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ORIGINAL RESEARCH

Incidence, Clinical Characteristics and Outcomes of Persistent *Staphylococcus aureus* Bacteremia in a Chinese Tertiary Care Hospital: A Single-Center Retrospective Study

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Purpose: Persistent *Staphylococcus aureus* bacteremia (pSAB) poses significant clinical challenges because of its association with poor outcomes, including relapse and mortality. Despite its clinical importance, data on pSAB in the mainland Chinese population remain limited. This study aimed to investigate the prevalence, clinical characteristics, and predictors of pSAB in a tertiary hospital in China.

Patients and Methods: We conducted a retrospective case–control study at a large tertiary-care hospital in China from 2020 to 2024. Patients with *Staphylococcus aureus* bacteremia (SAB) were categorized into persistent and nonpersistent groups on the basis of the duration of bacteremia (>48 hours). Clinical characteristics, management, and outcomes were compared. Multivariate logistic regression was used to identify independent risk factors for pSAB.

Results: Among 499 patients with SAB, 48 (9.6%) met the criteria for pSAB, with the incidence peaking at 13.9% in 2024. Compared with the non-pSAB group, the pSAB group had higher rates of infective endocarditis (p=0.002), a CCI ≥7 (p=0.036), metastatic infection (p=0.007), and preadmission fever ≥7 days (p=0.026). They more frequently underwent surgical intervention (p=0.041), received dual anti-MRSA therapy (p<0.001), and less often received β-lactam monotherapy (p=0.001). pSAB was associated with prolonged fever (p=0.014), a hospital stay ≥7 days after SAB onset (p=0.002), increased 30-day mortality (p=0.036), and increased 3-month relapse (p=0.001). Multivariate analysis revealed a CCI ≥7 (OR=4.09; 95% CI: 1.19–14.00; p=0.025), infective endocarditis (OR=8.66; 95% CI: 1.52–49.03; p=0.015), and preadmission fever ≥7 days (OR=5.06; 95% CI: 1.61–15.90; p=0.006) as independent predictors of pSAB.

Conclusion: The incidence of pSAB is increasing in China and is associated with complex clinical features and adverse outcomes. Severe comorbidities, infective endocarditis, and prolonged fever before admission are significant predictors of pSAB. Early identification and aggressive source control are critical for improving the outcomes of high-risk patients.

Keywords: persistent bacteremia, *Staphylococcus aureus*, predictor, mortality

Introduction

Persistent bacteremia (PB) is defined as the continued or recurrent presence of pathogens in the bloodstream despite appropriate antimicrobial therapy. It is closely associated with increased organ dysfunction, prolonged hospitalization, and significantly elevated mortality, contributing to greater clinical severity and poor prognosis.[1–3]

Staphylococcus aureus remains the most common pathogen responsible for cases of PB, accounting for 8–39% of all *S. aureus* bacteremia (SAB) episodes.[4] Its virulence factors—including hemolysins and coagulases—facilitate immune evasion and tissue invasion and promote the development of persister phenotypes following infection.[5] In addition, *S. aureus* can form unique biofilms—structured microbial communities encased in extracellular polymeric substances.

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Biofilms promote bacterial adherence to host tissues and medical devices, impede antibiotic penetration, and significantly reduce clearance by host phagocytes. Within biofilms, *S. aureus* can enter a metabolically dormant state as persister cells, further enhancing antimicrobial tolerance.[6] These complex mechanisms provide a biologically plausible and pathophysiological basis for persistent SAB (pSAB) and underscore the importance of early identification and management.

However, notably there is currently no globally unified standard for the diagnosis and management of pSAB.[7] Over the past two decades, the diagnostic criteria for PB have evolved.[8] Early definitions, such as that proposed by Fowler et al in the early 2000s, required the presence of bacteremia to persist for at least seven days.[9] However, more recent studies have demonstrated that a prolonged duration of SAB is significantly associated with increased mortality and a higher risk of metastatic infections.[2] In 2020, Kuehl et al published a multinational cohort study involving 1,588 SAB patients and reported that when the duration of bacteremia increased from 1 day to 2–4 days, the 90-day mortality rate nearly doubled from 22% to 39%, respectively. On the basis of these findings, the authors suggested redefining the cutoff duration for PB as 2 days or more despite active antibiotic therapy.[4]

Although previous studies have described the clinical characteristics of pSAB and suggested potential predictive factors—such as infective endocarditis, metastatic infection, cardiovascular implantable electronic devices (CIEDs), and delayed source control[5]—the evolving diagnostic thresholds may alter the interpretation and validity of these predictors, warranting reevaluation.

Moreover, the incidence of pSAB varies across regions and time periods. A 2012 study from South Korea reported that among 79 patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, 31 (39.2%) remained bacteremic for more than seven days.[10] In contrast, a 2023 Korean study analyzing 1,300 patients with SAB revealed that only 17% had positive blood cultures persisting beyond two days.[11] This shift may reflect changes in diagnostic criteria and advances in treatment strategies. Furthermore, two studies from Taiwan, China, reported lower rates of pSAB than those reported in South Korea,[12,13] suggesting notable differences in incidence across countries. However, epidemiological data on pSAB in mainland China remain limited.

To address this knowledge gap, we conducted a retrospective analysis to quantify the incidence of pSAB in a tertiary-care Chinese hospital from 2020 to 2024, and to identify clinical predictors through comparative and multivariate analyses.

Materials and Methods

Research Design and Population

This retrospective, case–control study was conducted at the Second Affiliated Hospital of Zhejiang University School of Medicine, a tertiary-care center in Zhejiang Province, China, with more than 2000 beds. The hospital microbiological database was screened to identify patients who had positive blood cultures for *S. aureus*. Based on prior studies and with appropriate adjustments for our patient population and research aims,[14–16] patients were included in the study if they met all of the following criteria: 1) Hospitalized and aged ≥18 years; 2) at least one positive blood culture yielding *S. aureus*; 3) clinical signs or symptoms consistent with SAB; 4) received appropriate antibiotic therapy for *S. aureus* after the index blood culture; and 5) blood cultures performed between 48 hours and 7 days after the initiation of appropriate antibiotic therapy. Patients were excluded if they met any of the following criteria: 1) Polymicrobial bacteremia (ie, *S. aureus* isolated together with other pathogens in the same episode); 2) absence of clinical manifestations consistent with bacteremia (suggesting contamination rather than true infection); 3) no follow-up blood cultures performed between 48 hours and 7 days after the initiation of appropriate antibiotic treatment; and 4) did not receive appropriate antimicrobial therapy or died or were lost to follow-up within 48 hours of treatment initiation. All eligible patients were categorized into two groups: pSAB and nonpersistent SAB (non-pSAB). pSAB was defined as at least one follow-up blood culture positive for *S. aureus* obtained between 48 hours and 7 days after the initiation of appropriate antimicrobial therapy.[4,14] Non-pSAB was defined as all follow-up blood cultures obtained between 48 hours and 7 days after the initiation of appropriate antimicrobial therapy being negative for *S. aureus*. As a retrospective case-control study, controls were randomly selected from the non-pSAB group at a 1:1 ratio to the number of pSAB cases.

Ethical Approval

This retrospective case–control study was approved by the Institutional Review Board of the Second Affiliated Hospital of Zhejiang University School of Medicine (Reference No. 2025–0034). The requirement for informed consent was waived because the study involved only a retrospective review of existing medical records and laboratory data, posed no potential risk to patients, and used de-identified information. All patient data were fully anonymized prior to analysis to ensure confidentiality. The study was conducted in accordance with the ethical standards of the institutional research committee and the principles of the Declaration of Helsinki (as revised in 2013).

Definitions and Data Collection

SAB is defined as patients fulfilling the diagnostic criteria for bloodstream infection, with blood cultures positive for *S. aureus*.[17] The duration of bacteremia was calculated from the day the first positive blood culture was collected to the day of the last positive follow-up blood culture.[11] Relapse was defined as the reoccurrence of SAB after two consecutive days of negative blood cultures.[18] Appropriate antibiotic therapy was defined as the administration of at least one intravenous agent within 24 hours after the index blood culture, which was subsequently confirmed to be active against the isolated *S. aureus* strain in vitro and recommended by current clinical guidelines.[19,20] Metastatic infection was defined as infection at a distant anatomical site unrelated to the primary source.[21] Sources of bacteremia were classified as either hospital-acquired or community-acquired; community-acquired SAB was diagnosed if positive blood cultures were obtained within 48 hours of admission, whereas hospital-acquired SAB was diagnosed when cultures became positive after 48 hours of hospitalization.[22] The primary outcome was 30-day mortality.

Clinical data were extracted from electronic medical records. The variables analyzed included demographics (age, sex, comorbidities) and infection severity scores.[16] (SOFA score, Pitt score), clinical manifestations (onset of bacteremia, metastatic lesions, fever duration, laboratory parameters, duration of bacteremia), treatments (surgical intervention, antibiotic regimens), and outcomes (hospital stay, 3-month relapse, and 30-day mortality).

Statistical Analysis

Categorical variables are expressed as counts and percentages, and continuous variables are expressed as the means with standard deviations or medians with interquartile ranges (IQRs), depending on the distribution. For univariate analysis, categorical variables were compared using the chi-square test or Fisher's exact test, and continuous variables were analyzed using Student's t test or the Mann–Whitney U-test, as appropriate. For multivariate analysis, logistic regression models were used to identify independent predictors, and p values were calculated using the Wald test. A two-tailed p value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA).

Results

Epidemiology and Demographics

Over a five-year period, 499 patients with blood culture-confirmed SAB were identified, including 48 patients (9.6%) with PB. The lowest incidence of pSAB was recorded in 2022 (4/80, 4.8%), while the highest was observed in 2024 (17/105, 13.9%). A gradual increase in incidence was noted over the past four years (Figure 1A).

Among the 48 patients included in the pSAB group, 26 were male (54.2%), with a median age of 61.5 years (IQR 54.0–71.0). These demographic characteristics were not significantly different from those of the non-pSAB group. However, the Charlson comorbidity index (CCI) was significantly greater in the pSAB group (median 4.0 [IQR 2.0–7.0] vs 3.0 [IQR 2.0–4.5], $p = 0.030$). Although the proportion of patients with a CCI ≥ 3 did not differ significantly between the two groups (70.8% vs 58.3%, OR=1.74; p=0.200), a significantly greater proportion of patients with a CCI ≥ 7 were in the pSAB group (27.1% vs 10.4%; OR = 3.19; $p = 0.036$). These findings indicate that patients with a greater burden of comorbidities were more prevalent in the pSAB group, suggesting that severe comorbidity may be a potential predictor of the development of pSAB (Table 1).

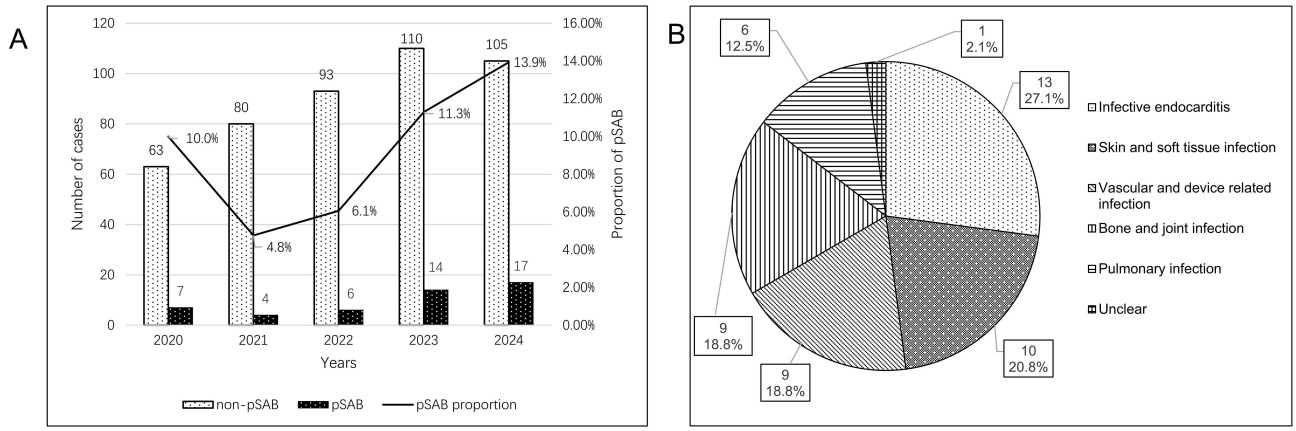

Figure 1 (**A**) Proportion of pSAB among all SAB cases over the past five years. (**B**) Composition of pSAB by onset of bacteremia.
Abbreviations: SA, Staphylococcus aureus; SAB, Staphylococcus aureus bacteremia; pSAB, persistent Staphylococcus aureus bacteremia.

Clinical Characteristics of pSAB

In the pSAB group, 18 patients (37.5%) were infected with MRSA, and 16 patients (33.3%) had community-acquired infections. In comparison, the corresponding proportions in the non-pSAB group were 47.9% and 31.3%, respectively. No significant differences were found between the pSAB and non-pSAB groups in these aspects.

Table 1 Baseline Characteristics and Clinical Features in Patients with pSAB vs Non-pSAB

Variables	pSAB (n=48)	non-pSAB (n=48)	OR (95% CI)	p value
Demographics				
Male, n (%)	26 (54.2)	30 (62.5)	0.71 (0.31–1.60)	0.408
Age, y, median (IQR)	61.5 (54.0–71.0)	61.0 (46.5–66.0)		0.577
CCI, median (IQR)	4.0 (2.0–7.0)	3.0 (2.0–4.5)		0.030
CCI ≥3, n (%)	34 (70.8)	28 (58.3)	1.74 (0.74–4.05)	0.200
CCI ≥7, n (%)	13 (27.1)	5 (10.4)	3.19 (1.04–9.83)	0.036
Onset of bacteremia				
IE, n (%)	13 (27.1)	2 (4.2)	8.54 (1.81–40.34)	0.002
SSTI, n (%)	10 (20.8)	10 (20.8)	1.00 (0.37–2.68)	1.000
VDI, n (%)	9 (18.8)	10 (20.8)	0.88 (0.32–2.40)	0.798
BJI, n (%)	9 (18.8)	11 (22.9)	0.78 (0.29–2.09)	0.615
PI, n (%)	6 (12.5)	9 (18.8)	0.62 (0.20–1.90)	0.399
Unknown, n (%)	1 (2.1)	6 (12.5)	0.31 (0.06–1.59)	0.268
Clinical manifestations				
CAI, n (%)	16 (33.3)	15 (31.3)	1.14 (0.48–2.68)	0.943
MRSA, n (%)	18 (37.5)	23 (47.9)	0.65 (0.29–1.47)	0.409
Metastasis, n (%)	11 (22.9)	2 (4.2)	6.84 (1.43–32.79)	0.007
Fever ≥7 d pre-admission, n (%)	15 (31.3)	6 (12.5)	3.18 (1.11–9.10)	0.026
WBC ($\times 10^9$/L), mean ± SD	19.7 ± 18.5	15.2 ± 8.9		0.147
CRP (mg/L), mean ± SD	175.1 ± 91.2	157.8 ± 93.3		0.378
PCT (ng/mL), mean ± SD	10.7 ± 20.0	18.7 ± 29.8		0.185
IL-6 (pg/mL), mean ± SD	2037.7 ± 8790.6	1148.7 ± 2023.5		0.533
PLT ($\times 10^9$/L), mean ± SD	146.1 ± 109.5	164.0 ± 124.1		0.464
D-dimer (μg/L), mean ± SD	6745.4 ± 5503.7	6437.9 ± 4982.5		0.701
Lactate (mmol/L), mean ± SD	3.8 ± 4.4	3.1 ± 1.8		0.404
SOFA, median (IQR)	3.5 (1.0–6.3)	4.0 (1.8–8.0)		0.676
SOFA ≥2, n (%)	34 (70.8)	36 (75.0)	0.81 (0.33–2.00)	0.646
Pitt, median (IQR)	1.0 (0.0–2.0)	2.0 (0.0–3.0)		0.529
Pitt ≥5, n (%)	7 (14.6)	2 (4.2)	3.93 (0.77–19.98)	0.159

(*Continued*)

Table 1 (Continued).

Variables	pSAB (n=48)	non-pSAB (n=48)	OR (95% CI)	p value
Treatment				
Surgery, n (%)	18 (37.5)	9 (18.8)	2.60 (1.03–6.60)	0.041
VAN, n (%)	4 (8.3)	3 (6.3)	1.36 (0.29–6.45)	1.000
VAN+BL, n (%)	13 (27.1)	13 (27.1)	1.00 (0.41–2.46)	1.000
DAP+BL, n (%)	3 (6.3)	0 (0.0)	/	0.241
LZD, n (%)	3 (6.3)	3 (6.3)	1.00 (0.19–5.22)	1.000
LZD+BL, n (%)	7 (14.6)	6 (12.5)	1.20 (0.37–3.86)	0.765
BL, n (%)	7 (14.6)	22 (45.8)	0.20 (0.08–0.54)	0.001
Two anti-MRSA agents, n (%)	11 (22.9)	0 (0.0)	/	<0.001
Outcomes				
LOS post-SAB, d, median (IQR)	22.5 (16.5–40.8)	18.0 (11.8–33.3)		0.140
LOS ≥7 d post-SAB, n (%)	37 (77.1)	22 (45.8)	3.98 (1.65–9.59)	0.002
Fever duration, d, median (IQR)	9.5 (7.0–15.0)	5.0 (1.0–12.0)		0.014
Relapse ≤3 months, n (%)	10 (20.8)	0 (0.0)	/	0.001
30-d mortality, n (%)	8 (16.7)	1 (2.1)	9.40 (1.13–78.41)	0.036

Note: p-values were calculated using the chi-square or Fisher's exact test for categorical variables, and the Student's t-test or Mann–Whitney U-test for continuous variables.

Abbreviations: pSAB, persistent *Staphylococcus aureus* bacteremia; SAB, *Staphylococcus aureus* bacteremia; CCI, Charlson Comorbidity Index; IE, infective endocarditis; SSTI, skin and soft tissue infection; VDI, vascular/device-related infection; BJI, bone and joint infection; PI, pulmonary infection; CAI, community-acquired infection; MRSA, methicillin-resistant *S. aureus*; WBC, white blood cell count; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; PLT, platelet count; SOFA, Sequential Organ Failure Assessment; Pitt, Pitt bacteremia score; VAN, vancomycin; BL, β-lactam; DAP, daptomycin; LZD, linezolid; d, days; LOS, length of Stay; OR, Odds Ratio; CI, Confidence Interval; IQR, Interquartile Range.

With respect to the onset of bacteremia, the most common primary site of infection in the pSAB group was infective endocarditis (IE) (13 cases, 27.1%), followed by skin and soft tissue infections (10 cases, 20.8%), vascular and device-related infections (9 cases, 18.8%), bone and joint infections (9 cases, 18.8%), and pulmonary infections (6 cases, 12.5%). In one case (2.1%), the primary source of infection was unknown (Figure 1B). With the exception of IE, which was significantly more common in the pSAB group (27.1% vs 4.2%, OR = 8.54; p = 0.002), there were no statistically significant differences between the two groups in terms of other primary infection sites.

With respect to clinical manifestations, patients in the pSAB group had a higher incidence of metastatic infections (22.9% vs 4.2%, OR=6.84; p=0.007), and a greater proportion had experienced persistent fever for ≥7 days prior to admission (31.3% vs 12.5%; OR=3.18; p=0.026). However, there were no significant differences between the pSAB and non-pSAB groups in terms of the levels of markers of infection severity, such as white blood cell count, C-reactive protein level, procalcitonin level, interleukin-6 level, platelet count, D-dimer level, blood lactate level, SOFA score, and Pitt score.

In terms of management, surgical intervention was more common in the pSAB group (37.5% vs 18.8%, OR=2.06; p=0.041). Combination therapy with two anti-MRSA agents was also more frequently utilized in the pSAB group (22.9% vs 0.00%, p<0.001), whereas β-lactam monotherapy was less common (14.6% vs 45.8%, OR=0.20, p=0.001). Other antibiotic agents, including vancomycin, daptomycin, and linezolid, as well as combination therapy with these agents and β-lactams, did not significantly differ between the two groups.

The clinical outcomes for pSAB patients were notably worse. The proportion of patients whose length of hospitalization was ≥7 days after SAB was significantly greater in the pSAB group than in the non-pSAB group (77.1% vs 45.8%, OR = 3.98; p = 0.002). Although the overall duration of postbacteremia hospital stay was not significantly different between the two groups (median 22.5 [IQR 16.5–40.8] vs 18.0 [IQR 11.8–33.3], p=0.140), patients in the pSAB group tended to have longer hospitalizations. Furthermore, the duration of fever was significantly longer in the pSAB group (median 9.5 [IQR 7.0–15.0] vs 5.0 [IQR 1.0–12.0], p=0.014). In addition, the pSAB group had higher 3-month relapse rates (20.8% vs 0.0%, p=0.001) and higher 30-day mortality rates (16.7% vs 2.1%, OR=9.40, p=0.036) (Figure 2), indicating significantly worse clinical outcomes in patients with pSAB.

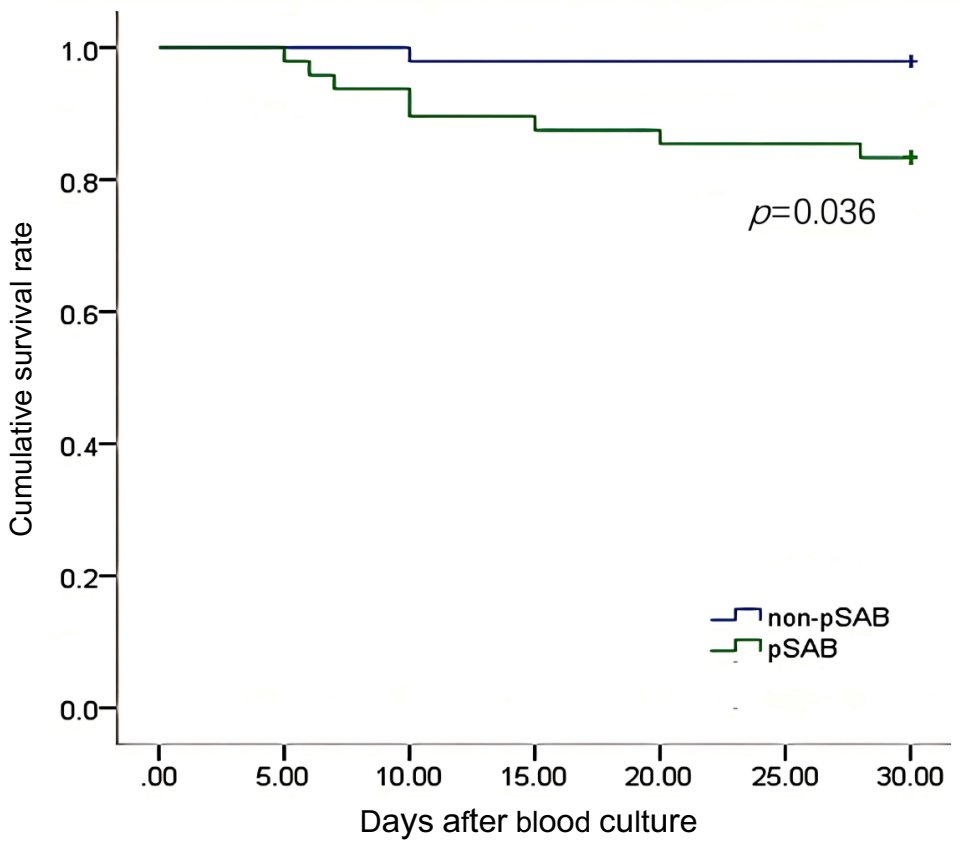

Figure 2 Thirty-day Kaplan-Meier survival curves for patients with pSAB.
Abbreviation: pSAB, persistent *Staphylococcus aureus* bacteremia.

Clinical Predictors of pSAB

Multivariate analysis revealed a Charlson comorbidity index ≥7 (OR=4.09; 95% CI: 1.19–14.00; p=0.025), infective endocarditis (OR=8.66; 95% CI: 1.52–49.03; p=0.015), and fever duration ≥7 days before admission (OR=5.06; 95% CI: 1.61–15.90; p=0.006) as clinical features that can predict pSAB presence (Table 2).

Discussion

The incidence of pSAB has recently increased,[20] a trend that was also observed in our study. As a highly virulent gram-positive pathogen, *S. aureus* accounts for 30%–40% of PB cases.[23] Despite active treatment, pSAB is significantly associated with poor clinical outcomes.[2] Similarly, in our study, patients in the pSAB group experienced a prolonged duration of fever and an extended hospital stay, and both the 30-day mortality rate and the 3-month recurrence rate were higher, highlighting the significantly worse clinical outcomes in patients with pSAB.

Table 2 Multivariate Analysis of Predictors for pSAB

Variables	OR (95% CI)	p value
Charlson comorbidity index ≥7	4.09(1.19–14.00)	0.025
Infective endocarditis	8.66(1.52–49.30)	0.015
Metastatic lesions	2.30(0.38–13.86)	0.364
Length of fever before hospitalization ≥7 days	5.06(1.61–15.90)	0.006

Note: p-values in the multivariate analysis were calculated using logistic regression with the Wald test to assess the significance of individual predictors.
Abbreviations: pSAB, persistent *Staphylococcus aureus* bacteremia; OR, Odds Ratio; CI, Confidence Interval.

We identified infective endocarditis, fever duration exceeding 7 days before admission, and a CCI ≥7 as clinical features that can predict the presence of pSAB, which is partially consistent with the findings of previous literature. For example, Fowler et al established infective endocarditis as a critical predictor of pSAB.[24] The CCI reflects the burden of comorbidities in patients. Previous reports have identified a CCI ≥6 as an independent risk factor for 30-day mortality in pSAB patients.[11] In our study, the proportion of patients with a CCI ≥7 was significantly greater in the pSAB group than in the non-pSAB group, suggesting that a high comorbidity burden may have predictive value for the development of pSAB. This may be related to impaired immune function and reduced infection control capacity in these patients. Notably, we identified prolonged fever prior to hospitalization as a novel predictive factor, suggesting that it may serve as a marker of refractory infections or delayed therapeutic intervention. Clinically, close attention should be given to patients with pSAB who present with prolonged fever at admission, with early evaluation and source control prioritized.

We observed a greater proportion of surgical interventions and increased use of combination therapy with two anti-MRSA antibiotics (such as vancomycin combined with linezolid or tigecycline) in the pSAB group, reflecting greater complexity in infection control. Nevertheless, patients with pSAB experienced longer fever durations and significantly higher rates of recurrence and short-term mortality, which is consistent with the findings of previous studies.[25,26] For example, Chang et al reported that even under optimized treatment conditions, patients with pSAB faced an elevated risk of treatment failure because of difficulty in lesion clearance or biofilm formation.[27] Our findings support this perspective and suggest that intensified antibacterial therapy alone may not compensate for inadequate source control. Therefore, in pSAB management, particular emphasis should be placed on early and effective lesion control, especially in patients with implant-related infections, abscesses, or endocarditis.

Unexpectedly, no significant differences were observed between the pSAB and non-pSAB groups regarding early inflammatory indicators (such as white blood cell count and procalcitonin) or severity scores (SOFA and Pitt scores) within 48 hours of bacteremia onset. These findings contrast with those of studies by Giannella et al, who reported stronger early inflammatory responses in patients with pSAB.[28] Our results suggest that the early inflammatory response to bacteremia may be similar regardless of subsequent persistence. Additionally, preadmission antibiotic use in some patients may have masked the true intensity of early infection responses.

This study had several limitations. First, it was a single-center, retrospective study with a relatively small sample size, potentially introducing selection bias. Second, variability in the timing and frequency of follow-up blood cultures during bacteremia may have influenced pSAB recognition. Furthermore, antibiotic regimens were not fully standardized, and individualized treatment decisions may have affected outcomes. Nonetheless, our study provides valuable clinical evidence for the identification and management of pSAB, particularly highlighting the importance of early detection and source control in high-risk populations.

Conclusion

This study revealed a rising incidence of pSAB in a tertiary-care hospital in China, with significantly higher 30-day mortality and 3-month relapse rates in patients with pSAB than in those without pSAB. We identified infective endocarditis, a CCI ≥7, and fever lasting ≥7 days before admission as independent clinical predictors of pSAB. Notably, our findings revealed prolonged fever before admission as a previously overlooked but significant predictor of pSAB. These findings underscore the importance of early identification and prompt source control, particularly in patients with complex comorbidities or prolonged febrile symptoms. The implementation of standardized screening protocols may help clinicians detect pSAB earlier and improve patient outcomes. Future multicenter and prospective studies are warranted to validate these findings and refine clinical decision-making strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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