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The 1st Cirebon International Health Symposium: Faculty of Medicine, Universitas Swadaya Gunung Jati
Update on Non-Communicable Diseases: Global Perspective on Health Challenges and Innovation

Correlation between *Methicillin-Resistant Staphylococcus aureus* Infection with Length of Stay and Mortality at Gunung Jati Regional Hospital, Cirebon, Indonesia: A Case Control Study with Total Sampling

Ranidaa' Diyaa' Azmi[1]*, Mohamad Erwin Indrakusuma[2], Taufan Herwindo Dewangga[3]

[1] Faculty of Medicine, Universitas Swadaya Gunung Jati, Indonesia,
[2] Department of Medical Education, Faculty of Medicine, Universitas Swadaya Gunung Jati, Indonesia.
[3] Department of Orthopaedic and Traumatology, Faculty of Medicine, Universitas Swadaya Gunung Jati, Indonesia

***Corresponding author's e-mail: ranidaa90@gmail.com**
DOI: 10.35898/ghmj-741116

ABSTRACT

Background: In 2017, WHO identified *Methicillin-Resistant Staphylococcus aureus* (MRSA) as a high-priority pathogen due to its antimicrobial resistance. MRSA prevalence has been rising since the 1960s, reaching 20% globally and over 80% in some countries. This increasing prevalence of MRSA is accompanied by higher morbidity, more challenging management with difficult treatment, and prolonged length of stay, and consequently increased mortality risk.

Aims: To determine the relationship between MRSA infection with length of stay and mortality at Gunung Jati Regional Hospital, Cirebon, Indonesia.

Methods: A case-control study was performed in 46 cases and 92 controls. This study used total sampling including 138 samples, selected population of MRSA patients between 2021-2023 at Gunung Jati Regional Hospital, Cirebon. Data was taken from medical record and WHONET data.

Results: The Mann-Whitney test results showed a significant correlation between MRSA infection and the length of stay compared to MSSA infection (p=0.003). Furthermore, the Chi-Square test revealed a significant correlation between MRSA infection and mortality (p=0.019; OR, 2.448; 95% CI, 1.151 – 5.205).

Conclusion: *Methicillin-Resistant Staphylococcus aureus* infection is associated with a longer length of stay and higher mortality compared to *Methicillin-Sensitive Staphylococcus aureus* infection.

Keywords: *Methicillin-Resistant Staphylococcus aureus (MRSA), Methicillin-Sensitive Staphylococcus aureus (MSSA), Length of Stay, Mortality.*

Received: 25 September 2024 **Reviewed:** 21 October 2024 **Revised:** 30 November 2024 **Accepted:** 15 December 2024

1. Introduction

Methicillin-Resistant Staphylococcus aureus (MRSA) is classified as part of the Multi-Drug Resistant (MDR) category due to its resistance to cefoxitin or oxacillin, rendering a wide range of beta lactam antibiotics ineffective, including penicillin, cephalosporin, beta-lactamase inhibitors, and carbapenems (Syahniar R et al., 2020). In 2017, the World Health Organization (WHO) classified *Methicillin-Resistant Staphylococcus aureus* (MRSA) as a high priority pathogen due to its resistance to various antimicrobial agents.

The prevalence of *Methicillin-Resistant Staphylococcus aureus* (MRSA) has steadily increased since the 1960s, reaching 20% globally and up to 80% in certain countries. This rise in *Methicillin-Resistant Staphylococcus aureus* (MRSA) prevalence is associated with higher morbidity, more challenging treatments, prolonged length of hospital stay, and an increased mortality rate. Currently, the prevalence of *Methicillin-Resistant Staphylococcus aureus* (MRSA) in Asia has reached 70%, while in Indonesia, it stands at 28%. The issue of antibiotic resistance in several developing countries, including Indonesia, contributes to prolonged treatments and increased healthcare costs, especially in the context of infectious diseases (Syahniar R et al., 2020).

Surveillance data from the Indonesian Society of Clinical Microbiologists (PAMKI) in 2022 revealed that the prevalence of MRSA infections in West Jawa reached 19%. Clinical microbiology laboratory data from RSD Gunung Jati Cirebon showed that in 2023, the incidence of *Methicillin-Resistant Staphylococcus aureus* (MRSA) in Cirebon reached 20%. Based on this background, the aim of this study is to investigate the correlation between *Methicillin-Resistant Staphylococcus aureus* (MRSA) infection with length of stay and mortality, compared to *Methicillin-Sensitive Staphylococcus aureus* (MSSA) infection at RSD Gunung Jati Cirebon.

2. Methods

Study design/ Research procedures

This study is an observational analysis utilizing a case-control design to investigate the correlation between *Methicillin-Resistant Staphylococcus aureus* (MRSA) infection with length of stay and mortality, compared to *Methicillin-Sensitive Staphylococcus aureus* (MSSA) at RSD Gunung Jati Cirebon. A total sampling method was used, comprising 138 samples, which were divided into 46 cases and 92 controls. The sample population was drawn from all MRSA patients who screened with culture test using the Vitek 2-*compact* method with the *Microbioth Dilution* (MIC) to identify MRSA or MSSA at RSD Gunung Jati Cirebon from 2021 to 2023 without any samples being excluded because the required data was complete (including data on gender, age, diagnosis, length of treatment, mortality, MRSA culture results, and other comorbidities in all samples). Data was taken from medical records and WHONET data.

Measurements

The independent variable in this study is *Methicillin-Resistant Staphylococcus aureus* (MRSA) infection, identified from *Methicillin-Resistant Staphylococcus aureus* (MRSA) patients as the case group and *Methicillin-Sensitive Staphylococcus aureus* (MSSA) as the control group. Additionally, the study examines length of stay, measured in days, as one dependent variable taken from the number of days the patient was hospitalized, from the day of admission to the day of discharge or going home. Another dependent variable is mortality, taken from the patient's condition after returning home from the hospital categorized as either alive and death. The data collected are secondary data, directly obtained by researchers at the hospital.

Statistical techniques

Two types of analysis were employed based on the data scale for each variable. The independent variable in this study is measured on an ordinal scale, while the length of stay is measured on a ratio scale, and mortality is measured on a nominal scale. Initially, data distribution was assessed using the Kolmogorov-Smirnov test due to the sample size being greater than 50, Data distribution is considered normal if *p-value* >0.05. Subsequently, bivariate analysis was conducted using the Mann-Whitney U test to examine the correlation between *Methicillin-Resistant Staphylococcus aureus* (MRSA) infection and length of stay, because the data distribution

was not normal with ordinal and ratio data scale. The Chi-Square test was used to analyze the relationship between MRSA infection and mortality, compared to *Methicillin-Sensitive Staphylococcus aureus* (MSSA) infection because the data scale is ordinal and nominal. In addition, the obtained data were analyzed using SPSS version 25.

Ethical clearance

The ethical principles of this research include permission, anonymity, and confidentiality. This study has been approved by the Health Research Ethics Committee (KEPK) of RSD Gunung Jati Cirebon and received Ethical Clearance, issued on May 6, 2024, under the number No.018/LAIKETIK/KEPPKRSGJ/V/2024.

3. Results

Respondent characteristics

Table 1 presents the characteristics of the respondents in this study, including sex, age, clinical diagnosis, and comorbidities. The total number of samples is 138, with 46 MRSA patients and 92 MSSA patients. In this study, the majority of MRSA infections occurred in females with 26 patients (66.7%), while 20 patients (43.5%) were male. For MSSA infections, most patients were also female with 50 patients (54.3%), while 42 patients (45.7%) were male. The age group most affected by MRSA was 25-64 years with 25 patients (53.3%), followed by patients aged ≥65 years with 10 patients (21.7%). Similarly, the majority of MSSA patients were in the age group 25-64 years with 61 patients (66.3%), followed by those aged ≥65 years with 9 patients (9.8%). Table 1 also includes clinical data such as clinical diagnosis and comorbidities. In this study, the most common clinical diagnosis among MRSA patients was sepsis, affecting 20 patients (43.5%), followed by cellulitis in 6 patients (13.0%), and pneumonia in 6 patients (13.0%). For MSSA patients the most frequent clinical diagnosis was sepsis, affecting 32 patients (34.8%), followed by abscesses in 25 patients (27.3%). Regarding comorbidities, the most prevalent comorbidity was diabetes mellitus, present in 13 MRSA patients (21.0%) and 33 MSSA patients (28.4%).

Bivariate analysis

Table 2 presents the results indicating that MRSA patients had a longer median length of stay at 5 days, compared to MSSA patients, who had a shorter median length of stay at 3 days. Based on the comparative analysis between MRSA infection and length of stay, the results showed a significant association (p=0.003), indicating that MRSA infection is associated with a longer hospital stay compared to MSSA infection.

Table 3 shows that the mortality rate was higher among MRSA patients, with 20 patients (43.5%) compared to 22 patients (23.9%) in the MSSA patients. Based on the comparative analysis between MRSA and MSSA infections regarding mortality, the results showed a statistically significant association (p=0.019; OR, 2.448; 95%CI, 1.151-5.205), indicating that MRSA infection increases the risk of mortality by nearly 2.5 times compared to MSSA infection.

4. Discussion

The analysis of this study reveals that the majority of patients with MRSA and MSSA infections are female, with 26 patients (56.5%) and 50 patients (54.3%) respectively. This prevalence may be attributed to hormonal factors, such as estrogen, which can influence virulence factors and make women more susceptible to infections. Additionally, the most common age range for MRSA infections is 25-64 years and age >65 years. The higher incidence in the 25-64 age group could be due to increased activity levels and more frequent exposure to potential sources of infection. As a result, MRSA transmission becomes more widespread in both work and residential environment.

Table 1. *Respondents' characteristic*

	MRSA	MSSA	Total
DEMOGRAPHIC DATA	46 (33.3)	92 (66.7)	138 (100)
Sex			
Male, n (%)	20 (43.5)	42 (45.7)	62 (44.9)
Female, n (%)	26 (56.5)	50 (54.3)	76 (55.1)
Age			
0-28 days, n (%)	2 (4.3)	1 (1.1)	3 (2.2)
29 days-1 years, n (%)	2 (4.3)	6 (6.5)	8 (5.8)
1-3 years, n (%)	3 (6.5)	6 (6.5)	9 (6.5)
3-5 years, n (%)	-	-	-
6-12 years, n (%)	-	1 (0.7)	1 (0.7)
13-18 years, n (%)	1 (2.2)	2 (2.2)	3 (2.2)
19-24 years, n (%)	3 (6.5)	6 (6.5)	9 (6.5)
25-64 years, n (%)	25 (54.3)	61 (66.3)	86 (62.3)
≥65 years, n (%)	10 (21.7)	9 (9.8)	19 (13.8)
CLINICAL DATA			
Clinical Diagnosis			
Abscess, n (%)	4 (8.7)	25 (27.2)	29 (21)
Sepsis, n (%)	20 (43.5)	32 (34.8)	52 (37.7)
Pneumonia, n (%)	6 (13.0)	9 (9.8)	15 (10.9)
Diabetic ulcer, n (%)	5 (10.9)	3 (3.3)	8 (5.8)
Cellulitis, n (%)	6 (13.0)	3 (3.3)	9 (6.5)
Respiratory failure, n (%)	1 (2.2)	1 (1.1)	2 (1.4)
Surgical site infection, n (%)	2 (4.3)	9 (9.8)	11 (8.0)
Osteomyelitis, n (%)	2 (4.3)	-	2 (1.4)
Bacterial Infection, n (%)	-	2 (2.2)	2 (1.4)
Gangrene, n (%)	-	5 (5.4)	5 (3.6)
Pleural effusion, n (%)	-	1 (1.1)	1 (0.7)
Fascitis necroticans, n (%)	-	2 (2.2)	2 (1.4)
Comorbidity			
Diabetes melitus, n (%)	13 (21.0)	33 (28.4)	46 (25)
Other metabolic endocrine, n (%)	8 (12.9)	1 (0.9)	9 (5.1)
Allergy/Immune, n (%)	2 (3.2)	1 (0.9)	3 (1.7)
Malignancy, n (%)	1 (1.6)	3 (2.6)	4 (2.2)
Cardiovascular, n (%)	4 (6.5)	5 (4.3)	9 (5.1)
Neurologic, n (%)	7 (11.3)	10 (8.6)	17 (9.6)
Malnutrition, n (%)	1 (1.6)	-	1 (0.6)
Anemia, n (%)	7 (11.3)	5 (4.3)	12 (6.7)
Chronic Kidney Disease, n (%)	3 (4.8)	13 (11.2)	16 (9.0)
Acute Kidney Injury, n (%)	3 (4.8)	12 (10.3)	15 (8.4)
Gynekology, n (%)	1 (1.6)	1 (0.9)	2 (1.1)
Urinary tract infection, n (%)	1 (1.6)	1 (0.9)	2 (1.1)
Tuberculosis, n (%)	1 (1.6)	2 (1.7)	3 (1.7)
Covid19, n (%)	2 (3.2)	1 (0.9)	3 (1.7)
Without Comorbidity, n (%)	8 (12.9)	28 (24.1)	36 (20.2)

Index: n = number, % = percentage

Table 2. Correlation between MRSA infection with length of stay

	MRSA	MSSA	*p-value*
Length of stay			
Median, days (95% CI)	5 (5.17-9.75)	3 (3.66-5.43)	0.003

*Mann-Whitney test

Table 3. Correlation between MRSA infection with mortality

Mortality	MRSA	MSSA	Total	*p- value*	OR (95% CI)
Death, n (%)	20 (43.5)	22 (23.9)	42 (30.4)	0.019	2.448
Alive, n (%)	26 (56.5)	70 (76.1)	96 (69.6)		(1.151 – 5.205)
Total, n (%)	46 (100)	92 (100)	138 (100)		

**Chi-Square test

From this recent study, it is noted that the elderly population (>65 years) experiences immune system declines with aging, which increases vulnerability to various diseases. This finding aligns with (Shiddiqui et al., 2023), who noted that whole aging does not always correlate with MRSA infection risk, both adults and the elderly exhibit a higher incidence of MRSA infections. In terms of clinical data, sepsis is the most common diagnosis for both MRSA and MSSA infections, with 20 patients (43.5%) and 32 patients (34.5%), respectively.

Staphylococcus aureus is a leading cause of sepsis. This infection often requires prolonged antibiotic therapy, which extend the length of hospital stay and adds to the diseases burden, contributing to increased risk of mortality. Length of stay and mortality are the crucial indicator for estimating the disease burden in healthcare settings (Tsuzuki S., et al 2021). Due to its virulence and adaptability, MRSA can lead to various infections, ultimately causing sepsis. Previous research indicates that MRSA has a mortality rate up to 60%. The Centers for Disease Control (CDC) reports approximately 80.000 cases of invasive MRSA infections and 11.000 death annually. The rising mortality rates are exacerbated by prolonged hospital stays and high treatment costs. Furthermore, diabetes mellitus is the most prevalent comorbidity among MRSA and MSSA infections, with 13 patients (21.0%) and 33 patients (28.4%), respectively (Mahjabeen M et al., 2022). Diabetes mellitus is known to be risk factor for MRSA infections. This finding is consistent with previous research, demonstrated that diabetes mellitus significantly impacts MRSA infection risk (p=0.044). Patients with comorbidities such as diabetes mellitus are more vulnerable to infection due to their compromised immune system (Indah L et al., 2022).

The results of this study indicate a significant association between MRSA infection and length of stay (p=0.003). This finding is consistent with research by (Rodrigues et al, 2020), which demonstrated that the average length of hospital stay for MRSA infection is longer compared to MSSA infections (p=0.002). Additionally, Joo EJ et al (2019) conducted a study on the impact of MRSA on patient outcomes, revealing that MRSA patients have worse clinical outcomes compared to MSSA patients since the year 2000. Staphylococcus aureus infections, particularly MRSA, are challenging to treat due to the development of antibiotic resistance, which often leads to therapeutic failure. This reduced drug sensitivity results in longer length of stay for MRSA patients, which is also associated with an increased risk of mortality during treatment (Stewart S et al., 2021)

Further analysis from this study shows a significant correlation between MRSA infection and mortality (p=0.019; OR, 2.448; 95%CI, 1.151-5.205). This indicates that MRSA infection increases the risk of mortality by nearly 2.5 times compared to MSSA infection. Globally, bacterial resistance to antimicrobials continue to rise, and infections caused by resistant bacteria offer limited therapeutic potions and can be severe. The severity of MRSA infections impacts the increased mortality rates observed in hospitals. MRSA infections generally have worse prognosis compared to MSSA infections. A previous meta-analysis study on the impact of MRSA infection on mortality from 1980 to 2000 revealed a significant increase in mortality associated with MRSA infections (p<0.001; OR, 1.93; 95% CI, 1.54-2.42). While a direct association between mortality and specific virulence genes has not been conclusively proven, some studies suggest that specific genes within the Staphylococcal cassette chromosome mec (SCCmec) are associated with higher mortality rates (Hirabayashi A et al., 2024). The release of beta-lactamase enzymes by Staphylococcus aureus is a major factor contributing to penicillin resistance, alongside the mecA gene, which encodes for Penicillin Binding Protein (PBP) and is responsible for methicillin

resistance. The mecA gene located on the MRSA chromosome or SCCmec (Alghamdi B et al., 2023).

MRSA is one of the most common pathogenic bacteria and continues to be a leading cause of morbidity and mortality worldwide. MRSA is a commensal bacterium in humans that can be transmitted within the community as well as in healthcare settings. Ensuring effective treatment for MRSA infections remains a challenge fir future medical practice. Antibiotics remain the primary agents for treating bacterial infections, essential for reducing mortality and improving life expectancy. MRSA poses a significant threat to life because it can evade the body's immune system, bypass epithelial barriers, and invade deeper tissues such as the bloodstream, heart valves, gastrointestinal tract, dermis, and bones (Lade H et al., 2021). This issue is exacerbated by the rapid emergence and spread of MRSA, which has developed resistance to nearly all beta-lactam antibiotics. Consequently, inadequate antibiotic therapy can fail to improve patient outcomes, prolong length of stay, and increase the risk of mortality if not managed properly.

This study has some limitations, such as the lack of further investigation into whether the MRSA infections examined were Hospital-Acquired Methicillin-Resistant Staphylococcus aureus (HA-MRSA) or Community-Acquired Methicillin-Resistant Staphylococcus aureus (CA-MSSA). Additionally, the study did not include genotypic testing for mecA gene in MRSA strains.

5. Conclusion

Methicillin-Resistant Staphylococcus aureus infection is associated with a longer length of stay and higher mortality compared to *Methicillin-Sensitive Staphylococcus aureus infection.* This study is expected that the results can be used as information material related to guidelines for prevention and control of infections in hospital and can conduct wider screening of MRSA patients with clinical infections so that MRSA patients can be treated earlier with appropriate therapy and that they can reduce the length of stay and mortality.

Conflict of Interest

There is no conflict of interest-nothing to disclosure.

References

Syahniar R, Rayhana, Kharisma DS, Khatami M, Duarsa DBB. *Methicillin-resistant staphylococcus aureus* among clinical isolates in Indonesia: A systematic review. Vol. 13, Biomedical and Pharmacology Journal. Oriental Scientific Publishing Company; 2020. p. 1871–8. https://doi.org/10.13005/bpj/2062

World Health Organization. WHO updates list of drug-resistant bacteria most threatening to human health [Internet]. 2024 [cited 2024 Sep 4]. Available from: https://www.who.int/news/item/17-05-2024-who-updates-list-of-drug-resistant-bacteria-most-threatening-to-human-health

Perhimpunan Dokter Spesialis Mikrobiologi Klinik Indonesia (PAMKI). Surveilans MRSA di Indonesia Tahun 2022. 2022.

Rodrigues R, Passadouro R, Gomes O, Castro R. Risk factors, length of stay and in-hospital mortality of *methicillin-resistant staphylococcus aureus* infections: A case-control study. Acta Med Port. 2020;33(3):174–82. https://doi.org/10.20344/amp.10952

Tsuzuki S, Yu J, Matsunaga N, Ohmagari N. Length of stay, hospitalisation costs and in-hospital mortality of *methicillin-susceptible and methicillin-resistant Staphylococcus aureus* bacteremia in Japan. Public Health. 2021 Sep 1;198:292–6. https://doi.org/10.1016/j.puhe.2021.07.046

Stewart S, Robertson C, Pan J, Kennedy S, Haahr L, Manoukian S, et al. Impact of healthcare-associated infection on length of stay. Journal of Hospital Infection. 2021 Aug 1;114:23–31. https://doi.org/10.1016/j.jhin.2021.02.026

Siddiqui AH, Koirala J. *Methicillin-Resistant Staphylococcus aureus*. National Library of Medicine. 2023 Apr 2. In: StatPerals [Internet]. Treasure Island (FL): StatPerals Publishing 2024 jan-.PMID: 29489200

Indah Lestari L, Umiana Soleha T, Utami N, Rahmayani Program Studi Pendidikan Dokter F, Kedokteran F, Lampung U, et al. Hubungan Faktor Risiko Dengan Angka Kejadian Infeksi Bakteri *Methicillin-Resistant Staphylococcus Aureus* (MRSA) Pada Penderita Ulkus. Jurnal Penelitian Perawat Nasional [Internet]. 2022; Available from: http://jurnal.globalhealthsciencegroup.com/index.php/JPPP

Joo EJ, Park DA, Kang CI, Chung DR, Song JH, Lee SM, et al. Reevaluation of the impact of methicillin-resistance on outcomes in patients with *staphylococcus aureus* bacteremia and endocarditis. Korean Journal of Internal Medicine. 2019 Nov 1;34(6):1347–62. https://doi.org/10.3904/kjim.2017.098

Ali Alghamdi B, Al-Johani I, Al-Shamrani JM, Musamed Alshamrani H, Al-Otaibi BG, Almazmomi K, et al. Antimicrobial resistance in *methicillin-resistant staphylococcus aureus*. Vol. 30, Saudi Journal of Biological Sciences. Elsevier B.V.; 2023. https://doi.org/10.1016/j.sjbs.2023.103604

Hirabayashi A, Yahara K, Oka K, Kajihara T, Ohkura T, Hosaka Y, et al. Comparison of disease and economic burden between MRSA infection and MRSA colonization in a university hospital: a retrospective data integration study. Antimicrob Resist Infect Control. 2024 Dec 1;13(1). https://doi.org/10.1186/s13756-024-01383-8

Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of Mortality Associated with *Methicillin-Resistant* and *Methicillin-Susceptible Staphylococcus aureus* Bacteremia: A Meta-analysis [Internet]. Vol. 36, Clinical Infectious Diseases. 2003. Available from: https://academic.oup.com/cid/article/36/1/53/283567 https://doi.org/10.1086/345476

Mahjabeen F, Saha U, Mostafa MN, Siddique F, Ahsan E, Fathma S, et al. An Update on Treatment Options for *Methicillin-Resistant Staphylococcus aureus* (MRSA) Bacteremia: A Systematic Review. Cureus. 2022 Nov 14; https://doi.org/10.7759/cureus.31486

Lade H, Kim JS. Bacterial targets of antibiotics in *methicillin-resistant staphylococcus aureus*. Antibiotics. 2021 Apr 1;10(4). https://doi.org/10.3390/antibiotics10040398

Cite this article as:

Azmi, R. D., Indrakusuma, M. E., & Dewangga, T. H. (2024). Correlation between Methicillin-Resistant *Staphylococcus aureus* Infection with Length of Stay and Mortality at Gunung Jati Regional Hospital, Cirebon, Indonesia: A Case Control Study with Total Sampling. *GHMJ (Global Health Management Journal)*, *7*(4), 308–314. https://doi.org/10.35898/ghmj-741116