

Epidemiology and Factors Associated With Discharging Patients After Blood Culture Collection in the Emergency Department: A Case-Control Study in Japan

Toshiki Miwa, Akane Takamatsu, and Hitoshi Honda®

Division of Infectious Diseases, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

Background. Some patients receive the diagnosis of bloodstream infection (BSI) after discharge from the emergency room (ER). Because the safety of discharging patients after a blood culture collection is unknown, the present study aimed to investigate the prevalence, outcomes, and factors associated with BSI diagnosed after ER discharge.

Methods. This monocentric, case-control study compared patients who received a BSI diagnosis after ER discharge with those who were admitted for BSI. Factors associated with ER discharge after a blood culture collection were identified using multivariate logistic regression analysis.

Results. Between January 2014 and December 2020, 5.5% (142/2575) of patients with BSI visiting the ER were initially discharged. This occurred more commonly during the coronavirus disease 2019 (COVID-19) pandemic in 2020. On multivariate analysis, factors independently associated with the discharge of patients with BSI were the absence of hypotension (adjusted odds ratio [aOR], 15.71 [95% confidence interval {CI}, 3.45–71.63]), absence of altered mental status in the ER (aOR, 8.99 [95% CI, 3.49–23.14]), unknown origin at ER discharge (aOR, 4.60 [95% CI, 2.43–8.72]), and low C-reactive protein (aOR, 3.60 [95% CI, 2.19–5.93]). No difference in 28-day mortality was observed between the groups.

Conclusions. BSI is occasionally diagnosed after ER discharge. The prevalence of BSI diagnosed after ER discharge may have increased during the COVID-19 pandemic. Normal vital signs, unknown origin at ER discharge, and low C-reactive protein were important considerations leading to the discharge of these patients.

Keywords. blood culture; emergency department; patient safety.

Bloodstream infections (BSIs) are commonly associated with sepsis, which is one of the leading causes of death worldwide [1–3]. Patients with BSI generally require hospitalization and need parenteral antimicrobial therapy during the early course of illness. Because delayed or inappropriate initial antimicrobial therapy for BSI is associated with poor clinical outcomes even in patients without sepsis, appropriate management, including close monitoring and prompt initiation of antimicrobial therapy, is essential, especially in the emergency room (ER) setting [4, 5]. Although a positive blood culture is the gold standard for diagnosing BSI, blood culture results are often not available quickly enough to impact clinical decision-

Open Forum Infectious Diseases[®]

making, particularly in the ER [6]. Moreover, the clinical manifestations of BSI vary widely, and predicting BSI at the initial presentation, especially in the ER, is difficult [7]. Thus, very often patients are discharged after a blood culture is drawn on the initial visit, only to be diagnosed later with a BSI.

Although several studies have demonstrated that patients discharged from the ER who later received a BSI diagnosis had less severe disease, fewer comorbidities, and more favorable outcomes, including a lower mortality rate [8–11], the practice of discharging patients after drawing a blood culture is controversial. Moreover, the coronavirus disease 2019 (COVID-19) pandemic, which increased the incidence of febrile illness, may have impeded visits to the ER by patients without COVID-19 [12]. COVID-19 has also led to a shortage of healthcare resources, such as hospitalization capacity, possibly prompting ER physicians to discharge patients, including those with undiagnosed BSI, more readily [13, 14].

The present study aimed to investigate the prevalence and outcomes of BSI diagnosed in patients after discharge from the ER and to identify the factors associated with patient discharge after blood culture collection.

Received 02 June 2022; editorial decision 06 July 2022

Correspondence: Hitoshi Honda, MD, PhD, Division of Infectious Diseases, Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan (hhhhonda@gmail.com).

[©] The Author(s) 2022. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons. org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com https://doi.org/10.1093/ofid/ofac342

METHODS

Study Design and Setting

The present study was conducted at Tokyo Metropolitan Tama Medical Center, a 790-bed tertiary care center located in Tokyo, Japan. The emergency department at the study center provides 24-hour service and receives approximately 20 000 patients annually. Only adult patients are admitted. Medical care in the ER is provided by the attending ER physicians, residents (postgraduate years 1–5), and consulting physicians from various subspecialties. The decision to admit patients is made at the discretion of the attending physicians. Blood culture results are recorded in the electronic medical records by the Department of Microbiology Laboratory. The Infectious Diseases Division at the study center routinely tracks all positive blood culture results and contacts the treating physicians for reevaluation if patients with BSI are discharged from the ER before the disease is diagnosed.

Participants

The present study included patients visiting the ER between January 2014 and December 2020 whose blood culture returned positive. Case patients were those with a diagnosis of BSI who were discharged from the ER. Three control subjects with BSI in the same year who were admitted immediately after their initial ER visit were randomly selected per case patient. If the patients visited the ER more than once and received a BSI diagnosis after each visit during the study period, only the first visit was included. BSI was defined as the growth of the causative pathogen in a blood culture. If common skin flora were isolated from a blood culture (eg, coagulase-negative staphylococci or Corynebacterium, Bacillus, Micrococcus, or Cutibacterium species), multiple, positive blood cultures were required to establish the diagnosis. A positive blood culture not meeting the definition of BSI was considered to have resulted from contamination [15].

The exclusion criteria were age <18 years, a positive blood culture resulting from contamination, and transfer to another hospital within 48 hours after blood culture collection. Because the present study aimed to compare patients with a positive blood culture following their initial discharge from the ER with patients who were admitted on their initial visit, patients with a severe illness at ER presentation, such as those directly admitted to the intensive care unit or who died within 48 hours after blood culture collection, were also excluded.

Data Collection

Demographic and clinical data on the study patients, including comorbidities, vital signs, consciousness status as measured by the Glasgow Coma Scale, laboratory data, the presumptive diagnosis in the ER, the subsequent diagnosis, details of the antimicrobial therapy given, and the clinical course and outcomes after the ER visit were retrospectively collected from electronic medical records. In the present study, septic status was defined as ≥ 2 on the quick Sequential Organ Failure Assessment score [16]. Twenty-eight-day mortality was tracked from the initial blood culture collection using the medical records. If no record was found, the patients were contacted by telephone to determine if they were alive 28 days after the date of their positive blood culture results.

Statistical Analysis

On univariate analysis, categorical variables were compared using the χ^2 test or Fisher exact test as appropriate, and continuous variables were compared using the Mann-Whitney U test. Multivariate logistic regression was performed to identify the factors associated with the discharge of patients with BSI. In previous studies, a history of cerebrovascular disease [10], chronic heart failure, chronic lung disease [9], and the initial diagnosis [8-11] were associated with discharge. These factors were therefore included in the prediction model in the present study. Furthermore, factors with P < .05 on univariate analysis with clinical plausibility were included. Before the multivariate analysis, multicollinearity was assessed using 2-by-2 tables and variance inflation factors to ensure that the factors were independent of each other. The Hosmer-Lemeshow test was performed to assess the goodness of fit for the logistic regression model. All statistical analyses were 2-tailed, and P < .05 was considered to indicate statistical significance. All the analyses were done using Stata version 16 (StataCorp, College Station, Texas).

Patient Consent Statement

Patient consent was waived because it was mainly associated with quality-improvement intervention introduced at the hospital level with negligible risk of harming patients. The institutional review board at Tokyo Metropolitan Tama Medical Center approved the study [3–25].

RESULTS

During the study period, 153 432 patients visited the ER. Blood cultures were collected in 19 010 patients (12.4%); 2575 (13.5%) of these had BSI, and of the latter, 142 (5.5%) were initially discharged from the ER. Of these 142 patients, 3 were excluded because of incomplete vital sign data, and 417 control subjects were randomly selected. Thus, 556 patients were finally included for analysis.

The COVID-19 pandemic year of 2020 saw an increase in the number of patients with BSI diagnosed after their ER discharge. The percentage of these patients in 2020 and 2014–2019 was 8.4% (40/475) and 4.9% (102/2100), respectively (odds ratio [OR], 1.80 [95% confidence interval {CI}, 1.23–2.63]).

Table 1. Characteristics of Patients With a Positive Blood Culture Collected in the Emergency Room

Characteristic	Total (N = 556)	Discharged From ER (n = 139)	Directly Admitted From ER (n = 417)	<i>P</i> Value
Patient demographics				
Age, y, median (IQR)	77 (67–84)	72 (57–81)	79 (69–85)	<.001
Age ≥65 y	432 (77.7)	92 (66.2)	340 (81.5)	<.001
Male sex	253 (45.5)	64 (46.0)	189 (45.3)	.883
Living status $(n = 463)^a$				
Alone	70/463 (15.1)	11/119 (9.2)	59/344 (17.2)	
With family	359/463 (77.5)	105/119 (88.2)	254/344 (73.8)	
Nursing facility	31/463 (6.7)	2/119 (1.7)	29/344 (8.4)	
Dormitory or shared housing	3/471 (0.7)	1/119 (0.8)	2/344 (0.6)	
ER visit day				.794
Weekday (Monday–Friday)	373 (67.1)	92 (66.2)	281 (67.3)	
Weekend (Saturday–Sunday)	183 (32.9)	47 (33.8)	136 (32.6)	
ER visiting time				.006
6:00 ам-5:59 рм	346 (62.2)	73 (52.5)	273 (65.5)	
6:00 pm-5:59 am	210 (37.8)	66 (47.5)	144 (34.5)	
Comorbidities				
CCI, median (IQR)	2 (0.5–3)	2 (0–3)	2 (1–3)	.186
History of solid malignancy				.922
None	364 (65.5)	90 (64.8)	274 (65.7)	
Localized	156 (28.1)	39 (28.1)	117 (28.1)	
Metastatic	36 (6.5)	10 (7.2)	26 (6.2)	
Diabetes mellitus	125 (22.5)	38 (27.3)	87 (20.9)	.113
Cerebrovascular disease	87 (15.7)	15 (10.8)	72 (17.3)	.069
Acute coronary syndrome	58 (10.4)	10 (7.2)	48 (11.5)	.149
Collagen vascular disease	50 (9.0)	6 (4.3)	44 (10.6)	.026
Chronic liver disease	38 (6.8)	12 (8.6)	26 (6.2)	.601
Chronic lung disease	32 (5.8)	11 (7.9)	21 (5.0)	.207
Renal function				.815
Normal	538 (96.8)	136 (97.8)	402 (96.4)	
Chronic renal failure ^b without dialysis	5 (0.9)	1 (0.7)	4 (0.96)	
Chronic renal failure ^b with dialysis	13 (2.3)	2 (1.4)	11 (2.6)	
Chronic heart failure	27 (4.9)	2 (1.4)	25 (6.0)	.038
Systemic corticosteroid use within the last 28 $\ensuremath{d^{\mathrm{c}}}$	14 (2.5)	2 (1.4)	12 (2.9)	.534
Other immunosuppressant use within the last 28 d	23 (4.1)	3 (2.2)	20 (4.8)	.223
Chemotherapy within the last 28 d	33 (5.9)	7 (5.0)	26 (6.2)	.604
Intravascular device ^d	37 (6.7)	6 (4.3)	31 (7.4)	.202
Prothesis other than intravascular device	62 (11.2)	8 (5.8)	54 (13.0)	.020

Data are presented as No. (%) unless otherwise specified.

Abbreviations: CCI, Charlson Comorbidity Index; ER, emergency room; IQR, interquartile range.

^aInformation on the living status of 93 patients, including 20 discharged patients and 73 directly admitted patients, was unable to be extracted.

^bChronic renal failure was defined as serum creatinine ≥3 mg/dL.

^cPatients receiving the equivalent of prednisolone ≥10 mg were included.

^dIntravascular device included central venous catheters, cardiac implantable electronic devices, and prosthetic vascular grafts.

Table 1 shows the demographic and clinical data on the patients. In total, 432 patients (77.7%) were aged 65 years or older. Approximately one-third had a history of solid organ malignancy, and one-fifth had diabetes mellitus. Univariate analysis identified the following factors as potentially associated with patient discharge: age <65 years, nighttime ER visit, absence of collagen vascular disease, chronic heart failure, prosthesis other than an intravascular device, absence of hypotension, absence of altered mental status, low C-reactive protein (CRP), a presumptive diagnosis of unknown origin, and intra-abdominal/hepatobiliary tract infection. All these factors were included in multivariate analysis. In addition, because a presumptive diagnosis of urinary tract infection was the exposure of interest in the present study, it was also included in the multivariate analysis.

Table 2 shows the results of the multivariate analysis of predictors of BSI diagnosis following ER discharge. Factors independently associated with discharge were the absence of hypotension (adjusted OR [aOR], 15.71 [95% CI, 3.45–71.63]), the absence of altered mental status (AMS) in the ER (aOR, 8.99 [95% CI, 3.49–23.14]), unknown origin at ER discharge

Table 2. Factors Associated With Emergency Room Discharge of Patients With a Subsequently Diagnosed Bloodstream Infection

			Univariate Analysis		Multivariate Analysis ^a	
Variables	Discharged From ER (n = 139)	Directly Admitted From ER (n = 417)	OR (95% CI)	<i>P</i> Value	Adjusted OR (95% CI)	<i>P</i> Value
Demographics						
Age ≥65 y	92 (66.2)	340 (81.5)	0.44 (.29–.68)	<.001	0.66 (.38–1.16)	.146
ER visiting time between 12:00 AM and 5:59 AM	20 (14.4)	33 (7.9)	1.96 (1.08–3.54)	.031	1.30 (.61–2.78)	.497
Comorbidities						
Cerebrovascular disease	15 (10.8)	72 (17.3)	0.58 (.32-1.05)	.060	0.71 (.34–1.49)	.369
Prothesis other than intravascular device ^b	8 (5.8)	54 (13.0)	0.41 (.19–.89)	.013	0.40 (.16–1.03)	.057
Collagen vascular disease	6 (4.3)	44 (10.6)	0.38 (.16–.92)	.017	0.31 (.11–.87)	.026
Chronic lung disease	11 (7.9)	21 (5.0)	1.62 (.76–3.45)	.222	2.27 (.84–6.12)	.106
Chronic heart failure	2 (1.4)	25 (6.0)	0.23 (.05–.98)	.015	0.24 (.05–1.17)	.077
History of solid malignancy						
None	90 (64.8)	274 (65.7)	Ref			
Localized	39 (28.1)	117 (28.1)	1.01 (.66–1.57)	.947		
Metastatic	10 (7.2)	26 (6.2)	1.17 (.54–2.52)	.687		
Diabetes mellitus	38 (27.3)	87 (20.9)	1.43 (.92–2.22)	.114		
Chemotherapeutic agent use within the last 28 d	7 (5.0)	26 (6.2)	0.80 (.34-1.88)	.598		
Systemic corticosteroid use within the last 28 d	6 (4.3)	37 (8.9)	0.46 (.19–1.12)	.065		
Other immunosuppressant use within the last 28 d	3 (2.2)	20 (4.8)	0.44 (.13-1.50)	.148		
Intravascular device ^b	6 (4.3)	31 (7.4)	0.56 (.23–1.34)	.207		
Clinical characteristics						
Body temperature in ER ≤36.0°C or ≥39.0°C	52 (37.4)	137 (32.9)	1.22 (.82–1.82)	.328		
Absence of hypotension in ER	137 (98.6)	336 (80.6)	16.51 (4.00–68.11)	<.001	15.71 (3.45–71.63)	<.001
Absence of altered mental status in ER ^c	133 (95.7)	318 (76.3)	6.90 (2.95–16.12)	<.001	8.99 (3.49–23.14)	<.001
White blood cells $\leq 10.0 \times 10^3 / \mu L$	67 (48.2)	169 (40.5)	1.37 (.93–2.01)	.114		
Platelets $≤15.0 \times 10^4/\mu$ L	49 (35.3)	178 (42.7)	0.73 (.49–1.09)	.120		
CRP ≤5.0 mg/dL	87 (62.6)	127 (30.5)	3.82 (2.56-5.71)	<.001	3.60 (2.19–5.93)	<.001
Presumptive diagnosis in the ER						
Unknown origin	65 (46.8)	51 (12.2)	6.30 (4.04–9.82)	<.001	4.60 (2.43-8.72)	<.001
Urinary tract infection	35 (25.2)	137 (32.9)	0.69 (.45–1.06)	.086	1.00 (.53–1.86)	.990
Intra-abdominal/hepatobiliary infection	6 (4.3)	120 (28.8)	0.11 (.05–.26)	<.001	0.14 (.05–.36)	<.001
Lower respiratory tract infection	13 (9.4)	32 (7.7)	1.24 (.63–2.44)	.536		
Skin and soft tissue infection	9 (6.5)	28 (6.7)	0.96 (.44-2.09)	.922		
Osteoarticular infection	0 (0.0)	16 (3.8)	1.00	NA		
Endovascular infection ^d	0 (0.0)	8 (1.9)	1.00	NA		
Other ^e	11 (7.9)	25 (6.0)	1.35 (.65–2.81)	.436		

Data are presented as No. (%) unless otherwise specified.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; ER, emergency room; OR, odds ratio; NA, not applicable; Ref, reference.

^aThe Hosmer-Lemeshow goodness of fit test revealed a P value of .87. All variables from previous studies [8–11] and univariate analysis were retained in the final model.

^bIntravascular device included central venous catheters, cardiac implantable electronic devices, and prosthetic vascular grafts.

^cAltered mental status was defined as a value of the Glasgow Coma Scale <15.

^dEndovascular infections included primary bacteremia, endocarditis, catheter-related bloodstream infection, cardiac implantable electronic device infection, and prosthetic vascular graft infection.

^eOther included upper respiratory tract infection (n = 9), bacterial colitis (n = 6), central nervous system infection (n = 4), febrile neutropenia (n = 4), acute hepatitis (n = 2), acute pancreatitis (n = 2), choledocholithiasis without bacterial cholangitis (n = 2), heatstroke (n = 2), deep neck infection (n = 1), drug-induced fever (n = 1), mastoiditis (n = 1), neoplastic fever (n = 1), and parotitis (n = 1).

(aOR, 4.60 [95% CI, 2.43–8.72]), and low CRP (aOR, 3.60 [95% CI, 2.19–5.93]). History of collagen vascular disease (aOR, 0.31 [95% CI, .11–.87]) and diagnosis of intra-abdominal/hepatobiliary infection in the ER (aOR, 0.14 [95% CI, .05–.36]) were independently associated with admission directly following the ER visit. Among the 139 patients discharged from the ER, those with unknown origin were later more likely to receive the diagnosis of endovascular infection than those with a diagnosis of BSI of known etiology at the initial ER visit (40.0% [26/65] vs 18.9% [14/74]; OR, 2.86 [95% CI, 1.33–6.14]).

The median delay in antimicrobial therapy, calculated as the interval between the ER visit and commencement of antimicrobial therapy, was 0 days in both the case and the control groups (interquartile range [IQR], 0–0 days and 0–1 days, respectively; P < .01). Data on 28-day mortality were unable to be tracked in 37 (6.7%) patients (7 were discharged from the ER, and 30 were

directly admitted). In the remaining 519 patients, the 28-day mortality rate was 3.9% (20/519), with no significant difference between the groups (1.5% [2/132] vs 4.7% [18/387]; P=.12).

Among the patients with BSI who were discharged from the ER (n = 139), nearly half (71/139 [51.1%]) received no antimicrobial therapy or antimicrobial prescription on discharge at the index ER visit. The median delay in antimicrobial therapy was 1 day (IQR, 1-2 days) in these patients, who more frequently returned to the ER with sepsis or died within 28 days, although the difference was nonsignificant (7.0% [5/71] vs 2.9% [2/68] in patients with and without antimicrobial therapy or antimicrobial prescription on discharge, respectively; P = .44). Two patients with BSI after their ER discharge, who later died within 28 days, had spontaneous bacterial peritonitis and infective endocarditis, respectively. Their blood culture returned positive on the day after their ER visit, and neither received antimicrobial therapy or an antimicrobial prescription on discharge at the first ER visit. Table 3 shows the clinical outcomes in patients with a BSI diagnosed after their ER discharge.

DISCUSSION

The present study demonstrated that approximately 5% of patients with a delayed BSI diagnosis received their diagnosis after their ER discharge. Moreover, the proportion of such patients increased during the pandemic. Most of these patients had a favorable outcome, although some who were discharged without antimicrobial therapy returned to the ER with sepsis or died within 28 days. Furthermore, changes in vital signs, laboratory values such as CRP, and diagnostic status in the ER were

Table 3.	Outcome in	Patients	With a	Bloodstream	Infection	Diagnosed
After Disc	harge From	the Emerg	gency R	oom (n = 139)		

Variables	With Antimicrobial Therapy in the ER (n = 68)	Without Antimicrobial Therapy in the ER (n = 71)	<i>P</i> Value
Sepsis ^a at time of revisit or death within 28 d of first blood culture collection $(n = 132)^b$	2 (2.9)	5 (7.0)	.442
Subsequent disposition after identifying BSI			
Inpatient treatment (n = 111)	52 (76.5)	59 (83.1)	.330
Outpatient treatment (n = 22)	16 (23.5)	6 (8.5)	.646
Treated with IV antimicrobial therapy	8/16 (50.0)	2/6 (33.3)	
Treated with oral antimicrobial therapy	8/16 (50.0)	4/6 (66.7)	
No treatment $(n = 6)$	0 (0.0)	6 (8.5)	.028

Data are presented as No. (%) unless otherwise specified.

Abbreviations: BSI, bloodstream infection; ER, emergency room; IV, intravenous

^aSepsis was diagnosed if a patient had quick Sequential Organ Failure Assessment Score ≥2 [16].

^bMortality data were missing for 7 patients

important determinants of the disposition of patients with BSI after their ER visit.

The prevalence of ER discharge followed by a BSI diagnosis varied among previous studies from 2% to 27% [9, 11, 17–21]. In the present study, the prevalence of discharge followed by a BSI diagnosis was nearly 5%, indicating that a relatively small proportion of patients with BSI were inadvertently discharged from the ER. However, despite BSI being generally considered a serious infection requiring management and careful observation, only a small number of discharged patients with subsequently diagnosed BSI received appropriate medical care.

The increase in the number of patients during the pandemic with a BSI diagnosed after ER discharge is a matter of serious concern. This increase is presumably caused by a rise in the incidence of febrile illnesses associated with COVID-19. Under these circumstances, the difficulty in distinguishing COVID-19 from other febrile illnesses, including BSI, might have led to a reduction in the number of admissions, as reported by previous studies for other illnesses [13, 14]. Changes in ER practices for coping with increased patient numbers may compromise the safety of patients with BSI.

Some previous studies noted that a milder severity of symptoms on ER presentation (as assessed using the Pittsburgh Bacteremia Score) was associated with the decision to discharge patients after blood culture collection [8, 9]. In the present study, the absence of abnormal vital signs, including hypotension and AMS, at ER presentation, likely indicated milder disease severity and was the most powerful factor in the discharge from the ER of patients who later received a BSI diagnosis. As hypotension and AMS are rapidly appearing manifestations of sepsis [16], the findings of the present study suggested that the clinical assessment of disease severity using the vital signs and clinical presentation was the most important aspect of ER practice in deciding whether patients should be discharged. In contrast, in the present study normal vital signs did not exclude BSI, suggesting that close follow-up is necessary even in patients with normal vital signs if these patients are discharged after a blood culture is drawn. The present study also demonstrated that low CRP was associated with discharge followed by BSI diagnosis. This may simply reflect the perception among physicians of low CRP as a surrogate marker of mild disease severity. However, caution should be exercised when interpreting CRP values; low CRP is also seen in patients with sepsis, which is associated with a high mortality rate at the time of admission [22], Thus, it may not necessarily be safe to discharge patients with low CRP.

The present study also demonstrated that patients who later received a diagnosis of BSI of unknown origin were more likely to be discharged than those with an identifiable etiology. This finding likely illustrates the practice of ER physicians of promptly discharging patients with occult infections leading to BSI of unknown origin who are not severely ill instead of admitting them for close observation. This challenge has important clinical implications: first, patients who receive a diagnosis of BSI of unknown origin after ER discharge frequently have an endovascular infection that may lead to a catastrophic outcome induced by treatment delay; and second, a BSI of unknown origin may cause a delay in administering appropriate antimicrobial therapy [20, 23]. Thus, understanding the potential pitfalls in managing febrile patients with BSI of unknown origin is crucial [20, 24]. Appropriate, post-ER follow-up visits (eg, follow-up with the primary care physician) may improve patient safety [18].

The present study found that overall mortality in patients with a BSI following ER discharge was low (3.9%) and no different from that in patients with a BSI who were admitted immediately. This finding is consistent with that of previous studies demonstrating that the mortality rate in patients with a BSI who were discharged from the ER ranged from 0% to 5.0% [5, 9, 11, 17, 18, 20]. However, our study also found that a higher proportion of patients discharged with no antimicrobial therapy (ie, no antimicrobials were given at the ER visit or were prescribed on discharge) returned to the ER with sepsis or died within 28 days. This finding raises the question of the potential value of routine antimicrobial therapy in patients discharged after a blood culture collection. Nevertheless, previous studies noted that patients with a BSI after ER discharge were less likely to receive appropriate antimicrobial therapy than those with a BSI who were admitted immediately [10, 11], and that inappropriate antimicrobial therapy was associated with a high mortality rate or urgent readmission [5, 9]. Moreover, antimicrobial therapy without appropriate diagnosis may counteract antimicrobial stewardship in the ER [25]. The present study also revealed that the subsequent diagnosis of BSI frequently differed from the initial, presumptive diagnosis made in the ER, possibly leading to inappropriate antimicrobial therapy, a finding corroborated by several, previous studies [17, 18, 20]. Thus, routine antimicrobial therapy before the discharge should be avoided in these patients.

The present study has several limitations. As a monocentric, retrospective study, the results may not be applicable to other healthcare settings due to differences in resource availability and practices. Although patient-related factors associated with the decision to discharge from ER were assessed, physician-related factors, such as variations in the quality of care among ER physicians, and healthcare system-related factors, such as accessibility of healthcare resources, which can potentially influence patient disposition, were not. Mortality data were unable to be tracked in 37 patients (6.7% of all patients), possibly impacting the findings of the present study. Last, because the overall mortality rate was low, factors associated with mortality were unable to be determined.

In conclusion, ER discharge with a subsequent BSI diagnosis occurs occasionally, but its prevalence may have increased during the current COVID-19 pandemic. The absence of hypotension and AMS at the ER visit, unknown origin at ER discharge, and low CRP were important factors associated with ER discharge with a subsequent BSI diagnosis. The importance of close follow-up in patients with a suspected BSI on their initial ER visit should be emphasized for patient safety.

Notes

Author contributions. T. M. contributed to the acquisition and interpretation of data and drafting of the manuscript. A. T. and H. H. contributed to the study design and data interpretation. All the authors critically reviewed the manuscript and approved the final version.

Acknowledgments. We thank Mr. James R. Valera for his assistance with editing the manuscript.

Financial support. This work was supported by Kakenhi (19K10501; principal investigator: Hitoshi Honda).

Potential conflicts of interest. T. M., A. T., and H. H. have no conflicts of interest relevant to the present study.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 1995; 273:117–23. doi:10.1001/jama.1995.03520260039030
- Jones GR, Lowes JA. The systemic inflammatory response syndrome as a predictor of bacteraemia and outcome from sepsis. QJM 1996; 89:515–22. doi:10.1093/ gjmed/89.7.515
- Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020; 395:200–11. doi:10.1016/S0140-6736(19)32989-7
- Lee CC, Lee CH, Chuang MC, Hong MY, Hsu HC, Ko WC. Impact of inappropriate empirical antibiotic therapy on outcome of bacteremic adults visiting the ED. Am J Emerg Med 2012; 30:1447–56. doi:10.1016/j.ajem.2011.11.010
- Chan J, Wong J, Saginur R, Forster AJ, van Walraven C. Epidemiology and outcomes of bloodstream infections in patients discharged from the emergency department. CJEM 2015; 17:27–37. doi:10.2310/8000.2013.131349
- Peker N, Couto N, Sinha B, Rossen JW. Diagnosis of bloodstream infections from positive blood cultures and directly from blood samples: recent developments in molecular approaches. Clin Microbiol Infect 2018; 24:944–55. doi:10.1016/j.cmi. 2018.05.007
- Hyernard C, Breining A, Duc S, et al. Atypical presentation of bacteremia in older patients is a risk factor for death. Am J Med 2019; 132:1344–52.e1. doi:10.1016/j. amjmed.2019.04.049
- Chang EK, Kao KL, Tsai MS, et al. Occult *Klebsiella pneumoniae* bacteremia at emergency department: a single center experience. J Microbiol Immunol Infect 2015; 48:684–91. doi:10.1016/j.jmii.2015.08.010
- Lee CC, Hong MY, Chan TY, Hsu HC, Ko WC. The impact of appropriateness of antimicrobial therapy in adults with occult bacteraemia. Emerg Med J 2014; 31: 53–8. doi:10.1136/emermed-2012-201941
- Fu CM, Tseng WP, Chiang WC, et al. Occult Staphylococcus aureus bacteremia in adult emergency department patients: rare but important. Clin Infect Dis 2012; 54:1536–44. doi:10.1093/cid/cis214
- Epstein D, Raveh D, Schlesinger Y, Rudensky B, Gottehrer NP, Yinnon AM. Adult patients with occult bacteremia discharged from the emergency department: epidemiological and clinical characteristics. Clin Infect Dis 2001; 32:559–65. doi:10. 1086/318699
- Mantica G, Riccardi N, Terrone C, Gratarola A. Non-COVID-19 visits to emergency departments during the pandemic: the impact of fear. Public Health 2020; 183:40–1. doi:10.1016/j.puhe.2020.04.046
- Blecker S, Jones SA, Petrilli CM, et al. Hospitalizations for chronic disease and acute conditions in the time of COVID-19. JAMA Intern Med 2021; 181: 269–71. doi:10.1001/jamainternmed.2020.3978
- Kapsner LA, Kampf MO, Seuchter SA, et al. Reduced rate of inpatient hospital admissions in 18 German university hospitals during the COVID-19 lockdown. Front Public Health 2020; 8:594117. doi:10.3389/fpubh.2020.594117
- 15. Doern GV, Carroll KC, Diekema DJ, et al. Practical guidance for clinical microbiology laboratories: a comprehensive update on the problem of blood culture

contamination and a discussion of methods for addressing the problem. Clin Microbiol Rev 2019; 33:e00009-19. doi:10.1128/CMR.00009-19

- Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801–10. doi:10.1001/jama.2016.0287
- Kenig A, Salameh S, Gershinsky Y, Amit S, Israel S. Blood cultures of adult patients discharged from the emergency department—is the safety net reliable? Eur J Clin Microbiol Infect Dis 2020; 39:1261–9. doi:10.1007/s10096-020-03838-3
- González-Del Vecchio M, Bunsow E, Sanchez-Carrillo C, Garcia Leoni E, Rodriguez-Creixems M, Bouza E. Occult bloodstream infections in adults: a "benign" entity. Am J Emerg Med 2014; 32:966–71. doi:10.1016/j.ajem.2014. 05.007
- Mountain D, Bailey PM, O'Brien D, Jelinek GA. Blood cultures ordered in the adult emergency department are rarely useful. Eur J Emerg Med 2006; 13:76–9. doi:10.1097/01.mej.0000188231.45109.ec
- 20. Ramos JM, Masia M, Elia M, et al. Epidemiological and clinical characteristics of occult bacteremia in an adult emergency department in Spain: influence of blood culture results on changes in initial diagnosis and empiric antibiotic

treatment. Eur J Clin Microbiol Infect Dis 2004; 23:881-7. doi:10.1007/ s10096-004-1235-0

- Sturmann KM, Bopp J, Molinari D, Akhtar S, Murphy J. Blood cultures in adult patients released from an urban emergency department: a 15-month experience. Acad Emerg Med 1996; 3:768–75. doi:10.1111/j.1553-2712.1996.tb03513.x
- Wasserman A, Karov R, Shenhar-Tsarfaty S, et al. Septic patients presenting with apparently normal C-reactive protein: a point of caution for the ER physician. Medicine (Baltimore) 2019; 98:e13989. doi:10.1097/MD.000000000013989
- Modol J, Tudela P, Sabrià M, Veny A. Patients with bacteremia who were discharged from the emergency department. Clin Infect Dis 2002; 35:899–900; author reply 900–1. doi:10.1086/342566
- Gur H, Aviram R, Or J, Sidi Y. Unexplained fever in the ED: analysis of 139 patients. Am J Emerg Med 2003; 21:230–5. doi:10.1016/S0735-6757(03) 00038-X
- Pulia M, Redwood R, May L. Antimicrobial stewardship in the emergency department. Emerg Med Clin North Am 2018; 36:853–72. doi:10.1016/j.emc.2018.06. 012