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RESEARCH ARTICLE OPEN ACCESS

Prevalence of *mecC* Gene in MRSA at A Tertiary Hospital in Medan, Indonesia

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to β-lactam antibiotics owing to the presence of *mecA* and *mecC* resistance genes. Resistance genes in MRSA are carried by a genetic component named staphylococcal cassette chromosome *mec* (SCC*mec*). The *mecC* gene showed 63% similarity with the *mecA* gene. This resulted in the *mecC* gene not being detected by routine PCR examination, which specifically detects *mecA*. Data regarding the epidemiology of molecular detection of the *mecC* gene in Indonesia are still very limited, especially in North Sumatra Province. This study aimed to characterize MRSA resistance genes in a tertiary hospital in Medan, North Sumatra. Clinical samples of the infection were collected and identified as MRSA using the VITEK-2 compact device. A total of 80 samples from bacteremia patients in our hospital were used in this research. The detection of resistance genes is performed using conventional Polymerase Chain Reaction (PCR). Visualization of the presence of genes was performed using electrophoresis. *The mec* gene was detected in 79 MRSA samples (98.75%). A total of 63 samples carried two resistance genes, *mecA* and *mecC* (78.75%), 15 samples carried only *mecC* (18.75%), one sample carried only *mecA*, and only one sample carried neither *mecA* nor *mecC*. The finding of the *mecC* gene is a cause for concern because it cannot be detected via routine PCR. This study showed that the majority of MRSA bacteria carry a mixture of *mecA* and *mecC* genes.

Keywords: Methicillin-resistant *Staphylococcus aureus*, Molecular Epidemiology, Polymerase Chain Reaction, Tertiary Hospital

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INTRODUCTION

Staphylococcus aureus is a gram-positive bacterium that is sphere-shaped with a diameter of approximately 1 µm and arranged in irregular clusters that resemble grapes. *Staphylococcus* spp. are naturally found on human skin and mucous membranes. However, certain *Staphylococcus* spp. can cause infections, with *Staphylococcus aureus* being potentially severe. Almost everyone has experienced an infection caused by these bacteria, and these may vary from food poisoning and minor wound infections to life-threatening infections.[1]

Penicillin and its derivatives are effective against Staphylococcal infections. However, shortly after the introduction of penicillin, resistant strains of *S. aureus* have emerged and spread globally. In 1961, methicillin-resistant *S. aureus* (MRSA) bacteria were discovered, posing a persistent global health problem.[2] According to previous studies, the prevalence of MRSA in Indonesia is relatively high, ranging from 17% to 26.6%.[3-5] This high prevalence in hospitals can lead to an increased economic burden on the healthcare sector and heightened use of specific antibiotics against MRSA. There is concern that this could also trigger the development of other resistant strains.[6]

MRSA carries the resistance gene *mecA*, which leads to the transformation of penicillin-binding protein (PBP) to PBP2a. PBP2a acts as an alternative transpeptidase with a low affinity for most β-lactam antibiotics. The resistance gene component is located in a mobile genetic element known as *Staphylococcal* Cassette Chromosome *mec* (SCC*mec*). The *mecC* resistance gene results from a mutation in the *mecA* resistance gene, exhibiting only 63% similarity to *mecA*. MRSA isolates carrying the *mecC* gene are known to originate from the transmission of livestock-associated MRSA or other Staphylococci to humans.[2] This also results in the *mecC* gene not being detected through routine PCR examination which usually specifically detects *mecA* or through the PBP2a slide agglutination test.[7]

Surveillance of MRSA infections in healthcare facilities is crucial for controlling the growth of antimicrobial-resistant bacteria. Additionally, it enables the administration of efficient antibiotic therapy and more effective infection control strategies.[8] Research detecting resistance genes in MRSA bacteria is still limited in Indonesia, especially in North Sumatra. Therefore, researchers aimed to determine the presence of *mecA* and *mecC* resistance genes in MRSA bacteria identified from clinical samples at Haji Adam Malik General Hospital, Medan, North Sumatra.

MATERIALS AND METHODS

Bacterial isolates

Isolated DNA samples were collected from our previous study.[9] A total of 80 samples were used in this research, collected from Haji Adam Malik General Hospital from September 2022 to January 2023. This study included the conventional detection of the *mec* gene using conventional Polymerase Chain Reaction (PCR), followed by electrophoresis and UV light visualization.

Detection method

For the detection of *mecA* and *mecC* genes, we used specific forward and reverse gene primers. The primers used in this study were previously used in another study. For primer specificity, we chose the primers by using the Basic Local Alignment Search Tool (BLAST) from NCBI. These primers were confirmed to be suitable for the detection of *the mec* gene. The primers used are described in Table 1.

The identification of the gene started by preparing the master mix used. The master mix for PCR was prepared by combining GoTaq Green Master Mix 2X, primers (forward and reverse), and nuclease-free water. The PCR mix contains 12.5 µl of GoTaq Green master mix 2X, 10 µM (1 µl) each forward and reverse primer, 8.5 µl of Nuclease-free Water, and 2 µl of DNA sample. The PCR mix was placed in each PCR tube. The mix was then vortexed for homogenization and spun down to put down the sample.

The PCR process began with an initial denaturation at 95 °C for 5 min to melt the DNA strands. Subsequently, 35 cycles of denaturation at 95 °C for 30 s, hybridization at 54 °C for 30 s, and extension at 72 °C for 1 min were performed. Finally, a final extension was carried out at 72 °C for 2 min. Each cycle produced a duplication of the

target DNA, and this process yielded the desired results after 35 cycles. The final PCR product then processed to electrophoresis.[2,9]

Electrophoresis

In the initial steps, a 1% agarose gel was prepared by combining Tris-acetate-ethylenediaminetetraacetic acid (EDTA) buffer and agarose in an Erlenmeyer flask. The solution was heated to boiling, followed by the addition of ethidium bromide and thorough mixing. Next, the solution was poured into a caster and cooled until it solidified for approximately 45 min. The prepared agar was then placed into the electrophoresis chamber, and subsequently, 1X TAE was added to the electrophoresis chamber until the agar was completely submerged.

The molecular detection of *mecA* and *mecC* was conducted by loading 5 µL of a 100 bp DNA ladder into the first well as a control, followed by subsequent wells filled with 7 µl of PCR amplification products. Electrophoresis was run at a voltage of 80 V for 75 min. Subsequently, DNA bands were visualized under ultraviolet light and documented using the Gel Doc system (BioRad, California, United States of America). Based on the expected size of the amplicon from PCR results, the *mecA* and *mecC* resistance genes could be detected by observing the presence of the *mecA* resistance gene band (~533 bp) and the *mecC* resistance gene band (~356 bp).[2,9,10]

Figure 1 shows the *mecA* gene band and Figure 2 shows the *mecC* gene band.

RESULTS

In this study, there were no differences between groups that exhibited *mecC* gene only

Table 1. Primers used in this study

Name	Primer sequence	Amplicons	Ref.
mecA Forward	AAAATCGATGGTAAAGGTTGGC-	533 bp	2
mecA Reverse	AGTTCTGGAGTACCGGATTTGC-		
mecC Forward	TCACCAGGTTCAAC[Y]CAAAA-	356 bp	2
mecC Reverse	CCTGAATC[W]GCTAATAATATTTC-		

Table 2. Demographic characteristics of patients with MRSA infection

Categories	*mecC* (+) only n = 15	Others variant n = 65	p-value
Sex			
• Male	10 (66.7%)	42 (64.6%)	0.881
• Female	5 (33.3%)	23 (35.4%)	
Age (years)			
• <18	8 (53.3%)	21 (32.3%)	0.118
• 18-59	0 (0%)	32 (49.2%)	
• ≥60	7 (46.7%)	12 (18.5%)	
Mean ± standard deviation	27.13 ± 19.07	36.29 ± 23.13	
Outcome			0.542
• Recovery	12 (80%)	47 (72.3%)	
• Death	3 (20%)	18 (27.7%)	
Leukocyte counts (× cell/mm^3)			0.342
• <4500	0 (0%)	5 (7.7%)	
• 4,500-11,000	8 (53.3%)	24 (36.9%)	
• >11,000	7 (46.7%)	36 (55.4%)	
Mean ± standard deviation	25.492 ± 5.090	15.048 ± 10.031	

compared with other variants proven with the bivariate chi-square test. Both groups had relatively similar proportions in terms of sex ($p > 0.05$), age ($p > 0.05$), outcome ($p > 0.05$) and leukocyte count ($p > 0.05$) (Table 2).

Of the 80 samples examined, most contained the *mec* gene, whereas one sample showed a negative result for the gene. Most samples (78.75%) had mixed resistance genes (*mecA* and *mecC*) (Table 3).

DISCUSSION

MRSA infections are often found both as community infections and as infections acquired from health services. The presence of *mecC* increases the number of antibiotic-resistant *S. aureus* bacteria. In this study, most MRSA isolates had a mixture of *mec* genes (78.75%). This is different when compared with research by Idrees et al., in a Pakistani hospital, the majority of MRSA bacteria (57.1%) had a mixture of *mecA* and *mecC* genes, and around 7.9% of isolates only had the *mecC* gene.[2] In a meta-analysis study by Diaz et al, (using data from studies in Europe, The United States, and Jordan) the prevalence of MRSA infections carrying *mecC* reached 0.004%.[11] Another study in a tertiary hospital in China using 212 *S. aureus* samples did not find the presence of the *mecC* gene.[12]

Table 3. Distribution of *mec* gene in this study

Variable	N (%)
mecA and *mecC*	63 (78.75)
mecA	1 (1.25)
mecC	15 (18.75)
None	1 (1.25)

Our studies found no difference in demographic and laboratory data between *S. aureus* that expressed *mecC* gene only and other phenotypes of *S. aureus*. This is a novel analysis that we presented. It must be emphasized that *mecC* has no role as a virulence factor. The *mecC* gene is a resistance gene that is primarily known to function as a *mecA* mutation, which encodes a trans-peptidase against β-lactam antibiotics.[2]

The presence of the *mecC* gene results in it not being detected through routine PCR examination. The PBP2c protein formed has

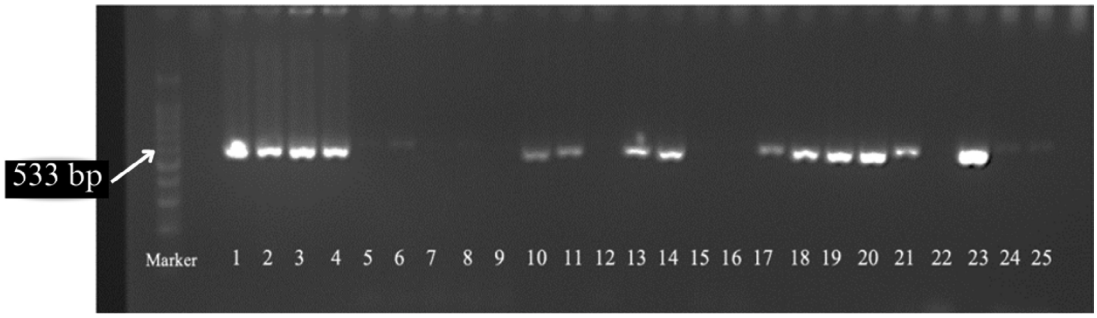

Figure 1. Gel electrophoresis of *mecA* gene

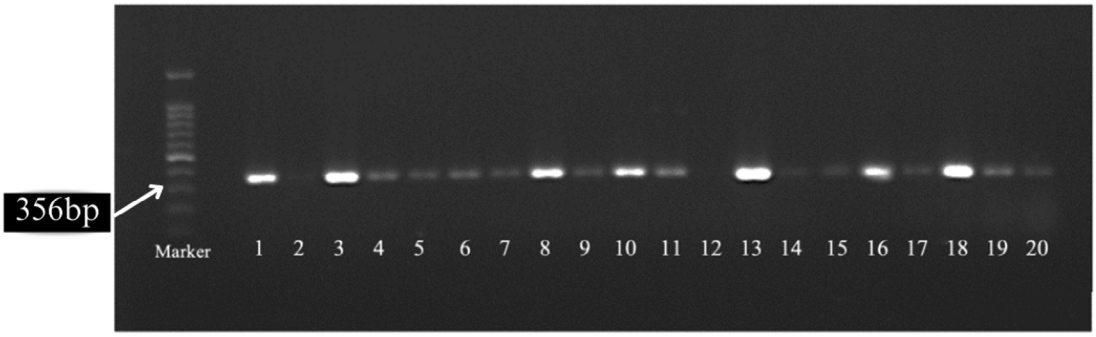

Figure 2. Gel electrophoresis of *mecC* gene

a higher affinity for oxacillin than cefoxitin; therefore, it can be said that PBP2c has a higher affinity for penicillins than cephalosporins.[13] *mecC* (previously named mecALGA251) is found in the mobile genetic element (MGE) called SCC*mec*, which is inserted at the 3'end of the orfX locus. The *mecC* gene is also known to be possessed by other Staphylococci bacteria such as *S. xylosus* and *S. saphrophyticus*.[14]

The origin of *mecC* is still debated. There is suspicion that the *mecC* gene comes from livestock due to the high number of cases occurring in people who have contact with livestock. MRSA with the *mecC* gene is also found in wild animals, such as red foxes, wild rabbits, wild boars, hedgehogs, and fallow deer. Another study reported that MRSA *mecC* was found in river water, where some wild animals (such as fallow deer) also carried MRSA *mecC*. This indicates that water can be a means of spreading MRSA bacteria into the environment that originate from various animal species.[15]

The high incidence of MRSA *mecC* findings has an impact on reducing the effectiveness of antibiotic therapy, and this will certainly affect patient recovery. MRSA *mecC* also carries other resistance genes along with regulators of their expression. In previous studies, MRSA was found to be resistant to many antibiotics. Antibiotics such as vancomycin, linezolid, teicoplanin, chloramphenicol, and clindamycin can be used because the resistance rate is lower in MRSA.[2] Therefore, routine molecular epidemiological examination of resistance genes such as *mec* needs to be carried out not only on MRSA bacteria, but also on other bacteria. This is necessary to avoid transmission of the *mecC* gene from one bacterium to another. These changes in MRSA molecular data will influence local antibiotic therapy guidelines and MRSA infection control.

The limitation of this study is that we did not examine the antibiotic resistance profiles of the isolates. Apart from that, we also did not carry out clonal complex analysis, so we do not know the origin of the MRSA *mecC* bacteria circulating in our tertiary hospital. However, this research can be used as the main basis for carrying out further molecular examinations not only in North Sumatra but also in other regions in Indonesia.

CONCLUSION

In this study, we concluded that *mecC* is highly prevalent in tertiary hospitals in the city of Medan, Indonesia. Our finding can be said to be very high compared to other studies. This study enforces the need for genetic surveillance in hospitals with high patient traffic, especially in urban regions. Multiple genotypic examinations may be necessary to ensure that no resistant strain can evade detection. Further research is needed on this particular topic.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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