase colonization risks, with effects lasting up to 360 days post-discharge [7], [12], [14].

3.5.2. Comparison with Other Studies in Southeast Asia

Studies from countries like Thailand and Vietnam have also highlighted prolonged hospitalization, ICU admission, and comorbidities as major risk factors for MDR infections in HAP. For instance, a study in Thailand reported that ICU stay was associated with a sixfold increase in the risk of MDR infections, comparable to the 18-fold increase observed in this study. Similarly, the role of recent antibiotic exposure is consistently emphasized across studies in the region. However, the prevalence of certain MDR pathogens, such as Acinetobacter baumannii and Pseudomonas aeruginosa, appears higher in Southeast Asia compared to other regions, which may reflect differences in healthcare practices, infection control measures, and antibiotic usage policies [4], [5], [15].

3.5.3. Clinical Implications

The findings underscore the importance of judicious antibiotic use to minimize the development of resistance and reinforce the need for careful nutritional assessment and support in hospitalized patients. The Charlson Comorbidity Index ≥3 was one of the strongest predictors of MDR infections in this study, consistent with prior findings that patients with multiple comorbidities are more vulnerable to resistant infections due to frequent healthcare exposure and impaired immunity. Furthermore, hypoalbuminemia emerged as a perfect predictor of MDR infections, aligning with evidence that low albumin levels reflect poor nutritional status and severe underlying illness, both of which increase susceptibility to infections.

The findings also highlight the need for region-specific strategies to combat MDR infections. In Southeast Asia, where healthcare-associated infections are a significant burden, proactive measures such as improved infection prevention protocols, antimicrobial stewardship programs, and education of healthcare workers are

essential. Strengthening laboratory capacities for pathogen identification and resistance.

3.5.4. Strengths and Limitations

This is the first study in Indonesia to describe the proportion of risk factors for MDR bacterial infections in HAP patients. It also evaluates under-researched factors such as Charlson Comorbidity Index and albumin levels. However, the retrospective design may limit data availability and accuracy. The single-center nature of the study may reduce generalizability, and the small sample size precluded statistical analysis beyond descriptive methods.

4. Conclusion

This study highlights the high proportion of HAP patients infected with MDR bacteria at Cipto Mangunkusumo General Hospital, with rates of 95% in 2015 and 82.1% in 2016. Among the identified risk factors, prior antibiotic use within 90 days before diagnosis (100%) and hypoaslbuminemia (albumin <2.5 g/dL, 100%) were the most significant contributors to MDR bacterial infections. Other notable risk factors included prolonged hospitalization (>5 days), ICU/HCU admission, nasogastric tube insertion, advanced age (>60 years), and high Charlson Comorbidity Index (CCI ≥3).

These findings provide valuable insights into the risk factors for MDR bacterial infections among HAP patients, which can guide institution-based empirical antibiotic treatment and preventive strategies. Targeting high-risk groups, such as patients with prior antibiotic use or hypoalbuminemia, and implementing stricter infection control measures in ICU settings may help reduce the burden of MDR bacterial infections in this population.

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