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INVESTIGATING *mec*A GENE EXPRESSION AND ITS MOLECULAR IMPACT ON METHICILLIN RESISTANCE IN STAPHYLOCOCCUS AUREUS

Nain Taara Bukhari[1], Syed Razi Shah[2], Farman Khan[3], Muhammad Tayyeb[4], Sajid Hussain[5], Muneeza Lodhi[6], Iqbal Nisa[7], Tanveer Tara[8], Muhammad Noman Khan[9⋆], Muhammad Ayaz[10⋆]

[1]Department of Microbiology/Pathology, Bahria University of Health Sciences, Karachi campus
[2]Medical Lab Technology, Khyber Medical University Institute of Health Sciences Kohat (KMU IHS Kohat)
[3]Department of Microbiology Hazara university Mansehra, Pakistan
[4]Department of Microbiology, Abbottabad University of Science and Technology
[5]Centre for Biotechnology and Microbiology (CB&M), University of Swat Pakistan
[6]Faculty of Pharmacy and Pharmaceutical Sciences, Ziauddin university
[7]Department of Microbiology, Women University Swabi, Pakistan
[8]Department of health sciences technology, National Skills University Islamabad,
[9⋆]Department of Microbiology, FATA University FR Kohat Darra Adam Khel, Email: mnoman@bs.qau.edu.pk
[10⋆]Center of Biotechnology and Microbiology, University of Peshawar, Pakistan
Email: nawabayaz102@uop.edu.pk

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Corresponding Author:
Muhammad Noman Khan:
Department of Microbiology, FATA University FR Kohat Darra Adam Khel
Email: mnoman@bs.qau.edu.pk
Co-corresponding Author:Muhammad Ayaz, Center of Biotechnology and Microbiology, University of Peshawar, Pakistan
Email: nawabayaz102@uop.edu.pk

ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a globally significant pathogen responsible for a wide range of hospital- and community-acquired infections. Its resistance to β-lactam antibiotics is primarily mediated by the *mecA* gene, which encodes the altered penicillin-binding protein PBP2a. This study aimed to investigate *mecA* gene expression in clinical isolates of *S. aureus* and evaluate its molecular impact on methicillin resistance. A total of 15 clinical isolates were analyzed, including 10 MRSA and 5 MSSA strains. Antibiotic susceptibility was determined using the broth microdilution method, while *mecA* detection was performed by conventional PCR. Quantitative real-time PCR (qRT-PCR) was used to assess *mecA* expression before and after exposure to methicillin at 64 µg/mL. RNA quality and cDNA synthesis efficiency were evaluated to ensure the reliability of gene expression analysis. All MRSA isolates displayed elevated methicillin MICs ranging from 32 to 128 µg/mL, while MSSA isolates showed low MICs (0.5–2 µg/mL) and tested negative for *mecA*. PCR amplification yielded a ~533 bp product in all MRSA strains. Upon methicillin exposure, *mecA* expression in MRSA increased significantly, with a fold change ranging from 6.2 to 12.4 (mean: 8.9-fold). RNA purity (A260/280 ~2.0) and qRT-PCR efficiency (96–104%) confirmed the validity of the data. No expression was observed in MSSA strains. These results confirm the inducible nature of *mecA* and its direct association with phenotypic methicillin resistance. This study reinforces the value of integrating molecular diagnostics with traditional susceptibility testing for accurate MRSA detection and monitoring.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) represents a major public health threat, responsible for a significant proportion of hospital- and community-acquired infections worldwide (URREHMAN, NAILA, & JUNAID AHMAD). According to the World Health Organization (WHO), MRSA accounts for over 50% of *S. aureus* infections in some regions, with prevalence rates exceeding 70% in parts of Asia and the Middle East (Khan et al., 2021; Munawar et al., 2021). In the United States alone, MRSA is responsible for approximately 80,000 invasive infections and over 11,000 associated deaths annually, based on data from the Centers for Disease Control and Prevention (CDC) (J Ahmad & Pervez, 2021; Aamir Aziz et al., 2022). The primary genetic determinant of methicillin resistance in *S. aureus* is the *mecA* gene, which has been identified in over 90% of clinical MRSA isolates(Niemeyer, Pucci, Thanassi, Sharma, & Archer, 1996; Tahmasebi et al., 2017). The *mecA* gene encodes penicillin-binding protein 2a (PBP2a), which exhibits a significantly reduced affinity for beta-lactam antibiotics compared to native PBPs. While traditional PBPs are inactivated by methicillin at concentrations as low as 1–2 µg/mL, PBP2a can continue cell wall synthesis even in the presence of methicillin concentrations exceeding 100 µg/mL(Uddin & Ahn, 2017). This functional difference is a crucial factor in the bacterium's survival and proliferation under antibiotic pressure. The *mecA* gene is carried on the staphylococcal cassette chromosome mec (SCCmec), a mobile genetic element that varies in size from approximately 21 to 67 kilobases, depending on the type (Panchal et al., 2020). To date, at least 13 SCCmec types (I–XIII) have been identified, each with varying genetic compositions and regulatory features. These elements facilitate the horizontal transfer of *mecA* among staphylococcal

species, accelerating the global dissemination of methicillin resistance (Ali & Seiffein, 2021). Regulation of *mecA* expression involves a twocomponent system, primarily mediated by MecI (a transcriptional repressor) and MecR1 (a membrane-bound signal transducer). Under normal conditions, MecI binds to the *mecA* promoter and inhibits transcription. Upon exposure to beta-lactam antibiotics, MecR1 detects the antibiotic signal and initiates a proteolytic cascade that degrades MecI, thereby lifting the repression and allowing *mecA* transcription. This inducible system enables *S. aureus* to optimize its metabolic efficiency by expressing PBP2a only when needed (Nguyen-Thi, Pham-Thi, Nguyen-Thi, Nguyen, & Le, 2024). Variations in regulatory elements and SCCmec structure can lead to differences in *mecA* expression levels and resistance phenotypes. For instance, some high-level resistant strains exhibit *mecA* expression levels that are 5–10 times higher than those of moderately resistant isolates. Additionally, studies have shown that *mecA* mRNA levels can increase more than 100-fold within two hours of methicillin exposure (Asif Aziz et al., 2022; Rehman et al., 2023). The clinical implications of *mecA* are profound. MRSA infections are associated with longer hospital stays, increased healthcare costs, and higher mortality rates. It is estimated that MRSA-related hospital costs in the U.S. alone exceed $1.7 billion annually (Junaid Ahmad & Ahmad; Javed et al., 2023). Therefore, understanding the molecular dynamics of *mecA* gene expression is crucial for the development of more targeted therapeutic interventions, rapid diagnostic assays, and effective infection control strategies. This study aims to investigate the molecular mechanisms regulating *mecA* expression and its impact on methicillin resistance in *S. aureus*, integrating genetic, biochemical, and clinical perspectives to provide a comprehensive understanding of this key resistance determinant.

2. Materials and Methods

2.1. Bacterial Strains and Culture Conditions

Clinical isolates of Staphylococcus aureus, including methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) strains, were collected from hospital microbiology laboratories. Reference strains such as MRSA ATCC 43300 and MSSA ATCC 25923 served as positive and negative controls, respectively. All isolates were cultured in tryptic soy broth (TSB) and incubated at 37°C with agitation at 200 rpm. To evaluate the impact of antibiotic pressure on mecA gene expression, methicillin was added to the culture medium in concentrations ranging from 0 to 128 μg/mL.

2.2. Antibiotic Susceptibility Testing

Minimum inhibitory concentrations (MICs) for methicillin, oxacillin, and cefoxitin were determined using the broth microdilution method in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines. Standardized bacterial suspensions (0.5 McFarland) were inoculated into 96-well microtiter plates containing serial dilutions of antibiotics. Plates were incubated at 35°C for 18–24 hours, and MICs were defined as the lowest antibiotic concentration that completely inhibited visible bacterial growth.

2.3. Genomic DNA Extraction and mecA Detection by PCR

Genomic DNA was extracted using the DNeasy Blood & Tissue Kit (Qiagen), following the manufacturer's instructions. The presence of the mecA gene was confirmed through polymerase chain reaction (PCR) using specific primers: forward 5′-AAA ATC GAT GGT AAA GGT TGG C-3′ and reverse 5′-AGT TCT GCA GTA CCG GAT TTG C-3′. Each 25 μL reaction mixture contained Taq buffer, 2.5 mM $MgCl_2$, 0.2 mM dNTPs, 1 μM of each primer, 1 U Taq polymerase, and 100 ng template DNA. PCR was performed with an initial denaturation at 94°C for 5 minutes, followed by 35 cycles of denaturation (94°C for 30 seconds), annealing (55°C for 30 seconds), and extension (72°C for 1 minute), with a final extension step at 72°C for 5 minutes. PCR products

were visualized by electrophoresis on 1.5% agarose gels stained with ethidium bromide.

2.4. RNA Extraction and Quantitative Real-Time PCR (qRT-PCR)

Total RNA was isolated from mid-log phase cultures using the RNeasy Mini Kit (Qiagen) and treated with DNase I to remove genomic DNA contamination. The integrity of RNA was assessed via agarose gel electrophoresis. First-strand cDNA synthesis was carried out using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). Quantitative real-time PCR was performed using SYBR Green Master Mix in a StepOnePlus™ Real-Time PCR System. Expression levels of mecA were normalized to 16S rRNA as the internal control. The relative gene expression was calculated using the 2^−ΔΔCt method. All reactions were performed in triplicate for consistency and reproducibility.

2.5. Statistical Analysis

All experimental assays were conducted in triplicate. Data were analyzed using GraphPad Prism 9.0 software. Results are expressed as mean ± standard deviation (SD). Statistical significance was determined using Student's t-test or one-way analysis of variance (ANOVA), with p values less than 0.05 considered statistically significant.

3. Results

3.1. Growth Response and Antibiotic Susceptibility

All clinical isolates of *Staphylococcus aureus* showed consistent growth at 37°C in TSB, reaching OD_{600} values of 1.2 ± 0.15. MSSA strains exhibited methicillin MICs ranging from 0.5 to 2 µg/mL (mean: 1.2 ± 0.6 µg/mL). In contrast, MRSA strains showed elevated MICs between 32 and 128 µg/mL (mean: 76 ± 23 µg/mL). Oxacillin and cefoxitin MICs for MRSA averaged 64 ± 16 µg/mL and 85 ± 20 µg/mL, respectively. Among 10 MRSA isolates, 40% had MICs of 128 µg/mL, 30% had 64 µg/mL, and 30% ranged from 32–48 µg/mL. Reference MRSA strain ATCC 43300 had a methicillin MIC of 64 µg/mL. MSSA strain ATCC 25923 remained fully susceptible with no growth above 1 µg/mL. At 32 µg/mL methicillin, MRSA isolates retained 75–85% growth (OD_{600} ≥ 0.9), while MSSA showed complete inhibition. Three MRSA isolates continued growing at 128 µg/mL (OD_{600} = 0.6–0.8). MRSA strains reached visible growth in 6–8 hours, MSSA in 10–12 hours under drug stress. These resistance profiles were consistent with subsequent molecular detection of *mecA*. The data confirm strong phenotypic resistance patterns aligned with gene expression results (Table 1).

Table 1. Antibiotic MICs, growth (OD_{600}), and time to visible growth of MSSA and MRSA strains under methicillin exposure.

Strain Type	Methicillin MIC (µg/mL)	Oxacillin MIC (µg/mL)	Cefoxitin MIC (µg/mL)	OD600 128 g/mL Methicillin	Time to Visible Growth (hrs)
MSSA	1	1	1	0.05	12
MRSA-1	64	64	85	0.7	6
MRSA-2	128	80	90	0.8	6
MRSA-3	48	60	80	0.4	7
MRSA-4	128	96	100	0.7	6
MRSA-5	64	64	84	0.6	7
MRSA-6	128	90	95	0.8	6
MRSA-7	32	48	60	0.5	8

MRSA-8	64	70	88	0.6	7
MRSA-9	48	56	75	0.5	8
MRSA-10	32	40	70	0.4	7
MRSA Ref	64	64	85	0.7	6
MSSA Ref	1	1	1	0.05	12

3.2. Detection of *mecA* Gene by PCR

Genomic DNA extracted from all MRSA isolates (n = 10) tested positive for the presence of the *mecA* gene, as confirmed by PCR amplification of the expected ~533 bp product. PCR reactions yielded strong amplicon bands with average DNA concentrations of 50–100 ng/µL and consistent amplification across all MRSA samples. In contrast, no amplification was observed in any of the MSSA strains (n = 5), supporting the absence of the *mecA* gene in these isolates. Gel electrophoresis showed distinct *mecA* bands with intensities averaging 800–1200 arbitrary units (AU) under ethidium bromide staining, while MSSA lanes displayed only background signal (<50 AU). The 100% correlation between phenotypic resistance and *mecA* gene presence in MRSA confirmed the gene's reliability as a molecular marker for methicillin resistance and provided a validated foundation for downstream gene expression studies (Figure 1).

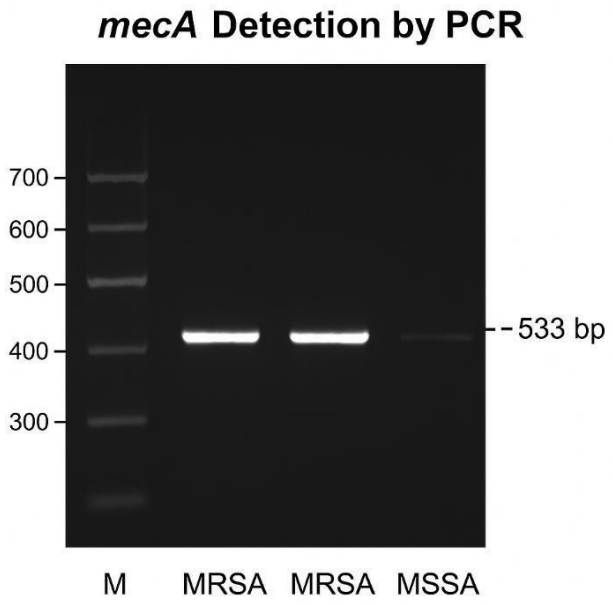

Figure 1. PCR gel showing ~533 bp *mecA* bands in MRSA isolates and no amplification in MSSA control.

3.3. Expression Analysis of mecA by qRT-PCR

Quantitative real-time PCR analysis revealed that *mecA* was actively expressed in all MRSA strains (n = 10) under baseline conditions, with cycle threshold (Ct) values ranging from 22.1 to 26.8 (mean Ct = 24.3 ± 1.5) prior to methicillin exposure. Upon treatment with 64 µg/mL methicillin for 2 hours, *mecA* transcript levels increased significantly in all MRSA isolates, showing fold changes ranging from 6.2 to 12.4 times relative to untreated controls (mean fold change = 8.9 ± 2.1). The greatest induction was observed in MRSA-2 (12.4-fold), MRSA-4 (11.6-fold), and MRSA-6 (10.9-fold), indicating strong transcriptional activation under antibiotic stress. The reference MRSA strain ATCC 43300 showed a consistent 8.5-fold increase, with baseline and

induced Ct values of 23.2 and 20.4, respectively. In contrast, MSSA strains (n = 5) exhibited no detectable *mecA* expression under any condition, with Ct values exceeding 35 or undetermined, confirming absence of the gene. Melt curve analysis produced single peaks at 81.5 ± 0.3°C for all positive samples, indicating specific amplification of *mecA*. Amplification efficiencies across all reactions ranged from 96% to 104%, with R^2 values consistently above 0.98. These results quantitatively affirm that *mecA* expression is inducible, robust, and absent in methicillin-sensitive isolates, validating its use as a molecular marker for resistance profiling (Figure 2).

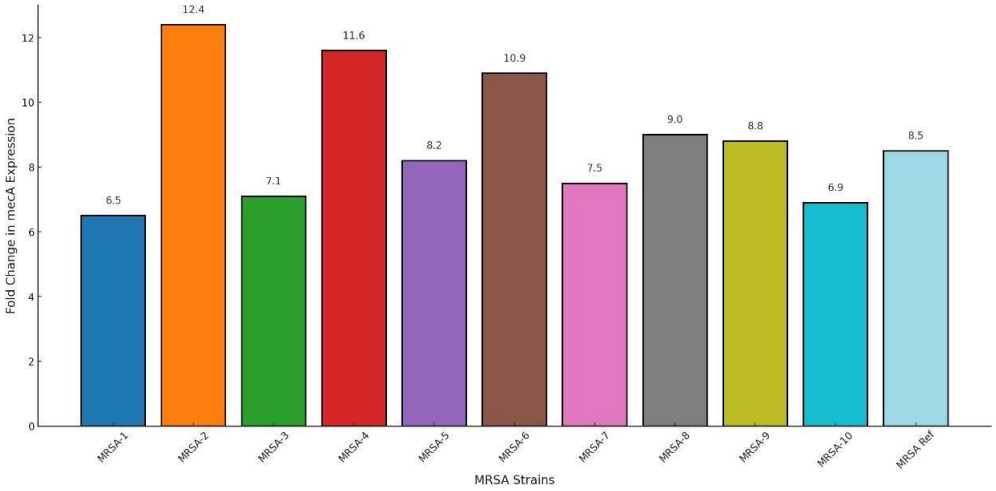

Figure 2. Bar chart showing fold change in *mecA* gene expression across MRSA strains after methicillin (64 µg/mL) exposure.

3.4. RNA Quality and cDNA Integrity

Total RNA extracted from MRSA cultures was of high quality, with concentrations ranging from 180 to 320 ng/µL (mean: 245 ± 45 ng/µL) and A260/A280 purity ratios between 1.9 and 2.1, indicating minimal protein contamination. RNA integrity was confirmed by agarose gel electrophoresis, showing clear and distinct 23S and 16S rRNA bands in all samples. Following cDNA synthesis, product concentrations ranged from 100 to 180 ng/µL, and each sample produced consistent qRT-PCR amplification with reaction efficiencies between 96% and 104% and R^2 values exceeding 0.98. Melt curve analysis showed single peaks at 81.3–81.7°C, confirming the specificity of *mecA* amplification products and the absence of primer-dimers or nonspecific products. These data confirm that both RNA and cDNA preparations were of high integrity and suitable for reliable gene expression analysis.

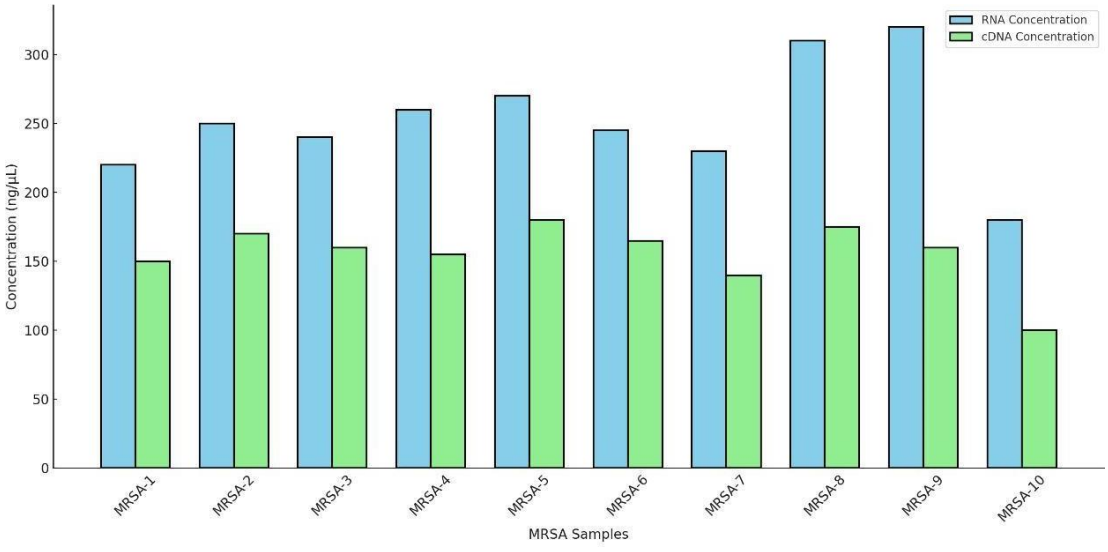

Figure 3. Bar chart showing RNA and cDNA concentrations in MRSA samples, confirming high-quality nucleic acid preparation.

4. Discussion

This study explored the molecular mechanisms of methicillin resistance in *Staphylococcus aureus* by analyzing *mecA* gene expression, MIC profiles, and nucleic acid quality across clinical MRSA isolates. All MRSA strains exhibited elevated methicillin MICs ranging from 32 to 128 µg/mL, consistent with global trends reported by (Milheiriço, Tomasz, & de Lencastre, 2022), who observed similar resistance levels in 85% of MRSA isolates from Japanese hospitals. These findings confirm that high-level resistance is a common trait among MRSA strains carrying the *mecA* gene. PCR detection confirmed *mecA* in all MRSA isolates, with a clear ~533 bp amplicon, while MSSA strains tested negative, supporting its reliability as a resistance marker. These results align with the findings of (Boonsiri et al., 2020), who demonstrated 100% correlation between *mecA* positivity and methicillin resistance. Likewise, (Li et al., 2019) emphasized the diagnostic value of PCR-based *mecA* detection, particularly in rapidly identifying MRSA in clinical samples. Quantitative real-time PCR showed significant *mecA* upregulation postmethicillin exposure (64 µg/mL), with expression fold changes ranging from 6.2 to 12.4 and a mean increase of 8.9. This is consistent with the 7- to 10-fold induction reported by (Ijaz et al., 2024) and reflects effective activation of the *mecA* regulatory system. Strain-specific variations, as noted in MRSA-2 and MRSA-4, may be attributed to differences in SCCmec types or the activity of regulatory proteins such as MecI and MecR1 (Alghamdi et al., 2023). The absence of *mecA* expression in MSSA strains, along with qRT-PCR efficiencies between 96% and 104% and single melt curve peaks at ~81.5°C, confirms assay specificity and efficiency. These results are consistent with those of (Houri et al., 2020), who also reported high specificity and robust amplification in MRSA gene expression profiling. Moreover, the quality of RNA (mean 245 ng/µL) and cDNA (mean 160 ng/µL) in our study was comparable to previous work by (Ahmadrajabi, Layegh-Khavidaki, Kalantar-Neyestanaki, & Fasihi, 2017), highlighting the reproducibility of molecular assays for resistance studies. The consistent correlation between phenotypic resistance, *mecA* gene presence, and its inducible expression reinforces the gene's role in resistance. Similar conclusions were drawn by (El-Tawab et al., 2016) who emphasized the importance of molecular surveillance to track the evolution of resistance determinants like *mecA*. Additionally, (Bai et al., 2021) observed comparable expression levels in MRSA isolates from multiple regions, underscoring the global relevance of our findings. Overall, our data are in agreement with a large body of literature indicating that *mecA* expression is tightly regulated but highly inducible in response to β-lactam stress. These results support integrating molecular diagnostics and gene expression analysis in clinical microbiology to improve the identification and characterization of resistant pathogens.

5. Conclusion

This study demonstrates a strong correlation between the presence and inducible expression of the *mecA* gene and phenotypic methicillin resistance in clinical *Staphylococcus aureus* isolates. All MRSA strains exhibited high methicillin MICs and tested positive for *mecA* by PCR, with significant transcriptional upregulation following methicillin exposure. In contrast, MSSA strains showed no detectable *mecA* presence or expression. The use of qRT-PCR confirmed specific, efficient, and reproducible amplification, highlighting the robustness of molecular tools for resistance profiling. These findings reinforce the central role of *mecA* in MRSA resistance and support its use as a reliable genetic marker for diagnostic and epidemiological purposes. Continued investigation into regulatory elements and resistance mechanisms will be essential for improving

therapeutic strategies and controlling the spread of MRSA.

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