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Research Article

# Prevalence of Methicillin-Resistant *Staphylococcus aureus* using Molecular Biological Methods and its Antibiotic Resistance Patterns in Al-Ahsa Region of Saudi Arabia

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**Abstract:** Methicillin-Resistant *Staphylococcus aureus* (MRSA) causes many clinical manifestations. In modern healthcare systems, the frequency of MRSA infections is used as the benchmark for the quality of healthcare. MRSA-associated clinical manifestations and antibiotic resistance differ in different regions of the world. No studies had previously been carried out on MRSA in Al-Ahsa Saudi Arabia. Therefore, we studied the prevalence and antibiotic resistance patterns of MRSA in our region. Overall, 2661 patients were tested for MRSA by employing GeneXpert-based PCR assay during Jan- Dec 2018, and data was analyzed using SPSS version 24. 146 patients were MRSA positive (5.48%), with a mean age of 45.17 years and a male to female ratio of 1:1.03. The highest frequency of MRSA was in the age group 60-79 years (25.43%) The prevalence of MRSA infection was highest between August to September (p-value < 0.001). Anemia, hypoalbuminemia, and leukocytosis were associated with MRSA infections ($p < 0.001$). 87.67% of patients had community-acquired infections (CA-MRSA) ($p < 0.001$). Prevalence of CA-MRSA was the highest among the age group 60-70 years while the patient age group ≥ 80 years had the highest frequency of hospital-acquired infections ($p = < 0.0003$). Vancomycin and Linezolid showed 100% susceptibility, Penicillin, Cefoxitin, and Cefazoline 100% resistance while Oxacillin showed 98.9% resistance. The highest frequency of MRSA was found during scorching summer while the majority of the patients had CA-MRSA which necessitates precautions to be taken during top summer months. MRSA infections were significantly associated with anemia, hypoalbuminemia, and leukocytosis. Vancomycin and Linezolid could be drugs of choice for MRSA infections.

**Keywords:** MRSA, Epidemiology, Co-morbidities, Antibiotic resistance, Electrolyte imbalance.

## 1. INTRODUCTION

*Staphylococcus aureus* is considered as one of the most clinically significant infectious agents due to its innate pathogenicity, leading to a lot of life-threatening infections [1-2]. It can adapt to a variety of environmental conditions that lead to MRSA infections in different parts of the world in every clinical setting [2-3]. Due to this, it is the major cause of inpatient clinical infections globally [4]. Nevertheless, as many patients are treated for infections outside hospitals (outpatient) as well, MRSA is rapidly increasing as community-acquired infection [5]. Although many antibiotics are available to treat *S. aureus*, including methicillin, tetracyclines, fluoroquinolones, linezolid, and daptomycin, most of these drugs quickly lose their clinical effectiveness as *Staphylococcus aureus* can develop drug resistance [1, 6].

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Methicillin-resistant *S. aureus* was reported in October 1960 when some *Staphylococcus aureus* strains were found to be resistant to new antibiotic methicillin discovered just a year before [7]. MRSA had been regarded as the serious nosocomial infectious agent causing infections throughout the world that has severely affected health care and resulted in tremendous increases in health care costs [7]. Therefore, the quality of healthcare is benchmarked against the frequency of MRSA infections in modern healthcare systems. Accordingly, reliable testing of MRSA infections and their antibiotic resistance patterns is an integral component of an infection control program at any good hospital [3-6].

*S. aureus* isolates develop methicillin resistance when staphylococcal cassette chromosome (SCCmec) with mecA gene is inserted in the bacteria. mecA gene transcribes a modified penicillin-binding protein (PBP-2a) that cannot be inhibited by methicillin and other b-lactam antibiotics, thus causing methicillin resistance [8–11]. Many methods are available to detect and diagnose MRSA, that include oxacillin screening test, oxacillin minimum inhibitory concentration test, and oxacillin and/or cefoxitin disk diffusion method [11-12]. Nevertheless, these standard antimicrobial tests are reported to have false positive and negative results [8-10]. On the other hand, molecular biological methods including PCR-based MRSA assays that directly detect mecA gene present only in all MRSA strains and completely absent in methicillin-sensitive *S. aureus* (MSSA) isolates are regarded as the most sensitive, specific, and reproducible tests for diagnosing MRSA [13-20]. Furthermore, PCR-based assays are also recommended as confirmatory tests for the detection of MRSA in clinical samples identified by standard MRSA detection methods [7, 14]. Therefore, we employed a PCR-based molecular biological assay for the detection of MRSA in our subjects. Clinical manifestations and comorbidities associated with MRSA were also studied along with antibiotic resistance patterns.

## 2. MATERIALS AND METHODS

Overall, all 2661 patients suspected of MRSA infections visiting King Abdulaziz Hospital in Al-Ahsa during January 2018 – December 2018 in Saudi Arabia were included in the study. To detect MRSA in clinical samples, a fully automated PCR-based molecular biological assay (GeneXpert® MRSA assay, Cepheid, Sunnyvale, CA, USA) was employed that carried out all steps of pre-PCR (DNA extraction), PCR amplification, and post-PCR (fluorescent detection of PCR-amplified fragments) per manufacturer's instructions [14]. All the specimens were processed by using standard microbiological methods and susceptibility testing for determining resistance to different antibiotics was carried out by broth microdilution using Vitek-II (fully-automated identification and susceptibility testing instrument) per Clinical and Laboratory Standards Institute (CLSI) guidelines 2012 [15].

Data obtained from the electronic medical records (EMR) was incorporated and stored in Microsoft excel. Statistical analysis was carried out using SPSS version 24 (IBM Corp., Armonk, N.Y., USA) and conducted in form of descriptive and inferential statistics. A p-value of equal to or less than 0.05 (corresponding to 95% confidence level) was taken as significant for all statistical tests. The study was approved from the Scientific Committee (SC) and Institutional Review Board (IRB) of our institute.

## 3. RESULTS

Out of a total of 2661 patients, 146 (5.45%) patients were detected positive for MRSA with 74 females (50.7%) and 72 males (49.3%). The ratio of male to female patients was 1:1.03 ($p = 0.47$). Patients' mean age in the study was 45.17 years. MRSA infections were most common in the age group 60-79 years (25.43%) Figure 1.

Out of 146 patients, 87.67% of patients had a community-acquired infection and 12.23% acquired during hospitalization (Figure 2: Table1) which was based on whether the infection was detected from the sample taken within 48 hours of hospital admission or later, respectively. Our result clearly illustrated a significantly higher incidence rate of community-acquired MRSA infections than hospital-acquired ($p < 0.001$).

Findings indicate that the patient group ≥ 80 years had the highest frequency of hospital-

**Table 1.** Frequency of hospital-acquired, and community-acquired MRSA infections

| Acquisition of infections | Number | Percentage % | P-value |
|---|---|---|---|
| Hospital-Acquired MRSA | 18 | 12.33% | <0.001 |
| Community-Acquired MRSA | 128 | 87.67% | |

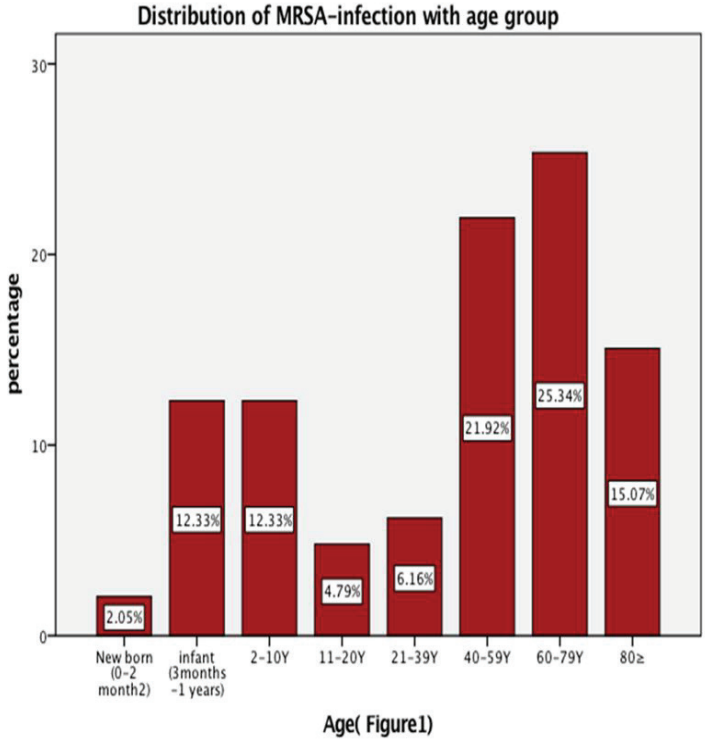


**Fig. 1.** Frequency of MRSA infections in different age groups

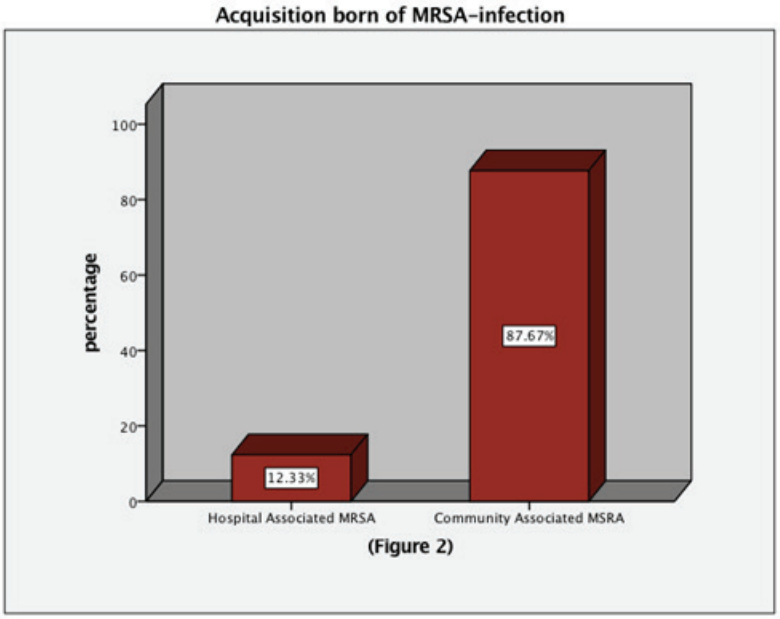


**Fig. 2.** Prevalence of hospital-acquired, and community community-acquired infections

acquired infections. However, in community-acquired MRSA age groups, 60-70 years had the highest frequency followed by 40-59 years age group with a ( p-value < 0.0003 ) Figure 3.

A high prevalence of MRSA infection was observed during the scorching summer of 2018. Out of 146 cases, 20 (13.70%) were diagnosed in August, and 17 (11.64%) cases were diagnosed in September. Thus, it indicates the highest rate of infection with MRSA was in the period between August to September with a p-value of < 0.001 (Figure 4).

The Association of MRSA infections with different hematological parameters was studied. MRSA patients had leukocytosis in 26 cases (16.4%), neutrophilia in 32 cases (20.1%), eosinopenia in 21 (13.2%) cases, low RBC count in 40 cases (25.2%), decreased hemoglobin in 62 cases (39%), and decreased hematocrit in 55 cases (34.6%) ($p < 0.001$) Table 2.

The effect of MRSA infection on different electrolytes was also studied in our patients. There was a decrease in carbon dioxide in 60 MRSA patients (37.7%), hypoalbuminemia in 39 patients (24.5%), hypocalcemia in 33 patients (20.8%), and hyponatremia in 58 patients (36.5%). On the other hand, there was a noted elevation in the anion gap in 59 patients (37.1%), and creatinine in 32 patients (20.1%) ($p < 0.001$) (Table 3).

There was a significant association between various age groups and albumin levels in MRSA patients. Among patients ≥60 years of age 25 patients (17.1%) presented hypoalbuminemia. (P=0.002) (Table 4).

Antimicrobial susceptibility minimum inhibitory concentration (MIC) testing for MRSA isolates indicated that all tested samples (100%) were resistant to Penicillin, Cefoxitin, Cefazoline, 98.9% resistant to Oxacillin, 22.3% resistant to Clindamycin, 29.4% resistant to Erythromycin, 27% resistant to Sulfamethoxazole, 12.9% resistant to Moxifloxacin, 8.2% resistant to Nitrofurantoin, 10.5% resistant to Gentamicin, and 1.1% resistant to Tigecycline. Our results were based on using *S.aureus* (ATCC29213, MRSA negative control), *S.aureus* (ATCC43300, MRSA positive control), and *S. aureus* (ATCCBAA-1026, Cefoxitin screen MRSA positive control) in MIC studies. Moreover, 77.6% of the isolates were susceptible to Clindamycin, 72.9% for Sulfamethoxazole 70.5% for Erythromycin 87% for Moxifloxacin, 91.7% for Nitrofurantoin, 89.4% for Gentamicin, 98.8% for Tigecycline, 98.9% for vancomycin, and 100% susceptibility to Linezolid. Therefore, our results indicate that Linezolid, vancomycin, and Tigecycline are the best treatment options for MRSA infections in our region. Because in the cases of vancomycin only one case 1.1% presented a resistance response however linezolid showed no resistance. No significant correlation was found between the acquisition of infection and the antimicrobial susceptibility (MIC) (Table 5).

## 4. DISCUSSION

Our findings show that the prevalence of Methicillin-Resistant *S. aureus* is higher in elderly patients in Al- Ahsa region. Our results are following a report from Kuwait documenting MRSA frequency of 81.6% infections in elderly patients [21]. The reason for the higher rate of infection among elderly patients might be due to a weakened immune system at older ages [21]. Our study also showed that community-acquired MRSA infections are significantly higher than hospital-acquired infections in our region, which has been reported by others as well [2, 3, 21]. The factors contributing to higher frequencies of community-acquired MRSA infections may be sharing of contaminated personal equipment, living in overcrowded poor areas, unsealed wounds, etc. [3, 21]. This necessitates the need to increase public awareness about MRSA as part of infection control programs at the community level.

We also report an increase in the incidence of MRSA infections in the warmer seasons especially between the months from August to September. Our results are endorsing other similar reports in this regard. For example, a study conducted in Iowa, in the USA showed 47.3% of MRSA patients infected during summer [22]. The heat rise and subsequently more sweating along with compromised personal hygiene increase chances of the infection transmission in summer [22]. The Centers for Disease Control and Prevention (CDC) and the National Collegiate Athletic Association

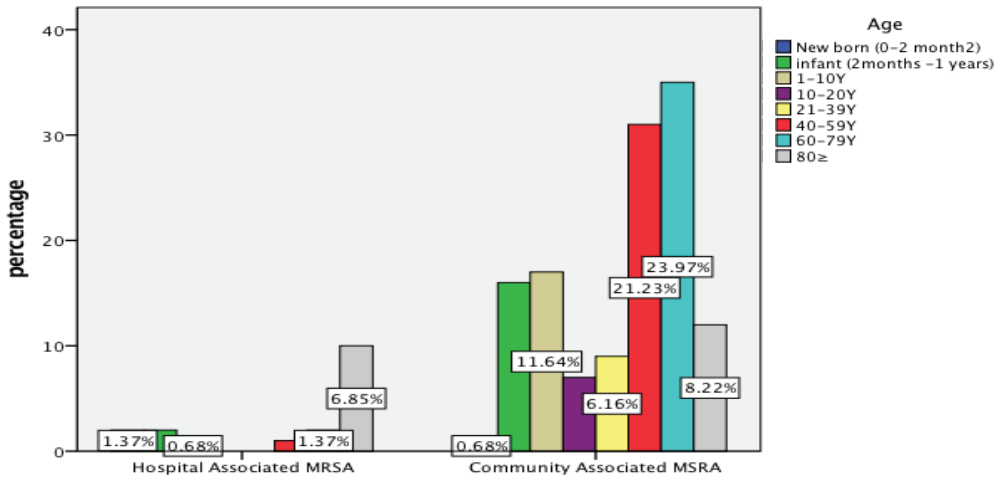


**Fig. 3.** Association of age groups with the hospital & Acquired MRSA infections

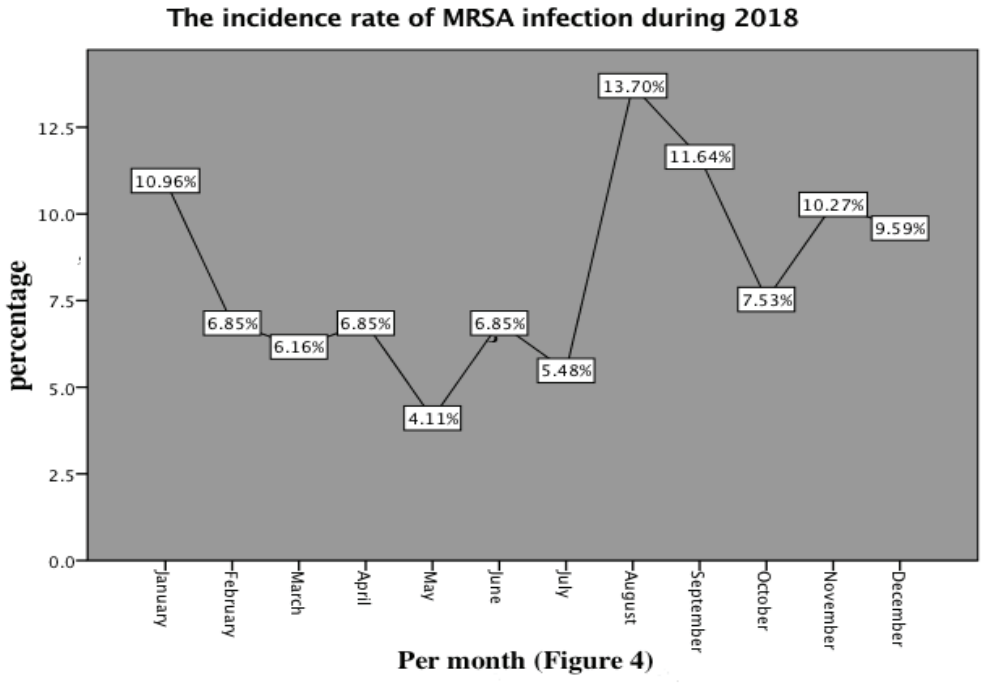


**Fig. 4.** Frequency of MRSA infections with different periods in the year

**Table 2.** Association of MRSA infections with different hematological parameters

| CBC Result | Low | High | Critical | P-value |
|---|---|---|---|---|
| White blood cell | 6 (3.8%) | 26 (16.4%) | 1 (0.6%) | < 0.001 |
| Neutrophil | 3 (1.9%) | 32 (20.1%) | 0% | < 0.001 |
| Eosinophil | 21 (13.2%) | 2 (1.3%) | 0% | < 0.001 |
| Red blood cell | 40 (25.2%) | 14 (8.8%) | 0% | < 0.001 |
| Hemoglobin | 62 (39%) | 3 (1.9%) | 6 (3.8%) | < 0.001 |
| Hematocrit | 55 (34.6%) | 3 (1.9%) | 0% | < 0.001 |

**Table 3.** Effect of MRSA infection on different electrolyte

| Chemistry results | Low | High | Critical | P-value |
|---|---|---|---|---|
| Carbon dioxide | 60 (37.7%) | 5 (3.1%) | 2 (1.3%) | (p < 0.001). |
| Anion gap | 1 (0.6%) | 59 (37.1%) | 0 (0 %) | (p < 0.001). |
| Albumin | 39 (24.5%) | 0 (0 %) | 0 (0 %) | (p < 0.001). |
| Calcium | 33 (20.8%) | 5 (3.1%) | 1 (0.6%) | (p < 0.001). |
| Sodium | 58 (36.5%) | 7 (4.4%) | 1 (0.6%) | (p < 0.001). |
| Creatinine | 6 (3.8%) | 32 (20.1%) | 5 (3.1%) | (p < 0.001). |

**Table 4.** Association between MRSA infection and hypoalbuminemia

| Age | Low | Normal | High | Not available |
|---|---|---|---|---|
| 60-79Y | 11 (7.5%) | 21 (14.4%) | 0 | 5 (3.4%) |
| ≥80Y | 14 (9.6%) | 6 (4.1%) | 0 | 2 (1.4%) |

**Table 5.** Antibiotic resistance and susceptibility patterns of MRSA isolates

| Antibiotic susceptibility | Cefazoline | Cefoxitin | Penicillin | Linezolid | Oxacillin | Tigecycline | Nitrofurantoin | Gentamicin | Moxifloxacin | Vancomycin | Clindamycin | Sulfamethoxazole | Erythromycin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Resistance** | **100%** | **100%** | **100 %** | **0%** | **98.8%** | **1.1%** | **8.2%** | **10.5%** | **12.9%** | **1..1%** | **22.3%** | **27%** | **29.4%** |
| **Susceptible** | **0%** | **0%** | **0%** | **100 %** | **1.1%** | **98.8%** | **91.7%** | **89.4%** | **87%** | **98.8%** | **77.6%** | **72.9%** | **70.5%** |

(NCAA) have formulated relevant guidelines to suppress the spread of MRSA among athletes by educating them on personal hygiene and taking showers after working out.

We studied the association of different hematological parameters with MRSA infections. Our findings showed that 25.2% of patients had anemia and 24.5% had hypo-albuminuria. A study conducted in Kuwait showed that "most patients were anemic and presented with hypoalbuminemia" [21] which supports our results. It has been reported in a study carried out by Japan Epidemiological Association that the patients with hypoalbuminemia had an enhanced risk for MRSA infections (P<0.005) [6]. A study conducted in India showed that low hemoglobin levels were significantly associated with MRSA infections [23]. These findings may have important implications in the characterization and clinical management of patients with MRSA infections.

In this study, we found that most of our MRSA isolates manifested resistance to Penicillin, Cefoxitin, Cefazoline, and Oxacillin. The process of the resistance is arbitrated through the "mec operon", a portion of the Staphylococcal cassette chromosome (SCCmec), and the resistance is manifested due to the expression of the mecA gene [8-11]. This gene transcribes penicillin-binding

protein 2a (PBP2a), a protein with reduced binding capacity for b-lactamase inhibitors including methicillin [24]. Moreover, our analyses showed that 27% of the cases presented resistance against sulfamethoxazole. On the other hand, several studies showed that sulfamethoxazole is as potent as vancomycin [25]. Some other studies reported an emerging resistance of MRSA against sulfamethoxazole globally and it was found to be low in developed countries (20% or less) as compared to developing countries, i.e. in India 85-97%% MRSA isolates were reported resistant to sulfamethoxazole [26, 27]. A possible cause for this resistance in developing countries could be the unregulated use of antibiotics [28]. In the present study, Clindamycin showed 77.6% Susceptibility (18). Inconsistent percentages of clindamycin resistance were revealed in two other countries, i.e. the USA and India [29, 30]. MRSA causing hospital-acquired infections are frequently resistant to erythromycin and clindamycin. (CDC) [28]. Furthermore, our findings show 89.4% susceptibility to Gentamycin. A similar study conducted in Egypt reported above 90% susceptibility to gentamycin and clindamycin by Community-acquired MRSA isolates [31], Therefore these antimicrobial agents are a better treatment choice for MRSA infections. In the same study carried out in Egypt, the optimal response elucidated by MRSA isolates was found to be for Linezolid (100 % susceptibility) and for Vancomycin and Tigecycline (98.8% susceptibility) [31] which is in accordance with our findings. It is globally acknowledged that Vancomycin is the gold standard for treating MRSA [32]. Nevertheless, the use of Vancomycin has some limitations, for example, it is expensive, causes toxicity, has a short half-life, and needs refrigeration [33]. Linezolid is a good substitute for vancomycin and it has got the USA and European drug regulatory authorities' approvals for the treatment of nosocomial pneumonia already [34]. Tigecycline has recently been reported to be a safe and potent antibiotic for the treatment of MRSA infections, with 99.9% effectiveness in a clinical setting that almost equals linezolid [35]. It shows the clinical significance of our studies to show other antibiotics as a substitute for vancomycin in case of resistance to this effective drug by MRSA in our region.

In the present study, a correlation between the hospital-acquired or community-acquired MRSA infections and susceptibility of different antibiotics was not statistically significant that could be attributed to the low number of patients with MRSA infections. Globally, various studies show that community acquired-MRSA strains manifest less resistance to non-beta-lactamase inhibitors than hospital-born MRSA strains due to intrinsic genetic differences between two types of MRSA isolates [36, 37]. A recent study carried out in Shandong China reported that most community-acquired MRSA isolates showed clindamycin and erythromycin resistance (88.6% and 78.3%, respectively) while 91.7% of hospital-acquired strains MRSA isolated showed resistance to clindamycin only. Nevertheless, it reported 100% susceptibility to vancomycin, linezolid, and tigecycline by the hospital- as well as community-acquired MRSA isolates [36] that are in accordance with our findings. Moreover, it further manifests the clinical significance of our studies that provides important information about the clinical management of antibiotic-resistant MRSA isolates.

## 5. CONCLUSION

The highest frequency of MRSA was found during the peak summer season. The majority of the patients had community-acquired MRSA infections which necessitate more hygienic habits to be adopted during scorching summer months, specifically for elderly patients who had statistically high infection rates. Our study finds that MRSA infections were significantly associated with anemia, hypoalbuminemia, and leukocytosis along with electrolyte imbalance that may help in the better clinical management of patients with MRSA infections. Vancomycin could be the most effective antibiotic while Linezolid and Tigecycline could be good options for treating MRSA infections in case of vancomycin resistance.

## 6. ACKNOWLEDGEMENTS

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## 7. CONFLICT OF INTEREST

The authors declare no conflict of interest.

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