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Original Article

Time to positivity for differentiating blood culture contamination: A 20-hour cutoff for major contaminants

Yohei Manabe [a], Hideharu Hagiya [b,*], Shinnosuke Fukushima [b], Kenta Nakamoto [b], Kohei Oguni [b], Hidemasa Akazawa [b], Yasushi Fujita [c], Takashi Kiguchi [c], Koji Iio [d]

[a] Department of Pharmacy, Okayama University Hospital, Okayama, Japan
[b] Department of Infectious Diseases, Okayama University Hospital, Okayama, Japan
[c] Department of Nursing, Okayama University Hospital, Okayama, Japan
[d] Microbiology Division, Clinical Laboratory, Okayama University Hospital, Okayama, Japan

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ABSTRACT

Background: Blood culture remains the gold standard for diagnosing bacteremia; however, contamination inevitably occurs in 2-3% of cases, requiring differentiation between true bacteremia and contamination. Although time to positivity (TTP) aids in this clinical decision, with detection after 24 hours generally indicating contamination, technological advances in blood culture systems may have shortened this threshold interval.
Methods: This study retrospectively analyzed blood culture data in our hospital from April 2023 to January 2025 to determine the optimal TTP cutoff. Patients with positive blood cultures for major contaminating bacteria were included. Cases were classified as true bacteremia or contamination based on a comprehensive chart review conducted by the antimicrobial stewardship audit, and TTP was compared between the groups. Sensitivity, specificity, and Youden index at various TTP cutoffs were utilized to determine the optimal threshold using the receiver operating characteristic curve analysis.
Results: Seventy-one patients were enrolled, with 34 cases classified as true bacteremia and 37 as contamination. Identified bacteria included coagulase-negative staphylococci (70.4%), viridans group streptococci (18.3%), and others (11.3%). The median TTP was significantly shorter in the true bacteremia group compared with the contamination group (18.6 vs.25.8 hours, $p < 0.001$). In the contamination group, 43.2% of the cases demonstrated positive growth within 24 hours. Based on sensitivity, specificity, and Youden index, the optimal threshold was estimated to be 20 hours. A subgroup analysis of the CNS-only cohort yielded concordant results.
Conclusion: This study suggests that a 20-hour TTP threshold could help effectively differentiate true bacteremia from contamination in current clinical settings.

1. Introduction

Blood culture is a fundamental diagnostic tool for patients suspected of bacteremia, providing crucial data that enables the identification of pathogenic organisms and guiding the administration of appropriate antimicrobial therapy [1]. Blood is inherently sterile, and all the detected isolates should be regarded as infectious bacteria. However, in real clinical settings, blood contamination can occur [2], with a generally observed rate of 2-3% [3], requiring the determination of true bacteremia and contamination. Blood culture contamination is possibly associated with several factors such as skin flora contamination, improper sampling techniques, and low compliance with hand hygiene. Decreasing the contamination is significantly important because it can lead to unnecessary treatments, prolonged hospital stays, and increased healthcare costs [4]. Also, the overuse of antibiotics associated with the false-positive blood culture results heightens the risk of adverse effects,

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* Corresponding author at: Hideharu Hagiya, M.D., Ph.D., Department of Infectious Diseases, Okayama University Hospital, Okayama, Japan, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.
E-mail addresses: ph20033@s.okayama-u.ac.jp (Y. Manabe), hagiya@okayama-u.ac.jp (H. Hagiya).

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including allergic reactions, *Clostridioides difficile* infection, and the emergence of antimicrobial resistance [5]. Thus, stringent measures to prevent blood culture contamination are essential.

The evaluation of blood culture results is critically important. Time to positivity (TTP), which is generally defined as the time difference between either the blood culture sampling or the initiation of incubation and the first identification of bacteria growth [6], aids in differentiating true bacteremia from contamination. Multiple microbiological and technical factors potentially influence TTP, including preceding administration of antimicrobials, heterogeneity of organisms, bacterial inoculum volume, and blood culturing systems used [1,7,8]. A cutoff threshold of >24 hours is generally applied as an indicator of contamination, and clinicians rely on this standard norm to determine treatment indication.

With advancements in blood culture systems, we hypothesize that the cutoff TTP for identifying blood culture contamination may have shortened. This study aimed to analyze our hospital data to propose an updated TTP cutoff, promoting more judicious use of antibiotics.

2. Methods

2.1. Study Design and Patient Eligibility

This single-center retrospective study was conducted at Okayama University Hospital, where we reviewed medical records of patients with positive blood cultures from April 1, 2023, to January 31, 2025. The study included patients who tested positive for common contamination-associated bacterial species, including coagulase-negative staphylococci (CNS), *Cutibacterium acnes, Micrococcus* spp., viridans group streptococci, *Corynebacterium* spp., and *Bacillus* spp. [3,9–12]. Patients were excluded if they met any of the following criteria: (i) age under 18 years, (ii) presence of multiple microorganisms species in the blood culture, (iii) administration of any antibiotic within 2 days prior to the blood culture testing date, or (iv) cases undeterminable as true bacteremia or contamination due to any reason such as transfer or discharge before antimicrobial stewardship team intervention. We extracted patient and treatment information from medical records, including age, gender, diagnosis, antimicrobial use, blood culture test date, TTP, detected bacterial species in blood culture, number of positive blood culture sets, any antimicrobial use before 2 days preceding the test date, and antimicrobial stewardship team's conference records regarding treatment strategies for blood culture-positive patients.

2.2. Microbiologic Methods

Blood culture samples were collected according to the standard protocols of our university hospital. Drawing two sets of blood cultures, with each bottle typically containing 8–10 mL of blood, is highly recommended. A "set" refers to a pair of aerobic and anaerobic bottles collected from a single venipuncture, and a "positive set" means that either one or both bottles in that set yielded positive culture results. In our facility, we use BD BACTEC™ Plus Aerobic/F and Anaerobic/F culture vials (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), which are processed using the BACTEC™ FX system—a fully automated instrument—immediately after submission to the microbiology division. During off-hours, the blood culture incubation starts with using BACTEC™ FX40 system. When blood cultures turned positive, bacterial identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI Biotyper, Bruker Daltonics, Bremen, Germany).

2.3. Determination of True Bacteremia or Contamination

True bacteremia or contamination was determined based on the antimicrobial stewardship team's conference records for each blood culture-positive patient. At our hospital, the antimicrobial stewardship team provides therapeutic recommendations for all blood culture-positive patients, documenting diagnoses and treatment strategies in the medical record. This multidisciplinary team, which includes infectious disease physicians, routinely evaluates the likelihood of contamination for each positive blood culture by considering factors such as the patient's clinical history, vital signs, laboratory data, number of positive blood culture bottles, culture results from other sites, imaging findings, and clinical course. Contamination was defined as cases in which the detected bacteria were classified as contaminants by the antimicrobial stewardship team, and no targeted antimicrobial therapy was initiated.

2.4. Definition and Analysis of TTP

TTP was defined as the shortest time to positivity among blood culture bottles when multiple bottles were positive. In this study, we calculated the median, interquartile range, maximum, and minimum of TTP values for both the true bacteremia and contamination groups. These values were plotted in box plots, and violin plots were used to visualize and compare the distribution density of TTP in each group. In the contamination group, the bacterial species detected and their proportion with TTP shorter than 24 hours were also analyzed.

In addition, we calculated the sensitivity and specificity at various TTP thresholds to distinguish between the true bacteremia and contamination groups. Based on these calculations, we drew the receiver operating characteristic (ROC) curve, with TTP as the independent variable and bacteremia/contamination as the dependent variable. To identify the optimal TTP cutoff value, we calculated the TTP value that maximized the sum of sensitivity and specificity, known as the Youden index, and defined this TTP as the optimal cutoff value. In a subgroup analysis focused on CNS—the most frequently detected contaminant—we performed the same analysis to determine the optimal cutoff value specifically for CNS-positive blood cultures.

2.5. Statistical analyses

Statistical analysis was performed between true bacteremia group and contamination group for each factor in the patient characteristics and TTP. Binary variables were evaluated with the Fisher's exact test. Continuous variables were analyzed using the Mann-Whitney U test. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and RStudio (RStudio, PBC, Boston, MA, USA), a graphical user interface for R (R Foundation for Statistical Computing version 4.4.1; Vienna, Austria) [13]. Statistical significance was set at two-sided p-values <0.05 for all analyses.

2.6. Ethics statement

Patient data were anonymized to avoid identification. Informed consent was obtained in an opt-out approach because this was a retrospective study. The research protocol was reviewed and approved by the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital Ethics Committee (K2412-014).

3. Results

3.1. Patients and isolated bacterial species

During the study period, the total number of patients with positive blood cultures was 816. Among them, we identified 248 blood culture-positive patients with major contaminating bacteria defined in the methodology section of the present study, including CNS, *Cutibacterium acnes, Micrococcus* spp., viridans group streptococci, *Corynebacterium* spp., and *Bacillus* spp., and consequently enrolled 71 patients based on eligibility assessment (Fig. 1). Of these, 34 patients were diagnosed with true bacteremia, while 37 were deemed to have positive cultures due to

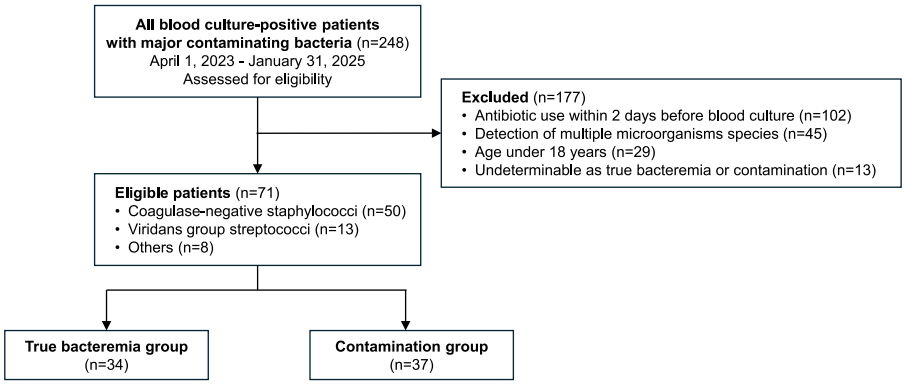

Fig. 1. Study Flowchart
The Fig. represents the flowchart diagram of patient selection.

contamination. The characteristics of all patients enrolled and those in each group are shown in Table 1. Of the 50 patients with only one set of positive blood cultures (including 1/1 set, 1/2 set, and 1/3 set), 37 (74.0%) were identified as contamination, while 13 (26.0%) were determined to be true bacteremia. All patients with multiple sets of positive blood culture were deemed as true bacteremia. Overall, CNS was detected in 50 patients (70.4%), making it the most frequently identified bacterial species. Viridans group streptococci was more frequently observed in the true bacteremia group, while other species such as *Cutibacterium acnes, Bacillus* spp., and *Corynebacterium* spp. were detected only in the contamination group. Next, patient characteristics in cases with CNS are shown in Table 2. In this cohort, although age tended to be higher in the contamination group, the distribution of gender and the number of positive blood culture sets in this cohort was similar to those observed in the all patient cohort. *Staphylococcus epidermidis* was detected in 56%, the most common of the CNS isolates.

Table 1
Clinical and microbiological characteristics in all patients.

	Overall	True bacteremia	Contamination	*p*-value
	n = 71	*n* = 34	*n* = 37	
Median age (IQR)	69 (57.5-78)	65 (53.25-75.75)	73 (59-79)	0.078
Gender (%)				0.807
Male	44 (62.0)	22 (64.7)	22 (59.5)	
Female	27 (38.0)	12 (35.3)	15 (40.5)	
Number of positive culture sets (%)				
1/1 set	9 (12.7)	4 (11.8)	5 (13.5)	
1/2 set	39 (54.9)	9 (26.5)	30 (81.1)	
1/3 set	2 (2.8)	0 (0)	2 (5.4)	
2/2 sets	21 (29.6)	21 (61.8)	0 (0)	
Bacterial species (%)				
Coagulase-negative staphylococci	50 (70.4)	23 (67.6)	27 (73.0)	
Staphylococcus epidermidis	28 (39.4)	15 (44.1)	13 (35.1)	
Staphylococcus capitis	10 (14.1)	3 (8.8)	7 (18.9)	
Staphylococcus hominis	5 (7.0)	1 (2.9)	4 (10.8)	
Staphylococcus caprae	3 (4.2)	1 (2.9)	2 (5.4)	
Staphylococcus lugdunensis	2 (2.8)	2 (5.9)	0 (0)	
Staphylococcus haemolyticus	1 (1.4)	1 (2.9)	0 (0)	
Staphylococcus simulans	1 (1.4)	0 (0)	1 (2.7)	
Viridans group streptococci	13 (18.3)	11 (32.4)	2 (5.4)	
Streptococcus anginosus	5 (7.0)	5 (14.7)	0 (0)	
Streptococcus constellatus	3 (4.2)	1 (2.9)	2 (5.4)	
Streptococcus oralis	2 (2.8)	2 (5.9)	0 (0)	
Streptococcus intermedius	1 (1.4)	1 (2.9)	0 (0)	
Streptococcus mitis/oralis	1 (1.4)	1 (2.9)	0 (0)	
Streptococcus sanguinis	1 (1.4)	1 (2.9)	0 (0)	
Others	8 (11.3)	0 (0)	8 (21.6)	
Cutibacterium acnes	3 (4.2)	0 (0)	3 (8.1)	
Bacillus subtilis	2 (2.8)	0 (0)	2 (5.4)	
Bacillus cereus	1 (1.4)	0 (0)	1 (2.7)	
Corynebacterium aurimucosum	1 (1.4)	0 (0)	1 (2.7)	
Corynebacterium striatum	1 (1.4)	0 (0)	1 (2.7)	

IQR, interquartile range.

Table 2
Clinical and microbiological characteristics in patients detected coagulase-negative staphylococci.

	Overall	True bacteremia	Contamination	*p*-value
	n = 50	*n* = 23	*n* = 27	
Median Age (IQR)	66 (55-78)	59 (47-70)	76 (58.5-79)	0.012*
Gender (%)				0.774
Male	30 (60.0)	13 (56.5)	17 (63.0)	
Female	20 (40.0)	10 (43.5)	10 (37.0)	
Number of positive culture sets (%)				
1/1 set	5 (10.0)	2 (8.7)	3 (11.1)	
1/2 set	28 (56.0)	6 (26.1)	22 (81.5)	
1/3 set	2 (4.0)	0 (0)	2 (7.4)	
2/2 sets	15 (30.0)	15 (65.2)	0 (0)	
Bacterial species (%)				
Staphylococcus epidermidis	28 (56.0)	15 (65.2)	13 (48.1)	
Staphylococcus capitis	10 (20.0)	3 (13.0)	7 (25.9)	
Staphylococcus hominis	5 (10.0)	1 (4.3)	4 (14.8)	
Staphylococcus caprae	3 (6.0)	1 (4.3)	2 (7.4)	
Staphylococcus lugdunensis	2 (4.0)	2 (8.7)	0 (0)	
Staphylococcus haemolyticus	1 (2.0)	1 (4.3)	0 (0)	
Staphylococcus simulans	1 (2.0)	0 (0)	1 (3.7)	

IQR, interquartile range. *A two-sided *p*-value <0.05 was considered statistically significant.

3.2. Comparison of TTP between the true bacteremia group and contamination group

Both in all patient cohort and in CNS-only cohort, the distribution of TTP was generally shorter in the true bacteremia group compared to the contamination group (Fig. 2). The median TTP in the true bacteremia group was significantly shorter than that in the contamination group (18.6 and 25.8 hours, respectively, $p < 0.001$; Table 3). However, the minimum TTP was 9.6 hours in both groups. The proportion of cases being positive <24 hours in the contamination group was 43.2 % (16/37 cases). Bacterial species in such cases included *Staphylococcus epidermidis* (37.5%), *Staphylococcus capitis* (25.0%), *Staphylococcus caprae* (6.3%), *Staphylococcus hominis* (6.3%), *Streptococcus constellatus* (6.3%), *Bacillus cereus* (6.3%), *Bacillus subtilis* (6.3%), and *Corynebacterium striatum* (6.3%). Similarly, in CNS cases, the median TTP in the true bacteremia group was significantly shorter than that in the contamination group (17.6 and 25.1 hours, respectively, $p < 0.001$; Table 3). The proportion of cases being positive <24 hours in the contamination group was 44.4% (12/27 cases). Bacterial species in such cases included *Staphylococcus epidermidis* (50.0%), *Staphylococcus capitis* (33.3%), *Staphylococcus caprae* (8.3%), and *Staphylococcus hominis* (8.3%).

Table 3
Comparison of the time to positivity (TTP) between true bacteremia and contamination group.

All cases	Overall	True bacteremia	Contamination	*p*-value
	$n = 71$	$n = 34$	$n = 37$	
Median TTP, hours (IQR)	22.1 (17.9-36.3)	18.6 (16.5-24.2)	25.8 (21.4-49.7)	<0.001*
Minimum	9.6	9.6	9.6	
Maximum	151.9	74.4	151.9	
Coagulase-negative staphylococci	Overall	True bacteremia	Contamination	*p*-value
	$n = 50$	$n = 23$	$n = 27$	
Median TTP, hours (IQR)	21.4 (17.6-30.1)	17.6 (16.5-21.3)	25.1 (21.3-39.6)	<0.001*
Minimum	9.6	9.6	16.6	
Maximum	84.7	39.5	84.7	

IQR, interquartile range. *A two-sided *p*-value <0.05 was considered statistically significant.

3.3. Sensitivity and specificity analysis

The ROC curves with TTP as the independent variable and presence or absence of contamination as the dependent variable are shown in Fig. 3. TTP above the cutoff was defined as the presence of contamination. In all patients, the Youden index was at a TTP of 20.7 hours, with sensitivity and specificity of 0.811 and 0.676, respectively (Fig. 3**A**). The area under the ROC curve was 0.770 (95% confidence intervals, 0.659-0.881). In patients with CNS, the Youden index was at a TTP of 19.9 hours, with sensitivity and specificity of 0.852 and 0.696, respectively (Fig. 3**B**). The area under the ROC curve was 0.808 (95% confidence intervals, 0.687-0.930).

3.4. Cutoff value for TTP to determine the blood culture contamination

Based on the present results, the sensitivity, specificity, and the sum of these values of the cutoff TTP were examined from 18 to 26 hours in 2-hour increments (Table 4). Both in all patient cohort and in patients with CNS, the sum of sensitivity and specificity was highest at a cutoff TTP of 20 hours, suggesting that the blood culture duration of 20 hours can be defined as an ideal cutoff TTP for differentiating the true bacteremia and contamination. Moreover, because a substantial number of cases represented contamination within 24 hours, the sensitivity for detecting contamination was higher when the cutoff TTP was 20 hours rather than 24 hours, the conventional threshold.

4. Discussion

In this study, we identified the optimal threshold for TTP to distinguish true bacteremia from contamination in the patients with major contaminating bacteria. Our data suggests that a 20-hour threshold is a clinically-applicable cutoff TTP both in the overall cases and the CNS subgroup. When identifying contamination, however, multiple factors such as the number of positive blood culture sets, clinical manifestations, laboratory data, and preceding administration of antimicrobials should also be taken into account.

Several studies have investigated TTP as the indicator for distinguishing true bacteremia from contamination. A retrospective, single-center study in Spain between 2011 and 2013 analyzed TTP across all bacterial and fungal species detected in blood cultures and reported that the TTP of less than 12 hours indicated true bacteremia (sensitivity: 45.3%, specificity: 95%) [14]. Similarly, another retrospective study using database of private clinical

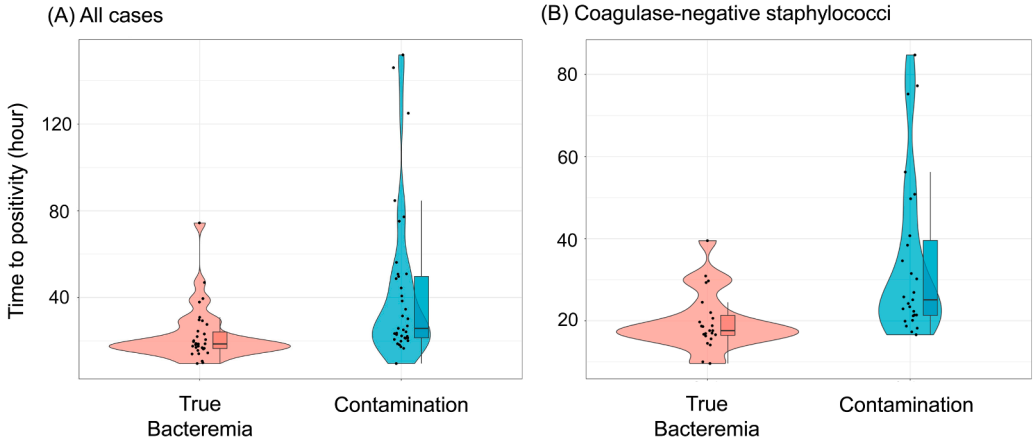

Fig. 2. Distribution of Time to Positivity in the True Bacteremia and Contamination Groups
The plots illustrate the distribution of time to positivity (TTP) in the true bacteremia group and contamination group in (A) all patients and (B) patients with coagulase-negative staphylococci. Strip plots represent the TTP of each sample and violin plots depict the distribution density of TTP in the true bacteremia group (pink) and contamination group (light blue). Within each box plot, horizontal bold lines denote the median values; boxes denote the interquartile range of each group; vertical extending lines denote the maximum and minimum values excluding outliers.

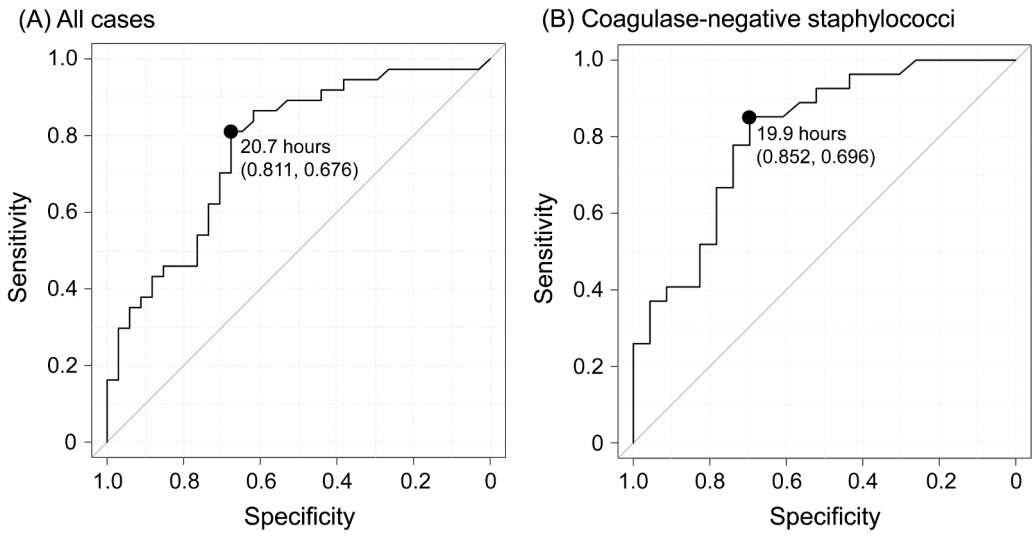

Fig. 3. Sensitivity and Specificity at Each Time to Positivity Cutoff
The receiver operating characteristic (ROC) curves illustrate sensitivity and specificity for different time to positivity (TTP) cutoff values in (A) all patients and (B) patients with coagulase-negative staphylococci. TTP above the cutoff is defined as contamination. Black circle markers on each curve indicate the point where the sum of sensitivity and specificity is maximized, known as the Youden index, and values beside markers represent the cutoff TTP along with the corresponding sensitivity and specificity.

Table 4
Sensitivity and specificity at each cutoff time to positivity (TTP).

All cases			
Cutoff TTP	Sensitivity	Specificity	Sum
18 hours	0.919	0.382	1.301
20 hours	0.865	0.618	1.483
22 hours	0.703	0.676	1.379
24 hours	0.595	0.735	1.330
26 hours	0.514	0.765	1.278
Coagulase-negative staphylococci			
Cutoff TTP	Sensitivity	Specificity	Sum
18 hours	0.926	0.435	1.361
20 hours	0.852	0.696	1.548
22 hours	0.667	0.739	1.406
24 hours	0.593	0.783	1.375
26 hours	0.481	0.826	1.308

laboratory in Peru between 2016 and 2021 included all bacterial and fungal species and proposed that the TTP of more than 16.5 hours indicated contamination (sensitivity: 85%, specificity: 63%) [15]. However, direct comparisons between these findings and those of the present study are not feasible due to methodological differences such as contamination determination methods, blood culture systems, and presence or absence of prior antibiotic administration. Furthermore, the most notable difference from our study is the microorganisms species analyzed. Growth rates vary by species; for example, *Streptococcus pneumoniae, Enterococcus faecalis*, and *Escherichia coli* exhibit rapid growth, whereas CNS grow at a moderate rate, and *Corynebacterium* spp., anaerobes, and yeasts, including *Candida* spp., have slow growth rates [14–16]. Consequently, the microorganisms included in a study can influence overall TTP values and affect the interpretation of results. However, in real-world clinical practice, contamination is a concern for only a limited number of bacterial species and specific clinical scenarios—primarily when contamination-associated bacteria, such as those in this study, are detected in one of two blood culture sets. To our knowledge, no recent study has compared the TTP of true bacteremia and contamination and proposed the cutoff threshold specifically for major contamination-associated bacteria.

Even in the CNS-only cohort, the present study suggests that the TTP of 20 hours is a reasonable cutoff. Previous studies have reported data supporting the TTP of 20-24 hours as an optimal cutoff, despite differences in study design, including contamination determination methods and patient characteristics [17–19]. Overall, our findings align with these previous results.

Our study showed that 43.2% and 44.4% of blood culture-positive samples classified as contamination turned positive within 24 hours, in the all patient cohort and in CNS-only cohort, respectively. Furthermore, the TTP cutoff of 20 hours appears more appropriate than 24 hours for distinguishing true bacteremia from contamination (Table 4). Although, among clinicians, the 24-hour TTP has been commonly considered a threshold to differentiate the contamination from true bacteremia, the present study indicates that nearly half of contamination cases turn positive earlier than 24 hours. One contributing factor may be advances in blood culture systems and blood culture bottles, which have led to shortened incubation times [8,20,21].

In July 2024, a global supply restriction on BD's blood culture bottles unexpectedly occurred [22], necessitating us to conserve the culture bottles in daily clinical practice. In such a situation, the understanding and clinical application of TTP in diagnosing the blood culture contamination becomes even more crucial.

This study has several limitations. First, due to the single-center retrospective design of this investigation, the generalizability of the presented data requires validation through additional multi-center studies. Second, the sample volume of blood culture, which can influence TTP [23], was not assessed. Third, the latent time interval from blood sampling to culture initiation was not recorded. However, institutional protocols mandate that blood culture specimens be transported to the microbiology laboratory immediately after collection during both daytime and nighttime hours, minimizing pre-analytical delays. Fourth, TTP can vary depending on the blood culture system used [1]. However, the BACTEC™ FX system employed in this study is one of the most commonly used blood culture systems; thus, the results can be relevant to many other institutions.

5. Conclusion

This study demonstrated that a 20-hour TTP threshold could help distinguish true bacteremia from contamination caused by major contaminating organisms. Our findings indicate that even when TTP is shorter than 24 hours, a substantial number of cases still represent contamination, highlighting the necessity of considering this possibility

in clinical decision-making. Our data would contribute to antimicrobial stewardship by reducing unnecessary antibiotic administration in cases of blood culture contamination.

CRediT authorship contribution statement

Yohei Manabe: Writing – original draft, Visualization, Investigation, Formal analysis. **Hideharu Hagiya:** Writing – review & editing, Visualization, Supervision, Project administration, Conceptualization. **Shinnosuke Fukushima:** Writing – review & editing, Conceptualization. **Kenta Nakamoto:** Writing – review & editing. **Kohei Oguni:** Writing – review & editing. **Hidemasa Akazawa:** Writing – review & editing. **Yasushi Fujita:** Writing – review & editing. **Takashi Kiguchi:** Writing – review & editing. **Koji Iio:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials

The datasets used in this study are available from the corresponding author upon request.

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