Open Forum Infectious Diseases

MAJOR ARTICLE

Sequential Time to Positivity as a Prognostic Indicator in *Staphylococcus aureus* Bacteremia

Isin Y. Comba,[1,a] John Raymond Go,[1,a] James Vaillant,[1] John C. O'Horo,[1] Ryan W. Stevens,[2] Raj Palraj,[1] and Omar Abu Saleh[1]

[1]Division of Public Health, Infectious Diseases, and Occupational Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA, and [2]Department of Pharmacy, Mayo Clinic, Rochester, Minnesota, USA

Background. We aimed to determine the factors associated with sequential blood culture time to positivity (STTP) and validate the previously defined time to positivity (TTP) ratio threshold of 1.5 in predicting adverse disease outcomes and mortality of *Staphylococcus aureus* bacteremia (SAB).

Methods. We conducted an observational study of adult patients with SAB. The TTP ratio was calculated by dividing the TTP of the second blood culture by that of the first.

Results. Of 186 patients, 69 (37%) were female, with a mean age of 63.6 years. Median TTP was 12 hours (interquartile range [IQR], 10–15 hours) from the initial and 21 hours (17–29) from sequential blood cultures. Methicillin-resistant *S aureus* (MRSA)–infected patients had significantly shorter STTPs ($P < .001$) and lower TTP ratios ($P < .001$) compared to patients with methicillin-susceptible *S aureus* (MSSA). A significant correlation between initial and STTP was observed in patients with MRSA ($r = 0.42$, $P = .002$) but not in those with MSSA. A higher rate of native valve endocarditis (NVE) significantly correlated with a TTP ratio of ≤1.5 (odds ratio, 2.65 [95% confidence interval, 1.3–5.6]; $P = .01$). The subgroup having an initial TTP <12 hours combined with a TTP ratio ≤1.5 showed the highest prevalence of NVE.

Conclusions. The STTP varies based on methicillin susceptibility of *S aureus* isolate. This study suggests a potential clinical utility of the STTP to identify patients at a higher risk of NVE. However, prospective studies are required to validate these findings.

Keywords. bacteremia; blood cultures; infective endocaditis; *Staphylococcus aureus*; time to positivity.

Staphylococcus aureus bacteremia (SAB) carries about a 10%–30% mortality rate [1]. Several clinical risk factors have been linked to poor outcomes, including advanced age, female sex, underlying comorbidities, immunosuppression, and methicillin resistance of the isolate [1, 2]. Given the significant morbidity and mortality associated with SAB, it is crucial to identify patients at higher risk for poor outcomes to optimize treatment and improve clinical outcomes.

Time to positivity (TTP) from initial blood cultures has been long recognized as a valuable surrogate marker for bacterial load and carries prognostic significance in SAB [3, 4]. A shorter TTP, defined as the growth of *S aureus* within 12 hours, has been shown to be an independent predictor for persistent and metastatic bacteremia, endovascular source of infection, complicated SAB, and higher mortality [4–10]. While a shorter initial blood culture TTP (ITTP) is predictive of adverse outcomes, there are limited existing data on the potential utility of sequential blood culture TTP (STTP) as a prognostic indicator [7]. A singular study has investigated the TTP ratio (second blood culture TTP to first blood culture TTP) in a cohort of 87 patients with persistent SAB, and the authors reported that a TTP ratio <1.5 is an independent predictor of mortality [11]. While the results are encouraging and indicate potential clinical value in disease prognosis, a caution is warranted in interpreting TTP, as it is influenced by various factors, including the volume of blood collected, delay in blood sample processing, or presence of antibiotics or antibiotic sequesters in blood [12, 13].

We hypothesized that STTP and TTP ratio can be informative of complex interaction among host-pathogen-antibiotic and offer clinicians a better understanding of the overall therapeutic response aiding in making clinical decisions. The primary objective of our study is to investigate the association between disease characteristics and outcomes in relation to STTP patterns in patients with SAB for ≥24 hours. As a secondary objective, we assessed the previously proposed TTP ratio of 1.5 as an indicator of adverse outcomes, aiming to validate of this threshold in a distinct cohort.

Received 30 November 2023; editorial decision 18 March 2024; accepted 19 March 2024; published online 21 March 2024

[a]I. Y. C. and J. R. G. contributed equally to this work.

Correspondence: Isin Yagmur Comba, MD, Division of Public Health, Infectious Diseases, and Occupational Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (comba.isin@mayo.edu); Omar M. Abu Saleh, MBBS, Division of Public Health, Infectious Diseases, and Occupational Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (abusaleh.omar@mayo.edu).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofae173

MATERIALS AND METHODS

Study Design

We conducted a single healthcare system, multisite, retrospective review of all adults (≥18 years old) with a positive blood culture for *S aureus* between January 2019 and December 2019 at Mayo Clinic sites in Arizona, Florida, and Minnesota and the Mayo Clinic Health System in the Midwest. Patients with SAB who had positive follow-up blood cultures for *S aureus* at least 24 hours after initial cultures were included in the analysis. Exclusions applied to patients who (1) declined research authorization, (2) were <18 years old, (3) did not have positive follow-up blood cultures, (4) had SAB lasting <24 hours, or (5) had inadequate medical records. We collected data from both electronic health records and the clinical microbiology laboratory. This study was reviewed by the Mayo Clinic Institutional Review Board and determined to be exempt from human subjects research per 45 Code of Federal Regulations 46.104, Category 4 research.

Microbiology

At least 2 blood culture sets comprised of 1 BD BACTEC lytic Anaerobic/F bottle and 1 or 2 BD BACTEC Plus Aerobic/F bottles, with each bottle containing approximately 8–10 mL of blood, were obtained from each patient. The Becton Dickinson BD BACTEC FX platform was used with a standard incubation period of 5 days. The system is continuously monitored, and if a blood culture bottle is flagged as positive on the BD BACTEC FX platform, TTP is automatically recorded and further workup is performed, including Gram staining and subculturing onto appropriate media. *Staphylococcus aureus* was identified using matrix-assisted laser desorption/ionization–time of flight mass spectrometry and/or with a combination of morphological and biochemical characteristics. Antimicrobial susceptibility testing was performed using agar dilution, and the results were interpreted per the guidelines of the Clinical and Laboratory Standards Institute [14].

Definitions

Baseline comorbidities were assessed using the Charlson Comorbidity Index [15]. SAB was defined as the growth of *S aureus* from a blood culture bottle. We adopted Friedman criteria [16] to classify the acquisition of bloodstream infection. The bacteremia source was determined through a manual chart review conducted by 2 infectious disease providers (J. R. G. and I. Y. C.). Bloodstream infections were classified as community-acquired with positive cultures within 48 hours of admission and no prior healthcare contact, healthcare-associated with prior healthcare exposure within the same timeframe of within the first 48 hours of admission, and nosocomial if detected after 48 hours of admission. We defined STTP as the TTP of successive blood cultures collected from patients with SAB lasting at least 24 hours. For cases wherein multiple subsequent sets of blood cultures were obtained, the earliest TTP, after 24 hours of bacteremia, was reported as the sequential TTP. Infective endocarditis (IE) was defined according to the modified Duke criteria [17]. Predicting risk of endocarditis using a clinical tool scores on days 1 and 5 were calculated [18]. Complicated SAB and persistent SAB definitions were employed from the Infectious Diseases Society of America guidelines [19]. We calculated the duration of bacteremia by measuring the time interval between the first positive blood culture and the first subsequent negative blood culture. We defined high-grade bacteremia as the organism's growth in 2 or more sets of blood cultures or >50% of all collected bottles [20].

Statistical Analysis

Descriptive statistics involved frequencies and proportions for categorical variables. Mean, median, standard deviation (SD), or interquartile range (IQR) were computed for continuous variables. To determine the factors associated with TTP ratio groups with a threshold of 1.5, logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). All covariates that were statistically significant ($P < .05$) in univariate analysis were included in the multivariate model. Adjustment for methicillin-resistant *S aureus* (MRSA)/methicillin-susceptible *S aureus* (MSSA) status was also employed to account for significant variability observed between TTP ratios and methicillin resistance of the isolates. Kaplan-Meier analysis was used to assess 30-day and 365-day survival, incorporating right censoring. A threshold of $P < .05$ was applied for statistical significance. All statistical analyses were performed using R statistical software (v4.2.3; R Core Team 2023) [21–25].

RESULTS

Study Cohort

Six hundred two patients with SAB were identified during the 1-year period, and 186 patients who met the study criteria were included in the analysis (Figure 1). Thirty-seven percent (n = 69) were female, and mean age was 63.6 years. The majority identified as White (96% [n = 179]). Among 186 patients with SAB, MSSA was detected in 73% (n = 135) and MRSA in 27% (n = 51). The primary mode of infection acquisition was healthcare-associated for 52% (n = 97), followed by community-acquired for 42% (n = 78) and nosocomial for 6% (n = 11). Among the sources of bacteremia, skin and soft tissue infections were the most prevalent at 33% (n = 62), followed by catheter-related infections at 15% (n = 27), osteoarticular infections at 9% (n = 16), and genitourinary/gastrointestinal infections at 6% (n = 12). Notably, 30% (n = 55) had indeterminate sources of bacteremia. Ninety percent (n = 168) underwent daily blood collection for bacterial cultures and 87% (n = 162) had high-grade bacteremia in initial blood cultures. The mean duration of bacteremia was 4 days (SD, 2.5 days).

Regarding the adverse outcomes, 89% (n = 169) had complicated bacteremia, 59% (n = 110) had persistent bacteremia, 31% (n = 57) had prosthetic device infection, 29% (n = 54) had IE, 22% (n = 40) had osteomyelitis, and 15% (n = 27) had septic emboli. For diagnostic evaluation of IE, 85 patients (46%) underwent both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), 46 (25%) had only TTE, and 48 (26%) had only TEE. Seven patients without echocardiograms were considered indeterminate for IE. Among the 54 IE cases, 42 involved native valves, and 12 were prosthetic valve endocarditis. One hundred thirty-one patients had a source of bacteremia identified, and 104 achieved source control. All patients were on appropriate antimicrobials between initial and sequential blood culture collections. Of the inpatient antimicrobial agents administered, cefazolin (48% [n = 89]) and vancomycin (20% [n = 38]) were the most common for MSSA and MRSA bacteremia, respectively. The average duration of inpatient intravenous antibiotics was 14 days (SD, 9 days), and outpatient was 29 days (SD, 18 days). Notably, 21% (n = 39) of patients received follow-up oral therapy, with 23 individuals transitioning to chronic suppression using oral agents. The most utilized oral suppressive agents were cefadroxil (n = 22) and doxycycline (n = 8).

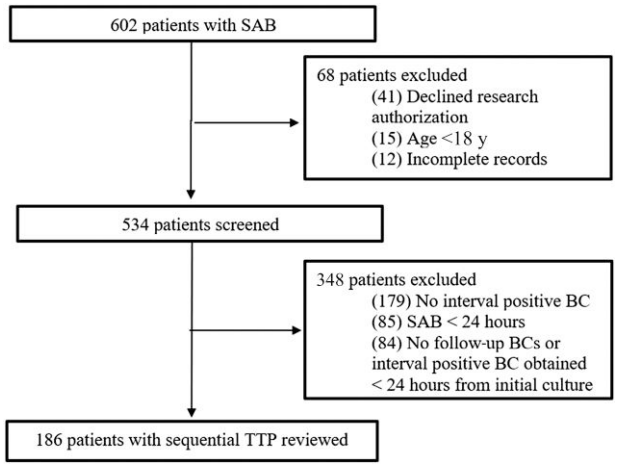

Figure 1 . Study cohort flowchart. Abbreviations: BC, blood culture; SAB, *Staphylococcus aureus* bacteremia; TTP, time to positivity.

TTP From Sequential Blood Cultures Differs Based on Methicillin Resistance

Median TTP was 12 hours (IQR, 10–15 hours) from the initial blood cultures and 21 hours (IQR, 17–29 hours) from sequential blood cultures. The median duration between initial and sequential blood culture collection was 1.1 days (IQR, 0.6–1.4 days). Interestingly, TTP from the initial and sequential blood cultures did not correlate (Spearman, $r = 0.12$, $P = .15$; Figure 2*A*). We then calculated the ratio of STTP to ITTP to better characterize the relative change in TTP. The distribution of the TTP ratio was heterogeneous across the cohort (Supplementary Figure 1), with a median of 1.7 (IQR, 1.3–2.4).

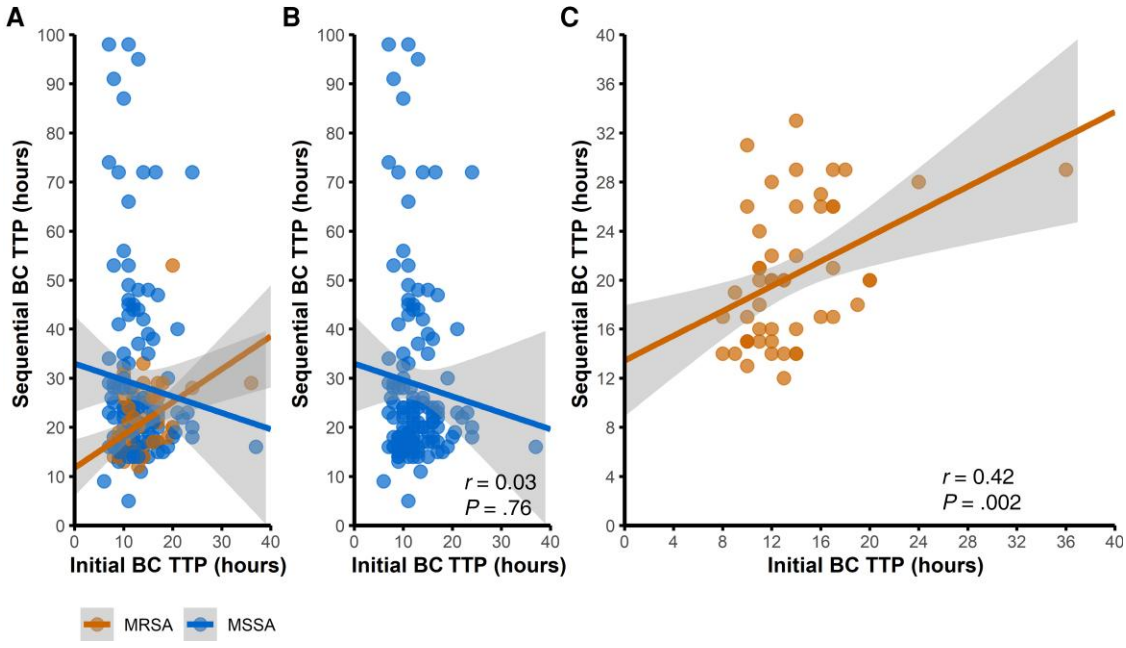

Figure 2. Correlation of time to positivity (TTP) between initial versus sequential blood cultures (BCs). The scatterplots illustrate the relationship between TTP in hours from initial BCs (x-axis) to sequential BCs (y-axis). *A*, Entire cohort. *B*, Methicillin-susceptible *Staphylococcus aureus* (MSSA) cohort, where no significant correlation was found (Spearman ρ = 0.03, $P = .76$). *C*, Methicillin-resistant *S aureus* (MRSA) cohort, revealing a moderate positive correlation (Spearman ρ = 0.42, $P = .002$). One influential point in (*C*), with a sequential TTP >50 h due to a delayed culture draw (72+ hours postinitial), was excluded to avoid overestimation of the correlation coefficient.

Table 1. Descriptive Characteristics of Study Cohort by Sequential Time to Positivity (TTP)/Initial TTP Ratio

Characteristic	STTP/ITTP ≤1.5 (n = 71)	STTP/ITTP >1.5 (n = 115)	Unadjusted Model			Adjusted Model[a]		
			OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
Age, y, mean ± SD	61.9 ± 17.0	64.6 ± 15.8	0.99	(.97–1.01)	.28	…	…	
Male sex	42 (59)	75 (65)	0.77	(.42–1.42)	.41	…	…	
BMI, kg/m^2, mean ± SD	28.4 ± 7.8	29.9 ± 7.1	0.97	(.93–1.01)	.20	…	…	
CCI score, mean ± SD	4.6 ± 3.0	5.5 ± 2.9	0.91	(.82–1.01)	.06	…	…	
Injection drug use	7 (10)	7 (6)	1.69	(.55–5.14)	.35	…	…	
Myocardial infarction	14 (20)	41 (36)	0.44	(.21–.87)	.02	0.50	(.21–1.10)	.09
CHF	20 (28)	43 (37)	0.66	(.34–1.23)	.20	…	…	
PVD	8 (11)	17 (15)	0.73	(.28–1.75)	.50	…	…	
CVA	7 (10)	15 (13)	0.73	(.26–1.83)	.51	…	…	
Dementia	3 (4)	6 (5)	…	…		…	…	
Liver disease	10 (14)	10 (9)	1.72	(.67–4.44)	.25	…	…	
Diabetes mellitus	20 (28)	32 (36.5)	0.68	(.35–1.28)	.24	…	…	
COPD	10 (14)	12 (10)	1.41	(.56–3.45)	.45	…	…	
Connective tissue disease	7 (10)	13 (11)	0.86	(.31–2.21)	.75	…	…	
Moderate to severe CKD	13 (18)	30 (26)	0.63	(.30–1.30)	.22	…	…	
Solid tumor	9 (13)	22 (19)	0.61	(.25–1.38)	.32	…	…	
Cardiac prosthetic device	9 (13)	30 (26)	0.41	(.17–.89)	.03	0.65	(.24–1.66)	.38
Prosthetic valve	5 (7)	10 (9)	0.83	(.24–2.34)	.69	…	…	
Permanent pacemaker	4 (6)	14 (12)	…	…		…	…	
AICD	1 (1)	8 (7)	…	…		…	…	
CRT	1 (1)	2 (2)	…	…		…	…	
VAD	1 (1)	2 (2)	…	…		…	…	
SAB within last 3 mo	7 (10)	5 (4)	2.41	(.74–8.42)	.15	…	…	

Data are presented as No. (%) unless otherwise indicated. Outcome labeling for logistic regression: "STTP/ITTP ≤1.5" = 1; "STTP/ITTP >1.5" = 0.

Abbreviations: AICD, automatic implantable cardioverter-defibrillator; BMI, body mass index; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CVA, cerebrovascular accident; ITTP, initial time to positivity; OR, odds ratio; PVD, peripheral vascular disease; SAB, *Staphylococcus aureus* bacteremia; SD, standard deviation; STTP, sequential time to positivity; VAD, ventricular assist device.

[a]All covariates that were statistically significant ($P < .05$) in univariate analysis (myocardial infarction, cardiac prosthetic device, high-grade bacteremia, native valve infective endocarditis), as well as methicillin-resistant/methicillin-susceptible *Staphylococcus aureus* status, were included in the adjusted model.

We then compared TTP metrics between patients with MRSA versus MSSA infection. ITTP did not differ based on MRSA/MSSA status (*t* test, $P = .24$). However, patients with MRSA infection had shorter STTP (*t* test, $P < .001$). Similarly, TTP ratio was significantly lower in the MRSA group (*t* test, $P < .001$). ITTP and STTP positively correlated in patients with MRSA infection (Spearman, $r = 0.42$, $P = .002$; Figure 2*C*). There were no differences in source control achievement between the MRSA and MSSA groups. Comparisons of clinical characteristics and disease outcomes between the MSSA and MRSA cohorts are presented in Supplementary Table 1. Overall, demographics and baseline comorbidities in the MRSA and MSSA cohorts were balanced. Patients with MSSA bacteremia had higher rates of high-grade bacteremia (Pearson χ^2, $P = .03$).

TTP Ratio and Clinical Characteristics

To investigate and validate the prognostic implications of the TTP ratio, we used a predefined cutoff value of 1.5. A TTP ratio of ≤1.5 correlated with lower rates of myocardial infarction at baseline (OR, 0.44 [95% CI, .21–.87]; $P = .02$) and cardiac prosthetic devices (OR, 0.41 [95% CI, .17–.89]; $P = .03$) (Table 1). Overall, 21% of the study cohort (n = 39) had at least 1 cardiac prosthetic device. In patients with a TTP ratio of ≤1.5, a bioprosthetic valve was the most common device (7% [n = 5]), whereas a permanent cardiac pacemaker was the most prevalent in the TTP ratio >1.5 group. Although patients with a TTP ratio of ≤1.5 tended to have a lower comorbidity score (OR, 0.91 [95% CI, .82–1.01]; $P = .06$), we did not see any significant correlation between the TTP ratio and other baseline clinical characteristics (Table 1).

TTP Ratio and SAB Outcomes

In adjusted analysis, native valve endocarditis (OR, 2.65 [95% CI, 1.3–5.6]; $P = .01$; Table 2), and high-grade bacteremia (OR, 0.3 [95% CI, .1–.7]; $P = .008$) (Table 2) were significant predictors of TTP ratio groups independent of MRSA/MSSA status, myocardial infarction, or cardiac prosthetic device. We then classified patients into 4 groups based on a flowchart using an ITTP cutoff of 12 hours, followed by a TTP ratio cutoff of 1.5 (Supplementary Figure 2). Significant differences were observed in native valve endocarditis proportions among these 4 groups (Pearson χ^2, $P = .02$). Notably, the group with an ITTP <12 hours and TTP ratio ≤1.5 exhibited the highest native valve endocarditis rates.

Table 2. *Staphylococcus aureus* Bacteremia Disease Characteristics and Outcomes of Study Population by Sequential Time to Positivity (TTP)/Initial TTP Ratio

Characteristic[a]	STTP/ITTP ≤1.5 (n = 71)	STTP/ITTP >1.5 (n = 115)	Unadjusted Model			Adjusted Model[b]		
			OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
MRSA	22 (31)	29 (25)	0.75	(.39–1.45)	.39	0.82	(.39–1.74)	.60
Vancomycin MIC ≥2 μg/mL	18 (25)	17 (15)	1.96	(.93–4.14)	.08	…	…	
Acquisition								
Community	32 (45)	46 (40)	…	Reference		…	…	
Healthcare-associated	37 (52)	60 (52)	0.89	(.48–1.63)	.70	…	…	
Nosocomial	2 (3)	9 (8)	0.32	(.05–1.34)	.16	…	…	
Ward								
General medicine floor	30 (42)	56 (49)	…	Reference		…	…	
PCU/telemetry	16 (23)	16 (14)	1.87	(.82–4.29)	.14	…	…	
ICU	25 (35)	43 (37)	1.08	(.56–2.11)	.81	…	…	
Duration of symptoms >7 d	33 (46.5)	57 (49.6)	0.88	(.49–1.60)	.7	…	…	
Daily blood cultures	64 (90)	104 (90)	0.97	(.36–2.75)	.95	…	…	
Duration of BSI, d, mean ± SD	4.4 ± 2.5	4.0 ± 2.5	1.06	(.95–1.20)	.29	…	…	
High-grade bacteremia	56 (79)	106 (92)	0.32	(.12–.76)	.01	0.27	(.10–.70)	.008
PREDICT score day 1, mean ± SD	1.6 ± 0.9	1.9 ± 1.1	0.78	(.57–1.04)	.10	…	…	
PREDICT score day 5, mean ± SD	2.8 ± 1.2	3.0 ± 1.5	0.88	(.71–1.09)	.24	…	…	
Complicated BSI	63 (89)	102 (89)	1.04	(.40–2.66)	.99	…	…	
Infective endocarditis	24 (36)	30 (27)	1.53	(.79–2.93)	.20	…	…	
Native valve	23 (34)	19 (17)	2.56	(1.27–5.23)	.009	2.65	(1.26–5.63)	.01
Prosthetic valve	1 (1.5)	11 (10)	…	…		…	…	
Osteomyelitis	18 (25)	22 (19)	1.43	(.70–2.91)	.32	…	…	
Persistent BSI	42 (59)	68 (59)	1.00	(.55–1.83)	.99	…	…	
Septic emboli	11 (15)	16 (14)	1.13	(.48–2.59)	.76	…	…	
Intravascular device	20 (28)	35 (30)	0.90	(.46–1.71)	.74	…	…	
Source control achieved	36 (51)	61 (53)	0.91	(.50–1.65)	.76	…	…	
Hospice	13 (19)	25 (22)	0.81	(.38–1.70)	.58	…	…	
Total antibiotic duration, mean ± SD	41.9 ± 25.2	39.8 ± 32.1	1.00	(.99–1.01)	.63	…	…	
Duration of hospital stay, d, mean ± SD	16.4 ± 10.3	15.4 ± 13.5	1.01	(.98–1.03)	.58	…	…	

Data are presented as No. (%) unless otherwise indicated. Outcome labeling for logistic regression: "STTP/ITTP ≤1.5" = 1; "STTP/ITTP >1.5" = 0.

Abbreviations: BSI, bloodstream infection; CI, confidence interval; ICU, intensive care unit; ITTP, initial time to positivity; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PCU, progressive care unit; PREDICT, predicting risk of endocarditis using a clinical tool; OR, odds ratio; SD, standard deviation; STTP, sequential time to positivity.

[a]One patient has missing duration of BSI and 2 patients have missing hospice status.

[b]All covariates that were statistically significant ($P < .05$) in univariate analysis (myocardial infarction, cardiac prosthetic device, high-grade bacteremia, native valve infective endocarditis), as well as MRSA/methicillin-susceptible *S aureus* status, were included in the adjusted model.

In this cohort, the in-hospital, 30-day, and 365-day all-cause mortality rates were 15%, 18%, and 42%, respectively. The Kaplan-Meier analysis of 30-day survival demonstrated that patients with an ITTP <12 hours had lower survival rates than those with ITTP ≥12 hours (log-rank test, $P = .04$; Figure 3*A*). However, no significant association was observed between the TTP ratio cutoff 1.5 and 30-day survival (Figure 3*B*).

DISCUSSION

In this observational study of 186 SAB patients, we assessed prognostic relevance of the TTP from sequential blood cultures. Major findings of the study revealed that STTP values vary based on the methicillin susceptibility of the *S aureus* isolate and should be interpreted cautiously. Although ITTP did not differ based on methicillin resistance, MRSA-infected patients exhibited significantly shorter STTPs and a lower TTP ratio than MSSA cases. Interestingly, while no correlation was observed between the TTP of initial and sequential blood cultures in MSSA isolates, a significant correlation was evident in MRSA isolates. These findings suggest that patients with MRSA infection experience a slower response to treatment. This may be due to several factors, including differences in the patient population, treatment with vancomycin, which is considered inferior to β-lactam therapy and associated with longer durations of bacteremia [26], and higher minimum inhibitory concentrations (MICs) to vancomycin, as the MRSA isolates in our cohort were twice as likely to have an MIC to vancomycin of ≥2 μg/mL compared to MSSA (15% vs 29%, respectively). This may have affected their growth kinetics on sequential blood cultures and resulted in lower STTP and TTP ratio. While antibiotics often reduce bacterial growth, the mechanisms in gram-positive isolates are less elucidated [27, 28].

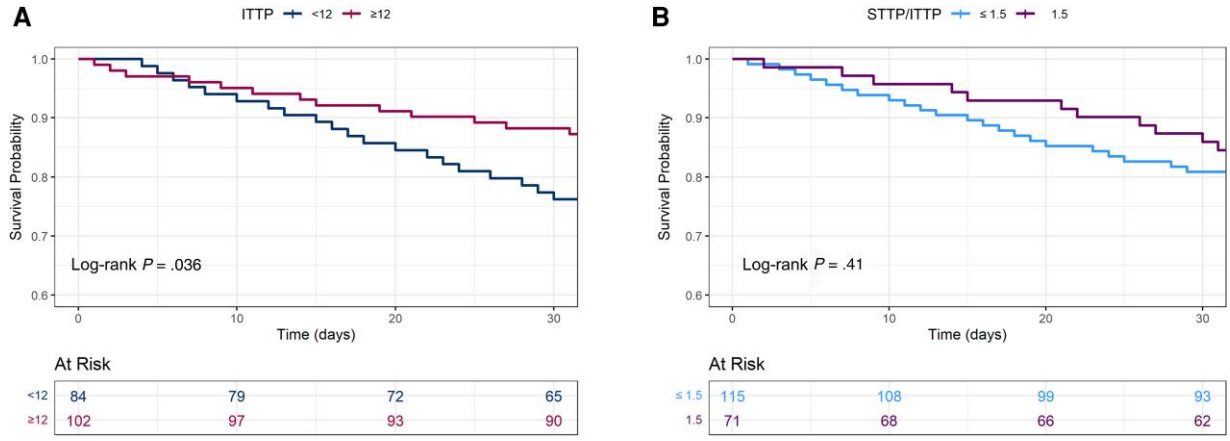

Figure 3. Kaplan-Meier curves for 30-day survival based on initial time to positivity (ITTP) and time to positivity (TTP) ratio groups using designated cutoff values. Plots display 30-day Kaplan-Meier survival curves between ITTP of <12 vs ≥12 h (*A*) and TTP ratio ≤1.5 vs >1.5 (*B*). Log-rank test *P* values are presented. Abbreviations: ITTP, initial time to positivity; STTP, sequential time to positivity.

The role of antibiotic type and timing on TTP, though crucial, remains an area needing further exploration.

Previous studies have demonstrated that a shorter ITTP correlates with an increased mortality [4, 5, 7]. Similarly, our study reveals a clear association between a shorter ITTP and higher 30-day mortality. Regarding the TTP ratio and mortality, Hsu et al studied a cohort of 87 SAB patients persisting for >48 hours, revealing a 40% in-hospital mortality rate. A TTP ratio <1.5 was an independent risk factor for mortality [11]. In another report involving 41 patients with persistent SAB, failure to observe a decrease in STTP postintervention correlated with higher rates of secondary foci of infection and 30-day mortality [29]. In contrast, the TTP ratio did not predict 30-day all-cause mortality in our study, which could be due to differences between study cohorts, underscoring the variability in TTP metrics that can be attributed to other clinical factors.

Regarding TTP and IE, Kahn et al [9] examined a cutoff value of 13 hours for the ITTP as a predictor of IE, demonstrating a sensitivity of 100% (95% CI, 91%–100%) and specificity of 52% (95% CI, 47%–57%). In our study, there was a significant association between a TTP ratio of ≤1.5 and native valve endocarditis. This relationship persisted regardless of MRSA/MSSA status and was evident after stratifying for ITTP groups with a 12-hour cutoff. Overall, current study findings support the potential utility of STTP-related indices in identifying patients at risk of developing native valve endocarditis.

In this observational study, which achieved a 96% echocardiography compliance rate, 54 cases of IE were identified among 186 patients with SAB. This represents the highest rate among observational SAB studies, providing a robust outcome investigation. The high compliance rate can be in part due to inherent cohort characteristics with persistent bacteremia. As the largest-scale investigation to date examining the clinical significance of STTP, the current study underscores the need for careful interpretation of these metrics, especially given the observed variability tied to bacterial methicillin resistance. The study results also emphasize the complexity of applying these metrics in clinical settings.

Our study has several limitations. Given the retrospective nature, we could not control or adjust for multiple potential confounders, including source control timing, antimicrobial selection, dose and administration schedules, and blood inoculation-to-incubation transport time. Additionally, the blood collection was not monitored, and the exact blood volume per bottle may impact TTP. The study specifically focused on SAB patients with positive follow-up blood cultures. Consequently, the applicability of our findings to patients without positive follow-up cultures remains uncertain. Last, the current study evaluated the TTP ratio of 1.5, a threshold based on previous research, despite its small sample size foundation. We highlighted the challenges of applying this ratio in clinical contexts, affected by *S aureus* susceptibility and patient characteristics. The findings advocate for future research to incorporate mathematical models merging microbiological, clinical, and pharmacokinetic/pharmacodynamic insights to refine the TTP ratio's predictive value in patient care and therapeutic decision-making.

CONCLUSIONS

The TTP from sequential blood cultures and the TTP ratio of sequential blood cultures to initial blood cultures vary based on *S aureus* isolates' methicillin susceptibility and should be interpreted cautiously. This study suggests a potential clinical utility of the TTP ratio in patients with SAB to identify those

at a higher risk of native valve endocarditis. However, prospective studies are needed to validate the study results.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Patient consent. The study was reviewed by the Mayo Clinic Institutional Review Board and was granted an exemption (IRB #19–005199). Patients who declined authorization to use their medical records for research purposes were excluded from the study.

Potential conflicts of interest. All authors: No reported conflict.

References

1. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in *Staphylococcus aureus* bacteremia. Clin Microbiol Rev **2012**; 25:362–86.
2. Mylotte JM, Tayara A. *Staphylococcus aureus* bacteremia: predictors of 30-day mortality in a large cohort. Clin Infect Dis **2000**; 31:1170–4.
3. Blot F, Schmidt E, Nitenberg G, et al. Earlier positivity of central-venous versus peripheral-blood cultures is highly predictive of catheter-related sepsis. J Clin Microbiol **1998**; 36:105–9.
4. Khatib R, Riederer K, Saeed S, et al. Time to positivity in *Staphylococcus aureus* bacteremia: possible correlation with the source and outcome of infection. Clin Infect Dis **2005**; 41:594–8.
5. Marra AR, Edmond MB, Forbes BA, Wenzel RP, Bearman GM. Time to blood culture positivity as a predictor of clinical outcome of *Staphylococcus aureus* bloodstream infection. J Clin Microbiol **2006**; 44:1342–6.
6. Sowden D, Anstey C, Faddy M. Blood culture time to positivity as a predictor of mortality in community acquired methicillin-susceptible *Staphylococcus aureus* bacteremia. J Infect **2008**; 56:295–6.
7. Kim J, Gregson DB, Ross T, Laupland KB. Time to blood culture positivity in *Staphylococcus aureus* bacteremia: association with 30-day mortality. J Infect **2010**; 61:197–204.
8. Fida M, Saleh OA, Baddour LM, et al. Re: 'Time to blood culture positivity in *Staphylococcus aureus* bacteraemia to determine risk of infective endocarditis' by Kahn et al. Clin Microbiol Infect **2021**; 27:1365–6.
9. Kahn F, Resman F, Bergmark S, et al. Time to blood culture positivity in *Staphylococcus aureus* bacteraemia to determine risk of infective endocarditis. Clin Microbiol Infect **2021**; 27:1345.e7–12.
10. Simeon S, Le Moing V, Tubiana S, et al. Time to blood culture positivity: an independent predictor of infective endocarditis and mortality in patients with *Staphylococcus aureus* bacteraemia. Clin Microbiol Infect **2019**; 25:481–8.
11. Hsu MS, Huang YT, Hsu HS, Liao CH. Sequential time to positivity of blood cultures can be a predictor of prognosis of patients with persistent *Staphylococcus aureus* bacteraemia. Clin Microbiol Infect **2014**; 20:892–8.
12. American Society for Microbiology. Predictive value of blood culture time to positivity. **2018**. Available at: https://asm.org/Articles/2018/November/Predictive-Value-of-Blood-Culture-Time-to-Positivi. Accessed 19 September 2023.
13. Lamy B. Blood culture time-to-positivity: making use of the hidden information. Clin Microbiol Infect **2019**; 25:268–71.
14. Clinical and Laboratory Standards Institute (CLSI). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 11th ed. CLSI standard M07. Wayne, PA: CLSI, **2018**.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
16. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med **2002**; 137:791–7.
17. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **2000**; 30:633–8.
18. Abu Saleh O, Fida M, Asbury K, et al. Prospective validation of PREDICT and its impact on the transesophageal echocardiography use in management of *Staphylococcus aureus* bacteremia. Clin Infect Dis **2021**; 73:e1745–53.
19. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. Clin Infect Dis **2011**; 52:285–92.
20. Tai DBG, Go JR, Fida M, Saleh OA. Management and treatment of *Aerococcus* bacteremia and endocarditis. Int J Infect Dis **2021**; 102:584–9.
21. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, **2023**.
22. Enzmann D, Schwartz M, Jain N, Kraft S. **2023**. descr: Descriptive statistics. R package version 1.1.7. Available at: https://CRAN.R-project.org/package=descr. Accessed 24 November 2023.
23. Kassambara A, Kosinski M, Biecek P. **2021**. survminer: Drawing survival curves using 'ggplot2'. R package version 0.4.9. Available at: https://CRAN.R-project.org/package=survminer. Accessed 24 November 2023.
24. Wickham H. Ggplot2: elegant graphics for data analysis. New York: Springer-Verlag; **2016**.
25. Therneau T. A package for survival analysis in R. R package version 3.5-5. 2023. Available at: https://CRAN.R-project.org/package=survival. Accessed 24 November 2023.
26. Wong D, Wong T, Romney M, Leung V. Comparative effectiveness of β-lactam versus vancomycin empiric therapy in patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia. Ann Clin Microbiol Antimicrob **2016**; 15:27.
27. Scheer CS, Fuchs C, Gründling M, et al. Impact of antibiotic administration on blood culture positivity at the beginning of sepsis: a prospective clinical cohort study. Clin Microbiol Infect **2019**; 25:326–31.
28. Rand KH, Beal SG, Rivera K, Allen B, Payton T, Lipori GP. Hourly effect of pretreatment with IV antibiotics on blood culture positivity rate in emergency department patients. Open Forum Infect Dis **2019**; 6:ofz179.
29. Choi SH, Chung JW. Time to positivity of follow-up blood cultures in patients with persistent *Staphylococcus aureus* bacteremia. Eur J Clin Microbiol Infect Dis **2012**; 31:2963–7.