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ORIGINAL ARTICLE

Outcome, diagnosis, and microbiological profile comparison of community- and hospital-acquired bacteremia: A retrospective cohort study

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Abstract

Background: Although bacteremia is one of the most pressing situation in the field of hospital medicine, little is known about the differences between community- and hospital-acquired bacteremia (CAB and HAB, respectively).

Methods: Objective is to know the epidemiologic characteristics of CAB and HAB. Study design is a single-center retrospective cohort study. Participants were all patients over the age of 16 years who were blood cultures positive at single acute care hospital from April 2013 to March 2018. HAB was defined as positive culture acquired at least 48 h after admission or blood culture-positive patients transferred from other hospital. The primary outcome was 30 day mortality, and the secondary outcome was 1 year mortality. We compared the primary and secondary outcomes between HAB and CAB using logistic regression analyses.

Results: There were 325 participants in this study. The number of patients with CAB was 189 (58.1%). HAB was associated with a higher 30 day mortality rate than CAB (n = 31, 22.8% vs. n = 9, 4.8%, adjusted odds ratio (AOR) 2.60; 95% confidence interval (CI) 1.04–6.53, $p < 0.05$). In the secondary outcome, HAB was also associated with a higher 1 year mortality rate (n = 61/110, 55.5% vs. n = 32/143, 22.4%, AOR 2.27; 95% CI: 1.12–4.58).

Conclusions: Our study showed that HAB was associated with higher mortality than CAB in 30 day mortality and in 1 yr mortality. Thus, we confirmed that HAB is distinct from CAB concerning the differences of outcomes.

KEYWORDS
bacteremia, community-acquired bacteremia, empiric therapy, hospital-acquired bacteremia, infectious disease, sepsis

1 | INTRODUCTION

In recent years, the opportunity to divide a specific infection into several subgroups has increased. A subgroup is defined as a group with characteristic clinical symptoms and outcomes divided according to the clinical background of patients with the same disease syndrome. For example, healthcare-associated pneumonia (HCAP) and pneumonia in younger patients are among the

proposed "subgroups".[1,2] Kollef et al.[1] showed that patients with HCAP faced higher mortality rates than those with community-acquired pneumonia (CAP). Hospital-acquired pneumonia (HAP) is one of the most common subgroups of pneumonia[3] and is associated with significant increases in cost, length of stay, and mortality.[4]

Each subgroup in one infectious category has different epidemiological characteristics and prognosis from other groups. Therefore, understanding the subgroup in infectious syndrome is critical. Without accurate information on epidemiology and microbiology, physicians cannot design and formulate an effective antibiotic regimen for likely pathogens.[5–7] We would be able to predict the microbiology, and prognosis and detere clinical treatment if we could recognize the subgroup.

Sepsis is a common and serious condition that causes systemic inflammation and organ dysfunction, which often leads to death. Numerous studies have described the epidemiology of severe sepsis. For this reason, various subgroups have been proposed for sepsis. Previous studies have shown that healthcare-associated sepsis or hospital-acquired sepsis is associated with increased resource utilization and mortality compared with community-acquired sepsis.[8,9]

However, studies to address the subgroup of bacteremia have been limited. Kollef et al.[10] observed that patients with healthcare-acquired bacteremia (HCAB) had higher mortality rates than those with community-acquired bacteremia (CAB). However, less is known about the significance of hospital-acquired bacteremia (HAB). A few literature showed that nosocomial onset in tertiary institutions[11] and healthcare-associated onset[12] are risk of short-term mortality. However, there were no studies that have investigated CAB and HAB in general acute care hospitals in Japan on mortality, epidemiological differences such as differences of diagnosis. Therefore, we investigated the clinical characteristics, microbiology of bacteremia and we verified the prognostic difference between CAB and HAB. We aimed to detere whether HAB is a unique subgroup and to describe its epidemiology and outcomes.

2 | METHODS

2.1 | Design and setting and study population

We conducted a retrospective cohort study at single acute care hospital that has 220 beds and no intensive care unit. We reviewed the electronic medical records of consecutive patients entering the hospital between April 2013 and March 2018. We investigated all patients over the age of 16 years who showed positive blood cultures including information on their gender, age, vital signs, laboratory data, comorbidities, measure of disease severity, microbiology, clinical diagnosis at admission, and bacteremia. All hospitalized patients and outpatients aged ≧16 years were screened for bacteremia, and eligible patients were identified using a standardized case definition.

2.2 | Definition

Bacteremia was determined using blood culture, and a patient was considered to be positive for bacteremia if one set of the blood cultures was positive regardless of the bacterial species. Such condition was defined as one bacteremic episode. However, even if the same bacterial species from the same patient was repeatedly detected within 30 days, assuming that the first positive day as day 0, subsequent detection after the second time was ignored.

2.3 | Contamination

Blood culture was considered contaminated if one or more of the following organisms were identified in only one of a series of blood culture specimens: coagulase-negative *Staphylococcus* species (CNS), *Propionibacterium acnes*, *Micrococcus* species, "viridans"-group *streptococci*, *Corynebacterium* species, or *Bacillus* species. A blood culture series was defined as one or more specimens collected serially within a 24 h period to detect a bacteremic episode.[13]

2.4 | Hospital-acquired bacteremia

Bacteremia was classified as CAB or HAB. We defined HAB as a positive blood culture infection that was acquired after at least 48 h of admission to the hospital. We also defined HAB as cases in which the patients were transferred to our hospital for examination and treatment from previous hospitals where they hospitalized over 48 h, and the blood culture collected within 48 h was positive. The rest were classified as CAB. This definition was based on the HAP criteria.[14]

2.5 | Outcomes

The primary outcome was 30 day mortality. The secondary outcome was 1 year mortality. Secondary outcomes were tracked by referring to the hospital history on the electronic medical record.

2.6 | Exposure

For the primary and secondary outcomes, we selected age, gender, consciousness disorder, albumin (g/dl), and Charlson Comorbidity Index (CCI) as confounding factors. We selected age and gender as basic information. In addition, we selected the following items to adjust the severity of the disease. Consciousness disorder has been known as an indicator of the severity of various diseases. For example, APACHE-2 score, which is the prediction criteria in ICU hospitalized patients, includes the consciousness disorder as severity index.[15] Serum albumin has been shown to increase mortality as it decreases.[16] CCI has been used as a tool to predict hospital

mortality.[17] Although we set many explanatory variables, they are within a statistically reliable range.

2.7 | Statistical analysis

HAB patients were compared with CAB patients concerning demographics, clinical and microbiological characteristics, and primary or secondary outcomes. Continuous normally distributed variables were compared using Student's *t* test, and the Mann-Whitney *U* test was used to compare nonparametric variables.

For the primary outcome, the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for the likelihood of 30 day mortality were estimated using a multiple logistic regression model. In the logistic regression model, we adjusted for the clinically relevant all confounding factors shown in an exposure. The same analysis was also performed on the secondary outcome. A *p*-value of <0.05 was considered statistically significant. All analyses were performed with multiple imputation methods using SPSS version 22.0 for Windows (SPSS Inc,). We could not neglect the missing values for certain variables such as albumin (9.0%). Therefore, we encoded these missing values as "unknown states" and included all patients in the analysis.

2.8 | Ethical consideration

This study was approved by the Institutional Review Boards of the surveyed Hospital. Since our research was a retrospective study, we did not obtain consent from the patients. However, we displayed a poster in the hospital for a certain period describing study contents and contact address for the rejection of participation in our study. We confirmed that the analysis results were correctly anonymized so that patients would not suffer privacy issues.

3 | RESULTS

3.1 | Baseline characteristics

The cohort study consisted of 396 patients. A total of 71 patients were excluded (15 patients were children, two patients lacked the outcome information, 10 patients with no antibiotics treatment, and 44 patients met the contamination criteria). As a result, 325 patients were enrolled in this study. Baseline characteristics were shown in Table 1. The median age of the participants was 76.0 years and 193 patients (59.4%) were men. The number of patients with HAB was 136 (41.8%). After 48 h or more of hospitalization, 134 patients were infected, and 2 patients were transferred from another hospital with 48 h or more hospital stay. We could follow the 30 day mortality of all patients and the 1-year mortality of 253 patients (77.8%).

The microbiology of CAB and HAB is displayed in Table 2. There were 332 pathogens isolated. *Escherichia coli* was the most common isolated bacteria in both CAB and HAB, and CNS was the most common in HAB. ESBL was found equally in the CAB and HAB groups, and however, the mortality in the HAB group was higher than that in the CAB group. Pathogens known as cause of nosocomial infection such as *Pseudomonas aeruginosa*, *Enterobacter* species, and CNS were more frequently cause of HAB than CAB (Table 2).

The diagnosis of bacteremia is displayed in Table 3. In HAB, there were significantly more catheter infections, suture failure, and significantly fewer cases of urinary tract infections, pyogenic spondylitis, and acute abdomen. Acute abdomen consisted of appendicitis, intestinal perforation, and intestinal necrosis. In addition, there were

TABLE 1 Characteristics of Participants at Baseline

	CAB (*n* = 189) (%)	HAB (*n* = 136) (%)	*p*-value	All Participants *n* = 325 (%)
Characteristic				
Age, years median(IQR)	76.0 (68.0–82.0)	77.0 (68.3–83.0)	0.36	76.0 (68.0–82.5)
Gender (male) (%)	111(58.7)	82(60.2)	0.78	193(59.4)
BMI (IQR)	22.3 (19.8–24.9) (*n* = 169)	22.4 (20.1–24.8) (*n* = 127)	0.95	22.3 (20.0–24.8) (*n* = 296)
Bedridden activity at admission (%)	70/186(37.6)	54(39.7)	0.71	124(38.2) (*n* = 322)
Consciousness disturbance (%)	26/188(13.8)	44(32.4)	<0.01	70(21.6) (*n* = 324)
Albumin (g/dl) (IQR)	3.5(2.9–3.9) (*n* = 176)	2.9(2.5–3.4) (*n* = 121)	<0.01	3.2(2.7–3.7) (*n* = 297)
eGFR (mL//1.73 m^3) (IQR)	44.3(26.0–67.1)	56.8(33.9–79.6) (*n* = 134)	<0.01	50.6(29.4–71.5) (*n* = 323)
CCI (IQR)	2.0(1.0–4.5)	4.0(2.0–7.0)	<0.01	3.0(2.0–6.0)
Outcome				
30 day mortality	9(4.8)	31(22.8)	<0.01	40(12.3)
1 year mortality	32/143(22.4)	61/110(55.5)	<0.01	93/253(36.8)

Note: Values for categorical variables indicate percentage; values for continuous variables indicate medican.

Abbreviations: BMI, body mass index BMI is the wight in kilograms divided by the square of the height in meters; CAB, community-acquired bacteremia; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; HAB, hospital-acquired bacteremia; IQR, interquartile range.

TABLE 2 Pathogens and mortality

	Incidence			Mortality	
	CAB	HAB		CAB	HAB
	(*n* = 192) (%)	(*n* = 140) (%)	*p*-value[a]	(*n* = 9) (%)	(*n* = 31) (%)
GPC					
S.aureus	20(10.4)	21(10.9)	0.21		2/21(9.5)
MRSA	6(3.1)	12(6.3)	<0.05		4/12(33.3)
S.pneumoniae	3(1.6)	2(1.4)	0.92		
Enterococcus sp.	6(3.1)	4(2.9)	0.89	1/6(16.7)	2/4(50.0)
CNS	15(7.8)	26(18.6)	<0.01	1/15(6.7)	1/26(3.8)
GNR					
E.coli	73(38.0)	28(20.0)	<0.01	1/73(1.4)	10/28(35.7)
ESBL	7(3.6)	3(2.1)	0.43		2/3(66.7)
K.pneumoniae	26(13.5)	9(6.4)	<0.05	2/26(7.7)	2/9(22.2)
K.oxytoca	6(3.1)	2(1.4)	0.32		
P.aeruginosa	1(0.5)	5(3.6)	<0.05		2/5(40.0)
Enterobacter sp.	5(1.8)	10(7.1)	<0.05		2/10(20.0)
B.fragilis	0(0.0)	3(2.1)	0.39		
Acinetobacter sp.	1(0.7)	2(1.4)	0.78		
Other	36(18.8)	28(20.0)		4/36(11.1)	4/28(14.3)

Abbreviations: CNS, Coagulase-negative *Staphylococci*; ESBL, extended spectrum β-lactamases; GNR, gram-negative rod; GPC, gram-positive cocci; MRSA, Methicillin-resistant *Staphylococcus aureus*.

[a]*p*-value were calculated using the chi-square test or Fisher's exact test for categorical variables as appropriate.

significantly more bacteremia cases in which the infected organ could not be identified in HAB.

3.2 | Primary and secondary outcomes

An unadjusted analysis showed that HAB had a higher mortality rate than CAB (Table 1). In a logistic regression analysis adjusting for possible confounders, HAB was associated with a higher 30 day mortality rate than CAB (*n* = 31, 22.8% vs. *n* = 9, 4.8%, adjusted odds ratio (AOR) 2.60; 95% confidence interval (CI) 1.04–6.53, $p < 0.05$). The consciousness disturbance (AOR 6.20; 95% CI: 2.69–14.22, $p < 0.01$) was suggested to relate to high mortality. High albumin (/g/dl) (AOR 0.49; 95% CI: 0.2–0.85, $p < 0.01$) was suggested to relate to low mortality. In the secondary outcome, HAB was also associated with a higher 1 year mortality rate (*n* = 61/110, 55.5% vs. *n* = 32/143, 22.4%, AOR 2.27; 95% CI: 1.12–4.58) (Table 4).

4 | DISCUSSION

We showed the clinical characteristics of CAB and HAB in a general hospital in this study. Furthermore, we confirmed that HAB is distinct from CAB concerning the differences between clinical characteristics and outcomes. There have been several studies on bacteremia; however, bacteremia has not been classified into subgroups in most of them. In recent years, classifications, such as HCAB, CAB, HAB, or nosocomial bloodstream infection, have been proposed as new classifications of bacteremia.[18,19] These classifications were made for the need for initial broad empiric antimicrobial therapy in patients with HAB or HCAB. Currently, many studies on sepsis and HCAB have been advancing.

Our study showed that HAB was associated with higher mortality than CAB. There are two possible reasons for this result. In our study, the rate of *E. coli* and *Klebsiella pneumoniae* was significantly lower in HAB, and the rate of *P. aeruginosa*, *Enterobacter* sp., MRSA and CNS was higher in HAB. Kollef et al. indicated a higher proportion of MRSA in HCAB than CAB.[10] The characteristic of the bacteria found in HAB is that it can quickly develop resistance to various antibiotics. The mortality rate of patients with *P. aeruginosa* and *Enterobacter* sp. was high in our study. Bacteremia with multidrug-resistant bacteria was shown to have a worse prognosis than bacteremia with multidrug-sensitive bacteria, due to failure of initial empiric therapy.[20] This suggests that empiric therapy at the start of antibiotics start may not cover the cause of bacteria.

However, HAB caused by CNS, MRSA, *Enterococcus* sp., *E. coli*, and *K. pneumoniae*, tended to have a higher mortality rate than CAB with the same bacteria. We could not explain this difference only

TABLE 3 Diagnosis of bacteremia

	Incidence			Mortality	
	CAB	HAB	*p*-value[c]	CAB	HAB
	(*n* = 189) (%)	(*n* = 136)(%)		(*n* = 9) (%)	(*n* = 31) (%)
Catheter-related infection	2(1.0)	17(12.5)	<0.01		2/17(11.8)
Pneumonia	15(7.9)	17(11.8)	0.22	1/15(6.7)	5/17(29.4)
Cholangitis	26(13.6)	14(10.4)	0.28		3/14(21.4)
Suture failure[a]	0(0.0)	13(9.0)	<0.01		1/13(7.7)
Urinary tract infection	56(29.3)	8(5.6)	<0.01		
Febrile Neutropenia	2(1.0)	3(2.1)	0.43		1/3(33.3)
Infective endocarditis	8(4.2)	3(2.1)	0.28		2/3(66.7)
Cholecystitis	3(1.6)	2(1.4)	0.84		
Pyogenic spondylitis	11(5.8)	2(1.4)	<0.05		
Liver abscess	2(1.0)	1(0.7)	0.73		
Acute abdomen[b]	7(3.7)	0(0.0)	<0.05		
Cellulitis	3(1.6)	0(0.0)	0.13		
Emphysematous cystitis	2(1.0)	0(0.0)	0.22		
Other infection	13(6.8)	5(3.5)	0.18	3/13(23.1)	
Unknown bacteremia	39(21.5)	51(39.6)	<0.01	5/39(12.8)	17/51(33.3)

[a]Sture failure; Intra-abdoal abscess or peritonitis due to suture failure after intra-abdoal surgery. All diagnosis were postoperative diagnosis.

[b]Acute abdomen; appendicitis, intestinal perforation, intestinal necrosis

[c]*p*-value were calculated using the chi-square test or Fisher's exact test for categorical variables as appropriate.

TABLE 4 Adjusted OR (AOR) of 30 day mortality and 1 year mortality

	Adjusted		
	OR	95% CI	*p*-value
30 day mortality			
HAB	2.60	1.04–6.53	<0.05
Age per y	1.00	0.96–1.04	0.85
Gender(male)	1.76	0.73–4.21	0.21
Consciousness disturbance	6.20	2.69–14.22	<0.01
Albumin (/g/dl)	0.49	0.21–0.85	<0.05
CCI (/per one score)	1.05	0.91–1.22	0.49
1 year mortality			
HAB	2.27	1.12–4.58	<0.05
Age per y	1.06	1.01–1.10	<0.01
Gender(male)	1.12	0.55–2.26	0.76
Consciousness disturbance	4.60	1.97–10.79	<0.01
Albumin (/g/dl)	0.44	0.24–0.79	<0.01
CCI (/per one score)	1.40	1.21–1.62	<0.01

Abbreviations: CI, confidence interval; OR, odds ratio.

by the difference of bacterial species. Therefore, it is possible that differences in infected organs may affect mortality even with the same species. Compared with CAB, HAB had more catheter-related infections, suture failures, and bacteremia with unknown infected organs, and fewer cases of urinary tract infections, pyogenic spondylitis, and acute abdomen.

In addition, the difference in mortality was shown between HAB and CAB, even in the same infected organs. This result could not be explained only by the resistance of the bacteria or difference of the infected organs. We considered the reason for this result was the background of the patients. HAB had lower albumin and higher CCI than CAB in univariate analyses of patient backgrounds. Although these two factors did not make a significant difference in the multivariate analysis for primary outcomes, lower albumin showed a tendency to decrease mortality at a high level, and CCI showed a tendency to increase mortality at a high level. Hypoalbuemia has a poor prognostic risk factor in various diseases.[16,21,22] Originally, CCI was developed to classify comorbid conditions to estimate the risk of mortality.[23] Therefore, HAB patients are considered likely to have poor general condition than CAB patients at bacteremia diagnosis. These differences might lead to prognostic differences between HAB and CAB. For example, in our study, pneumonia with HAB had a higher mortality rate than pneumonia with CAB. This might be because pneumonia with HAB was HAP and pneumonia with CAB was CAP. HAP has been shown to have higher mortality than CAP,[24] and it has been confirmed that having bacteremia does not change the trend.

In this study, it was suggested that 30 day mortality was associated with a consciousness disorder and hypoalbuemia (per g/dl). In

addition, it was suggested that 1 year mortality was associated with old age (per year), consciousness disorder, hypoalbuemia (per g/dl), and high CCI level (per one score). Aging and consciousness disturbance are prognostic factors in various diseases, for example, both factors were included in CURB65,[25] a prognostic tool in pneumonia. Thus, they represented the severity of the disease itself. It would be natural that factors with high severity were mortality predictors.

5 | LIMITATIONS

This study has several limitations. This was a retrospective study, and it is possible that a selection bias affected the results. Patient severity scores such as Pitt bacteremia score and APACHE-2 score should be included in the covariates as known factors related to bacteremia mortality. However, since we collected data on electronic medical records in this study, we could not clarify these scoring. We could only follow 78.5% of the participants with 1 year mortality, and the results may differ if all participants were pooled. In addition, this study was a single-center study, and the results might change in tertiary facilities and community-based institutions. Because it is originally a single-center study, the quality of treatment must be assessed to ensure external validity. For example, an assessment of whether empirical treatment for multidrug-resistant bacteria was appropriate would be necessary. Empiric therapy should be compared with the drug susceptibility of the causative organism to verify whether the treatment was appropriate. However, this was not possible because this study is a retrospective study. Although MRSA and ESBL could be traced, other multidrug-resistant bacteria and two-drug resistant *Pseudomonas aeruginosa* could not be exaed. In this study, we adopted a reliable diagnosis name with the electronic medical record. Thus, for example, most of the CNS infections in CAB may not adopt a presumed diagnosis, such as being classified as unknown bacteremia rather than Catheter-related infection. Finally, as with other cohort studies, confounding factors might be a threat to validity. We carefully exaed the validity; however, there is a possibility of confounding, including unknown health risks. Based on our findings, it is necessary to conduct prospective study on bacteremia.

6 | CONCLUSIONS

We investigated the clinical characteristics, bacteremia's microbiology, and verified the prognostic difference between community-acquired bacteremia (CAB) and hospital-acquired bacteremia (HAB). Compared with CAB, HAB had more catheter-related infections, suture failures, and bacteremia with unknown infected organs. On the other hand, HAB had fewer cases of urinary tract infections, pyogenic spondylitis, and acute abdomen. The rates of E. coli and K. pneumoniae were significantly lower in HAB, while P. aeruginosa, Enterobacter sp., and CNS were higher in HAB. Our study also showed that HAB was associated with higher mortality in 30 day and 1 yr than CAB. Thus, we confirmed that HAB is distinct from CAB concerning the differences between clinical characteristics and outcomes.

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CONFLICT OF INTEREST

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