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ORIGINAL ARTICLE

Timing and prediction of secondary bacteremia in patients with COVID-19: A retrospective cohort study

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Abstract

Background: We aimed to aid the appropriate use of antimicrobial agents by determining the timing of secondary bacteremia and validating and updating clinical prediction models for bacteremia in patients with COVID-19.

Methods: We performed a retrospective cohort study on all hospitalized patients diagnosed with COVID-19 who underwent blood culture tests from January 1, 2020, and September 30, 2021, at an urban teaching hospital in Japan. The primary outcome measure was secondary bacteremia in patients with COVID-19.

Results: Of the 507 patients hospitalized with COVID-19, 169 underwent blood culture tests. Eleven of them had secondary bacteremia. The majority of secondary bacteremia occurred on or later than the 9th day after symptom onset. Positive blood culture samples collected on day 9 or later after disease onset had an odds ratio of 22.4 (95% CI 2.76–181.2, $p < 0.001$) compared with those collected less than 9 days after onset. The area under the receiver operating characteristic curve of the modified Shapiro rule combined with blood culture collection on or after the 9th day from onset was 0.919 (95% CI, 0.843–0.995), and the net benefit was high according to the decision curve analysis.

Conclusions: The timings of symptom onset and hospital admission may be valuable indicators for making a clinical decision to perform blood cultures in patients hospitalized with COVID-19.

KEYWORDS
blood stream infection, clinical prediction model, COVID-19, secondary bacteremia

1 | INTRODUCTION

Secondary bacteremia in patients hospitalized with coronavirus disease 2019 (COVID-19) is a significant concern and has been reviewed globally since the COVID-19 pandemic period. Complications of bloodstream infections (BSI) have been reported in approximately 5.2% of patients with COVID-19 admitted to the intensive care unit (ICU) and are associated with high in-hospital mortality and increased antimicrobial use.[1]

Many national guidelines do not recommend systematic empirical antibiotic therapy for patients hospitalized with COVID-19. Depending on the setting, the prevalence of bacterial co-infection

and hospital-acquired infection (HAI) was 3.5% and 15%, respectively, and it was higher in patients in the ICU.[2] Bacteremia accounted for 1% and 7.3% of co-infections and HAIs, respectively.[3,4] Nevertheless, 60%–98% of patients hospitalized with COVID-19 receive empirical antibiotic treatment.[5] There is a gap between the prevalence of bacterial infections and antibiotic use for treatment in hospitalized patients with COVID-19, which highlights the potential for inappropriate use and leads to antimicrobial resistance due to increased utilization. To improve antibiotic stewardship, clinicians should reduce antibiotic use and understand the patterns of secondary infections in hospitalized patients with COVID-19 to identify targets for antibiotic use.[6]

Secondary infections in hospitalized patients with COVID-19 have often been diagnosed based on limited clinical and scientific evidence and without considering the time of occurrence of secondary bacteremia, which could help determine the potential usefulness of initiating empiric antibiotic treatment in hospitalized patients with COVID-19.[7,8] The analysis of blood cultures is essential for diagnosis and management and for recognizing the occurrence time of secondary bacteremia, which supports the development of appropriate antimicrobial stewardship interventions even during the COVID-19 pandemic.[9] A study conducted at a tertiary hospital in Israel found that the median (interquartile range) time of onset of secondary bacterial infection in hospitalized patients with influenza and COVID-19 was 1 (1–3) day and 4 (1–8) days, respectively.[10] These findings suggest that patients with influenza are typically hospitalized after developing bacterial complications, whereas patients with COVID-19 are often admitted with severe symptoms of the viral infection, and secondary bacterial infection arises as complications after hospitalization. We hypothesized that the number of days from the onset of illness or hospitalization could predict secondary bacterial infections in COVID-19 patients. To assist in the appropriate use of antimicrobial agents, our study aimed to determine whether the timing of blood culture collection provides additional predictive value to existing clinical prediction models for bacteremia in patients with COVID-19.

2 | METHODS

We included patients aged ≥18 years with confirmed COVID-19 infection by a positive SARS-CoV-2 polymerase chain reaction (PCR) or rapid antigen test who were admitted to the Kyoto City Hospital in Japan between January 1, 2020, and September 30, 2021, and had blood culture results. Blood samples were collected before initiating antimicrobial agents from patients suspected of having bacteremia on admission or during hospitalization.

We evaluated eligible patients with COVID-19 on admission using the Ordinal Scale for Clinical Improvement[11] and severity of illness categories.[12] The Ordinal Scale was stratified from OS-1 (not hospitalized and having no limitation in activities) to OS-8 (death). Additional categories were as follows: 2, not hospitalized and activities limited; 3, hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care; 4, hospitalized and not requiring supplemental oxygen but requiring ongoing medical care; 5, hospitalized and requiring supplemental oxygen; 6, hospitalized and requiring noninvasive ventilation or use of high-flow oxygen devices; and 7, ventilation + additional organ support pressors, renal replacement therapy (RRT), or extracorporeal membrane oxygenation (ECMO). On admission, the illness severity of the patients with COVID-19 was stratified as mild, moderate, severe, and critical. The categories were as follows: mild, any of the various signs and symptoms of COVID-19 but no shortness of breath, dyspnea, or abnormal chest images; moderate, evidence of lower respiratory disease during clinical assessment or imaging and oxygen saturation (SpO_2) ≥94% in room air at sea level; severe, SpO_2 <94% in room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory rate >30 breaths/min, or lung infiltration >50%; and critical, respiratory failure, septic shock, and/or multiple organ dysfunction.

In this retrospective cohort study, we collected the following data from electronic medical records: patient demographics, clinical manifestations of COVID-19 on admission, days from COVID-19 onset (typical clinical signs or symptoms started), number of days of hospitalization from the day of admission, comorbidities, treatments undertaken for COVID-19, antibiotics initiated within 3 days of the drawing of blood culture samples, ICU status, laboratory parameters, and vital signs as soon as possible but within 24 h of blood culture (no later than 24 h after the test).

Multiple board-certified infectious disease specialists (S. Y. and K. T) reviewed all the cases to determine the presence and source of the secondary bacteremia. Blood culture contamination was defined as the presence of one or more of the following organisms it was found in only one blood culture set out of a series of two or three blood culture sets: coagulase-negative staphylococci, *Micrococcus* spp., viridans group streptococci, *Cutibacterium acnes*, *Corynebacterium* spp., and *Bacillus* spp.[13] Blood cultures were performed using a BACTECTM blood culture system. For patients who had multiple episodes of blood sample collection, the data from the first collection were included if the patient had bacteremia. For patients without bacteremia, the data from the first collection are presented.

The statistical analysis was performed in three steps. First, we described the time of occurrence of secondary bacteremia from the day of COVID-19 onset and the day from hospital admission. Second, we validated the existing bacteremia prediction rules in patients with COVID-19 by modified Shapiro rule (Table S1)[14] and the ID-BactER score (Table S2),[15] which have been validated for patient populations other than those of COVID-19. Third, we evaluated whether combining a validated prediction model with the number of days of blood culture collection since onset or hospitalization would improve prediction. Because we were unable to establish a cutoff for the number of days from onset or hospitalization to blood culture collection based on the findings of previous studies, we described them in quartiles separately and set the median values to their respective cutoffs. The performance of each model was evaluated

using the area under the receiver operating characteristic curve (AUC) for discrimination, a calibration plot, net reclassification improvement (NRI) for reclassification, and a decision curve analysis (DCA) for clinical usefulness.[16]

Continuous variables were compared using Wilcoxon rank-sum tests. Categorical and binary variables were compared using Fisher's exact test. Statistical significance was defined as a two-sided *p*-value <0.05. We did not conduct formal sample size calculations, and all available data were used to maximize the power. In terms of handling missing values, we performed a complete case analysis because missing values were below 5%, as such an analysis might then be feasible.[17] Stata software (version 17.0; StataCorp., College Station, TX, USA) was used for statistical analysis.

This protocol was approved by the Ethics Committee of Kyoto City Hospital. As the study used anonymously collected observational data, the institutional review board waived the need for patient consent. Instead, we provided enrolled patients the opportunity to disclaim their participation using the hospital website.

3 | RESULTS

In total, 507 patients with COVID-19 were hospitalized between January 1, 2020, and September 30, 2021. Among those aged ≥18 years, blood cultures were performed in 169 patients; 224 blood cultures were performed during the study period, including 55 multiple blood cultures. Among the 169 hospitalized patients with COVID-19, 11 (6.5%) had secondary bacteremia, and 158 (93.5%) gave a negative blood culture test (Figure 1). Among the COVID-19 population, 88.1% of patients scored 3–4 on the World Health Organization (WHO) ordinal scale, and 78.1% had moderate-to-severe illness severity at admission. The average body temperature of the patients whose blood cultures were drawn when they were clinically suspected of having secondary bacteremia was 37.8°C (interquartile range (IQR) 37.0–38.3). Of the 158 patients without secondary bacteremia, 62 (39.2%) were treated with antimicrobials (Table 1).

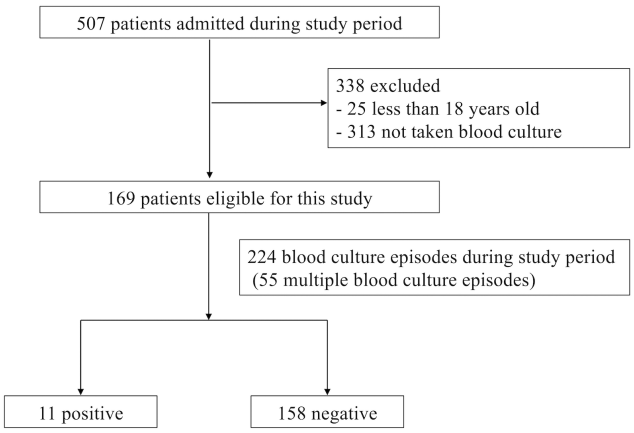

FIGURE 1 Patient selection flow.

3.1 | Days from COVID-19 onset and days from hospitalization and secondary bacteremia

The median durations from COVID-19 symptom onset and hospitalization to secondary bacteremia were 12.5 days (IQR, 12–19.5) and 6 days (IQR, 5–9), respectively. Figure 2A shows the proportion of secondary bacteremia in hospitalized patients with COVID-19 suspected of having bacteremia with blood cultures drawn by quartile days from the onset of symptoms. By univariable logistic regression, positive blood culture tests collected on day 9 or later after disease onset had an odds ratio of 22.4 (95% CI 2.76–181.2, $p < 0.001$), compared to those collected within the first 8 days. Figure 2B shows the proportion of secondary bacteremia divided by quartile of days from admission. The odds ratio for a positive blood culture taken on or after the 2nd day of hospitalization was 41.0 (95% CI 0.505–332.2, $p < 0.001$), compared to those obtained on or before the first day of hospitalization.

Overall, the proportion of secondary bacteremia in hospitalized patients with COVID-19 suspected of having bacteremia based on blood cultures was 4.9%. Pathogens isolated from the blood culture and the presumed sources of the 11 secondary infections were as follows: three cases of pneumonia, two catheter-related blood stream infections, one case of both pneumonia and catheter-related bloodstream infection, and two urinary tract infections (UTIs). Among the 11 cases of secondary bacteremia, six cases occurred in the ICU, and there were five deaths before discharge (Table S3).

3.2 | Validation of existing prediction rules

The AUCs of the modified Shapiro's rule and ID-BactER score in our patient population were 0.906 (95% CI, 0.828–0.983) and 0.772 (95% CI, 0.556–0.989), respectively (Figures S1a and S2a), and the calibration plots are shown in Figures S1b and S2b, respectively. The modified Shapiro rule exhibited good discrimination and calibration.

3.3 | Adding information on the number of days for blood culture collection from onset of illness or hospitalization to the modified Shapiro's rule

When the modified Shapiro rule was combined with blood culture collection at or beyond 9 days after onset, AUC was 0.919 (95% CI, 0.843–0.995) (Figure S3a,b); continuous NRI was 1.170 (95% CI 0.141–1.530); and reclassification was improved. On the other hand, the AUC was 0.921 (95% CI, 0.849–0.993) when the modified Shapiro rule was combined with blood culture collection on or after the 2nd hospital day, while the continuous NRI was 1.146 (95% CI −0.471 to 1.630) and reclassification was not improved.

TABLE 1 Patient characteristics, underlying diseases, severity, treatments, and time of admission based on Japanese epidemiology.

	Total	Without bacteremia	With bacteremia	
	N = 169	*N* = 158	*N* = 11	*p* Value
Demographics				
Age (years), median (IQR)	68 (54–81)	68 (53–81)	75 (59–83)	0.27
Male, *n* (%)	112 (66.3%)	105 (66.5%)	7 (63.6%)	1.00
Body mass index	24.6 (22.3–27.2)	24.2 (22.5–27.3)	25.0 (18.8–27.1)	0.92
Time of admission				
First wave (January–May 2020)	18 (10.7%)	18 (11.4%)	0 (0.0%)	0.51
Second wave (June–October 2020)	16 (9.5%)	15 (9.5%)	1 (9.1%)	
Third wave (November–February 2020)	40 (23.7%)	38 (24.1%)	2 (18.2%)	
Forth wave (March–June 2021)	44 (26.0%)	42 (26.6%)	2 (18.2%)	
Fifth wave (July–September 2021)	51 (30.2%)	45 (28.5%)	6 (54.5%)	
Underlying disease, *n* (%)				
Myocardial infarction	4 (2.4%)	4 (2.5%)	0 (0.0%)	1.00
Cerebrovascular disease	17 (10.1%)	16 (10.1%)	1 (9.1%)	1.00
Chronic lung disease	15 (8.9%)	15 (9.5%)	0 (0.0%)	0.60
Chronic liver disease	3 (1.8%)	2 (1.3%)	1 (9.1%)	0.18
Diabetes mellitus	35 (20.7%)	32 (20.3%)	3 (27.3%)	0.70
Chronic kidney disease	6 (3.6%)	6 (3.8%)	0 (0.0%)	1.00
Malignancy	21 (12.4%)	19 (12.0%)	2 (18.2%)	0.63
Hypertension	69 (40.8%)	64 (40.5%)	5 (45.5%)	0.76
Immunocompromised	4 (2.4%)	4 (2.5%)	0 (0.0%)	1.00
WHO ordinal scale on admission				
3	82 (48.5%)	79 (50.0%)	3 (27.3%)	<0.001
4	67 (39.6%)	64 (40.5%)	3 (27.3%)	
5	16 (9.5%)	14 (8.9%)	2 (18.2%)	
6	4 (2.4%)	1 (0.6%)	3 (27.3%)	
Severity on admission				
Mild	17 (10.1%)	16 (10.1%)	1 (9.1%)	0.016
Moderate	64 (37.9%)	62 (39.2%)	2 (18.2%)	
Severe	68 (40.2%)	65 (41.1%)	3 (27.3%)	
Critical	20 (11.8%)	15 (9.5%)	5 (45.5%)	
Respiratory support received				
None	55 (32.5%)	54 (34.2%)	1 (9.1%)	<0.001
Simple oxygen	101 (59.8%)	98 (62.0%)	3 (27.3%)	
High flow nasal cannula	5 (3.0%)	4 (2.5%)	1 (9.1%)	
Invasive mechanical ventilation	8 (4.7%)	2 (1.3%)	6 (54.5%)	
Vital sings				
Body temperature (°C), median (IQR)	37.8 (37.0–38.3)	37.8 (37.1–38.3)	36.8 (36.2–38.3)	0.089
Respiratory rate (breaths/min), median (IQR)	20 (18–24)	20 (18–24)	20 (16–21)	0.57
Systolic blood pressure (mmHg), median (IQR)	123 (110–140)	124 (110–140)	103 (98–113)	0.004
Heart rate, median (IQR)	89 (76–100)	90 (76–100)	72 (59–109)	0.22
Altered mental status, *n* (%)	16 (9.5%)	10 (6.3%)	6 (54.5%)	<0.001
Laboratory data				
White blood cell count (10^9/L), median (IQR)	5.9 (4.4–8.7)	5.7 (4.4–8.0)	11.9 (8.7–25.4)	<0.001
Neutrophils (%), median (IQR)	77.3 (67.9–86.4)	76.5 (67.3–84.5)	89.0 (84.8–95.0)	<0.001

(Continues)

TABLE 1 (Continued)

	Total	Without bacteremia	With bacteremia	
	N = 169	*N* = 158	*N* = 11	*p* Value
Platelet count (10^9/L), median (IQR)	178 (127–232)	179 (129–235)	128 (91–207)	0.18
Serum creatinine (mg/dL), median (IQR)	0.8 (0.7–1.1)	0.8 (0.7–1.1)	0.8 (0.6–0.9)	0.35
Serum C reactive protein (mg/L), median (IQR)	46 (17–108)	50 (18–111)	20 (3.0–32)	0.022
Serum lactate dehydrogenase (IU/L), median (IQR)	325 (232–463)	319 (232–452)	516 (228–911)	0.10
D dimer (mcg/mL), median (IQR)	1.1 (0.6–2.4)	1.0 (0.6–2.2)	3.2 (2.7–6.6)	<0.001
Serum ferritin (ng/mL), median (IQR)	549.5 (251.1–995.7)	538.7 (238.8–938.8)	728.1 (548.5–1109.7)	0.12
Intravenous catheter	24 (14.2%)	14 (8.9%)	10 (90.9%)	<0.001
Treatments				
Remdesivir	19 (11.2%)	10 (6.3%)	9 (81.8%)	<0.001
Corticosteroids	25 (14.8%)	16 (10.1%)	9 (81.8%)	<0.001
Tocilizumab	11 (6.5%)	4 (2.5%)	7 (63.6%)	<0.001
Baricitinib	3 (1.8%)	2 (1.3%)	1 (9.1%)	0.18
Anticoagulant	24 (14.2%)	16 (10.1%)	8 (72.7%)	<0.001
Antibiotics	73 (43.1%)	62 (39.2)	11 (100%)	<0.001

Note: Data are presented as percentages or medians (IQR). Continuous variables are compared using the Wilcoxon rank-sum test. Categorical and binary variables are compared using Fisher's exact test. For patients with multiple episodes of blood culture sample collection, data from the first collection were included if the patient had true bacteremia. For patients without bacteremia, the data from the first collection were included.
Abbreviation: IQR, interquartile range.

3.4 | Decision curve analysis

We used DCA to evaluate the net benefit of combining the modified Shapiro rule with blood culture collection on or after the 9th day from the onset of illness and on or after the 2nd day from admission. Information on blood culture collection on or after the 9th day from disease onset was shown to have an additional net benefit over the modified Shapiro rule (Figure 3).

4 | DISCUSSION

We analyzed the occurrence of secondary bacteremia in patients hospitalized with mild-to-critical COVID-19 and found that secondary bacteremia occurred on or after 9th day from the onset of COVID-19 symptoms and on or after the 2nd day from hospitalization. The median time of occurrence of secondary bacteremia was 6 days (IQR, 5–9) from the day of admission. Of the 11 patients with secondary bacteremia, one patient who was fully vaccinated with the primary series of COVID-19 vaccinations presented with fever without any other symptoms of COVID-19 infection. The patient's initial findings, such as pyuria, indicated a UTI, although SARS-CoV-2 PCR gave positive results as the patient was screened for COVID-19 on admission. Finally, the patient was diagnosed with UTI, *Escherichia coli* bacteremia, and asymptomatic COVID-19. Therefore, except in this case, our findings suggest that secondary bacteremia is less likely to occur until at least 2 days after hospitalization.

Buetti et al. indicated that ICU-BSIs among patients with COVID-19 occurred at a median of 12 days (IQR 9–16) after ICU admission compared to 6.5 days (IQR 5–12.5) in patients in the ICU without COVID-19, which showed that patients with COVID-19 had a higher probability of developing ICU-BSIs, especially 7 days after ICU admission.[18] Pasquini et al. reported a difference in the number of days between hospital admission and BSI occurrence in patients with and without COVID-19 (i.e., days 16 and 5), respectively.[19] As mentioned earlier, bacterial infections occur later after hospitalization in COVID-19 compared to influenza.[10] These results, as well as our own, suggest that bacterial infections in COVID-19 are more likely to occur as a healthcare-associated complication after hospitalization rather than as a complication early in the course of illness. In addition, a Japanese single-center study reported that clinically diagnosed concurrent infections in patients with COVID-19 during hospitalization occurred in 0.2% of patients with mild-to-moderate disease and 5.2% of patients with severe-to-critical disease.[20] Based on these previous studies and the results of the present study, the routine use of antimicrobial agents in patients with COVID-19 at the early onset and mild-to-moderate stages of the disease is not justified.

We validated the clinical prediction model for blood culture positivity in patients with COVID-19. Validation of the existing rules developed in the pre-COVID-19 era showed that Shapiro's rule had good discriminative power, but the ID-BactER score was poor. DCA helps to assess the clinical utility of the predictive model by weighting benefits and harms and considering risk thresholds.[16] From the DCA results, it is more likely that the number of days from onset and the number of days from hospitalization are additional predictors to modified Shapiro's rule for bacteremia. However, according to the NRI, days from admission did not improve reclassification. During

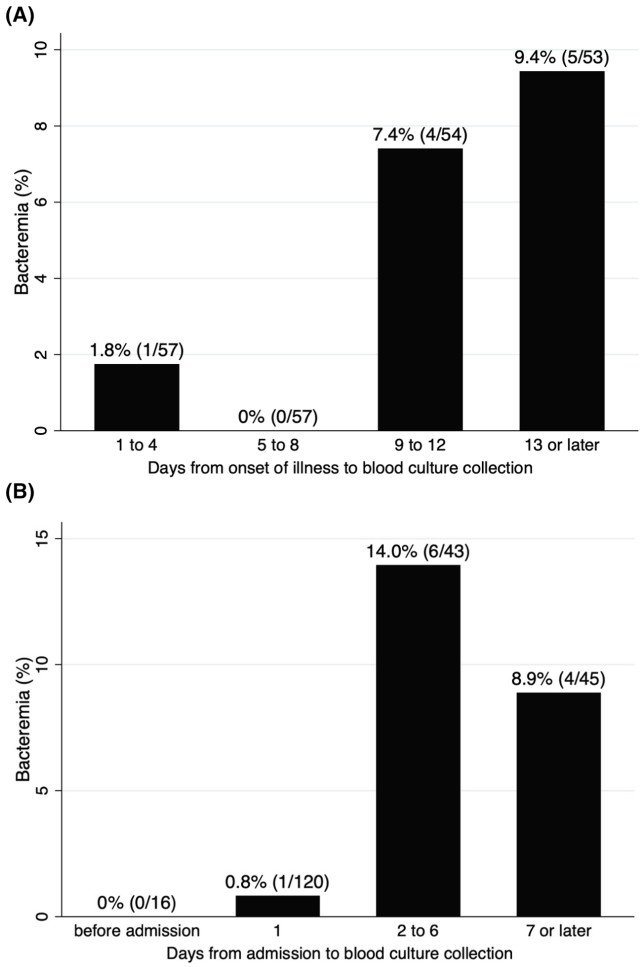

FIGURE 2 (A) Days from onset of illness to blood culture collection. *Note*: One patient presented with urinary tract infection with *E. coli* bacteremia on the admission day when the SARS-CoV-2 PCR test gave a positive result. (B) Days from admission to blood culture collection. *Note*: Blood culture samples were drawn from 16 patients with COVID-19 before hospital admission as outpatient medical service.

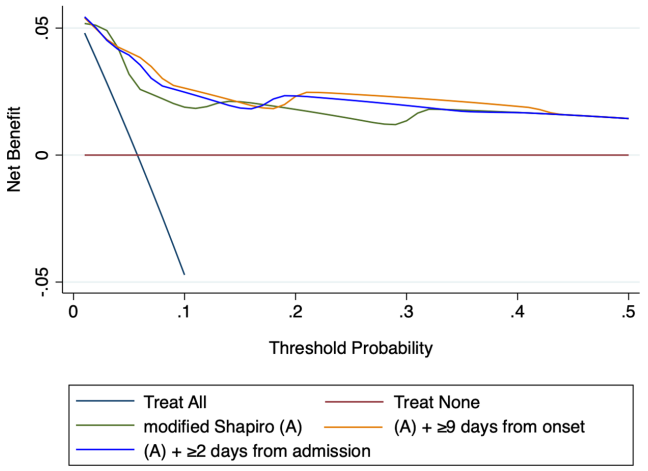

FIGURE 3 Decision curves for the modified Shapiro (A), (A) combined with blood culture collection on or after the 9th day from symptom onset, and (A) combined with blood culture collection on or after 2nd day from admission. *Note*: The brown line is the net benefit of treating no patients, assuming that none would have bacteremia; the navy blue line is the net benefit of treating all patients similarly regardless of their severity, assuming that all would have bacteremia; the green line is the net benefit of treating patients according to the modified Shapiro rule (model A); the orange line is the net benefit of treating patients based on the model A combined with blood culture collection on or after the 9th day from symptom onset; and the blue line is the net benefit for treating patient based on the model A combined with blood culture collection on or after the 2nd day from hospital admission.

the period of the present study, when the decision on the indication for hospitalization was made by the administration, patients at high risk for severe disease were often hospitalized before they became severely ill. Therefore, this may have led to the dissociation between DCA and NRI results for the number of days from hospitalization.

Among the 158 patients with COVID-19 without secondary bacteremia in our study, 62 (39.2%) received antimicrobial therapy within 3 days of blood culture. Antimicrobial stewardship is an essential strategy for appropriate antibiotic use even in hospitalized patients with COVID-19. Moretto et al. showed that antibiotic treatment was frequently administered to patients with more severe presentation on admission but was not associated with death or transfer to the ICU.[8] Langford et al. demonstrated that antibiotics are prescribed more frequently to older patients and those requiring mechanical ventilation.[6] Deciding the delivery of antibiotic therapy may still be challenging in hospitalized patients with COVID-19. Adding information on the number of days since onset to modified Shapiro's rule may improve prediction of bacteremia and may be useful in determining blood culture collection time and the appropriate use of antimicrobial agents.

Our study had several limitations. First, this retrospective observational study was conducted at a single center with a relatively small sample size of patients with bacteremia in hospitalized patients with COVID-19. Further external validation using a larger sample from multiple institutions is required. Second, we did not perform blood cultures for all hospitalized patients with COVID-19. In addition, there were no definitive criteria for blood cultures to be drawn when patients were suspected of having secondary bacteremia, as this depended on the clinician's judgment. Therefore, undocumented secondary bacteremia may have existed, and the reported amount could have been underestimated. However, most blood cultures were drawn if the patient's fever hit the median temperature (37.8°C). Third, throughout our study period between January 1, 2020, and September 30, 2021, there were several significant changes in the COVID-19 pandemic situation, such as epidemiology in Japan and treatment options. The COVID-19 infection in patients might have been less severe in the early phase of our study. The patients did not receive corticosteroids before the RECOVERY trial[21] and tocilizumab before December 2020. In our study period, cases caused by the Omicron variant did not exist. Therefore, our results may not be generalizable to currently hospitalized patients with COVID-19. Fourth, we did not analyze the secondary infections

without bacteremia. In our data, approximately 40% of patients admitted with COVID-19 without bacteremia were treated with antimicrobials for suspected secondary bacterial infections. Secondary bacterial pneumonia could not be adequately investigated because sputum cultures of COVID-19 patients were not accepted in the laboratory during this study period due to infection control problems. Fifth, the median was used as the cutoff for the number of days from onset or hospitalization to blood culture collection because we were unable to set in advance based on previous studies. The present findings need to be validated in another population.

In conclusion, patients with COVID-19 were more likely to have positive blood cultures collected on day 9 or later of disease onset. The modified Shapiro's rule for predicting bacteremia in COVID-19 hospitalized patients has high discriminatory power, and the net benefit could be improved by adding information on the number of days from onset.

AUTHOR CONTRIBUTIONS

A. Y., K. T., and S. Y. conceived and designed the study. A. Y. wrote the manuscript. A.Y., K. T., and S.Y. analyzed the data and prepared all figures and tables. All the authors reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethics approval statement: This protocol was approved by the Ethics Committee of Kyoto City Hospital.

Patient consent statement: Not applicable.

Clinical trial registration: We did not register with the Clinical Trial Registry.

A CHECKLIST FOR THE REPORTING STATEMENT

TRIPOD statement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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