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Original Article

Factors for mortality in patients with persistent *Staphylococcus aureus* bacteremia: The importance of treatment response rather than bacteremia duration

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Abstract *Background:* The criteria for antibiotic failure in persistent *Staphylococcus aureus* bacteremia (SAB) are unclear, but treatment response and bacteremia duration are commonly used indicators of antibiotic failure. We evaluated the effects of treatment response and bacteremia duration on mortality in persistent SAB.
Methods: We retrospectively identified patients with persistent SAB in four university-affiliated hospitals between 2017 and 2021. Bacteremia duration was calculated from the first day of active antibiotic therapy, and persistent SAB was defined as bacteremia lasting for 2 or more days. Defervescence and Pitt bacteremia score (PBS) were used to evaluate treatment response at treatment day 4. The primary outcome was 30-day in-hospital mortality. Time-dependent multivariable Cox regression analysis and subgroup analysis according to methicillin resistance were performed.
Results: A total of 221 patients was included in the study, and the 30-day in-hospital mortality was 28.5%. There was no significant difference in bacteremia duration between survived and deceased patients. Independent factors for mortality included age, Charlson comorbidity index, initial PBS, pneumonia, and removal of the eradicable focus. PBS at treatment day

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$4 \geq 3$ was the strongest risk factor (adjusted hazard ratio [HR] = 4.260), but defervescence was not. Bacteremia duration was not an independent factor except for 13 days or more of methicillin-resistant SAB (adjusted HR = 1.064).
Conclusions: In patients with persistent SAB, PBS at treatment day 4 was associated with 30-day in-hospital mortality rather than defervescence and bacteremia duration. The results of this study could help determine early intensified treatment strategies in persistent SAB patients.

Introduction

Staphylococcus aureus bacteremia (SAB) is one of the most common bloodstream infections contributing to mortality and has been consistently associated with high mortality.[1–3] In patients with SAB, the distinction between complicated and uncomplicated bacteremia is important for treatment decisions and prognosis, and persistent bacteremia is a criteria for complicated bacteremia.[4,5] The current guidelines suggest persistent bacteremia as positive follow-up blood cultures 2–4 days after the initial set, but previous studies have used various definitions and criteria.[4,5] Recently, two large-scale studies have been conducted to clarify the definition of persistent SAB.[6,7] One study demonstrated that every continued day of bacteremia was associated with an increased relative risk of death.[6] Another study suggested a duration of persistent SAB as two or more days despite active antibiotic therapy.[7] These results indicate that identification of persistent SAB should be made early, even one day after initiation of antibiotic therapy.[8]

For patients with persistent SAB, a thorough evaluation of the source and extent of infection, active removal of the eradicable focus, and extended treatment duration are recommended to improve prognosis.[4,8] In addition, a change to antimicrobial salvage therapy or implementation of positron emission tomography/computed tomography (PET/CT) can be considered promising management options, but it remains unclear when such treatment strategies should be considered.[8,9] Therefore, additional risk stratification in persistent SAB is necessary to determine these treatment strategies. To help with this risk stratification, we evaluated risk factors for mortality in patients with persistent SAB, including treatment response and bacteremia duration, commonly used as indicators of antibiotic failure.[8–10]

Methods

Study design and patients

The study retrospectively identified patients (age $\geq$18 years) with *S. aureus* isolated from $\geq$1 blood culture from January 2017 to December 2021 at four university-affiliated hospitals in Republic of Korea. Only patients with confirmed persistent SAB were included in the study. Persistent bacteremia was defined as bacteremia lasting for two days or more despite active antibiotic therapy.[7] Patients with non-persistent bacteremia or polymicrobial bacteremia (isolation of more than one microbial species from an episode) were excluded in the study. We also excluded patients who were lost to follow-up within 14 days from the first positive blood culture. Clinical data were collected from electronic medical records. This study was approved by the Institutional Review Board (IRB) of each participating hospital with a waiver of consent (IRB number of BP Hospital: BPIRB 2022-07-013).

Definitions and outcome

Bacteremia duration was calculated from the first day of active antibiotic therapy after collection of the first positive blood culture to the day of the last positive follow-up blood culture.[7] A positive follow-up culture within 14 days after a negative follow-up culture was considered a continuing bacteremic episode.[7] Active antibiotic therapy was defined as administration of at least one intravenous glycopeptide or beta-lactam antibiotic with in vitro activity against isolated *S. aureus*. Treatment response was evaluated in two ways at the fourth day of active antibiotic therapy (treatment day 4): 1) confirmation of defervescence and 2) Pitt bacteremia score (PBS). Defervescence was defined as an afebrile state in which the body temperature remained lower than 38.0 °C for at least 48 h.[11,12] The PBS included five criteria: fever, hypotension, mechanical ventilation, cardiac arrest, and mental status.[13] Among them, the criterion for fever was decreased by 0.6 °C because the axillary temperature was mainly used for body temperature measurement in the hospitals.[11,14,15] Immunosuppression was defined as the use of steroids (prednisolone >0.5 mg/kg/d or equivalent for >1 month), chemotherapy, or anti-tumor necrosis factor therapy within the past three months. Metastatic infection was defined as distant foci anatomically distinct from the implicated source of bacteremia.[16] Eradicable focus was defined as that with surgically removable infection or indwelling foreign body such as intravenous catheter and drainable abscess.[17] Non-eradicable foci included unknown primary sites, osteomyelitis, meningitis, pneumonia, septic arthritis, and endocarditis. Sources of bacteremia were classified as nosocomial, healthcare-associated, or community-acquired.[18] The primary outcome was 30-day in-hospital mortality.[19] We defined favorable outcomes as

survival beyond 30 days from the first positive blood culture in the hospital or live discharge.

Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]) and categorical variables as frequency count (percentage). Continuous variables were compared using Mann—Whitney U tests according to the results of the normality tests. Fisher's exact test or chi-square test was used to compare categorical variables. The cut-off value of continuous variables was determined using a receiver operating characteristic (ROC) curve with the Youden Index. Cut-off values for bacteremia duration were determined considering the distribution of 30-day in-hospital mortality. Variables with a $P < .1$ in univariable Cox regression analysis were included in the multivariable model, and forward conditional selection was used to identify significant variables. Subgroup analysis was conducted comparing risk factors between patients with methicillin-resistant *S. aureus* (MRSA) and those with methicillin-susceptible *S. aureus* (MSSA) bacteremia. To assess the effect of bacteremia duration after adjusting for immortal-time bias, time-dependent multivariable Cox regression analysis was conducted. *P* values were two-tailed, and *P* values $< .05$ were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software for Windows, Version 25.0 (2017, IBM Corp., Armonk, NY, USA).

Results

Study population and patient characteristics

Of the 1300 patients with SAB, 221 were included in the study: 73 patients from BP Hospital, 65 from SC Hospital, 48 from KS Hospital, and 35 from DK Hospital (Fig. 1). Eight patients were discharged within 30 days from onset of bacteremia, and the median follow-up duration of these patients was 25.5 days (IQR 22.25—29).

One hundred twenty-nine (58.4%) patients were male, and the median age of all patients was 69 years (IQR 58—79.5). The median Charlson comorbidity index (CCI) of the patients was 5 (IQR 4—7), and 91 patients had at least one prosthesis. Seventy-nine (35.7%) patients were admitted to the intensive care unit (ICU) within 24 h from onset of bacteremia, and the median initial PBS was 1 (IQR 0—3). Common sources of bacteremia were osteoarticular focus (29.9%), unknown focus (17.6%), and intravascular catheter (16.7%). Metastatic infection was identified in 56 patients (25.3%). Of the source of bacteremia, nosocomial bacteremia represented 36.7% and community-acquired bacteremia 35.3%. Bacteremia due to MRSA occurred in 112 (50.7%) patients, and the median bacteremia duration was 5 days (IQR 3—8).

The median time from onset of bacteremia to administration of active antibiotics was one day (IQR 0—2), and the most common initial antibiotic therapy was glycopeptide plus beta-lactam (56.6%). One hundred seventy patients (76.9%) underwent echocardiography, and the proportion of patients who underwent infectious diseases consultations within seven days of onset of bacteremia was 64.7%.

Sixty-three (28.5%) patients died within 30 days from onset of bacteremia, with a median time to death of 12 days (IQR 8—21) (Table 1). Among the deceased patients, negative conversion of blood cultures was identified in 33 (52.4%). Mortality rates in patients with MSSA and MRSA bacteremia were 21.1% and 35.7%, respectively.

The deceased patients consisted of more females, were older, and exhibited higher CCI and initial PBS than the surviving patients. Furthermore, in the deceased patients, MRSA bacteremia, pneumonia, unknown focus, metastatic infection, and initial glycopeptide and beta-lactam therapy were more common, while skin and soft tissue infections, removal of the eradicable focus, and performance of transthoracic echocardiography were less common.

Bacteremia duration and treatment response

There was no significant difference in bacteremia duration between the deceased and surviving patients (Table 1). However, in the deceased patients, there were significantly more patients with 4—12 days of bacteremia and fewer patients with 13 days or more of bacteremia. There was a significant difference in bacteremia duration between patients with MSSA and MRSA bacteremia (median 4 [IQR 3—6] and 6 [IQR 3—12.75] days, $P < .001$).

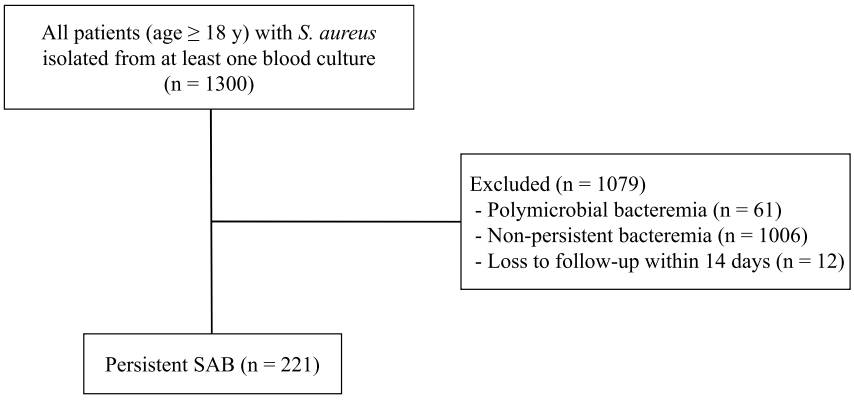

Figure 1. The study population. SAB, *Staphylococcus aureus* bacteremia.

Table 1 Clinical characteristics of patients with persistent *Staphylococcus aureus* bacteremia.

Characteristics	Survived (n = 158)	Deceased (n = 63)	*P* value
Male	100 (63.3)	29 (46.0)	.019
Age, years, median (IQR)	67.5 (55.75–77.25)	75 (62–82)	.003
Comorbidities			
Charlson comorbidity index, median (IQR)	5 (4–7)	6 (5–8)	.001
Diabetes	63 (39.9)	21 (33.3)	.366
Diabetes with end-organ damage	24 (15.2)	10 (15.9)	.899
Moderate or severe liver disease	5 (3.2)	2 (3.2)	>.999
Moderate or severe renal disease	39 (24.7)	18 (28.6)	.551
Hemodialysis dependence	29 (18.4)	13 (20.6)	.696
Metastatic solid tumor	15 (9.5)	8 (12.7)	.481
Hematologic malignancy	4 (2.5)	2 (3.2)	>.999
Immunosuppression	20 (12.7)	12 (19.0)	.223
Prostheses			
Orthopedic device	28 (17.7)	10 (15.9)	.742
Cardiovascular device	9 (5.7)	3 (4.8)	>.999
Long-term CVC	29 (18.4)	12 (19.0)	.905
Other prosthesis[a]	5 (3.2)	1 (1.6)	.677
ICU admission within 24 h[b]	42 (26.6)	37 (58.7)	<.001
Pitt bacteremia score, initial, median (IQR)	1 (0–2)	3 (1–4)	<.001
White blood cell count (/μL), median, (IQR	12,920 (10,120–18080)	13,130 (9360–19,390)>	.902
C-reactive protein (mg/dL), median, (IQR)	19.38 (7.31–27.72)	20.66 (9.73–27.99)>	.450
Focus of infection			
Endocarditis	15 (9.5)	10 (15.9)	.176
Osteoarticular focus	53 (33.5)	13 (20.6)	.058
Pneumonia	4 (2.5)	10 (15.9)	.001
Surgical wound infection	4 (2.5)	0 (0)	.580
Skin and soft tissue infection	22 (13.9)	2 (3.2)	.020
Intravascular catheter	28 (17.7)	9 (14.3)	.537
Unknown focus	22 (13.9)	17 (27.0)	.021
Others[c]	11 (7.0)	2 (3.2)	.358
Metastatic infection	33 (20.9)	23 (36.5)	.016
Onset of bacteremia			
Nosocomial	56 (35.4)	25 (39.7)	.555
Healthcare-associated	46 (29.1)	16 (25.4)	.579
Community-acquired	56 (35.4)	22 (34.9)	.942
Methicillin resistance	72 (45.6)	40 (63.5)	.016
Bacteremia duration, days, median (IQR)	5 (3–8.25)	5 (3–8)	.874
2–3 days	60 (38.0)	21 (33.3)	.518
4–12 days	71 (44.9)	39 (61.9)	.023
≥13 days	27 (17.1)	3 (4.8)	.016
Removal of eradicable focus (n = 128)			
No removal	38 (24.1)	16 (25.4)	.833
Removal of focus after day 3[b]	29 (18.4)	5 (7.9)	.053
Removal of focus before day 3[b]	34 (21.5)	6 (9.5)	.037
Time to active antibiotics, days, median (IQR)[b]	1 (0–2)	1 (0–2)	.303
Initial active antibiotic therapy			
Glycopeptide monotherapy	33 (20.9)	7 (11.1)	.088
Glycopeptide and beta-lactam	82 (51.9)	43 (68.3)	.027
Anti-staphylococcal beta-lactam	6 (3.8)	3 (4.8)	.717
Other beta-lactams	37 (23.4)	10 (15.9)	.216
Transthoracic echocardiography	128 (81.0)	42 (66.7)	.022
Transesophageal echocardiography	16 (10.1)	2 (3.2)	.088
ID consultation within 7 days[b]	104 (65.8)	39 (61.9)	.582
Treatment response at treatment day 4			

Table 1 (*continued*)

Characteristics	Survived (n = 158)	Deceased (n = 63)	*P* value
Defervescence (n = 220)[d]	104 (65.8)	41 (66.1)	.966
Pitt bacteremia score, median (IQR)(n = 220)[d]	0 (0–1)	3 (0.75–5)	<.001

[a] Other prostheses included central nervous system shunts and ureteral double J stents.
[b] Time points were calculated from the onset of bacteremia.
[c] Other infections included urinary tract infections, intra-abdominal infections, and vascular graft infections.
[d] One patient died at treatment day 3.
Data are presented as the numbers (%) unless otherwise indicated.
Abbreviations: CVC, central venous catheter; ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range.

Table 2 Univariable and multivariable analyses for 30-day in-hospital mortality in total patients with *S. aureus* bacteremia.

Variable	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Female	1.752 (1.067–2.876)	.027		
Age ≥74 years[a]	2.801 (1.683–4.661)	<.001	2.250 (1.318–3.839)	.003
CCI ≥ 6[a]	2.687 (1.591–4.540)	<.001	1.973 (1.152–3.378)	.013
Methicillin resistance	1.778 (1.064–2.970)	.028		
ICU admission within 24 h	2.931 (1.773–4.844)	<.001		
Initial PBS ≥ 3[a]	3.614 (2.198–5.942)	<.001	1.951 (1.117–3.408)	.019
Osteoarticular focus	0.579 (0.314–1.066)	.079		
Pneumonia	4.540 (2.295–8.981)	<.001	2.724 (1.313–5.654)	.007
Skin and soft tissue infection	0.232 (0.057–0.950)	.042		
Unknown focus	1.975 (1.132–3.446)	.017		
Removal of eradicable focus	0.366 (0.191–0.701)	.002	0.449 (0.231–0.870)	.018
Glycopeptide monotherapy	0.512 (0.233–1.123)	.095		
Glycopeptide and beta-lactam	1.809 (1.064–3.076)	.029		
Metastatic infection	1.752 (1.049–2.927)	.032		
Transthoracic echocardiography	0.512 (0.303–0.865)	.012		
PBS at treatment day 4 ≥ 2[a]	6.314 (3.723–10.710)	<.001	4.260 (2.369–7.466)	<.001

[a] The cut-off value was determined using a receiver operating characteristic (ROC) curve with the Youden Index.
Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; ICU, intensive care unit; HR, hazard ratio; PBS, Pitt bacteremia score.

At treatment day 4, defervescence exhibited no significant difference between the two groups, but PBS was significantly higher in the deceased patients than in the surviving patients (Table 1). Between patients with MSSA and MRSA bacteremia, defervescence revealed no significant difference ($P = .737$), but PBS at treatment day 4 was significantly higher in patients with MRSA bacteremia (median 1 [IQR 0–3] and 0 [IQR 0–1], $P = .005$).

Table 3 Univariable and multivariable analyses for 30-day in-hospital mortality in patients with MRSA bacteremia.

Variable	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age ≥73 years[a]	2.432 (1.290–4.585)	.006	2.128 (1.115–4.061)	.022
CCI ≥ 6[a]	2.494 (1.301–4.780)	.006		
ICU admission within 24 h	2.383 (1.264–4.492)	.007		
Initial PBS ≥ 3[a]	2.831 (1.514–5.294)	.001		
Pneumonia	4.717 (2.150–10.349)	<.001	2.920 (1.302–6.548)	.009
Glycopeptide and beta-lactam	2.483 (1.042–5.918)	.004		
Transthoracic echocardiography	0.378 (0.202–0.707)	.002		
PBS at treatment day 4 ≥ 3[a]	5.260 (2.794–9.904)	<.001	4.796 (2.519–9.131)	<.001

[a] The cut-off value was determined using a receiver operating characteristic (ROC) curve with the Youden Index.
Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*; HR, hazard ratio; PBS, Pitt bacteremia score.

Risk factors for 30-day in-hospital mortality

In univariable Cox regression analysis, 16 possible risk factors were identified (Table 2). In the final multivariable model, age ≥74 years, CCI ≥6, initial PBS ≥3, pneumonia, removal of the eradicable focus, and PBS at treatment day 4 ≥ 2 were included as significant risk factors. Among the identified risk factors, PBS at treatment day 4 ≥ 2 was the strongest factor (adjusted hazard ratio: 4.260; $P < .001$). In the subgroup analysis of patients with MRSA bacteremia, age ≥73 years, pneumonia, and PBS at treatment day 4 ≥ 3 were significant risk factors (Table 3). In patients with MSSA bacteremia, significant risk factors included age ≥74 years, initial PBS ≥2, removal of the eradicable focus, and PBS at treatment day 4 ≥ 2 (Table 4).

Considering bacteremia duration as the time-dependent variable, there was no significant association between bacteremia duration and 30-day in-hospital mortality in the total patients with SAB (Table 5). Only in patients with MRSA bacteremia, 13 days or more of bacteremia was associated with increased mortality (adjusted hazard ratio: 1.064; $P = .040$).

Table 4 Univariable and multivariable analyses for 30-day in-hospital mortality in patients with MSSA bacteremia.

Variable	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age ≥74 years[a]	3.902 (1.603–9.496)	.003	3.292 (1.301–8.333)	.012
CCI ≥ 6[a]	3.051 (1.255–7.419)	.014		
ICU admission within 24 h	3.576 (1.567–8.163)	.002		
Initial PBS ≥ 2[a]	5.450 (2.022–14.691)	.001	2.975 (1.026–8.624)	.045
Unknown focus	2.940 (1.245–6.940)	.014		
Removal of eradicable focus	0.149 (0.035–0.635)	.001	0.180 (0.041–0.790)	.023
Metastatic infection	2.380 (1.029–5.502)	.043		
PBS at treatment day 4 ≥ 2[a]	12.110 (4.721–31.067)	<.001	7.836 (2.897–21.197)	<.001

[a] The cut-off value was determined using a receiver operating characteristic (ROC) curve with the Youden Index.
Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; ICU, intensive care unit; MSSA, methicillin-susceptible *S. aureus*; HR, hazard ratio; PBS, Pitt bacteremia score.

Table 5 Thirty-day in-hospital mortality by duration of bacteremia.

		Duration, days	Total, n	Death, n (%)	Adjusted HR (95% CI)	*P* value
Total[a]	1)[d]	2–3	81	21 (25.9)	Reference	
		4+	140	42 (30.0)	1.007 (0.971–1.044)	.707
	2)	2–3	81	21 (25.9)	Reference	
		4–6	62	22 (35.5)	1.015 (0.972–1.059)	.502
		7+	78	20 (25.6)	1.003 (0.964–1.043)	.891
	3)	2–3	81	21 (25.9)	Reference	
		4–12	110	39 (35.5)	1.017 (0.980–1.055)	.366
		13+	30	3 (10.0)	0.961 (0.902–1.024)	.223
MRSA[b]	1)	2–3	29	11 (37.9)	Reference	
		4+	83	29 (34.9)	0.998 (0.952–1.046)	.917
	2)	2–3	29	11 (37.9)	Reference	
		4–6	28	14 (50.0)	1.012 (0.957–1.070)	.679
		7+	55	15 (27.3)	0.991 (0.943–1.042)	.735
	3)	2–3	29	11 (37.9)	Reference	
		4–12	55	26 (47.3)	1.049 (0.980–1.124)	.167
		13+	28	3 (10.7)	1.064 (1.003–1.129)	.040
MSSA[c]	1)	2–3	52	10 (19.2)	Reference	
		4+	57	13 (22.8)	0.983 (0.928–1.042)	.569
	2)	2–3	52	10 (19.2)	Reference	
		4–5	25	8 (32.0)	0.972 (0.908–1.042)	.423
		6+	32	5 (15.6)	0.994 (0.932–1.060)	.855

[a] Covariates: age ≥74 years, CCI ≥6, initial PBS ≥3, pneumonia, removal of the eradicable focus, and PBS at treatment day 4 ≥ 2.
[b] Covariates: age ≥73 years, pneumonia, and PBS at treatment day 4 ≥ 3.
[c] Covariates: age ≥74 years, initial PBS ≥2, removal of the eradicable focus, and PBS at treatment day 4 ≥ 2.
[d] The cut-off value was determined using a receiver operating characteristic (ROC) curve with the Youden Index.
Abbreviations: CI, confidence interval; HR, hazard ratio; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Discussion

We evaluated the effects of treatment response and bacteremia duration on 30-day in-hospital mortality in patients with persistent SAB. Defervescence and PBS were used to evaluate treatment response, and PBS at treatment day 4 was a significant risk factor. Bacteremia duration was not associated with 30-day in-hospital mortality except for a duration of 13 days or more in patients with MRSA bacteremia.

The 30-day in-hospital mortality of patients with persistent SAB in this study was 28.5%. This result is higher than that of all SAB patients (18.1%)[1] and is consistent with that of a previous study (28.5%).[7] In another study, the 30-day mortality of persistent SAB was as low as 13.6%, but there was a difference in the median age of patients (69 years vs. 57 years).[6] Furthermore, the proportion of patients with persistent SAB in this study was relatively low (17.8% vs. 31.9%).[7] This result may be due to our identification of all patients with *S. aureus* isolated from blood cultures regardless of signs and symptoms of bacteremia and might have missed patients with persistent SAB who did not undergo early follow-up blood cultures. On the other hand, the proportion of patients with seven days or more of bacteremia was relatively high (35.3% vs. 8.9%).[7] This difference may be due to higher rates of metastatic infection (25.3% vs. 12.7%) and MRSA (50.7% vs. 10.8%) in the patients of this study.

We evaluated the association of bacteremia duration with 30-day in-hospital mortality using several cut-off values. Although there was a tendency for increased mortality in patients with 4—12 days of bacteremia, this duration was not significantly associated with mortality after adjusting for immortal-time bias. Only 13 days or more of MRSA bacteremia was significantly associated with a slight increase in mortality. These results suggest that the effect of bacteremia duration on 30-day mortality may not be significant after persistent SAB is established. However, since we assessed 30-day mortality, the effect of bacteremia duration in this study may have been attenuated, considering the association between bacteremia duration and relapse.[20] Further large-scale studies assessing long-term outcomes such as 90-day mortality or relapse are needed to identify an optimal cutoff value for bacteremia duration for determining treatment failure in persistent SAB.

In this study, PBS at treatment day 4 was the strongest risk factor for 30-day in-hospital mortality, but defervescence was not a significant factor. PBS is a scoring system developed to measure the acute severity of disease in patients with bacteremia and has been used primarily to predict prognosis at initial presentation.[21] However, since this scoring system includes several patient-specific variables such as fever, hypotension, and mental status, it may also be useful for evaluating treatment response.[21,22] Furthermore, we evaluated PBS on the fourth day of treatment. The time points for evaluating early treatment response in bacteremia were variously suggested in previous studies, ranging from 2 to 5 days after the onset of bacteremia or the initiation of treatment.[23] Considering the time-to-positivity of blood cultures,[24] a positive signal from blood cultures on treatment day 2, which is used as the criterion for persistent SAB, would typically be confirmed on treatment day 3 or 4. Thus, PBS at treatment day 4 can be timely used as an early indicator of treatment failure in persistent SAB. On the other hand, defervescence is one of the criteria of complicated SAB, but it is not well-defined for temperature and duration.[4,25] We assessed defervescence over two days but did not observe a significant difference between the two groups. Although defervescence is a commonly used clinical parameter for evaluating treatment response, it alone may not be reliable to predict prognosis.[10]

In addition, age, CCI, initial PBS, and pneumonia were significant risk factors, and these results are consistent with those of previous studies.[6,7,26] In patients with persistent SAB who have these risk factors, additional therapeutic interventions prior to the fourth day of antibiotic treatment may be beneficial. Removal of the eradicable focus was a negative risk factor, which highlights the importance of adequate source control.[8] Furthermore, there were differences in these risk factors and cut-off values for PBS (3 points in the MRSA subgroup; 2 points in the MSSA subgroup) according to methicillin resistance. These differences may be due to pathogen-specific or antibiotic-related factors such as virulence factors and antimicrobial bactericidal activity.[3] Thus, considering the differences in bacteremia duration and mortality together, different treatment strategies according to methicillin resistance may be needed in persistent SAB, including cut-off values for PBS.

This study has several limitations. First, changes in antibiotic regimens after initial active antibiotic therapy were not evaluated. However, this was a retrospective study, and it was difficult to evaluate such changes uniformly because they were determined based on clinical judgments. In addition, daptomycin, another agent approved for SAB treatment, was rarely used due to delays in its domestic introduction and the non-applicability of national insurance. A previous study also did not show significant differences in duration of bacteremia according to change of antibiotics after initial empiric therapy.[6] Second, negative conversion of blood cultures was not identified in half of the patients who died, and it is possible that the duration of bacteremia was censored in these patients. Among these patients, the median interval between the date of death and the last positive blood culture was 1 days (IQR 0—2). However, due to the retrospective nature of this study, rigorous follow-up of blood cultures could not be conducted. Third, data on serum vancomycin concentration were not included in the analysis. During the study period, vancomycin therapeutic drug monitoring based on trough concentrations was available in all hospitals, but this method is no longer preferred under recent guidelines.[27] In addition, teicoplanin was administered as glycopeptide antibiotics in some patients. Fourth, because transesophageal echocardiography was performed infrequently in the patients, the diagnosis of infective endocarditis may have been missed.

We confirmed that more than one-quarter of the patients with persistent SAB died within one month. This, together with a recent study showing that infection-related deaths in SAB occur mainly within one month,[28] underscores the need for early intensified treatment strategies other than prolonged antibiotic therapy in persistent SAB. PET/CT and early antimicrobial salvage therapy have recently emerged as promising therapeutic options,[8,9] and the risk factors identified in this study could be used as indicators for the decision on such treatment strategies in persistent SAB.

Ethical approval

This study was approved by the Institutional Review Board (IRB) of each participating hospital with a waiver of consent (IRB number of BP Hospital: BPIRB 2022-07-013).

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Declaration of competing interest

The authors have no competing interests to declare.

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