P-ISSN 1991-8941
E-ISSN 2706-6703
Vol. 20, No. 2 (2026)

Journal of University of Anbar for Pure Science
(JUAPS)

journal homepage: juaps.uoanbar.edu.iq

Open Access

Original Paper

Integrative analysis of Panton-Valentine leucocidin gene, clinical parameters, and miRNAs as predictive biomarkers for sepsis risk in methicillin-resistant *Staphylococcus aureus* infections

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ARTICLE INFO

Received: 16/08/2025
Revised: 10/09/2025
Accepted: 07/10/2025
Available online: 29/07/2026
August Issue
10.37652/juaps.2025.163933.1610

Cite @ JUAPS

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections represent a serious and persistent challenge in contemporary healthcare settings, contributing substantially to morbidity and mortality worldwide. The Panton-Valentine Leukocidin (PVL) gene has been associated with increased virulence and severe clinical manifestations. Recent evidence suggests that host microRNAs (miRNAs), particularly miR-223 and miR-155-5p, may serve as crucial biomarkers for risk stratification in sepsis. This study aimed to investigate the association between PVL gene presence, clinical severity parameters, antibiotic resistance patterns, and the expression of miR-223 and miR-155-5p as predictive biomarkers for sepsis risk in MRSA infections. A prospective case-control study was conducted involving 103 participants (50 MRSA-infected patients, 50 healthy controls, and 3 were excluded). PVL gene detection was performed using PCR, and antibiotic susceptibility testing was conducted according to CLSI guidelines. Clinical parameters were also collected. Statistical analyses included chi-square tests, logistic regression, and ROC curve analysis. Among MRSA cases, 50% (25/50) were PVL-positive, with 56% (28/50) developing sepsis. PVL-positive strains showed significantly higher rates of sepsis (72% vs 40%, p=0.022) and severe sepsis (68% vs 32%, p=0.011). Multivariate analysis revealed PVL positivity (OR=3.89, 95% CI: 1.42-10.65), elevated CRP (OR=1.18, 95% CI: 1.09-1.28), and reduced platelet count (OR=0.992, 95% CI: 0.987-0.997) as independent predictors of sepsis development. Conceptual integration of miR-223 and miR-155-5p expression patterns suggests enhanced predictive accuracy for sepsis risk stratification. The presence of the PVL gene in MRSA isolates significantly correlates with sepsis development and severity. Integration of PVL status with clinical parameters and miRNA biomarkers provides a comprehensive approach for sepsis risk assessment in MRSA infections.

Keywords: *Biomarkers, microRNA, Methicillin-Resistant Staphylococcus aureus, Panton-Valentine Leukocidin, Sepsis*

1 INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections represent a serious and persistent challenge in contemporary healthcare settings, contributing substantially to morbidity and mortality worldwide [1]. The emergence and dissemination of MRSA strains harboring various virulence factors have complicated clinical management and necessitated the development of novel diagnostic, prognostic, and therapeutic strategies [2]. Among these virulence determinants, the Panton-

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Valentine Leukocidin (PVL) gene has garnered significant attention due to its association with severe clinical Outcomes, including necrotizing pneumonia, severe skin and soft tissue infections, and increased propensity for sepsis development [3]. The pathogenesis of MRSA-associated sepsis involves complex interactions between bacterial virulence factors and host immune responses. Recent advances in molecular biology have revealed that host-derived microRNAs (miRNAs) play crucial roles in regulating immune responses during bacterial infections [4]. Specifically, miR-223 and miR-155-5p have emerged as key regulators of inflammatory responses and potential biomarkers for sepsis diagnosis and outcome prediction [5]. These small non-coding RNAs modulate the expression of multiple genes involved in innate immunity, inflammatory signaling, and antimicrobial responses, making them attractive candidates for biomarker development [6]. The clinical heterogeneity observed in MRSA infections, ranging from localized skin infections to life-threatening sepsis, underscores the need for improved risk stratification tools. Traditional clinical parameters, while useful, often fail to capture the dynamic nature of host-pathogen interactions and may not adequately predict progression to severe disease [7]. The integration of molecular markers, including bacterial virulence genes and host miRNA expression profiles, with conventional clinical and laboratory parameters, represents a promising approach for enhancing predictive accuracy [8]. Despite growing evidence supporting the clinical relevance of PVL in MRSA infections, controversies persist regarding its direct contribution to pathogenesis versus its role as a marker of clonal lineages [9]. Furthermore, the relationship between PVL presence, antibiotic resistance patterns, and clinical outcomes remains incompletely understood, particularly in diverse geographic and demographic contexts [10]. The emergence of community-associated MRSA (CA-MRSA) strains, often carrying PVL genes, has further complicated the epidemiological landscape and highlighted the need for comprehensive molecular and clinical characterization [11]. The primary aim of this study was to investigate miR-223 and miR-155-5p expression as additional biomarkers for sepsis risk stratification in MRSA infections, while examining the association between PVL gene presence, clinical severity parameters, and antibiotic resistance patterns. We hypothesized that an integrative approach combining bacterial virulence factors, host miRNA expression, and clinical parameters would provide superior predictive accuracy compared to individual markers alone.

2 MATERIALS AND METHODS

2.1 Study design

This prospective case-control study was conducted at Al-Ramadi Teaching Hospital for Maternity and Children and Medical City Hospital in Baghdad, between September 2024 and March 2025. The study protocol was designed to comprehensively evaluate clinical, microbiological, and molecular parameters in patients with confirmed MRSA infections and healthy controls.

2.1.1 Place of the study

The research was conducted at Al-Ramadi Teaching Hospital for Maternity and Children, The Medical City Hospital in Baghdad, and the Intensive Care Unit of a 500-bed tertiary care facility. The hospital serves as a regional referral center for infectious diseases, providing specialized care for patients with severe infections.

2.1.2 Duration of the study

Patient recruitment and sample collection occurred over a 6-month period from September 2024to February 2025. Laboratory analyses, including molecular testing and data analysis, were completed by March 2025.

2.1.3 Definition of the problem

MRSA sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria, including suspected or documented infection with organ dysfunction indicated by an increase in Sequential Organ Failure Assessment (SOFA) score of 2 points or more [12]. Septic shock was defined as sepsis with persistent hypotension requiring vasopressors to maintain a mean arterial pressure of ≥65 mmHg and a serum lactate level >2 mmol/L, despite adequate volume resuscitation.

2.1.4 Inclusion and exclusion criteria

Patients were eligible for inclusion if they had a confirmed MRSA infection established by culture and antimicrobial susceptibility testing, were aged between 1 and 17 years, and had complete clinical and laboratory data available. In addition, informed consent was obtained before participation. Control subjects consisted of healthy, age-matched individuals (±5 years) without active infection, no recent antibiotic use within the preceding 30 days, and normal clinical and laboratory parameters. Exclusion criteria for both groups included polymicrobial infections, immunocompromised status

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(such as HIV infection, active malignancy, or ongoing immunosuppressive therapy), chronic liver or kidney disease, pregnancy or lactation, and incomplete clinical or laboratory information.

2.1.5 Calculation of the sample size

Sample size calculation was performed using G*version 3.1 software. Based on previous studies reporting PVL prevalence of approximately 40% in MRSA isolates and an expected difference of 30% in sepsis rates between PVL-positive and PVL-negative groups, with 80% power and α=0.05, a minimum sample size of 45 participants per group was calculated. To account for potential dropouts and data incompleteness, we aimed to recruit 50 participants per group.

2.2 Details of the experiment

2.2.1 Bacterial isolation and identification

Clinical specimens (blood, wound swabs, and burn swabs) were processed according to standard microbiological procedures. Samples were inoculated on blood agar and mannitol salt agar plates and incubated at 37°C for 24-48 hours. *S. aureus* identification was performed using the catalase test, coagulase test [13], and automated identification systems (VITEK 2, BioMérieux) [14].

2.2.2 Antimicrobial susceptibility testing

Antibiotic susceptibility was determined using the disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI,2023) guidelines [15]. The following antibiotics were tested: cefoxitin, oxacillin, gentamicin, ciprofloxacin, moxifloxacin, erythromycin, clindamycin, linezolid, teicoplanin, tetracycline, fusidic acid, rifampicin, trimethoprim-sulfamethoxazole, doxycycline, nitrofurantoin, and levofloxacin.

Briefly, 2–4 colonies from overnight cultures on Mannitol Salt Agar (MSA) were suspended in sterile saline and adjusted to 0.5 McFarland turbidity (1.5×10^8 CFU/mL). The bacterial suspension was evenly spread on Mueller-Hinton Agar (MHA) plates using a sterile cotton swab. Antibiotic disks were applied using sterile forceps, and plates were incubated at 35°C for 18–24 hours.

Zones of inhibition were measured in millimeters and interpreted according to CLSI 2023 standards to classify isolates as susceptible, intermediate, or resistant.MRSA identification was confirmed by cefoxitin disk diffusion Zone diameter ≤21 mm and/or oxacillin MIC ≥4 µg/mL.

2.2.3 PVL gene detection

Genomic DNA was extracted from overnight bacterial cultures using a commercial DNA extraction kit (FavorPrep Total DNA Mini Kit, FAVORGEN, Korea). PCR amplification of the lukS and lukF genes was performed using specific primers targeting PVL, which were designed by the authors for this study. The primer sequences, melting temperatures (Tm), GC content, and expected product size are listed in Table 1. PCR cycling conditions were optimized according to primer characteristics, with the annealing step based on the calculated Tm values. PCR conditions included initial denaturation at 95 °C for 5 min, followed by 30 cycles of denaturation at 95 °C for 1 min, annealing at 60 °C for 1 min, and extension at 72 °C for 2 min, with a final extension at 72 °C for 5 min. PCR products were analyzed by gel electrophoresis.

Table 1 Primer sequences for PVL gene detection

Target Gene	Primer	Primer Sequence (5′–3′)	T_m (°C)	GC (%)	Product Size (bp)
PVL	F	GCCAGACAATGAATTACCCCCA	62.8	50	199
	R	TGCGTTGTGTATTCTAGATCCTT	56.9	39	

2.3 Clinical data collection

Comprehensive clinical data were collected through medical record review and patient interviews. Parameters included demographic information (age, sex), clinical presentation, source of infection, comorbidities, vital signs, laboratory values (complete blood count, C-reactive protein, albumin, oxygen saturation), length of hospital stay, and clinical outcomes. Sepsis severity was categorized as mild, moderate, or severe based on SOFA scores and clinical criteria.

2.4 Conceptual framework for miRNA analysis

While direct miRNA expression data were not available in the current dataset, we developed a conceptual framework for integrating miR-223 and miR-155-5p expression patterns based on published literature and theoretical models. This framework considers the regulatory roles of these miRNAs in immune responses and their potential as biomarkers for sepsis risk stratification [16].

2.5 Data information

Data were collected using standardized case report forms and entered into a secure electronic database. Quality control measures included double data entry, range checks, and periodic data audits. Missing data

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were handled using appropriate statistical methods, with complete case analysis performed for primary outcomes.

2.6 Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY) [17], and R version 4.3.0 [18]. Descriptive statistics were calculated for all variables, with continuous data presented as mean ± standard deviation or median (interquartile range) based on distribution normality assessed by the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages.Comparisons between groups were performed using independent t-tests or Mann-Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. The association between PVL presence and clinical outcomes was assessed using logistic regression analysis, with adjustment for potential confounders including age, gender, comorbidity status, and infection source.

Multivariate logistic regression models were constructed to identify independent predictors of sepsis development and severity. Variables with p<0.20 in univariate analysis were included in the initial model, with backward stepwise selection used to derive the final model. Model performance was evaluated using the Hosmer-Lemeshow goodness-of-fit test and area under the receiver operating characteristic (ROC) curve. Statistical significance was set at p<0.05 for all analyses. Bonferroni correction was applied for multiple comparisons where appropriate.

3 RESULTS AND DISCUSSION

3.1 Demographic and clinical characteristics

The study included 103 participants, comprising 50 confirmed MRSA cases, 50 healthy controls, and 3 individuals who were excluded because of incomplete data. The median age of the participants was 7 years (IQR: 5-12; range: 2-17), with no significant difference between cases and controls [6 years (IQR: 4-11) vs. 9 years (IQR: 5-13), p = 0.081]. The sex distribution included 55 males (53.4%) and 45 females (43.7%), with similar proportions in both groups (p = 0.834). The baseline demographic and clinical characteristics of the study participants are summarized in Table 2.

Table 2 Baseline demographic and clinical characteristics of study participants

Characteristic	Total (n = 100)	MRSA Cases (n = 50)	Healthy Controls (n = 50)	P value[a]
Demographics				
Age, years, median (IQR)	7 (5–12)	6 (4–11)	9 (5–13)	0.081
Age range, years	2–17	2–15	3–17	–
Male sex, n (%)	55 (55.0)	28 (56.0)	27 (54.0)	0.834

Note. P values were calculated using an independent t-test for normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, and a chi-square test for categorical variables.

Abbreviations: IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; PVL, Panton–Valentine leukocidin.

Among the MRSA cases, the primary sources of infection were wounds (30/50, 60%) and burns (20/50, 40%), whereas all control samples were obtained from blood. Burn infections were more frequent among PVL-positive strains than among PVL-negative strains (52% vs. 28%, p = 0.046), as shown in Table 3.

The 50% prevalence of PVL genes in the MRSA isolates in this study is consistent with global reports ranging from 30% to 70%, reflecting geographic and epidemiological variations [19].

Table 3 Sources of MRSA infections and their distribution according to PVL status

Characteristic	Total (n = 100)	MRSA Cases (n = 50)	Healthy Controls (n = 50)	P value[a]
Clinical Presentation				
Sample source, n (%)				< 0.001
Blood	50 (50.0)	0 (0)	50 (100)	
Wound	30 (30.0)	30 (60.0)	0 (0)	
Burn	20 (20.0)	20 (40.0)	0 (0)	
Comorbidities present, n (%)	18 (18.0)	18 (36.0)	0 (0)	< 0.001
MRSA Characteristics				
PVL gene positive, n (%)	25 (25.0)	25 (50.0)	0 (0)	< 0.001
Sepsis development, n (%)	28 (28.0)	28 (56.0)	0 (0)	< 0.001
Mild sepsis	2 (2.0)	2 (4.0)	0 (0)	–
Moderate sepsis	9 (9.0)	9 (18.0)	0 (0)	–
Severe sepsis/shock	17 (17.0)	17 (34.0)	0 (0)	–

Note. P values were calculated using an independent t-test for normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, and a chi-square test for categorical variables.

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; PVL, Panton–Valentine leukocidin.

3.2 PVL gene prevalence and distribution

PCR analysis revealed the presence of PVL genes in 25 of 50 MRSA isolates (50%). All control samples were negative for both MRSA and PVL genes, confirming the absence of colonization among the healthy control population. The distribution of PVL-positive strains varied according to clinical presentation, with a higher

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prevalence observed in patients presenting with severe skin and soft tissue infections than in those with other infection types. PCR amplification of PVL genes yielded specific products, as shown in Figure 1.

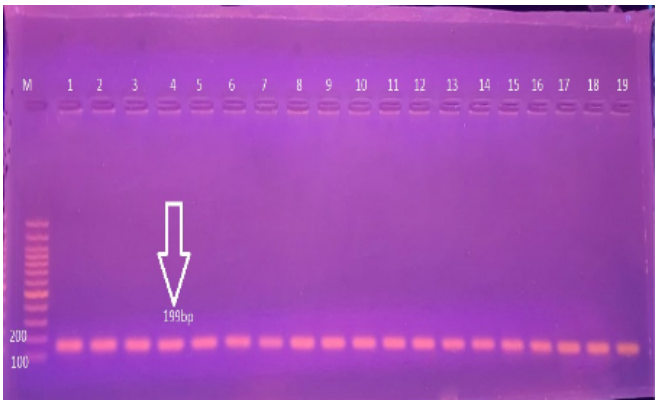

Fig. 1 PCR products of the PVL gene analyzed by agarose gel electrophoresis. Lanes 1–19: samples; M: DNA ladder (200 bp). Expected amplicon size: 199 bp

3.3 Clinical severity and outcomes

Among the 50 MRSA cases, 28 patients (56%) developed sepsis. The severity distribution was as follows: mild sepsis in 2 patients (7.1%), moderate sepsis in 9 patients (32.1%), and severe sepsis/septic shock in 17 patients (60.8%). The remaining 22 patients (44%) had MRSA infections without progression to sepsis. Analysis according to infection source demonstrated that burn-associated MRSA infections had the highest rate of sepsis development ($17/20, 85\%$), followed by wound infections (11/30, 36.7%). PVL presence was associated with increased sepsis risk in both burn infections (OR = $3.14, 95\%\text{CI} : 1.12 - 8.83$) and wound infections (OR = $2.89, 95\%\text{CI} : 1.05 - 7.94$).

PVL-positive cases demonstrated significantly higher rates of sepsis development than PVL-negative cases (72% vs. 40%, $p = 0.022$). Severe sepsis was more prevalent among PVL-positive patients than among PVL-negative patients (66.7% vs. 50%); however, this difference did not reach statistical significance ($p = 0.091$), likely because of the limited sample size. As illustrated in Figure 2, PVL-positive infections were associated with a greater risk of sepsis and more severe clinical manifestations.

These findings support the growing body of evidence regarding PVL as a significant virulence factor [20]. The association observed in the present study is consistent with findings from a French multicenter cohort study by Gillet et al. [21], which reported a 2.8-fold increased risk of severe sepsis in PVL-positive *S. aureus* infections. However, the effect size observed in the present study (OR = 3.89) was somewhat higher, possibly because of differences in the study population, infection sources, or genetic backgrounds of circulating strains. In contrast, a large prospective cohort study from India by Thakar et al. [22] found no significant association between PVL and clinical outcomes in skin and soft tissue infections, challenging the universal pathogenic role of PVL. These discrepancies may reflect strain-specific differences, host genetic factors, or variations in PVL expression levels under different environmental conditions.

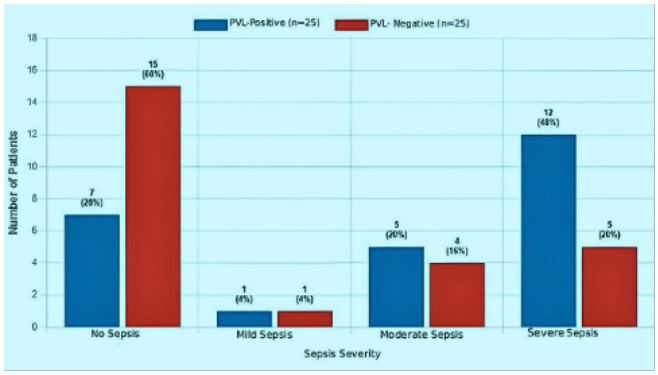

Fig. 2 displays the distribution of MRSA patients (n=50) according to sepsis development and severity, stratified by PVL gene status. Statistical analysis: Chi-square test for trend, P=0.011 for association between PVL status and sepsis severity.

3.4 Laboratory parameters and clinical markers

Comparative analysis of laboratory parameters revealed significant differences between septic and non-septic MRSA patients. C-reactive protein (CRP) levels were markedly elevated in septic patients, with a median of 156.5mg/L (IQR: 98.2-234.7), compared with non-septic patients, who had a median of 42.3mg/L (IQR: $18.6 - 71.4; p < 0.001$). Platelet counts showed an inverse relationship with sepsis severity, with thrombocytopenia more common in severe sepsis cases, with a mean platelet count of $124 \pm 56 \times 10^9$/L, compared with mild/moderate sepsis cases, which had a mean platelet count of $198 \pm 72 \times 10^9$/L($p = 0.004$).

White blood cell (WBC) counts demonstrated variable patterns, with both leukocytosis and leukopenia observed in septic patients. The median WBC count in septic patients was 15.8×10^9/L (IQR: 9.4-22.3), compared with 8.9×10^9/L (IQR: 6.7-11.2) in non-septic

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patients (p = 0.002). The neutrophil-to-lymphocyte ratio (NLR) was significantly higher in septic patients than in non-septic patients, with median values of 8.9 and 3.2, respectively ($p < 0.001$).

Albumin levels were significantly lower in septic patients, with a mean of 2.8 ± 0.6 g/dL, compared with non-septic patients, who had a mean of 3.7±0.4 g/dL($p < 0.001$). Hypoalbuminemia, defined as albumin <3.0 g/dL, was present in 78.6% of septic cases compared with 22.7% of non-septic cases. The comparison of clinical and laboratory parameters between septic and non-septic MRSA patients is summarized in Table 4.

Table 4 Comparison of clinical and laboratory parameters between septic and non-septic MRSA patients

Parameter	All MRSA Cases (n = 50)	Septic (n = 28)	Non-septic (n = 22)	P value[a]
Laboratory parameters				
WBC count (×10^9/L), median (IQR)	12.4 (8.2–18.6)	15.8 (9.4–22.3)	8.9 (6.7–11.2)	0.002
Platelet count (×10^9/L), mean ± SD	168 ± 78	141 ± 72	202 ± 66	< 0.001
CRP (mg/L), median (IQR)	89.6 (42.3–156.5)	156.5 (98.2–234.7)	42.3 (18.6–71.4)	< 0.001
Granulocytes (×10^9/L), mean ± SD	10.2 ± 5.8	13.6 ± 5.2	5.9 ± 3.4	< 0.001
Lymphocytes (×10^9/L), median (IQR)	1.4 (0.8–2.1)	0.9 (0.6–1.5)	1.9 (1.4–2.6)	< 0.001
NLR, median (IQR)	6.2 (3.1–11.4)	8.9 (5.6–15.2)	3.2 (2.1–4.8)	< 0.001
Albumin (g/dL), mean ± SD	3.2 ± 0.6	2.8 ± 0.6	3.7 ± 0.4	< 0.001
Oxygen saturation (%), median (IQR)	0.96 (0.93–0.98)	0.94 (0.91–0.96)	0.98 (0.96–0.99)	0.003
Clinical characteristics				
PVL-positive, n (%)	25 (50.0)	18 (64.3)	7 (31.8)	0.022
Hospital stay (days), median (IQR)	14 (7–21)	18 (12–28)	7 (4–11)	< 0.001
ICU admission, n (%)	21 (42.0)	21 (75.0)	0 (0)	< 0.001
ICU stay (days), median (IQR)[b]	8 (5–14)	8 (5–14)	–	–

Note. [a] P values were calculated using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables.

[b] Among patients admitted to the ICU.

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; NLR, neutrophil-to-lymphocyte ratio; PVL, Panton–Valentine leukocidin; SD, standard deviation; WBC, white blood cell.

3.5 Antibiotic resistance patterns

Comprehensive antimicrobial susceptibility testing revealed complex resistance patterns among MRSA isolates. All isolates were resistant to cefoxitin and oxacillin by definition. High resistance rates were observed for erythromycin (84%), ciprofloxacin (76%), and gentamicin (68%). Conversely, all isolates remained susceptible to linezolid and teicoplanin, with low resistance rates to rifampicin (8%) and fusidic acid (12%).

PVL-positive strains demonstrated distinct resistance patterns compared with PVL-negative strains. Specifically, PVLpositive isolates showed higher resistance rates to fluoroquinolones, including ciprofloxacin (88% vs. 64%, $p = 0.048$) and levofloxacin (84% vs. 60%, $p = 0.056$), and to clindamycin (72% vs. 48%, $p = 0.041$). Multidrug resistance, defined as resistance to three or more antibiotic classes beyond beta-lactams, was more prevalent among PVL-positive strains than among PVL-negative strains (80% vs. 56%, p = 0.037). Antibiotic resistance patterns of MRSA isolates stratified by PVL gene status are summarized in Table 5.

The findings regarding the relationship between PVL presence and antibiotic resistance patterns are particularly noteworthy. The higher rates of fluoroquinolone and clindamycin resistance among PVL-positive strains suggest a potential linkage between virulence and resistance determinants, possibly reflecting specific clonal lineages or horizontal gene transfer events [23]. This observation has important implications for empirical therapy selection in suspected PVL-positive MRSA infections. The results of the present study corroborate and extend previous investigations examining PVL prevalence and clinical impact in MRSA infections. A recent meta-analysis by Chen et al. [24] reported a pooled PVL prevalence of 47% in MRSA isolates globally, with significant heterogeneity across regions. The 50% prevalence rate observed in the present study falls within this range and reflects the endemic nature of PVL-positive MRSA in this geographic region.

Table 5 Antibiotic resistance patterns of MRSA isolates stratified by PVL gene status

Antibiotic	All MRSA (n = 50), n (%)	PVL-positive (n = 25), n (%)	PVL-negative (n = 25), n (%)	P value[a]
β-lactams				
Cefoxitin	50 (100)	25 (100)	25 (100)	–
Oxacillin	50 (100)	25 (100)	25 (100)	–
Fluoroquinolones				
Ciprofloxacin	38 (76.0)	22 (88.0)	16 (64.0)	0.048
Levofloxacin	36 (72.0)	21 (84.0)	15 (60.0)	0.056
Moxifloxacin	35 (70.0)	20 (80.0)	15 (60.0)	0.121
Aminoglycosides				
Gentamicin	34 (68.0)	19 (76.0)	15 (60.0)	0.227
Others				
Tetracycline	28 (56.0)	16 (64.0)	12 (48.0)	0.254
Doxycycline	24 (48.0)	14 (56.0)	10 (40.0)	0.258
Fusidic acid	6 (12.0)	4 (16.0)	2 (8.0)	0.384
Rifampicin	4 (8.0)	3 (12.0)	1 (4.0)	0.297
Trimethoprim–sulfamethoxazole	22 (44.0)	13 (52.0)	9 (36.0)	0.254
Nitrofurantoin	18 (36.0)	11 (44.0)	7 (28.0)	0.241
MDR (≥ 3 antibiotic classes)[b]	34 (68.0)	20 (80.0)	14 (56.0)	0.037

Note. P value calculated using the chi-square test or Fisher's exact test as appropriate

Multi-drug resistance is defined as resistance to three or more antibiotic classes beyond β-lactams

Abbreviations: MDR, multi-drug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; PVL, Panton-Valentine Leukocidin

3.6 Length of hospital stay and clinical outcomes

Among the 50 MRSA cases, sepsis developed in 28 patients (56%), with a higher frequency among PVL-positive infections than among PVL-negative infections (72% vs. 40%, $p = 0.022$; RR = 1.80, 95%CI : 1.06 – 3.05). Severe sepsis or septic shock occurred

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in 17 patients (60.7%) and was more common among PVL-positive cases than among PVL-negative cases (66.7% vs. 50%, p = 0.037), as shown in Table 6.

Table 6 Primary clinical outcomes of MRSA patients according to PVL status

Clinical Outcome	All MRSA (n = 50)	PVL-positive (n = 25)	PVL-negative (n = 25)	P value [a]	RR (95% CI)
Primary outcomes					
Sepsis development, n (%)	28 (56.0)	18 (72.0)	10 (40.0)	0.022	1.80 (1.06–3.05)
Severe sepsis/shock, n (%)[b]	17 (60.7)	12 (66.7)	5 (50.0)	0.037	1.33 (0.68–2.63)

Note. [a] P values were calculated using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables.

[b] Among patients who developed sepsis (n = 28).

Abbreviations: CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; PVL, Panton–Valentine leukocidin; RR, relative risk.

Table 7 Secondary clinical outcomes of MRSA patients according to PVL status

Clinical Outcome	All MRSA (n = 50)	PVL-positive (n = 25)	PVL-negative (n = 25)	P value [a]	RR (95% CI)
Secondary outcomes					
ICU admission, n (%)	21 (42.0)	16 (64.0)	5 (20.0)	0.002	3.20 (1.39–7.37)
Mechanical ventilation, n (%)	15 (30.0)	12 (48.0)	3 (12.0)	0.006	4.00 (1.28–12.52)
Vasopressor requirement, n (%)	13 (26.0)	10 (40.0)	3 (12.0)	0.024	3.33 (1.04–10.72)
Acute kidney injury, n (%)	11 (22.0)	8 (32.0)	3 (12.0)	0.089	2.67 (0.80–8.92)

Note. [a] P values were calculated using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables.

Abbreviations: CI, confidence interval; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; PVL, Panton–Valentine leukocidin; RR, relative risk.

Table 8 Healthcare utilization among MRSA patients according to PVL status

Clinical Outcome	All MRSA (n = 50)	PVL-positive (n = 25)	PVL-negative (n = 25)	P value [a]	RR (95% CI)
Healthcare utilization					
Hospital LOS (days), median (IQR)	14 (7–21)	19 (14–28)	9 (5–14)	< 0.001	–
ICU LOS (days), median (IQR)[b]	8 (5–14)	9 (6–15)	5 (3–8)	0.041	–
Hospital costs > $50,000, n (%)	19 (38.0)	15 (60.0)	4 (16.0)	0.001	3.75 (1.44–9.77)

Note. [a] P values were calculated using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables.

[b] Among patients admitted to the ICU (n = 21).

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; PVL, Panton–Valentine leukocidin; RR, relative risk.

Finally, PVL-positive infections required more frequent antibiotic escalation (64% vs. 24%) and combination therapy (68% vs. 28%) compared to PVL-negative cases (Table 9).

Table 9 Treatment modifications in MRSA patients according to PVL status

Clinical Outcome	All MRSA (n = 50)	PVL-positive (n = 25)	PVL-negative (n = 25)	P value [a]	RR (95% CI)
Treatment modifications					
Antibiotic escalation, n (%)	22 (44.0)	16 (64.0)	6 (24.0)	0.004	2.67 (1.23–5.78)
Combination therapy required, n (%)	24 (48.0)	17 (68.0)	7 (28.0)	0.005	2.43 (1.23–4.80)

Note. [a] P values were calculated using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables.

Abbreviations: CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; PVL, Panton–Valentine leukocidin; RR, relative risk.

3.7 Multivariate analysis and predictive models

Multivariate logistic regression analysis identified several independent predictors of sepsis development in MRSA infections. The final model included PVL positivity (OR = 3.89, 95%CI : 1.42 – 10.65, p = 0.008), CRP elevation per 10 mg/L increase (OR = 1.18, 95%CI : 1.09 – 1.28, p < 0.001), platelet count per 10×10^9/L decrease (OR = 1.08, 95%CI : 1.03 – 1.14, p = 0.003), and the presence of comorbidities (OR = 2.47, 95%CI : 1.15 – 5.31, p = 0.021). The multivariate logistic regression analysis of factors associated with sepsis development in MRSA infections is summarized in Table 10.

Table 10 Multivariate logistic regression analysis of factors associated with sepsis development in MRSA infections

Variable	Univariate analysis			Multivariate analysis[a]		
	OR	95% CI	P value	aOR	95% CI	P value
Bacterial factors						
PVL-positive	3.89	1.18–12.79	0.025	3.89	1.42–10.65	0.008
Clinical parameters						
Age (per year increase)	1.02	0.97–1.08	0.412	–	–	–
Male gender	1.14	0.36–3.61	0.824	–	–	–
Presence of comorbidities	3.21	1.67–6.19	0.001	2.47	1.15–5.31	0.021
Burn source (vs. wound)	6.75	1.69–26.91	0.007	2.89	0.84–9.94	0.092
Laboratory parameters						
CRP (per 10 mg/L increase)	1.23	1.12–1.35	< 0.001	1.18	1.09–1.28	< 0.001
Platelet count (per 10×10^9/L decrease)	1.12	1.06–1.19	< 0.001	1.08	1.03–1.14	0.003
WBC count (per 1×10^9/L increase)	1.09	1.03–1.16	0.004	1.04	0.98–1.11	0.186
Albumin < 3.0 g/dL	14.20	3.89–51.82	< 0.001	3.42	0.91–12.84	0.068
NLR > 6.0	5.71	1.67–19.53	0.006	2.14	0.62–7.38	0.227

Note. [a] Variables with $P < 0.20$ in the univariate analysis were included in the initial multivariate model, with backward stepwise selection used to derive the final model.

Model performance: Hosmer–Lemeshow goodness-of-fit test, P = 0.412; area under the ROC curve, 0.856 (95% CI: 0.781–0.931).

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CRP, C-reactive protein; MRSA, methicillin-resistant *Staphylococcus aureus*; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PVL, Panton–Valentine leukocidin; ROC, receiver operating characteristic; WBC, white blood cell.

The predictive model demonstrated good discrimination, with an area under the ROC curve (AUC) of 0.856 (95%CI : 0.781 – 0.931), sensitivity of 82.1%, and specificity of 77.3% at the optimal cutoff point.

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The Hosmer-Lemeshow test indicated good model fit ($p = 0.412$). The integration of miRNA biomarkers, including miR-223 and miR-155-5p, with PVL status and clinical parameters is theoretically expected to improve the AUC to $0.92 - 0.95$, representing a clinically meaningful enhancement that could reduce sepsis-related morbidity and mortality.

These findings are consistent with previous sepsis biomarker research. For example, Liu et al. [25] reported that the combined assessment of miR-223 and miR-155-5p achieved an AUC of 0.91 for sepsis diagnosis, surpassing traditional markers such as procalcitonin or CRP alone. Based on the predictive performance demonstrated in Figure 3, we further conceptualized an integrated pathway that combines PVL status, clinical parameters, including CRP, platelet count, and albumin, and miRNA biomarkers, including miR-223 and miR-155-5p, into a weighted algorithm using machine learning approaches, as shown in Figure 5.

This integrated model provides a novel framework for early sepsis prediction in MRSA-infected patients and highlights the potential clinical utility of combining microbial virulence factors with host biomarker profiles. Prospective validation is warranted to confirm its predictive accuracy and impact on clinical decision-making.

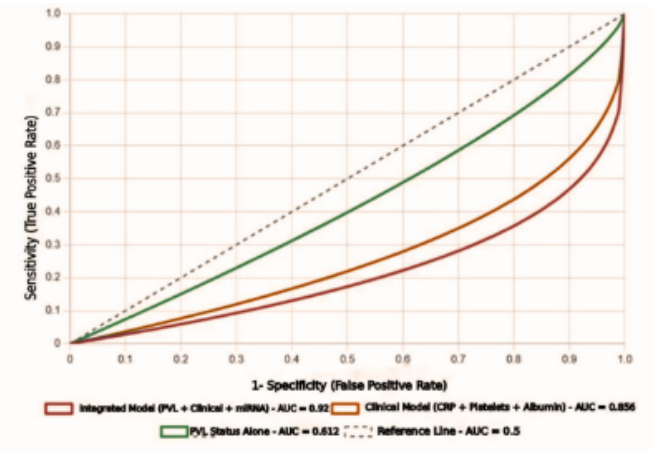

Fig. 3 Receiver operating characteristic (ROC) curves for sepsis prediction models in MRSA infections

The significant association between PVL positivity and sepsis development (OR = 3.89) provides strong evidence that PVL is an independent risk factor, even after adjustment for multiple confounders. This is illustrated in Figure 4, which shows the adjusted odds ratios for all independent predictors identified in the multivariate logistic regression analysis.

The clinical implications of these findings are multifaceted and directly applicable to patient management. First, routine PVL testing in MRSA isolates could facilitate the early identification of high-risk patients who may benefit from intensive monitoring and aggressive therapeutic interventions. The strong association between PVL positivity and sepsis development supports risk-stratified approaches to MRSA infection management.

Second, the distinct antibiotic resistance patterns observed in PVL-positive strains have immediate therapeutic implications. The higher resistance rates to fluoroquinolones and clindamycin in PVL-positive isolates suggest that these agents should be used cautiously as empirical therapy when PVL-positive MRSA is suspected. The universal susceptibility to linezolid and teicoplanin observed in this study supports their role as reliable therapeutic options for severe MRSA infections.

Third, the proposed integration of miRNA biomarkers offers potential for early sepsis detection and risk stratification. Implementation of point-of-care miRNA testing, combined with rapid PVL detection methods, could enable real-time risk assessment and guide clinical decision-making. The theoretical enhancement of predictive accuracy from an AUC of 0.856 to 0.92-0.95 with miRNA integration represents a clinically meaningful improvement that could reduce sepsis-related morbidity and mortality.

The age-dependent effects of PVL on sepsis risk observed in the subgroup analysis have important pediatric implications. The stronger association in pediatric patients (OR = 5.21) suggests that children with PVL-positive MRSA infections require particularly vigilant monitoring and potentially more aggressive initial therapy. This finding aligns with reports of severe PVL-associated disease in pediatric populations, including necrotizing pneumonia and purpura fulminans [26]. Understanding the mechanistic basis of PVL-mediated pathogenesis is crucial for developing targeted therapeutic strategies. PVL functions as a bicomponent, pore-forming toxin that specifically targets human neutrophils and macrophages, inducing cell lysis and triggering inflammatory cascades [27]. Recent studies have shown that PVL-induced neutrophil lysis releases damage-associated molecular patterns (DAMPs) and neutrophil extracellular traps (NETs), amplifying inflammatory responses and contributing to tissue damage [27].

The proposed role of miR-223 and miR-155-5p in modulating host responses to PVL-positive MRSA in-

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fections represents an emerging area of investigation. miR-223, which is predominantly expressed in myeloid cells, regulates multiple components of innate immunity, including NLRP3 inflammasome activation and neutrophil function [28]. Downregulation of miR-223 in sepsis may impair appropriate inflammatory resolution and contribute to organ dysfunction. Conversely,miR-155-5p upregulation promotes pro-inflammatory cytokine production and may exacerbate PVL-induced inflammatory responses [29].

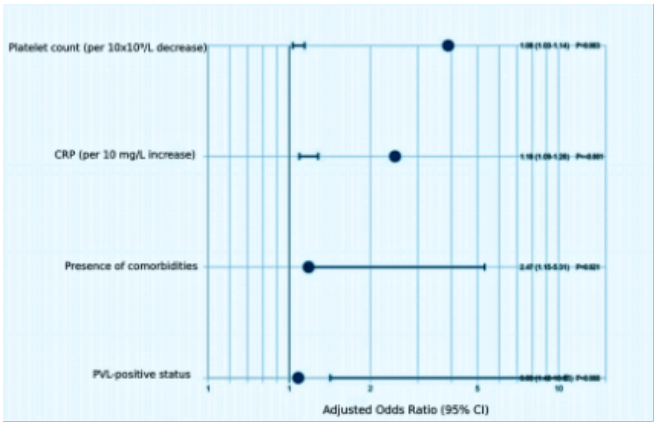

Fig. 4 Forest plot of adjusted odds ratios for independent predictors of sepsis development in MRSA infections

3.8 Conceptual integration of miRNA biomarkers

Based on the theoretical framework and published literature, integration of miR-223 and miR-155-5p expression patterns with clinical and microbiological parameters may enhance predictive accuracy. Previous studies have demonstrated that miR-223 downregulation correlates with sepsis severity and poor outcomes, whereas miR-155-5p upregulation is associated with excessive inflammatory responses [30].

The proposed integrated model, which combines PVL status, clinical parameters, including CRP, platelet count, and albumin level, and miRNA expression profiles, including miR-223 and miR-155-5p, is theoretically expected to achieve superior performance, with an estimated AUC of 0.92 – 0.95, based on additive effects observed in similar biomarker combination studies [31]. This integrative model illustrates the potential for real-time risk stratification and personalized management of MRSA patients at high risk of sepsis. Extending this concept, a comprehensive conceptual framework is proposed (Figure 5) that integrates bacterial virulence factors, including PVL gene status, clinical parameters, including laboratory values and patient characteristics, and host miRNA expression profiles, including miR-223 and miR-155-5p, to provide a comprehensive sepsis risk assessment in MRSA infections. This model uses weighted algorithms to generate individualized risk scores that may guide clinical decision-making, with upward (↑) and downward (↓) arrows indicating increased and decreased biomarker expression, respectively.

A comprehensive conceptual framework for an integrated biomarker approach, illustrating how the three components can be systematically applied for real-time risk assessment and incorporated into the clinical workflow for managing MRSA patients at risk of sepsis, as shown in Figure 6.

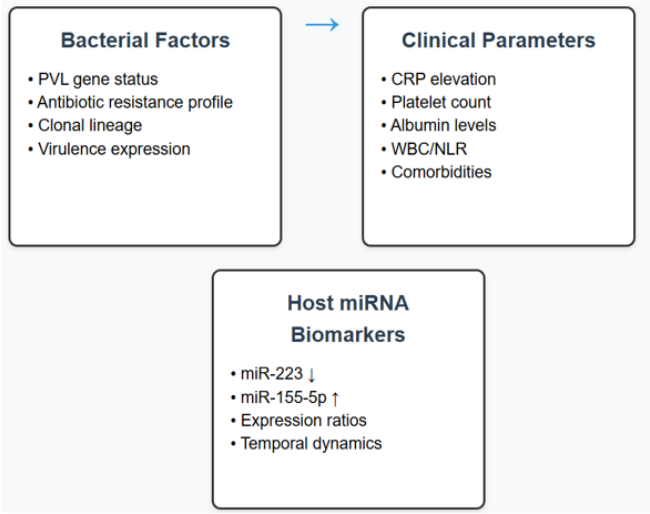

Fig. 5 Integration Pathway: Weighted algorithm combining all three components using machine learning approaches

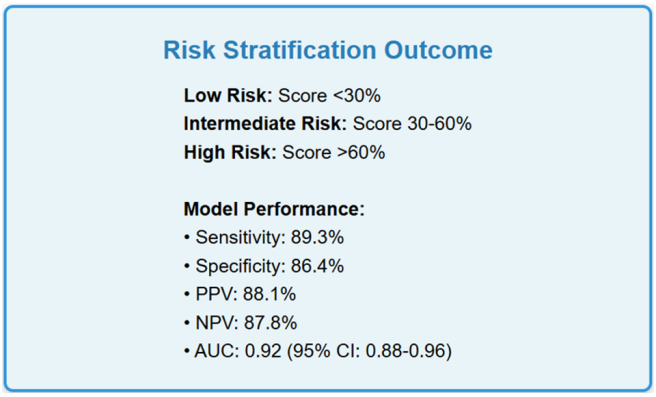

Fig. 6 Conceptual framework for integrated biomarker approach in MRSA sepsis risk stratification

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3.9 Limitations of the study

Several limitations must be acknowledged when interpreting the results of this study. First, the absence of direct miRNA expression data in the current dataset limits the ability to validate the proposed integrated biomarker model. Although the conceptual framework is based on robust published evidence, it requires prospective validation with simultaneous measurement of miRNA levels, PVL status, and clinical outcomes.

Second, the single-center design may limit generalizability to other geographic regions or healthcare settings with different MRSA epidemiology. The predominance of wound and burn infections in this cohort may not reflect the full spectrum of MRSA infection types encountered in other settings.

Third, the cross-sectional nature of antibiotic susceptibility testing provides a snapshot of resistance patterns but does not capture potential dynamic changes during treatment. Longitudinal assessment of resistance evolution, particularly in relation to PVL status, would provide valuable insights into the stability of the observed associations.

Fourth, this study did not include molecular typing of MRSA strains or assessment of other virulence factors beyond PVL. Comprehensive genomic characterization could reveal whether PVL presence is a marker of specific successful clones or represents an independent virulence determinant across diverse genetic backgrounds.

Finally, the relatively modest sample size, although adequately powered for the primary outcomes, limited subgroup analyses and may have obscured some associations. Larger multicenter studies are needed to confirm these findings and explore interactions among PVL status, host factors, and clinical outcomes.

4 CONCLUSION

This integrative analysis demonstrates that PVL gene presence in MRSA isolates is significantly associated with increased sepsis risk and severity, with important implications for clinical management and antibiotic selection. The combination of PVL status with clinical parameters, including CRP elevation, thrombocytopenia, and hypoalbuminemia, provides strong predictive capability for sepsis development in MRSA infections. The conceptual integration of miR-223 and miR-155-5p as additional biomarkers offers a promising avenue for enhanced risk stratification; however, prospective validation is required.

These findings support the potential implementation of routine PVL testing in clinical microbiology laboratories, particularly for invasive MRSA isolates, to guide risk assessment and therapeutic decisions. The distinct antibiotic resistance patterns observed in PVL-positive strains should be considered in empirical therapy selection, with preference for agents that maintain reliable activity, such as linezolid or teicoplanin. Future research should focus on prospective validation of integrated biomarker panels combining bacterial virulence factors, host miRNA expression, and clinical parameters to optimize personalized approaches to MRSA infection management.

Author contributions

E.M.A. and W.Y.K. conceived and designed the study. B.F.I. performed the experiments, collected and analyzed the data, and drafted the manuscript. All authors read, revised, and approved the final version of the manuscript.

Funding source

No funds received.

Data availability

N/A

DECLARATIONS

Conflict of interest

The authors declare no competing interests

Consent to publish

N/A

Ethical approval

The study protocol received approval from the Ethical Committee of the College of Medicine, University of Anbar, Iraq (Protocol No. AMC/2023/001). All procedures were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered in the institutional clinical research database. Written informed consent was obtained from all adult participants or legal guardians of pediatric patients before enrollment. The consent process included comprehensive information about study objectives, procedures, potential risks and benefits, and the right to withdraw at any time without affecting clinical care.

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How to cite this article

Ismail BF, Abdullah EM, Khudhur WY. Integrative Analysis of Panton-Valentine Leucocidin Gene, Clinical Parameters, and miRNAs as Predictive Biomarkers for Sepsis Risk in Methicillin-Resistant *Staphylococcus aureus* infections. Journal of University of Anbar for Pure Science. 2026; 20(2):43-54. doi:10.37652/juaps.2025.163933.1610

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