

# Antimicrobial Resistance Characteristics of *Staphylococcus aureus* Isolated From Both Tertiary Hospitals, One Western Medicine Hospital and One Traditional Chinese Medicine Hospital, in Shanghai, China From 2014-2023

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**Purpose:** Methicillin-resistant *Staphylococcus aureus* (MRSA) represents a growing threat to global public health. The aim of this study was to characterize the epidemiology and resistance of *Staphylococcus aureus* (*S. aureus*) collected between 2014 and 2023 from two Grade A tertiary hospitals in Shanghai: Shanghai Municipal Hospital of Traditional Chinese Medicine (STCMH), and Shanghai General Hospital (SGH).

**Methods:** A total of 9816 non-duplicate *S. aureus* isolates (STCMH: n=2714; SGH: n=7102) were retrospectively analyzed. Antimicrobial susceptibility testing was conducted following CLSI guidelines. Predictors of bacterial clearance in *S. aureus*-infected patients were identified using univariate and LASSO regression and incorporated into a nomogram model.

**Results:** *S. aureus* was primarily isolated from sputum and wound secretions, largely from the Intensive Care Medicine (ICU) and surgical departments, and most frequently affected patients aged  $\geq 65$  in both institutions. Compared to STCMH, SGH isolates exhibited higher resistance rates to penicillin G (91.00% vs 70.12%), levofloxacin (57.27% vs 49.48%), moxifloxacin (55.34% vs 46.54%), gentamicin (40.07% vs 36.77%), and rifampin (3.17% vs 1.58%). The MRSA prevalence declined markedly at STCMH, dropping from 67.70% in 2017 to 33.30% in 2023, but remained elevated at SGH (54.79% to 69.00%). Furthermore, MRSA isolates from SGH showed higher resistance to levofloxacin (80.75% vs 76.71%), but lower resistance to erythromycin (84.37% vs 87.68%) and moxifloxacin (65.03% vs 74.26%) compared to those from STCMH. After 2016, STCMH revealed accelerated declines in MRSA resistance to erythromycin, clindamycin, and rifampin. Both hospitals maintained 100% susceptibility to vancomycin, linezolid, and quinupristin/dalfopristin. The nomogram (AUC=0.654) identified combined antibiotic-TCM therapy, leukocyte and lymphocyte counts, and C-reactive protein levels as independent predictors of bacterial clearance.

**Conclusion:** STCMH had lower MRSA prevalence and *S. aureus* resistance rates than SGH, and TCM-antibiotic combination therapy might promote bacterial clearance, suggesting TCM's potential in combating antimicrobial resistance, which needs further multicenter validation to support the implementation of antimicrobial stewardship strategies.

**Keywords:** *Staphylococcus aureus*, methicillin-resistant *S. aureus*, antimicrobial resistance, traditional Chinese medicine, model for bacterial clearance

## Introduction

*Staphylococcus aureus* (*S. aureus*), a Gram-positive coccus, is a prevalent commensal organism colonizing the cutaneous and mucosal surfaces of both humans and animals. However, *S. aureus* can become a significant cause of serious hospital-acquired

infections, such as pneumonia, bloodstream infections, and infective endocarditis.<sup>1,2</sup> The increasing use of antimicrobial agents has driven the selection and spread of drug-resistant *S. aureus* strains, with methicillin-resistant *S. aureus* (MRSA) representing a critical public health threat.<sup>3</sup> Globally, MRSA strains are now endemic in hospital-associated (HA-MRSA), community-associated (CA-MRSA), and livestock-associated (LA-MRSA) settings, creating substantial clinical and public health challenges.<sup>4</sup>

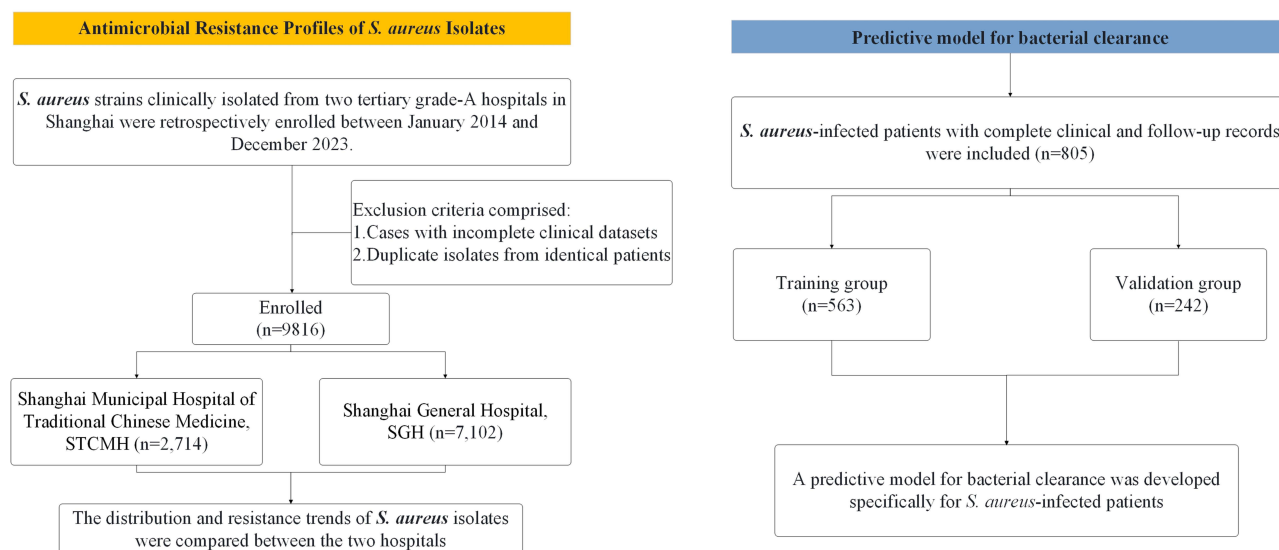
MRSA strains resist antibiotics by acquiring the *mecA* gene. This gene encodes the penicillin-binding protein 2a (PBP2a). PBP2a reduces binding affinity for  $\beta$ -lactams antibiotics and prevents these drugs from effectively disrupting bacterial cell wall synthesis.<sup>5</sup> Studies showed that MRSA infections are a major factor driving high mortality rates in hospital settings.<sup>6–8</sup> Healthcare institutions in different countries reported that MRSA accounts for over 50% *S. aureus* isolated from clinical samples.<sup>9</sup> The US Centers for Disease Control and Prevention (CDC) estimates that MRSA infections kill 10,600 people in the US each year, with direct medical costs exceeding US\$1.7 billion.<sup>10</sup> The 2024 data from China's Antimicrobial Resistance Surveillance Network (CHINET) showed that *S. aureus* accounts for 9.1% of total clinical detections, ranking it among the top three clinical pathogens. Notably, the MRSA detection rate rose from 28.7% in 2022 to 29.2% in 2024. A comparative analysis of 29,539 methicillin-sensitive *S. aureus* (MSSA) and 11,729 MRSA isolates revealed significantly higher resistance rates in MRSA to almost all tested antimicrobial agents, except for trimethoprim–sulfamethoxazole (MRSA 6.7% vs MSSA 11.9%). MRSA exhibited high resistance to erythromycin (76.4%) and clindamycin (53.8%), along with moderate resistance to levofloxacin (25.6%), ciprofloxacin (25.4%), gentamicin (12.3%), and fosfomycin (6.8%). In contrast, all MRSA isolates remained fully susceptible to vancomycin, norvancomycin, linezolid, teicoplanin, tigecycline, and rifampin.<sup>11</sup> Differences in MRSA resistance occur across regions and can be influenced by factors such as population density, intensity of antimicrobial use, and the availability of healthcare resources.<sup>12–14</sup>

In this context, the present study analyzes the distribution and susceptibility of antimicrobial resistance in *S. aureus* isolates from two tertiary Grade A hospitals in Shanghai: the Shanghai Municipal Hospital of Traditional Chinese Medicine (STCMH), which specializes in traditional Chinese medicine (TCM), and the Shanghai General Hospital (SGH), which focuses on Western medicine. Our analysis covered the period from 2014 to 2023 to identify the clinical characteristics and resistance patterns of *S. aureus*, particularly MRSA. These findings provide valuable insights to optimize antimicrobial stewardship and help mitigate the spread of resistant strains.

## Material and Methods

### Study Design

This study analyzed *S. aureus* isolates from both outpatient and inpatient departments of two tertiary Grade A hospitals in Shanghai over the period from January 2014 to December 2023 (Figure 1). Clinical data were retrospectively collected, covering patient demographics (age and gender), infection sites, pre-treatment blood test results [including C-reactive protein (CRP), complete blood count parameters (white blood cell (WBC) count, lymphocyte count, neutrophil%, lymphocyte%, monocyte%, eosinophil%, basophil%, hemoglobin (Hb), red blood cell count (RBC), hematocrit (HCT), platelet count (PLT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), plateleterit (PCT), absolute neutrophil count (ANC), absolute monocyte count, eosinophil count, basophil count) and derived ratios (neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR)], isolate's characteristics, antimicrobial susceptibility profiles, treatment details (including specific note of synergistic therapy combining antibiotics and TCM), and post-treatment bacterial clearance status. Among all enrolled patients, 259 cases received antibiotic monotherapy and 546 cases received combination therapy with TCM and antibiotics. Clinical outcomes, including bacterial clearance rates, were compared between the groups. Data were extracted using the WHONET 5.3 database and electronic medical records and resulted in the inclusion of 805 patients diagnosed with *S. aureus* infections. The present research received approval from the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2025SHL-KY-26-01) and was conducted in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the cohort study.



**Figure 1** Study design flowchart. A 10-year retrospective cohort study comparing antimicrobial resistance patterns between Shanghai Municipal Hospital of Traditional Chinese Medicine (STCMH) and Shanghai General Hospital (SGH).

**Abbreviations:** STCMH, Shanghai Municipal Hospital of Traditional Chinese Medicine; SGH, Shanghai General Hospital.

## Bacterial Identification and Antimicrobial Susceptibility Testing

Isolates were cultured and purified following standard microbiological protocols. Species identification and antimicrobial susceptibility testing were performed using the VITEK-2 Compact automated system (bioMérieux, France). Antibiotics tested included: penicillin (PEN), oxacillin (OXA), erythromycin (ERY), clindamycin (CLI), ciprofloxacin (CIP), levofloxacin (LVX), moxifloxacin (MXF), gentamicin (GEN), trimethoprim/sulfamethoxazole (SXT), rifampicin (RIF), vancomycin (VAN), linezolid (LZD) and quinupristin/dalfopristin (Q/D). *S. aureus* ATCC 29213 served as the quality control strain. Testing procedures followed the Clinical and Laboratory Standards Institute (CLSI) guidelines<sup>15</sup> and the manufacturer's instructions. Resistance rates were calculated using the formula:  $Resistance\ rate\ (\%) = (Number\ of\ resistant\ isolates / Total\ tested\ isolates) \times 100$ . Microbiological clearance was assessed based on culture results and complete clearance was defined as a negative bacterial culture following treatment. Total clearance rate was calculated as:  $Total\ clearance\ rate\ (\%) = (Number\ of\ cleared\ cases / Total\ cases) \times 100$ .<sup>15</sup>

## MRSA Detection

MRSA was defined per CLSI criteria:<sup>15</sup> cefoxitin disk diffusion inhibition zone diameter  $\leq 21$  mm or an oxacillin minimum inhibitory concentration (MIC)  $\geq 4$   $\mu\text{g/mL}$ . An oxacillin MIC of  $\leq 2$   $\mu\text{g/mL}$  defined MSSA.

## Development and Validation of a Bacterial Clearance Prediction Model

We used LASSO (Least Absolute Shrinkage and Selection Operator) regression combined with univariate logistic analysis to screen for independent predictors of bacterial clearance in patients infected with *S. aureus*. A multivariate logistic regression model was developed and represented through a nomogram. The model's ability to discriminate was assessed by calculating the area under the receiver operating characteristic (ROC) curve (AUC) and the calibration curve assessed the alignment between predicted probabilities and actual clearance rates.

## Statistical Analysis

We used WHONET 5.3 for preliminary screening of isolate distribution and resistance rates. We then performed in-depth analysis with R 4.2.1 and SPSS 24.0. Categorical data were expressed as frequencies (percentages) and comparisons between groups were analyzed using the  $\chi^2$ -test or Fisher's exact test. The Cochran-Armitage trend test analyzed the temporal trends in resistance rates. All statistical tests were two-tailed, with a significance threshold set at  $\alpha=0.05$  ( $P<0.05$ ).

## Results

### Distribution of *S. Aureus* and Changing Trends of MRSA in Two Hospitals

From 2014 to 2023, STCMH collected a total of 2,714 *S. aureus* isolates and SGH obtained 7102 samples. SGH recorded an annual *S. aureus* growth rate of 4.20% and STCMH presented a decline over the same period (Table 1).

The analysis of clinical samples revealed that sputum and wound secretions were the most prevalent, representing 67.18% and 20.24% of the samples in STCMH (Figure 2A), and 76.70% and 8.84% from SGH (Figure 2B). Other notable sample types included blood (5.06% in STCMH and 1.79% in SGH), urine (2.72% in STCMH and 6.52% in SGH), pus (2.83% in STCMH and 2.00% in SGH), and alveolar lavage fluid (1.17% in STCMH and 1.04% in SGH), as shown in Figure 2A and B.

At STCMH, the Department of Intensive Care Medicine (ICU) had the highest number of isolates (798, 27.40%), followed by Surgery (350, 12.02%), and Emergency Medicine (330, 11.33%). Neurology (237, 8.14%), Hematology (177, 6.08%), and Oncology (129, 4.43%) had fewer isolates. In SGH, the ICU had the most isolates (2897, 40.79%), followed by Surgery (2243, 31.58%), and Respiratory Medicine (Pulmonology) (180, 2.53%). The distribution of *S. aureus* across the various wards is illustrated in Figure 2C.

Figure 2D shows *S. aureus* infections primarily affected elderly patients ( $\geq 75$  years) in both hospitals. However, SGH had a significant lower proportion of these patients compared to STCMH (42.97% vs 53.98%,  $P < 0.01$ ). Furthermore, SGH had a higher percentage of infected patients aged 19–64 years than in STCMH (36.55% vs 21.11%,  $P < 0.01$ ) (Figure 2D). Infections among children and adolescents (0–18 years) were more frequent in SGH and three times that of STCMH (1.37% vs 3.91%,  $P < 0.01$ ) (Figure 2D).

From 2014 to 2023, MRSA detection differed between STCMH and SGH. STCMH experienced an upward trend from 46.80% in 2014 to 67.70% in 2017, where rates decreased from 66.40% in 2018 to 56.90% in 2021. These rates culminated in a significant drop to 33.30% in 2023. SGH showed a relatively stable increase from 54.79% to 61.24% during the period between 2014 and 2016 followed by a decline between 2017 (56.30%) and 2019 (48.80%). SHG then displayed a notable increase from 71.63% by 2021, followed by a period of relative stability around 67.80% to 69.00% through 2023 (Figure 3).

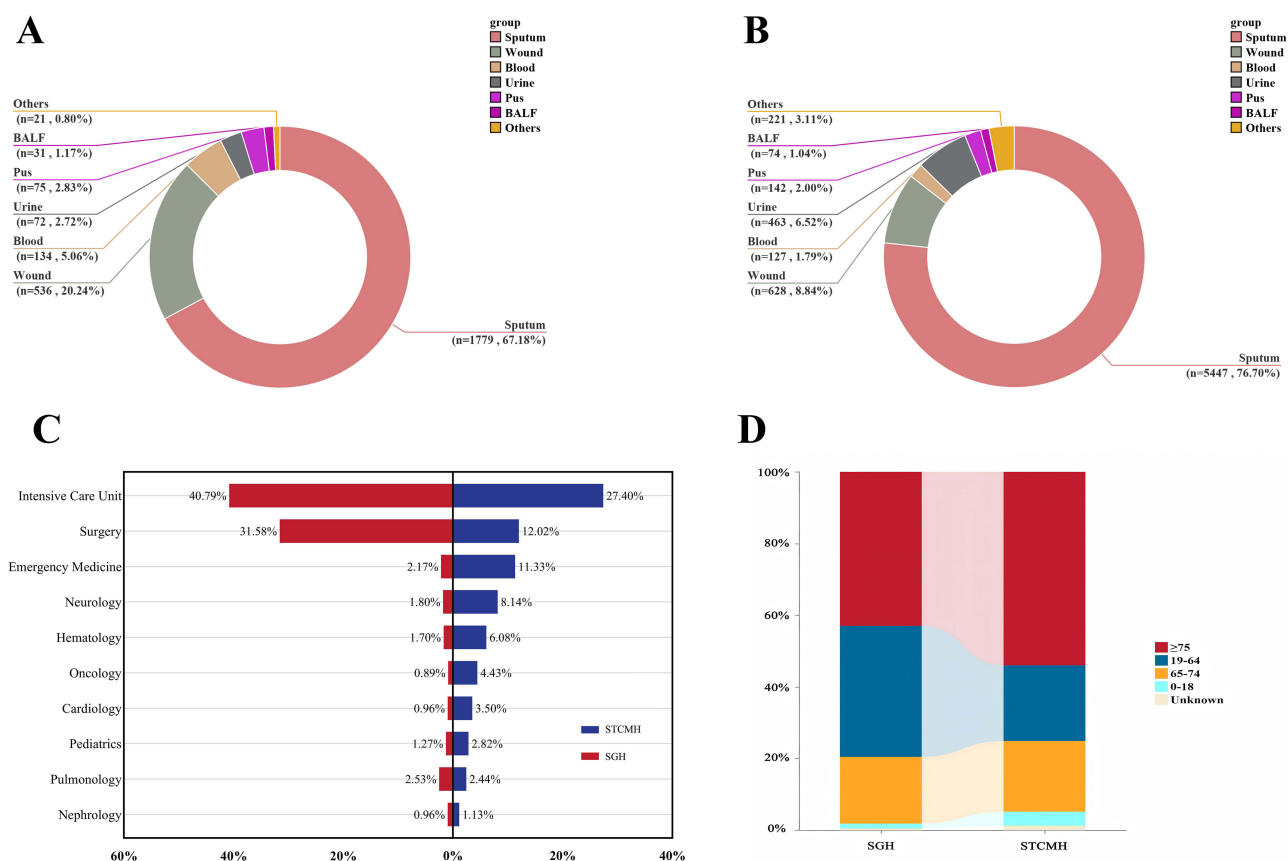
### Antimicrobial Resistance Profiles of *S. Aureus* From Two Hospitals

Table 2 shows high resistance rates among *S. aureus* isolates from SGH that exceeded 50% for several antibiotics: penicillin G (PEN, 91.00%), erythromycin (ERY, 66.42%), clindamycin (CLI, 63.50%), and levofloxacin (LVX,

**Table 1** Annual Distribution of Clinical Isolates of Staphylococcus Aureus in STCMH and SGH From 2014 to 2023

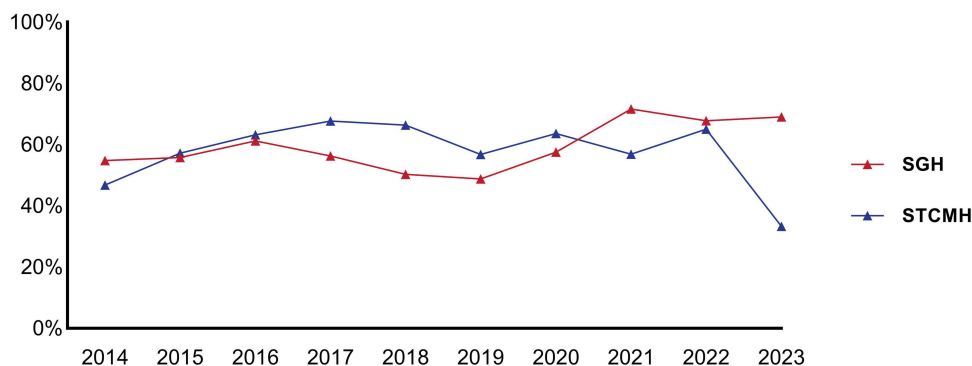
Year	SGH		STCMH	
	No. of Isolates	%	No. of Isolates	%
2014	553	7.80	297	11.20
2015	625	8.80	353	13.30
2016	644	9.10	220	8.30
2017	690	9.70	263	9.90
2018	718	10.10	295	11.10
2019	789	11.10	329	12.40
2020	720	10.10	269	10.20
2021	778	11.00	281	10.60
2022	702	9.90	203	7.70
2023	883	12.40	204	5.20
Total	7102		2714	

**Abbreviations:** SGH, Shanghai General Hospital; STCMH, Shanghai Municipal Hospital of Traditional Chinese Medicine.



**Figure 2** Distribution of specimen sources, clinical departments, and patient age groups of *Staphylococcus aureus* isolates from STCMH and SGH. Source and proportion of total culture specimens. Proportions of *S. aureus* isolates from different specimen types in STCMH and SGH. Sputum accounted for the highest proportion in both hospitals (A and B). Distribution of isolates among departments. The intensive care unit (ICU) and surgical departments were the primary sources of *S. aureus* isolates in both hospitals. At STCMH, the top three departments were ICU (27.40%), Surgery (12.02%), and Emergency Medicine (11.33%), while SGH showed a higher concentration in ICU (40.79%) and Surgery (31.58%), with Respiratory Medicine as the third most common source (2.53%) (C). Age distribution of the *S. aureus* infected population. Comparison of age groups (0–18, 19–64, and ≥75 years) among *S. aureus*-infected patients. Elderly patients (≥75 years) composed the largest proportion in both hospitals (D).

**Abbreviations:** STCMH, Shanghai Municipal Hospital of Traditional Chinese Medicine; SGH, Shanghai General Hospital; *S. aureus*, *Staphylococcus aureus*.



**Figure 3** Trends in MRSA detection rates (2014–2023). Annual MRSA detection rates (%) in STCMH and SGH. STCMH showed a significant decline after 2017, while SGH exhibited persistent high rates (Cochran-Armitage trend test,  $P < 0.05$ ).

**Abbreviations:** STCMH, Shanghai Municipal Hospital of Traditional Chinese Medicine; SGH, Shanghai General Hospital.

57.27%). MRSA accounted for a significant portion of these isolates (4,369, 61.5%) and MSSA represented a smaller fraction (1086, 15.3%). Furthermore, SGH-derived MRSA isolates exhibited high resistance to ERY (84.37%), CLI (82.76%), LVX (80.75%), moxifloxacin (MXF, 65.03%), and gentamicin (GEN, 58.78%). Conversely, *S. aureus* isolates

**Table 2** Comparison of *Staphylococcus Aureus* and MRSA Antimicrobial Susceptibility Between STCMH and SGH

Antibiotic	<i>Staphylococcus aureus</i>								Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)							
	SGH (n=7102)			STCMH (n=2714)			$\chi^2$	P	SGH (n=4369)			STCMH (n=1550)			$\chi^2$	P
	R	S	%	R	S	%			R	S	%	R	S	%		
PEN	6463	639	91.00	1903	811	70.12	27.56	<0.001	4369	0	100	1550	0	100	NA	NA
ERY	4717	2385	66.42	1779	935	65.55	0.63	0.427	3686	683	84.37	1359	191	87.68	9.961	<0.001
CLI	4510	2592	63.5	1651	1063	60.83	8.13	0.004	3616	753	82.76	1291	259	83.29	0.223	0.637
LVX	4067	3035	57.27	1343	1371	49.48	69.12	< 0.001	3528	841	80.75	1189	361	76.71	11.54	0.001
MXF	3930	3172	55.34	1263	1451	46.54	86.34	< 0.001	2841	1528	65.03	1151	399	74.26	44.41	<0.001
GEN	2846	4256	40.07	998	1716	36.77	12.89	< 0.001	2568	1801	58.78	918	632	59.23	0.095	0.758
SXT	312	6790	4.39	152	2562	5.6	6.92	0.009	120	4249	2.75	91	1459	5.87	32.49	<0.001
RIF	225	6877	3.17	43	2671	1.58	29.29	< 0.001	204	4165	4.67	33	1517	2.13	19.21	<0.001
VAN	0	7102	0	0	2714	0	NA	NA	0	4369	0.00	0	1550	0.00	NA	NA
LZD	0	7102	0	0	2714	0	NA	NA	0	4369	0.00	0	1550	0.00	NA	NA
Q/D	0	7102	0	0	2714	0	NA	NA	0	4369	0.00	0	1550	0.00	NA	NA

**Abbreviations:** STCMH, Shanghai Municipal Hospital of Traditional Chinese Medicine; SGH, Shanghai General Hospital. PEN, Penicillin; ERY, Erythromycin; CLI, Clindamycin; LVX, Levofloxacin; MXF, Moxifloxacin; GEN, Gentamicin; SXT, Trimethoprim/Sulfamethoxazole; RIF, Rifampin; VAN, Vancomycin; LZD, Linezolid; Q/D, Quinupristin/Dalfopristin; MRSA, Methicillin-resistant *Staphylococcus aureus*; NA, Not applicable.

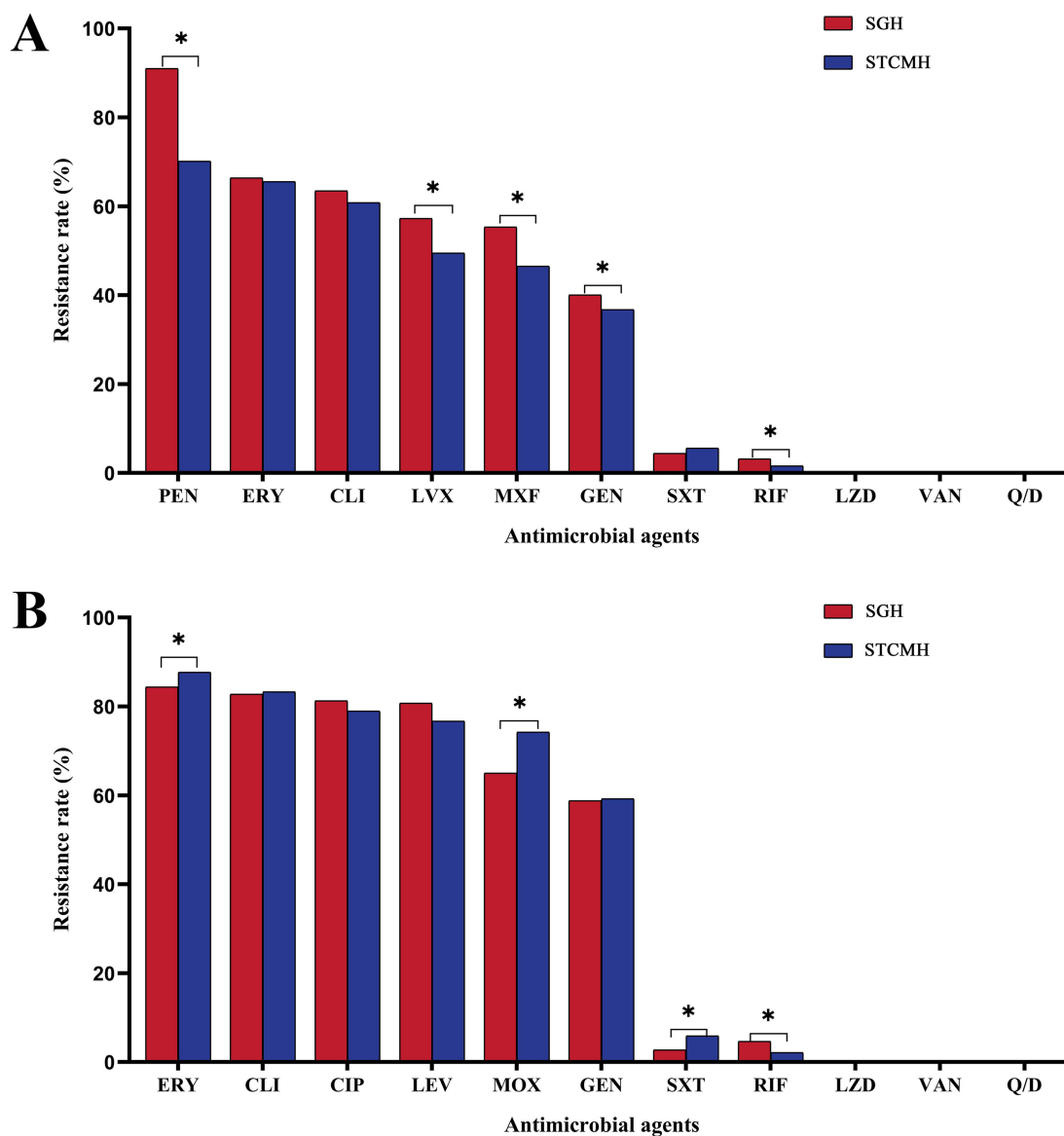
from STCMH showed comparatively lower resistance for PEN (70.12%), ERY (65.55%), CLI (60.83%), and LVX (49.48%). MRSA accounted for 1,550 (57.1%) of these STCHM isolates and MSSA totaled 619 (22.8%). STCMH-derived MRSA samples presented a higher resistance to ERY (87.68% vs 84.37%,  $P < 0.01$ ) and MXF (74.26% vs 65.03%,  $P < 0.01$ ) and a lower resistance to LVX (76.71% vs 80.75%,  $P < 0.01$ ) compared to SGH MRSA samples. Isolates from both hospitals exhibited low resistance rates (below 5.0%) for rifampicin (RIF), linezolid (LZD), vancomycin (VAN), and quinupristin/dalfopristin (Q/D) (Figure 4).

## Susceptibility for Antibiotic

Figure 5 shows that both hospitals experienced a decline in antibiotics resistance. At SGH, *S. aureus* exhibited high levels of resistance to multiple antibiotics. *S. aureus* resistance to RIF increased from 3.40% in 2014 to 4.80% in 2023 ( $P < 0.05$ ). However, resistance decreased for ERY (69.80% to 61.60%;  $P < 0.05$ ), GEN (48.60% to 35.40%;  $P < 0.05$ ), and SXT. In STCMH, resistance rates declined for PEN, ERY, CLI, LVX, GEN, SXT, and RIF ( $P < 0.05$ ) after 2016. Both hospitals reported no resistance to LZD, Q/D, and VAN, indicating their continued effectiveness (Figure 5). Both hospitals observed a decline in MRSA resistance. SGH presented a decrease in resistance rates for ERY, CLI, LVX, MXF, and GEN, while RIF resistance rose from 3.90% to 6.90% ( $P < 0.05$ ). MRSA resistance to ERY, CLI, LVX, MXF, GEN, SXT, and RIF declined ( $P < 0.05$ ) in STCMH. Resistance rates for VAN, LZD, and Q/D remained low and stable across isolates from both hospitals (Figure 5).

## Clinical Efficacy Analysis

This study included 805 patients infected with *S. aureus* with complete clinical and follow-up data. We randomly allocated these patients to a training cohort (n=563, 70%) and a validation cohort (n=242, 30%), as detailed in Supplementary Table 1. Lasso regression was used to screen the predictive variables. As the penalty coefficient lambda ( $\lambda$ ) increased, the penalization effect on variable selection intensified, causing the coefficients of non-relevant variables to approach zero. Through analysis indicated that a  $\lambda$  value of 0.042 provided the optimal accuracy for the Lasso regression model, with the results of variable selection shown in Figure 6A and B. The combination of univariate logistic analysis with LASSO regression for dimensionality reduction allowed four variables from 37 candidate predictors for stepwise screening: synergistic therapy combining antibiotics and TCM, WBC, lymphocyte number (Lym) and CRP (Figure 6C). The predictive formula for assessing bacterial clearance in *S. aureus*-infected patients was derived as follows:  $Z = -0.708 + 0.916$  (Therapy Combining Antibiotics and TCM)  $-0.005$  (CRP)  $+ 0.04$  (WBC)  $+ 0.225$  (Lym).



**Figure 4** Comparison of the resistance rates of *S. aureus* and MRSA in STCMH and SGH. **(A)**, Comparison of the resistance rates of *S. aureus*. SGH showed higher resistance rates than STCMH for penicillin (PEN), levofloxacin (LVX), moxifloxacin (MXF) and gentamicin (GEN); **(B)**, Comparison of the resistance rates of MRSA. STCMH MRSA exhibited higher resistance to erythromycin (ERY) and moxifloxacin (MXF) compared to SGH, whereas SGH had a higher levofloxacin (LVX) resistance rate.

**Notes:** \*Statistical significance:  $P < 0.05$ .

**Abbreviations:** STCMH, Shanghai Municipal Hospital of Traditional Chinese Medicine; SGH, Shanghai General Hospital; PEN, penicillin; ERY, erythromycin; CLI, clindamycin; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; GEN, gentamicin; SXT, trimethoprim/sulfamethoxazole; RIF, rifampicin; VAN, vancomycin; LZD, linezolid; Q/D, quinupristin/dalfopristin.

## Predictive Model for Bacterial Clearance

A nomogram predictive model was developed using the identified variables to estimate the probability of bacterial clearance in *S. aureus*-infected patients (Figure 6D). To calculate the total score, the scores of the identified risk factors are summed, and the corresponding value is located on the risk axis. The resulting value represents the probability of bacterial clearance for *S. aureus*. The model's discriminatory power was evaluated using the receiver operating characteristic (ROC) curve, with the area under the curve (AUC) quantifying predictive accuracy. The ROC curve analysis revealed that the constructed nomogram prediction model achieved an AUC of 0.654 (95% CI: 0.609–0.699) (Figure 6E). The DCA results indicated that the nomogram provides a high clinical net benefit, as illustrated in Figure 6F and G.

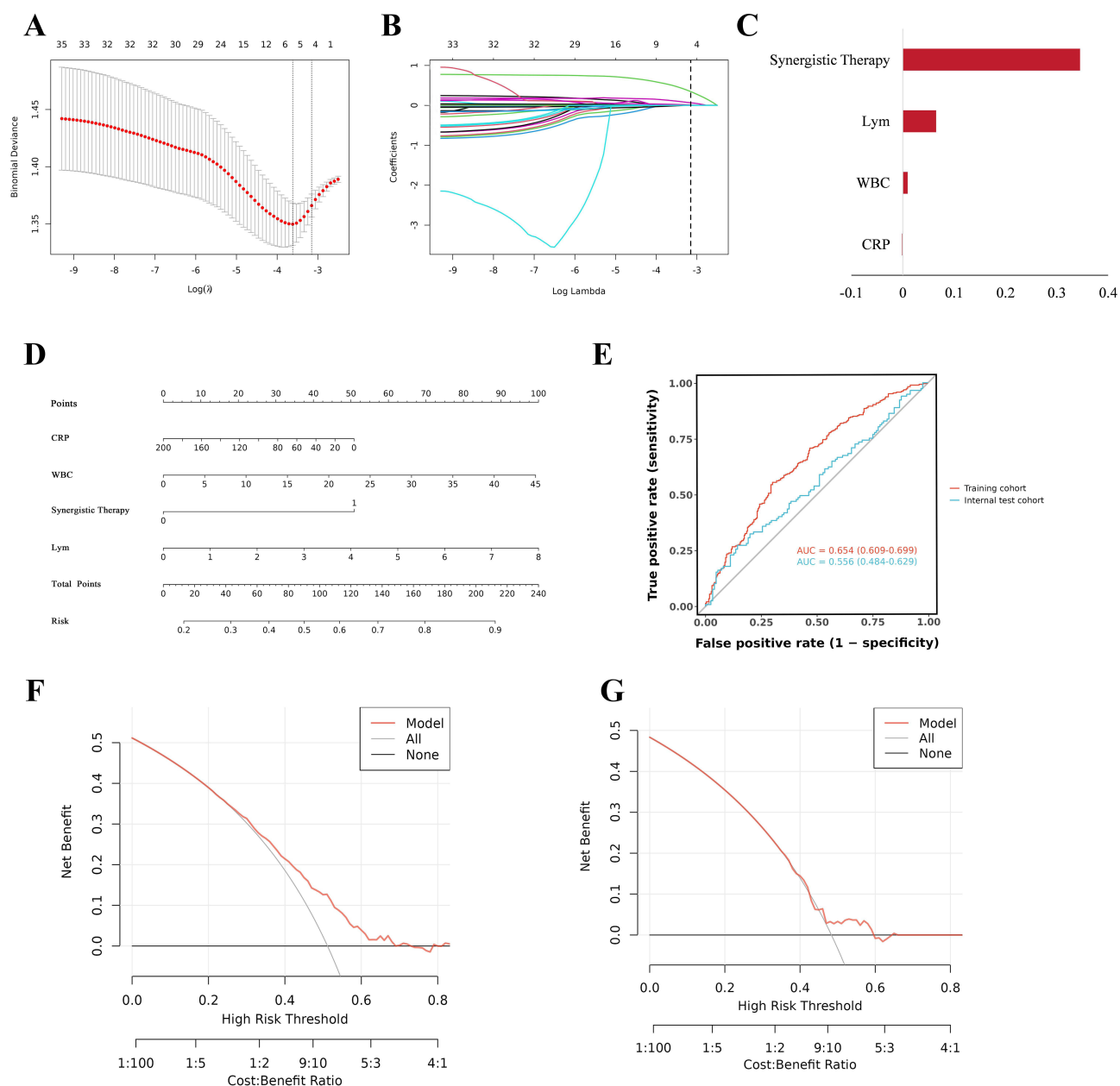


**Figure 5** Antibiotic resistance patterns of *S. aureus* and MRSA isolates from STCMH and SGH.

**Abbreviations:** STCMH, Shanghai Municipal Hospital of Traditional Chinese Medicine; SGH, Shanghai General Hospital; MRSA, Methicillin-resistant *Staphylococcus aureus*; *S. aureus*, *Staphylococcus aureus*.

## Discussion

Antimicrobial resistance (AMR) poses a major public health threat in the 21st century, significantly impacting society and the economy. *Staphylococcus aureus* remains a leading cause of infections and deaths in both hospitalized and outpatients across developing countries.<sup>16,17</sup> The World Health Organization's Global Antimicrobial Resistance and Use Surveillance System (GLASS) 2021 report indicated a 33.3% detection rate of MRSA in low- and middle-income countries. This rate exceeds the 15.0% prevalence reported in high-income countries across 109 participating nations and regions.<sup>18</sup> A systematic review and meta-analysis covering 16 African countries<sup>19</sup> showed a 4.1% MRSA carriage rate among healthy community residents. This prevalence is 2.05 times higher than the Centers for Disease Control and Prevention (CDC) estimates for the general US population (2%).<sup>20</sup> Furthermore, the study found a concerning 13.6% MRSA carriage rate among healthcare workers in Africa, exceeding the 1.8% pooled prevalence among healthcare workers in Europe and the United States.<sup>21</sup> The Global Research on Antimicrobial Resistance (GRAM) Project analyzed trends in antimicrobial resistance (AMR) from 1990 to 2021 and projected a significant global health impact through 2050 across 204 countries and territories. In 2021, MRSA caused 130,000 deaths, a 127% surge from the 57,200 fatalities it caused in 1990, establishing it as the fastest-growing AMR (antimicrobial resistance) threat. The persistent high mortality of AMR in low- and middle-income countries is driven by systemic challenges, including unequal distribution of medical resources, inadequate ICU facilities, shortages of healthcare workers, and limited microbiological diagnostic capabilities.<sup>22</sup> The emergence of MRSA during the 1990s led to improvements in both clinical hospitals and community healthcare facilities, along with the implementation of infection control strategies to prevent nosocomial transmission.<sup>23</sup> Furthermore, the ST8 (USA300 clone) strain, responsible for community outbreaks in the United States from the late 1990s to the early 2000s, rapidly became the dominant CA-MRSA clone in North America. This strain exhibits *mecA*-mediated methicillin resistance and often carries genetic factors such as *erm* and *msrA*, which confer cross-resistance to macrolides, tetracyclines, and other antibiotics.<sup>24</sup> A multicenter study found that CC59-ST59-t437-IV, CC8-ST239-t030-



**Figure 6** The cross-validation plot for Lasso regression. LASSO coefficient profiles for 37 candidate predictors of bacterial clearance (**A**). At  $\lambda = 0.042$ , four variables (synergistic antibiotic-TCM therapy, WBC, lymphocyte count, and CRP) were retained for model construction (**B**). Histogram of the coefficients of the selected features (**C**). Nomogram predictive model for evaluating bacterial clearance of *S. aureus*. This clinical decision tool integrates four independent predictors: synergistic antibiotic-TCM therapy (combination treatment), WBC count, lymphocyte levels, and CRP concentration. Each variable is assigned a weighted score on the scale; the cumulative total score corresponds to the predicted probability of successful bacterial eradication. Higher total scores indicate greater likelihood of microbiological clearance, supporting personalized therapeutic strategies for *S. aureus* infection management (**D**). Coefficient stability analysis of the bacterial clearance model. AUCs of the prediction models (**E**), DCA curve based on the training group (**F**), DCA curve based on the validation group (**G**).

**Abbreviations:** LASSO, Least Absolute Shrinkage and Selection Operator; TCM, Traditional Chinese Medicine; WBC, White Blood Cell; CRP, C-Reactive Protein; AUC, Area Under the Curve; DCA, Decision Curve Analysis.

III, and CC5-ST5-t2460-II strains are the predominant MRSA clones in China, although their prevalence varies across different administrative divisions.<sup>25</sup>

Multiple surveillance datasets showed a significant decline in MRSA infection rates in US healthcare facilities from 2005 to 2012.<sup>26</sup> This reduction has been attributed to improvements in surveillance, infection prevention, and control practices, and responsible antibiotic stewardship.<sup>27</sup> MRSA detection rates in China have steadily declined in recent years, falling from 36% in 2014 to 28.9% in 2022. However, detection rate climbed to 30.0% in 2024.<sup>11</sup> In the present study, both SGH and STCMH

hospitals reported MRSA detection rates exceeding the national average. Furthermore, the SGH hospital presented persistent high MRSA infection rates, displaying an initial decline followed by an upward trajectory with accelerated growth in later phases. The STCMH showed an initial increase in MRSA detection rates of 56.8% in 2018 to 66.4% in 2022, followed by a significant reduction to 33.3% in 2023. This decline may be associated to improved infection control measures implemented at the TCM hospital, which includes rigorous hygiene and disinfection protocols. Meanwhile, MRSA strains isolated from both SGH and STCMH showed significantly higher resistance rates to multiple antibiotics—including erythromycin, clindamycin, levofloxacin and gentamicin—compared to the national average.<sup>11</sup>

The present study examined *S. aureus* and MRSA resistance rates in a Western medicine hospital and a traditional Chinese medicine hospital from 2014 to 2023. Both hospitals recorded MRSA detection rates higher than the national average, but STCMH showed a steeper decline in these rates. Furthermore, resistance rates to multiple antibiotics decreased in both hospitals, with STCMH achieving a greater reduction. This study innovates by providing the first comparative analysis of MRSA detection and resistance patterns between Western medicine and TCM hospitals, revealing STCMH's advantages in controlling MRSA resistance. These findings offer new insights for clinical treatment and serve as critical references for optimizing antibiotic use and infection control measures. Two main factors explain these differences. First, patient characteristics. STCMH prioritize patients with chronic diseases and undergoing rehabilitation, as they often have longer stays but require fewer invasive interventions, which may reduce MRSA infection risks. Conversely, SGH focuses on acute and postoperative patients who frequently undergo invasive interventions, inherently increasing MRSA transmission risks. Second, antibiotic use. Certain natural compounds from plants exhibit synergistic effects with antibiotics to target MRSA.<sup>28</sup> STCMH's strategy of combining traditional Chinese and Western medicines is more effective to manage MRSA infections and reduce the need for antibiotics. This integrated approach reduces the development of antibiotic-resistant bacteria. The heavy reliance on broad-spectrum antibiotics in SGH, particularly during the COVID-19 pandemic (2020–2023), raised concerns about overuse and potential acceleration of MRSA dissemination. The combined use of herbal medicine and antibiotics may improve therapeutic efficacy, leading to shorter antibiotic courses and decrease antibiotic dosage. Data from Taxifulati et al<sup>29</sup> found that the integrative use of TCM with antibiotic therapy (AeTCMs) in China increased from 4.07 daily defined doses per 1000 inhabitants per day (DID) in 2011 to 6.82 DID by 2015. This represents a 13.75% annual growth rate. Antibiotic consumption during the same period showed a smaller increase, from 7.97 DID to 10.08 DID, with a 4.81% annual growth rate.<sup>30</sup> This difference suggests that antimicrobial stewardship policies might be influencing a shift, with increased AeTCM utilization and offsetting antibiotic use. This may be due to the synergistic or complementary benefits of AeTCM in managing infection.

This study investigated the predictors of bacterial clearance in *S. aureus* infections using real-world clinical data to develop a predictive model for initial treatment efficacy. LASSO regression identified four independent predictors: combined antibiotic and TCM therapy, WBC, lymphocyte count, and CRP levels. The combined antibiotic and TCM therapy significantly improved treatment success. However, elevated CRP levels decreased the likelihood of bacterial clearance, reflecting its value as a marker for inflammatory damage. The model presented moderate predictive performance (AUC = 0.654), suggesting its potential as an adjunctive tool for clinical risk stratification. Limitations, such as sample size, retrospective data bias, and the absence of critical host immune markers, prevent its use for individualized precision prediction at this time. Future research will focus on prospective, multi-center validation, and the identification of additional biomarkers to improve predictive accuracy.

The combination of TCM and antibiotic therapy for treating *S. aureus*, especially drug-resistant strains like MRSA, has become a prominent area of research.<sup>28</sup> This approach aims to improve antibiotic efficacy, reduce the emergence of resistance, and mitigate antibiotic side effects through synergistic interactions between herbal components and antibiotics.<sup>31</sup> While real-world evidence supports the clinical utility of combining TCM with antibiotics for treating *Staphylococcus aureus* infections, this study has several inherent limitations. First, the retrospective design introduces risks of unmeasured confounders. Additionally, potential sampling bias due to uneven isolate distribution and the restriction to Shanghai-based samples limit the generalizability of the findings to other regions. Second, the absence of molecular typing data impedes the discrimination between clonal transmission dynamics and spontaneous resistance mutations, thereby obscuring strain-specific epidemiological patterns. Third, incomplete documentation of treatment parameters—such as antibiotic dosing, TCM formulation compositions, and pharmacokinetic interactions—compromises

a quantitative assessment of therapeutic synergy. To address these limitations, the following steps should be undertaken in subsequent research: First, *in vitro* time-kill assays and murine infection models need to be employed to investigate the mechanisms of action of selected TCM monomers and their synergistic effects with antibiotics. Second, large-scale, multicenter randomized controlled trials (RCTs) need to be conducted across various regions using standardized TCM–antibiotic combination regimens to evaluate clinical efficacy and examine the resistance profiles of different bacterial clonal lineages to various antibiotics. Third, a comprehensive cost-effectiveness analysis also requires to be performed to compare integrated TCM–antibiotic therapy with current standard care, quantifying key clinical and economic outcomes including duration of hospitalization, healthcare costs, and rates of antibiotic resistance development.

In summary, our real-world study reveals that STCMH outperformed SGH in reducing MRSA detection rates and antimicrobial resistance. This success appears attributable to STCMH’s optimized infection control practices and the integration of TCM with Western medical approaches. Furthermore, our findings suggest that the combined analysis of antibiotic treatment with TCM usage, WBC, CRP levels, and lymphocyte count holds potential as a predictive tool for bacterial clearance in *S. aureus*-infected patients.

## Abbreviations

AMR, Antimicrobial Resistance; AUC, area under the ROC curve; AZM, azithromycin; CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; CDC, Centers for Disease Control and Prevention; CHINET, China Antimicrobial Resistance Surveillance Network; CIP, ciprofloxacin; CLI, clindamycin; CLSI, Clinical and Laboratory Standards Institute; CRP, C-reactive protein; DRSA, daptomycin-resistant *Staphylococcus aureus*; ERY, erythromycin; GEN, gentamicin; HA-MRSA, hospital-acquired methicillin-resistant *Staphylococcus aureus*; hVISA, heterogeneous vancomycin-intermediate *Staphylococcus aureus*; LA-MRSA, livestock-associated methicillin-resistant *Staphylococcus aureus*; LASSO, least absolute shrinkage and selection operator; LRSA, linezolid-resistant *Staphylococcus aureus*; LZD, linezolid; LVX, levofloxacin; *mecA*, methicillin resistance gene; MCV, mean corpuscular volume; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MXF, moxifloxacin; *msrA*, macrolide-streptogramin B resistance gene; NorA, norfloxacin resistance efflux pump; OXA, oxacillin; PBP2a, penicillin-binding protein 2a; PEN, penicillin; Q/D, quinupristin/dalfopristin; RCT, randomized controlled trial; RIF, rifampicin; ROC, receiver operating characteristic; SXT, trimethoprim/sulfamethoxazole; TCM, traditional Chinese medicine; STCMH, Shanghai Municipal Hospital of Traditional Chinese Medicine; VAN, vancomycin; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*; SGH, Shanghai General Hospital.

## Data Sharing Statement

All data used to support the findings of this study are available from the corresponding author on request.

## Ethics Approval and Consent to Participate

This study was approved by the Ethics Review Committee of the Shanghai Municipal Hospital of Traditional Chinese Medicine (2025SHL-KY-26-01). The Ethics Review Committee of the Shanghai Municipal Hospital of Traditional Chinese Medicine has waived the requirement for informed consent because this is a retrospective analysis, all personally identifiable information has been anonymized to protect patient privacy, and there were no additional interventions or risks to participants in this study. All procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no competing interests in this work.

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