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# Association of Meca and Lukf-PV Gene Profiles in Clinical Staphylococcus Aureus Isolates with Patient Clinical Outcomes

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**ABSTRACT:**

**Background:** The combined contribution of antimicrobial resistance and virulence determinants to the clinical outcomes of *Staphylococcus aureus* infection remains poorly understood. This study investigated the association of mecA and lukF-PV gene profiles in clinical *Staphylococcus aureus* isolates with patient clinical outcomes

**Methods:** This retrospective observational analytical study included 47 hospitalized adult patients with culture-confirmed *Staphylococcus aureus* infection at Hasanuddin University Hospital, Indonesia. Clinical and microbiological data from January 2022 to December 2025 were retrospectively retrieved from electronic medical records, while molecular analyses were performed between January and May 2026.

**Results:** The mecA (+)/lukF-PV (+) gene profile was significantly associated with prolonged hospitalization (OR, 31.17; 95% CI, 4.46–217.60; p = 0.001), prolonged antibiotic therapy (OR, 12.75; 95% CI, 2.33–69.87; p = 0.003), and antimicrobial resistance (OR, 10.21; 95% CI, 1.75–59.65; p = 0.010). The mecA (-)/lukF-PV (+) profile was independently associated with prolonged hospitalization (OR, 9.17; 95% CI, 1.15–73.24; p = 0.037), whereas the mecA (+)/lukF-PV (-) profile was associated only with antimicrobial resistance (OR, 27.50; 95% CI, 2.00–378.84; p = 0.013).

**Conclusions:** Combined molecular profiling of mecA and lukF-PV identified distinct *Staphylococcus aureus* strains associated with different clinical outcomes. The mecA (+)/lukF-PV (+) profile showed the strongest association with prolonged hospitalization, prolonged antibiotic therapy, and antimicrobial resistance, suggesting that simultaneous assessment of resistance and virulence determinants may improve risk stratification and complement routine microbiological evaluation in patients with *Staphylococcus aureus* infection. Prospective multicentre studies with larger sample sizes are warranted to validate these findings

## 1. INTRODUCTION

*Staphylococcus aureus* is a major human pathogen responsible for a wide spectrum of infections ranging from superficial skin and soft tissue infections to severe invasive diseases, including bacteremia, pneumonia, endocarditis, osteomyelitis, and sepsis. The remarkable ability of *Staphylococcus aureus* to acquire antimicrobial resistance and express diverse virulence determinants has contributed substantially to its persistence in both healthcare and community settings, resulting in increased morbidity,

mortality, prolonged hospitalization, and healthcare costs worldwide. Among antimicrobial-resistant strains, methicillin-resistant *Staphylococcus aureus* (MRSA) remains a global public health concern. Methicillin resistance is primarily mediated by the mecA gene, which encodes penicillin-binding protein 2a (PBP2a), conferring resistance to nearly all β-lactam antibiotics and serving as the molecular gold standard for MRSA identification. [1,2] In addition to antimicrobial resistance, bacterial virulence is a major determinant of disease severity. The lukF-PV gene, encoding one component of Panton–Valentine leukocidin (PVL), promotes leukocyte destruction and tissue necrosis and has been associated with severe skin and soft tissue infections as well as necrotizing pneumonia.[3]

Although mecA and lukF-PV represent distinct biological characteristics of S. aureus—antimicrobial resistance and virulence, respectively—their combined contribution to patient outcomes remains poorly understood. Most previous studies have investigated these genes separately, focusing either on the prevalence of mecA for MRSA identification or the distribution of PVL genes as virulence markers, with limited evaluation of their combined clinical significance. [4,5] Moreover, evidence regarding the relationship between combined resistance–virulence gene profiles and clinically relevant outcomes, such as prolonged hospitalization, duration of antibiotic therapy, and antimicrobial resistance, is still scarce, particularly in low- and middle-income countries. This knowledge gap limits the understanding of how bacterial molecular characteristics contribute to disease progression and treatment outcomes beyond conventional microbiological classification.

Therefore, this study investigated the association between combined mecA and lukF-PV gene profiles in clinical *Staphylococcus aureus* isolates and patient clinical outcomes. Specifically, we evaluated whether different resistance–virulence gene combinations were associated with prolonged hospital stay, extended antibiotic use, and antimicrobial resistance. By integrating molecular characterization with clinically relevant outcomes, this study aims to provide evidence that may improve risk stratification, support antimicrobial stewardship, and enhance infection prevention and control strategies for *Staphylococcus aureus* infections, particularly in resource-limited healthcare settings.

## 2. MATERIALS AND METHODS

### 2.1 Study design and subjects

This retrospective observational analytical study and was conducted at Hasanuddin University Hospital, Makassar, Indonesia, between October 2022 and December 2025. A total sampling approach was used to include all pus specimens obtained from hospitalized adult patients with culture-confirmed *Staphylococcus aureus* infection during the study period. Patients aged ≥18 years with positive *Staphylococcus aureus* cultures and complete microbiological and clinical records were eligible for inclusion. Isolates with inadequate bacterial growth, poor DNA quality, or incomplete laboratory and clinical data were excluded from the molecular analysis.

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University (Approval No. 326/UN4.6.4.5.31/PP36/2026; approval date: 5 March 2026). Patient confidentiality was maintained by anonymizing all microbiological and clinical data prior to analysis.

### 2.2 Data collection

Clinical and microbiological data were retrospectively collected from hospitalized adult patients with culture-confirmed *Staphylococcus aureus* infection at Hasanuddin University Hospital. Eligible cases were identified from the hospital microbiology database and electronic medical records between January 2022 and December 2025. Demographic and clinical information, including age, length of hospital stays, intensive care unit (ICU) admission, use of invasive medical devices, duration of systemic antibiotic therapy, history of surgery, underlying comorbidities, and antimicrobial susceptibility results, were retrieved from electronic medical records. The primary clinical outcomes evaluated were prolonged hospitalization (>5 days), prolonged antibiotic therapy (>7 days), and antimicrobial resistance. Clinical data were linked to the corresponding microbiological isolates using unique laboratory and medical record identifiers after patient information had been anonymized.

Comorbidities were identified retrospectively from diagnoses documented in the patients' electronic medical records during the index hospitalization. Diabetes mellitus, chronic kidney disease, and hypertension were considered present when the corresponding diagnosis was documented by the treating physician in the medical record. Other documented comorbidities, including malignancy, heart failure, dyslipidemia, and obesity, were also recorded. Patients with more than one documented

condition were classified as having multiple comorbidities; therefore, individual comorbidity categories were not mutually exclusive.

The molecular laboratory analysis was performed between January and May 2026. Pus specimens collected during routine clinical care had been cultured on Blood Agar Plate (BAP) and Mannitol Salt Agar (MSA) and incubated aerobically at 35–37°C for 18–24 h. *Staphylococcus aureus* isolates were identified using standard microbiological procedures based on colony morphology, Gram staining, catalase testing, and coagulase testing. Antimicrobial susceptibility testing was performed using the Kirby–Bauer disk diffusion method on Mueller–Hinton agar according to the Clinical and Laboratory Standards Institute (CLSI) M100, 35th edition guidelines. Phenotypic methicillin resistance was determined using the cefoxitin (30 µg) disk diffusion test. *Staphylococcus aureus* ATCC 25923 was used as the quality-control strain throughout bacterial identification and antimicrobial susceptibility testing.

Genomic DNA was extracted from confirmed *Staphylococcus aureus* isolates using the Geneaid Genomic DNA Mini Kit (Geneaid Biotech Ltd., Taiwan) according to the manufacturer's instructions. Multiplex polymerase chain reaction (PCR) was subsequently performed to detect the spa gene for species confirmation, the mecA gene as a marker of methicillin resistance, and the lukF-PV gene as a marker of PVL virulence. PCR amplification was carried out in a final reaction volume of 25 µL containing GoTaq® Green Master Mix, gene-specific primers, template DNA, and nuclease-free water. The cycling conditions consisted of an initial denaturation at 94°C for 5 min, followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 59°C for 1 min, extension at 72°C for 1 min, and a final extension at 72°C for 10 min. PCR products were separated by electrophoresis on a 2% agarose gel prepared in 0.5× Tris–borate–EDTA (TBE) buffer, stained with ethidium bromide, and visualized under ultraviolet illumination using a GelDoc XR Imaging System (Bio-Rad Laboratories, Hercules, CA, USA). Based on PCR findings, isolates were categorized into four molecular profiles: mecA (−)/lukF-PV (−), mecA (+)/lukF-PV (−), mecA (−)/lukF-PV (+), and mecA (+)/lukF-PV (+).

### 2.3 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Associations between mecA/lukF-PV gene profiles and clinical outcomes, including prolonged hospitalization (>5 days), prolonged antibiotic therapy (>7 days), and antimicrobial resistance, were evaluated using univariable binary logistic regression. The mecA (-)/lukF-PV (-) group was designated as the reference category. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated to estimate the strength of association between each molecular profile and the clinical outcomes. Statistical significance was defined as a two-sided p value $<0.05$.

## 3. RESULTS AND DISCUSSION

### 3.1 Baseline Characteristics of the Study

A total of 47 patients with culture-confirmed *Staphylococcus aureus* infection were included in the study. As shown in Table 1, most patients were aged <60 years (72.3%), had a hospital stay of ≥5 days (55.3%), and received antibiotic therapy for ≥7 days (57.4%). ICU admission was observed in only 6.4% of patients, whereas 38.3% required invasive medical devices. Comorbidities were present in 66.0% of patients, and 83.0% had a history of surgery. Antimicrobial susceptibility testing demonstrated that 48.9% of isolates were resistant, while molecular analysis identified the mecA and lukF-PV genes in 53.2% and 59.6% of isolates, respectively (Table 1).

**Table 1.** Baseline characteristics of the study population (N = 47)

| Characteristic | Overall, n (%) |
|---|---|
| **Age** | |
| < 60 years | 34 (72.3) |
| ≥ 60 years | 13 (27.7) |
| **Length of hospital stay** | |
| < 5 days | 21 (44.7) |
| ≥ 5 days | 26 (55.3) |
| **ICU admission** | |
| No | 44 (93.6) |

| | |
|---|---|
| Yes | 3 (6.4) |
| **Use of invasive devices** | |
| No | 29 (61.7) |
| Yes | 18 (38.3) |
| **Duration of antibiotic therapy** | |
| < 7 days | 20 (42.6) |
| ≥ 7 days | 27 (57.4) |
| **Comorbidity** | |
| No | 16 (34.0) |
| Yes | 31 (66.0) |
| **History of surgery** | |
| No | 8 (17.0) |
| Yes | 39 (83.0) |
| **Antimicrobial susceptibility** | |
| Susceptible | 24 (51.1) |
| Resistant | 23 (48.9) |
| **mecA gene** | |
| Negative | 21 (46.8) |
| Positive | 26 (53.2) |
| **lukF-PV gene** | |
| Negative | 19 (40.4) |
| Positive | 28 (59.6) |
| Abbreviations: ICU, intensive care unit. | |

The clinical diagnoses of the study population are summarized in Table 2. Skin and soft tissue abscess was the most common diagnosis, accounting for 19 patients (40.4%), followed by double lumen catheter infection (18 patients, 38.3%) and surgical site infection (5 patients, 10.6%). Osteomyelitis and other diagnoses each accounted for 2 patients (4.3%), whereas diabetic foot ulcer was identified in 1 patient (2.1%).

**Table 2.** Clinical diagnoses of patients with *Staphylococcus aureus* infection (N = 47)

| **Clinical diagnosis** | **n (%)** |
|---|---|
| Skin and soft tissue abscess* | 19 (40.4) |
| Double lumen catheter infection | 18 (38.3) |
| Surgical site infection (SSI) | 5 (10.6) |
| Osteomyelitis | 2 (4.3) |
| Diabetic foot ulcer | 1 (2.1) |
| Other diagnoses** | 2 (4.3) |
| * Skin and soft tissue abscesses included gluteal, buccal, cervical, thoracic, scrotal, labial, and other anatomical locations.<br>** Other diagnoses included infected soft tissue tumors and skin ulcers associated with scrofuloderma. | |

The distribution of comorbidities is presented in Table 3. Diabetes mellitus was the most common comorbidity, affecting 20 patients (42.6%), followed by chronic kidney disease (19 patients, 40.4%) and hypertension (6 patients, 12.8%). Malignancy was present in 4 patients (8.5%), whereas heart failure, dyslipidaemia, and obesity were each identified in 1 patient (2.1%). Overall, 16 patients (34.0%) had no documented comorbidities.

**Table 3.** Comorbidities of the study population (N = 47)

| **Comorbidity** | **n (%)** |
|---|---|
| Diabetes mellitus | 20 (42.6) |

| | |
|---|---|
| Chronic kidney disease | 19 (40.4) |
| Hypertension | 6 (12.8) |
| Malignancy | 4 (8.5) |
| Heart failure | 1 (2.1) |
| Dyslipidemia | 1 (2.1) |
| Obesity | 1 (2.1) |
| No comorbidity | 16 (34.0) |
| Percentages may exceed 100% because some patients had more than one comorbidity. | |

### 3.2 Association of Gene Profiles with Prolonged Hospitalization

As shown in Table 4, univariable binary logistic regression analysis demonstrated that the mecA(-)/lukF-PV(+) and mecA(+)/lukF-PV(+) gene profiles were significantly associated with prolonged hospitalization (>5 days) compared with the reference mecA(-)/lukF-PV(-) profile (OR, 9.17; 95% CI, 1.15–73.24; p = 0.037 and OR, 31.17; 95% CI, 4.46–217.60; p = 0.001, respectively). No significant association was observed for the mecA(+)/lukF-PV(-) profile (OR, 2.75; 95% CI, 0.28–26.61; p = 0.382).

**Table 4.** Univariable logistic regression for prolonged hospital stay

| Gene profile | OR (95% CI) | P value |
|---|---|---|
| mecA(-)/lukF-PV(-) | Reference | — |
| mecA(+)/lukF-PV(-) | 2.75 (0.28–26.61) | 0.382 |
| mecA(-)/lukF-PV(+) | 9.17 (1.15–73.24) | 0.037 |
| mecA(+)/lukF-PV(+) | 31.17 (4.46–217.60) | 0.001 |
| Abbreviations: OR, odds ratio; CI, confidence interval. | | |

As shown in Table 5, univariable binary logistic regression analysis demonstrated that the mecA(+)/lukF-PV(+) gene profile was significantly associated with prolonged antibiotic therapy (>7 days) compared with the reference mecA(-)/lukF-PV(-) profile (OR, 12.75; 95% CI, 2.33–69.87; p = 0.003). In contrast, neither the mecA(+)/lukF-PV(-) profile (OR, 2.25; 95% CI, 0.31–16.41; p = 0.424) nor the mecA(-)/lukF-PV(+) profile (OR, 1.35; 95% CI, 0.21–8.62; p = 0.751) showed a significant association with prolonged antibiotic therapy.

**Table 5.** Univariable logistic regression for prolonged antibiotic therapy

| Gene profile | OR (95% CI) | P value |
|---|---|---|
| mecA(-)/lukF-PV(-) | Reference | — |
| mecA(+)/lukF-PV(-) | 2.25 (0.31–16.41) | 0.424 |
| mecA(-)/lukF-PV(+) | 1.35 (0.21–8.62) | 0.751 |
| mecA(+)/lukF-PV(+) | 12.75 (2.33–69.87) | 0.003 |
| Abbreviations: OR, odds ratio; CI, confidence interval. | | |

As shown in Table 6, univariable binary logistic regression analysis demonstrated that the mecA(+)/lukF-PV(-) gene profile was significantly associated with antimicrobial resistance compared with the reference mecA(-)/lukF-PV(-) profile (OR, 27.50; 95% CI, 2.00–378.84; p = 0.013). Likewise, isolates harboring the mecA(+)/lukF-PV(+) gene profile had significantly higher

odds of antimicrobial resistance (OR, 10.21; 95% CI, 1.75–59.65; p = 0.010). In contrast, no significant association was observed for the mecA(-)/lukF-PV(+) profile (OR, 1.83; 95% CI, 0.20–16.51; p = 0.589).

**Table 6.** Univariable logistic regression for antimicrobial resistance

| Gene profile | OR (95% CI) | P value |
|---|---|---|
| mecA(-)/lukF-PV(-) | Reference | — |
| mecA(+)/lukF-PV(-) | 27.50 (2.00–378.84) | 0.013 |
| mecA(-)/lukF-PV(+) | 1.83 (0.20–16.51) | 0.589 |
| mecA(+)/lukF-PV(+) | 10.21 (1.75–59.65) | 0.01 |

Abbreviations: OR, odds ratio; CI, confidence interval.

### 3.4 Discussion

The present study demonstrated that the combined mecA(+)/lukF-PV(+) gene profile was consistently associated with adverse clinical outcomes, including prolonged hospitalization, prolonged antibiotic therapy, and antimicrobial resistance. In contrast, the mecA(-)/lukF-PV(+) profile was associated only with prolonged hospitalization, whereas the mecA(+)/lukF-PV(-) profile was associated only with antimicrobial resistance. These findings indicate that resistance and virulence determinants may contribute differently to the clinical course of *Staphylococcus aureus* infection and that simultaneous molecular characterization provides more clinically relevant information than assessment of either determinant alone.

The association between the mecA (+)/lukF-PV (+) profile and prolonged hospitalization is biologically plausible. Methicillin resistance mediated by mecA reduces the effectiveness of β-lactam antibiotics, frequently necessitating the use of second-line agents and potentially delaying microbiological clearance. Meanwhile, PVL encoded by lukF-PV induces neutrophil destruction, promotes extensive tissue necrosis, and amplifies local inflammatory responses. Although previous studies have consistently reported that MRSA infections are associated with longer hospital stays than MSSA infections. [4,6] relatively few investigations have specifically examined the combined contribution of mecA and lukF-PV. Similarly, Shallcross et al. (2013) reported that PVL-positive *Staphylococcus aureus* strains were associated with more severe skin and soft tissue infections requiring more intensive clinical management. Our findings extend these observations by demonstrating that the coexistence of resistance and virulence determinants is associated with substantially increased odds of prolonged hospitalization.[3]

Only isolates carrying the mecA (+)/lukF-PV (+) profile showed a significant association with prolonged antibiotic therapy. This finding suggests that extended treatment duration may reflect the combined effects of antimicrobial resistance and enhanced bacterial virulence. Resistant isolates frequently require alternative antimicrobial regimens with longer treatment courses, whereas severe tissue destruction induced by PVL may delay clinical resolution despite microbiological control. To date, evidence directly linking combined mecA/lukF-PV profiles with antibiotic duration remains scarce. Most published studies have evaluated antimicrobial resistance or virulence independently rather than their combined influence on treatment course. Therefore, our findings provide novel evidence supporting the hypothesis that concurrent resistance and virulence determinants contribute to more complex therapeutic management.

As expected, isolates harboring the mecA(+)/lukF-PV(-) profile exhibited the strongest association with antimicrobial resistance. This observation is consistent with the established biological function of mecA, which encodes penicillin-binding protein 2a (PBP2a) and serves as the principal molecular mechanism underlying methicillin resistance 1. Previous epidemiological studies have shown that MRSA isolates frequently exhibit multidrug-resistant phenotypes because SCCmec elements often harbor additional resistance determinants. [4,7] Interestingly, although the mecA(+)/lukF-PV(+) profile was also significantly associated with antimicrobial resistance, its odds ratio was lower than that observed for mecA(+)/lukF-PV(-) isolates. Given the wide confidence intervals observed in both groups, this difference should be interpreted cautiously and is most likely attributable to the relatively small sample size rather than a true biological difference.

To our knowledge, few previous studies have simultaneously evaluated mecA and lukF-PV gene profiles in relation to multiple clinically relevant outcomes, including hospitalization duration, antibiotic use, and antimicrobial resistance. Most investigations have focused on the prevalence of mecA as a marker of MRSA or PVL as an indicator of virulence without integrating these

molecular characteristics into a unified prognostic model. Consequently, the present study addresses an important knowledge gap by demonstrating that combined molecular profiling may provide additional prognostic information beyond conventional phenotypic susceptibility testing.

These findings have potential clinical implications. Early identification of isolates carrying both resistance and virulence determinants may facilitate risk stratification, optimize empirical antimicrobial selection, and support infection prevention strategies, particularly in tertiary referral hospitals where severe *Staphylococcus aureus* infections remain common. Incorporating molecular characterization into routine microbiological workflows may therefore improve individualized patient management and strengthen antimicrobial stewardship programs.

Several limitations should be acknowledged. First, this was a single-centre retrospective study with a relatively small sample size, resulting in wide confidence intervals and limited statistical precision. Second, only univariable logistic regression was performed; therefore, the observed associations were not adjusted for potential confounding factors such as age, ICU admission, invasive device use, comorbidities, or history of surgery. Third, only mecA and lukF-PV were investigated, whereas other resistance and virulence determinants, including mecC, spa, hla, and biofilm-associated genes, were not evaluated. Future multicentre studies with larger sample sizes and multivariable analyses are warranted to validate these findings and clarify the independent contribution of combined molecular profiles to patient outcomes.

## 4. CONCLUSION

Combined molecular profiling of mecA and lukF-PV identified clinically distinct *Staphylococcus aureus* strains associated with different patient outcomes. The mecA (+)/lukF-PV (+) profile consistently demonstrated the strongest association with prolonged hospitalization, extended antibiotic therapy, and antimicrobial resistance, highlighting the complementary roles of resistance and virulence determinants in disease progression. These findings support the potential value of integrating molecular characterization into routine microbiological evaluation to improve risk stratification and guide clinical management of Staphylococcus aureus infections. Further prospective multicenter studies are needed to confirm these associations and establish their clinical applicability.

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## AUTHOR CONTRIBUTIONS

**Dhevie Gianfranco Lumalessil:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft.

**Risna Halim Mubin**: Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft.

**Wasis Udaya:** Methodology, Investigation, Writing – review & editing.

**Syakib Bakri:** Supervision, Conceptualization, Writing – review & editing.

**Eliana Muis:** Supervision, Validation, Writing – review & editing.

**Arifin Seweng:** Formal analysis, Validation, Methodology, Writing – review & editing.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ETHICS STATEMENT

This study has been approved by the Research Ethics Committee of the Faculty of Medicine, Hasanuddin University, through the issuance of an ethics approval letter Number: 326/UN4.6.4.5.31/PP36/2026; approval date: 5 March 2026. This study complies with ethical principles, ensuring the protection of participants' rights and confidentiality.

## DATA AVAILABILITY STATEMENT

The study protocol was reviewed and approved by the Human Biomedical Research Ethics Committee, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia (ethical approval No. 689/UN.4.6.4.5.31/PP36/2026). The requirement for informed consent was waived by the ethics committee because of the retrospective nature of the study and the use of routinely collected clinical data. All patient data were anonymized prior to analysis and handled confidentially to protect participant privacy.

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