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Original Article

Shift in risk factors for mortality by period of the bloodstream infection timeline

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Abstract *Background:* This study was designed to determine changes in risk factors on the prognosis of patients during each period of the bloodstream infection (BSI) timeline.
Methods: Through an integrated study of multivariable regressions with machine learning techniques, the risk factors for mortality during each period of BSI were analyzed.
Results: A total of 302,303 inpatients who underwent blood cultures during 2011—2021 were enrolled. More than 8 % of BSI cases progressed to subsequent BSI, and risk factors were identified as gut colonization with vancomycin-resistant enterococci (aOR 1.82; 95 % CI 1.47—2.24), intensive care unit admission (aOR 3.37; 95 % CI 3.35—4.28), and current cancer chemotherapy (aOR 1.54; 95 % CI 1.36—1.74). The mean SOFA score of the deceased patients during the first 7 days was 10.6 (SD 4.3), which was significantly higher than those on days 8—30 (7.0 ± 4.2) and after Day 30 (4.0 ± 3.5). BSIs caused by *Acinetobacter baumannii* and *Candida albicans* were more likely to result in deaths of patients for all time periods (all, $P < 0.001$). BSIs caused by *Enterococcus faecalis* and *Enterococcus faecium* were associated with a poor outcome in the period after Day 30 (both, $P < 0.001$). Nonsusceptible phenotypes to β-lactam/β-lactamase inhibitors of *Escherichia coli* and *Klebsiella pneumoniae* influenced the prognoses of patients with BSI in terms of high mortality rates during both days 8—30 and after Day 30.
Conclusion: Influence of microbiological factors on mortality, including BSI-causative microorganisms and their major antimicrobial resistance, was emphasized in both periods of days 8—30 and after Day 30.

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Introduction

Bacterial and fungal bloodstream infections (BSIs) are an important cause of mortality and morbidity, prolonged length of stay (LOS) in hospital, and rising medical costs.[1–5] Based on the well-established practice in the field of infectious disease that measures the 30-day mortality rate, many previous studies have identified prognostic risk factors for patients with BSI.[4,6,7] However, some studies have argued that the burden of BSI is not limited to short-term outcomes and that there are parts that can only be assessed via long-term observations.[1,8,9] This is because the evaluation of short-term outcomes can be strongly influenced by the patient's baseline severity, as BSI occurs more commonly among patients with predisposing comorbidities with a high risk of early mortality.[10]

Patient-related variables, such as the patient's age and sex, intensive care unit (ICU) admission, and underlying illness, have repeatedly been reported to be associated with high short-term mortality rates among patients with BSI.[1,3,5,10] However, whether BSI-causative microorganisms and their antimicrobial resistance (AMR) are associated with an increased mortality rate among patients has been debated.[11–14] The impact of microbiological factors on patient prognosis could be masked by patient factors when comparing only 30-day mortality rates as an outcome of interest. However, an approach that compares the priority risk factors for mortality during each period by dividing the BSI timeline into several periods is still lacking.

We hypothesized that risk factors associated with mortality among patients with BSI might vary by the time period of infection, and microbiological factors could be considered as a risk factor for mortality at the late phase rather than the acute phase of BSI. This study was designed to determine the impact of variables, including patient conditions, causative microorganisms, and their AMR, on the prognosis of patients stratified by period of the BSI timeline.

Methods

Study population and data collection

Data on all adult patients who underwent blood cultures from two tertiary care hospitals (Hospital A and Hospital B in South Korea with 2000 and 800 beds, respectively) during 2011–2021 were retrospectively collected. Patients with a history of hospitalization within three months, transferred from long-term care facilities, and those with invasive catheterization were screened for gut colonization with antibiotic-resistant bacteria. The exclusion criteria were patients with no demographic information, $\geq$20 % missing values, or contaminated blood cultures. Patient-level data were collected, including demographics, underlying comorbidities with age-adjusted Charlson comorbidity index (CCI) score, baseline Sequential Organ Failure Assessment (SOFA) score, LOS in hospital, total medical costs, date of blood culture collection, and date of patient death. To obtain the most abnormal values within 24 h of sampling index blood cultures (Day 0), the maximum and minimum values of vital signs and laboratory test results were extracted. In addition, the use of antimicrobial agents, vasopressors, mechanical ventilators, and indwelling catheters was also investigated.

According to the Centers for Disease Control/National Healthcare Safety Network surveillance definitions,[15] contamination was defined as the isolation of the following microorganisms from the blood cultures: coagulase-negative staphylococci, diphtheroids, *Bacillus* species, *Propionibacterium* species, viridans group streptococci, *Aerococcus* species, or *Micrococcus* species. Polymicrobial infection refers to the isolation of two or more microorganisms from blood cultures within 24 h, and secondary BSI was indicated when a BSI was presumed to have originated from a site-specific infection in another body site. We also defined subsequent BSI (sBSI) as additional isolation of microorganisms other than those identified in index blood cultures from subsequent blood cultures.[3] Empirical therapy was considered as appropriate if the initial regimen included one or more antimicrobial agents susceptible to the causative pathogen. Total medical costs were presented in euros and US dollars by applying exchange rates of 1360.50:1 and 1127.26:1 (average of the study period) to Korean won, respectively.

The primary outcome was patient all-cause mortality during each period of the BSI timeline. To compare very short-term, short-term, and long-term prognostic risk factors, the in-hospital mortality rates during the first 7 days, Day 8 to Day 30 (days 8–30), and after Day 30 from the index blood culture date were calculated. LOS in hospital and medical costs were also assessed as secondary outcomes.

Propensity score matching

To reduce selection bias in imbalanced data and to analyze the impact of BSI on clinical outcomes, propensity score (PS) matching was conducted. The nearest neighbor matching method was used to match each patient group (1:1 match) based on five baseline variables: patient age, sex, admission year, CCI score, and baseline SOFA score. Matching was conducted so that the logit difference of the PS was less than 0.2 times the standard deviation (SD).

Statistical analysis

All variables were evaluated by the Kolmogorov–Smirnov test to assess Gaussian distributions. Descriptive statistics are described either as numbers and percentages for categorical variables or as the means and SDs [or medians and interquartile ranges (IQRs) in the case of nonparametric variables] for continuous variables. The statistical significance between groups was tested with either the chi-square test (or Fisher's exact test) for qualitative data or Student's t test (or the Mann–Whitney U test) for quantitative data.

Both logistic regression and Cox regression were performed for univariable and multivariable analyses to identify the risk factors for the occurrence of sBSI and mortality. Because numerous variables were significantly associated with clinical outcomes in univariable analyses, machine learning techniques were used in the variable selection processes for multivariable analysis models. The

dataset was randomly split into 4:1 and assigned to a training set and a test set. Candidate algorithms were the Attentive Interpretable Tabular Learning neural network (TabNet), K-nearest neighbor, light gradient boosting, and extreme gradient boosting (XGBoost). For each model, hyperparameter tuning was conducted through optima or grid search and fivefold cross-validation. To select the top parameters for multivariable analyses, we interpreted our machine learning models via Shapley additive explanation (SHAP) summary plots. Machine learning analyses were conducted using Python programming software version 3.7.12 (Python Software Foundation, Wilmington, DE).

The Kaplan—Meier estimator was employed to analyze outcomes, and differences between groups were assessed using the log-rank test. All reported p values were two-sided, and $p < 0.05$ was assumed to be statistically significant. Statistical analyses and graphic compositions were conducted using R statistical software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

This study was approved by the Institutional Review Board (approval no.: 3-2021-0373) of Yonsei University Gangnam Severance Hospital (Seoul, Republic of Korea).

Results

Baseline characteristics of the study population

A total of 302,303 unduplicated adult inpatients (231,035 in Hospital A and 71,268 in Hospital B) were enrolled in this study, excluding 24,341 by exclusion criteria among 326,644 patients who underwent blood cultures during the study period (Fig. 1). Positive blood cultures for bacterial and/or fungal pathogens (25,041/302,303, 8.3 %) were frequently identified among patients of male sex, old age, and/or with high CCI and baseline SOFA scores (all $p < 0.001$; Table 1 and Table S1). Urogenital tract was the most common source of secondary BSI (25.1 %), followed by respiratory tract (12.1 %) and gastrointestinal tract (10.7 %). PS matched analyses showed that positive blood cultures were associated with not only a significantly increased 30-day mortality rate and LOS of patients but also significantly elevated total medical costs (all $p < 0.001$; Fig. 2).

Index BSI

Escherichia coli was the most common index BSI-causative microorganism (32.3 %), followed by *Klebsiella pneumoniae* (15.5 %), *Staphylococcus aureus* (10.4 %), and *Enterococcus faecium* (7.4 %) (Fig. 3 and Table S2). *E. coli*-BSI was prominent among patients ≥65 years of age, among females, and among patients with CCI scores <5.6 and baseline SOFA scores <5.2 (both were below average in patients with BSI). In contrast, *Enterococcus*-BSI and candidemia were frequent among patients with high CCI scores, and BSIs caused by glucose-nonfermenting Gram-negative bacilli, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, were frequently identified among patients with high baseline SOFA scores. BSIs showed discriminatory clinical outcomes by causative microorganism (Fig. 4 and Table S3). While both the adjusted hazard ratio (aHR) for 30-day mortality and consequent medical costs of *E. coli*-BSI were low, those of *A. baumannii*-BSI and candidemia were high.

Subsequent BSI

Of 25,041 patients with BSI, 2034 (8.1 %) progressed to sBSI, which occurred frequently among patients with long LOS, medical devices including mechanical ventilators, arterial/venous catheters, and indwelling catheters, and high CCI and baseline SOFA scores. After adjusting for other confounders, risk factors for sBSI were identified as gut colonization with vancomycin-resistant enterococci (VRE) [adjusted odds ratio (aOR) 1.82; 95 % confidence interval

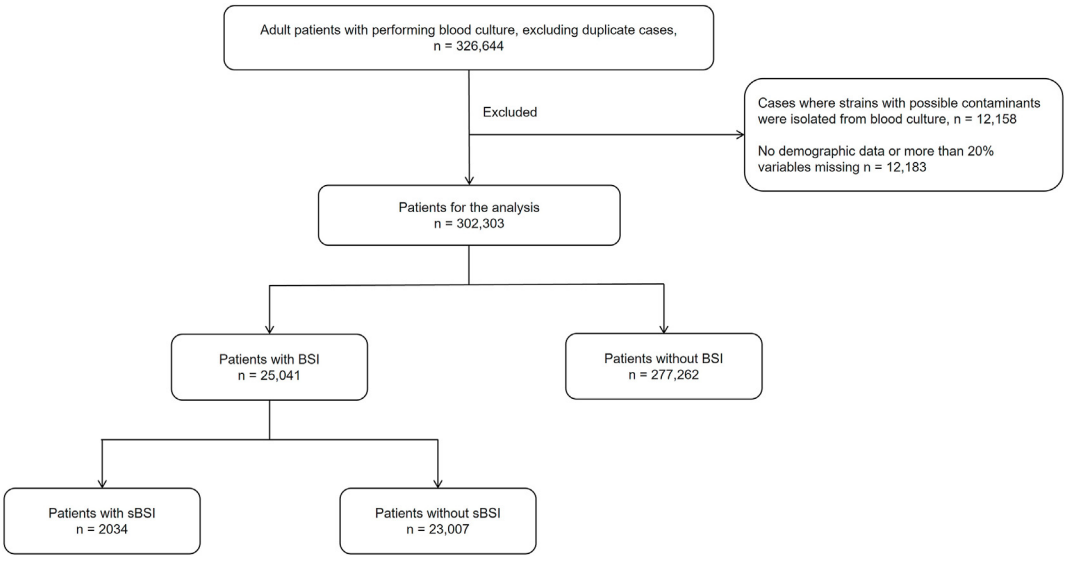

Figure 1. Flowchart of patient selection process. BSI, bloodstream infection; sBSI, subsequent BSI.

Table 1 Baseline characteristics of patients with and without BSI.

Characteristics	Total	No BSI	BSI	p
	(N = 302,303)	(N = 277,262)	(N = 25,041)	
Patient's age	60.5 ± 17.2	60.0 ± 17.4	65.5 ± 14.4	<0.001
Female sex	140,138 (46.4 %)	128,793 (46.5 %)	11,345 (45.3 %)	0.01
ICU admission	38,660 (12.8 %)	33,005 (11.9 %)	5655 (22.6 %)	<0.001
Hospital length of stay	8 [3–17]	7 [3–15]	16 [7–34]	<0.001
7-day mortality	10,126 (3.3 %)	7324 (2.6 %)	2802 (11.2 %)	<0.001
Mortality date, average ± SD	3.0 ± 2.2	3.1 ± 2.2	2.6 ± 2.1	<0.001
Mortality during days 8–30	13,224 (4.4 %)	10,870 (3.9 %)	2354 (9.4 %)	<0.001
Mortality date, average ± SD	17.5 ± 6.6	17.7 ± 6.6	17.0 ± 6.6	<0.001
In-hospital mortality after Day 30	38,317 (12.7 %)	33,748 (12.2 %)	4569 (18.2 %)	<0.001
Mortality date, average ± SD	140.8 ± 95.0	142.0 ± 92.4	131.9 ± 111.9	<0.001
Total medical costs (USD $)	3736.8 [1488.6–9033.0]	3502.9 [1389.0–8408.5]	7725.4 [3389.4–19266.7]	<0.001
Total medical costs (euro €)	4509.9 [1796.6–10902.0]	4227.7 [1676.3–10148.3]	9323.9 [4090.8–23253.2]	<0.001
SOFA score	1 [0–4]	1 [0–3]	4 [2–8]	<0.001
Infection sources (may be multiple)				
Gastrointestinal tract	–	–	2673 (10.7 %)	–
Catheter-related			1430 (5.7 %)	
Respiratory tract			3020 (12.1 %)	
Urogenital tract			6282 (25.1 %)	
Skin and soft tissue			1128 (4.5 %)	
Other sites			104 (0.4 %)	
Charlson comorbidity index score	4.5 ± 2.7	4.4 ± 2.7	5.6 ± 2.6	<0.001
Solid cancer	117,549 (38.9 %)	105,748 (38.1 %)	11,801 (47.1 %)	<0.001
Diabetes mellitus	40,049 (13.2 %)	35,203 (12.7 %)	4846 (19.4 %)	<0.001
Chronic obstructive pulmonary disease	9920 (3.3 %)	9167 (3.3 %)	753 (3.0 %)	0.01
Leukaemia	4359 (1.4 %)	3685 (1.3 %)	674 (2.7 %)	<0.001
Liver disease	24,945 (8.3 %)	21,317 (7.7 %)	3628 (14.5 %)	<0.001
Kidney disease	16,943 (5.6 %)	14,956 (5.4 %)	1987 (7.9 %)	<0.001
Devices				
Ventilator	15,337 (5.1 %)	12,233 (4.4 %)	3104 (12.4 %)	<0.001
Arterial line	16,541 (5.5 %)	14,261 (5.1 %)	2280 (9.1 %)	<0.001
Central venous line	35,083 (11.6 %)	29,161 (10.5 %)	5922 (23.6 %)	<0.001
Indwelling catheter	78,794 (26.1 %)	68,749 (24.8 %)	10,045 (40.1 %)	<0.001
COVID-19	655 (0.2 %)	596 (0.2 %)	59 (0.2 %)	0.547
CRE/CPE colonization	1249 (0.4 %)	750 (0.3 %)	499 (2.0 %)	<0.001
Clostridioides difficile infection	2336 (0.8 %)	1827 (0.7 %)	509 (2.0 %)	<0.001
VRE colonization	1920 (0.6 %)	1194 (0.4 %)	726 (2.9 %)	<0.001

Data are presented as numbers (%), means ± standard deviations, or medians [1st-3rd quartiles].
BSI, bloodstream infection; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; COVID-19; coronavirus diseases-19; CRE, carbapenem-resistant Enterobacteriaceae; CPE, carbapenemase-producing Enterobacteriaceae; VRE, vancomycin-resistant enterococci.

(CI) 1.47–2.24], and current cancer chemotherapy (aOR 1.54; 95 % CI 1.36–1.74) (Table S4).

The relative frequency of causative microorganisms in the sBSI was significantly different from that of the index BSI. *E. faecium* was identified with the highest frequency of 20.3 %, followed by *K. pneumoniae* (9.5 %), *A. baumannii* (8.6 %), and *Candida albicans* (7.5 %); however, *E. coli* and *S. aureus* were low at <5 % (Table S5). While index BSIs caused by *Candida* species, *E. coli*, or *K. pneumoniae* frequently progressed to *E. faecium*-sBSI, those caused by *Serratia* species and *Streptococcus pneumoniae* frequently progressed to *A. baumannii*-sBSI (Fig. S1). It was noteworthy that the index BSI caused by *E. coli* nonsusceptible to third-generation cephalosporins (3GCs) and *K. pneumoniae* nonsusceptible to 3GCs, β-lactam/β-lactamase inhibitors (BLBLIs), and/or carbapenems showed a positive correlation with the occurrence of *E. faecium*-sBSI (Table S6).

Mortality attributed to patient factors by period of the BSI timeline

The crude mortality rates of the patients with BSI during each period of the BSI timeline, during the first 7 days, days 8–30, and after Day 30, were 11.2 %, 9.4 %, and 18.2 %, respectively (Table 1), which were significantly higher for all the time periods compared with those of the non-BSI patients ($p < 0.001$ for all). The baseline characteristics of the deceased patients were different by time period (Table 2). In particular, the mean SOFA score of the

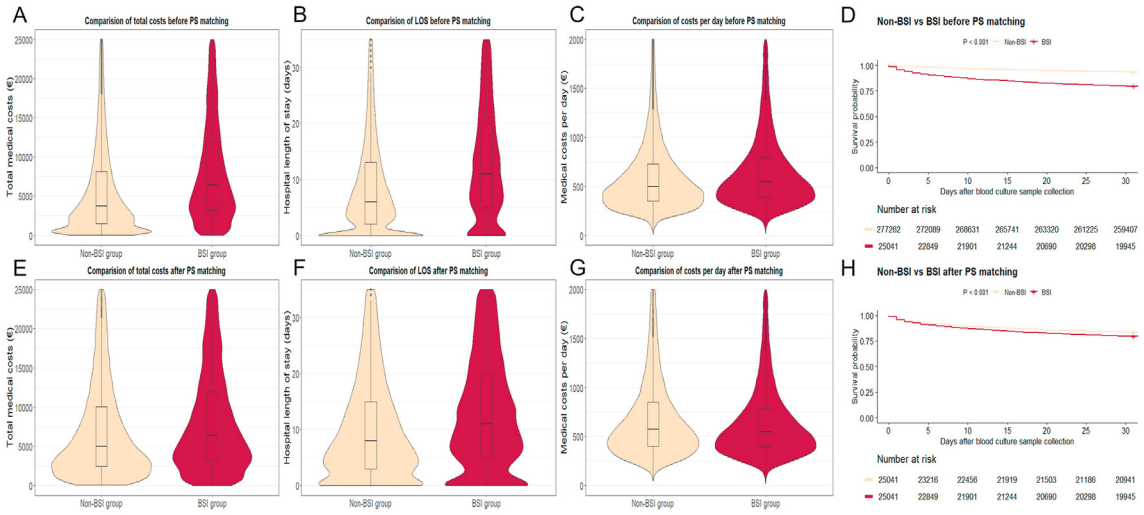

Figure 2. Comparison of medical costs, hospital length of stay and 30-day mortality between patients with and without BSI. Comparison of medical costs, hospital length of stay and 30-day mortality between patients with and without BSI before propensity score matching (A—D) and after propensity score matching (E—H).

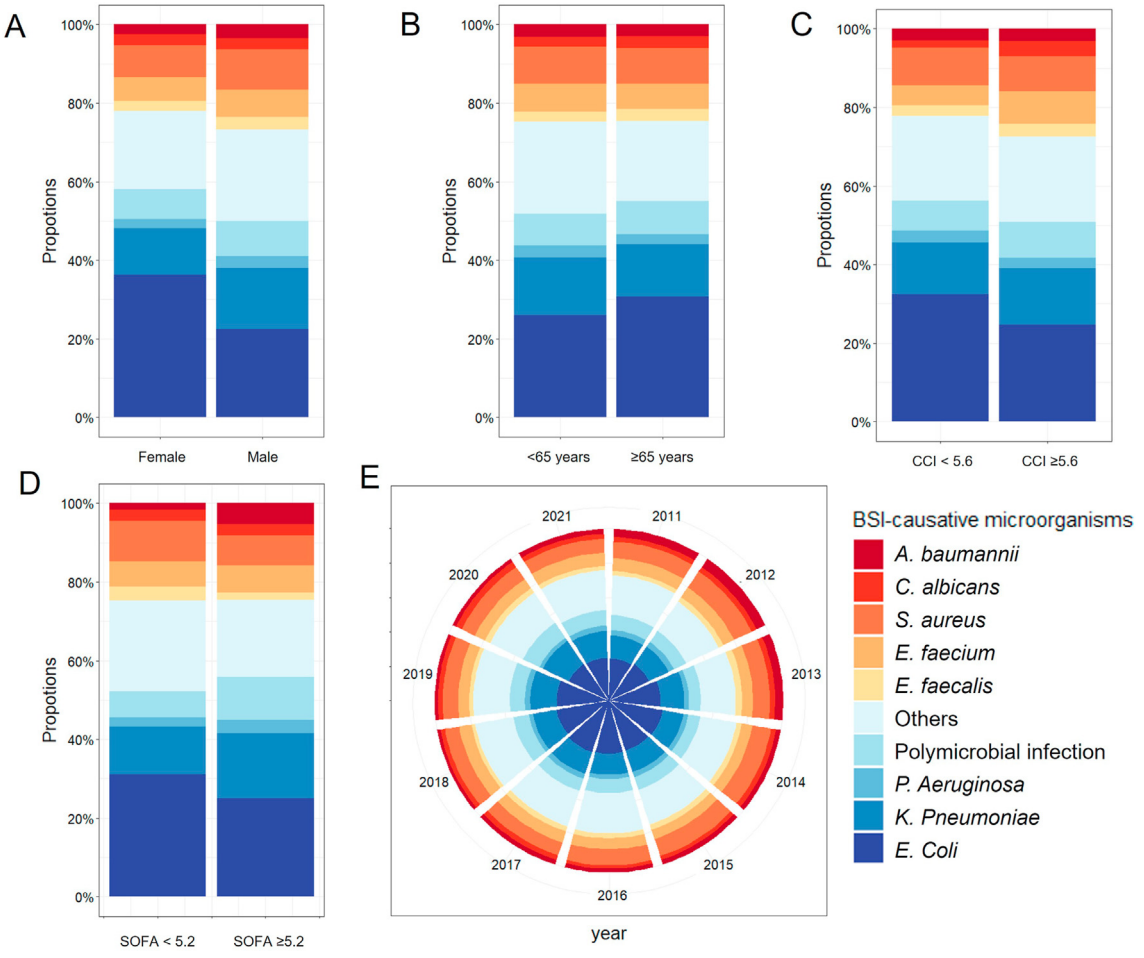

Figure 3. Distribution of BSI-causative microorganisms by sex (A), age group (B), groups above and below the mean Charlson comorbidity index score (C), SOFA score (D), and the year of disease onset. Data in each column are presented as a proportion of total BSI cases. All microorganisms, accounting for less than 1 % of the total cases, were clustered together as "Others"; detailed data are expressed in Table S2.

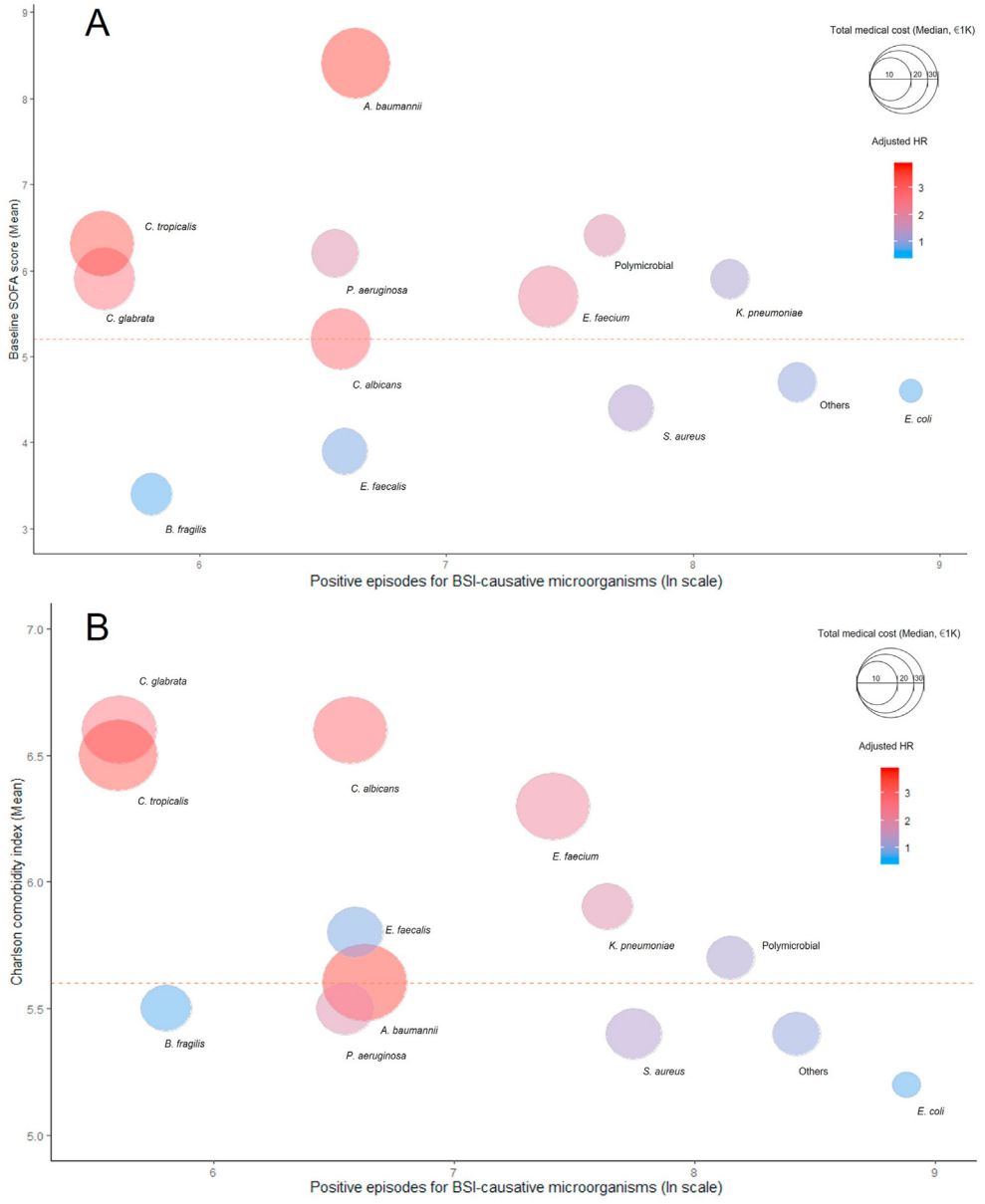

Figure 4. Incidence of BSI and its clinical progression stratified by BSI-causative microorganisms. In these bubble plots, the x axis expresses the total number (natural log scale) of cases of each BSI-causative microorganism infection, the y axis represents the baseline SOFA score (A) or Charlson comorbidity index score (B) for patients with BSI, and the red dotted lines indicate the mean scores for each among all cases. The bubble area is scaled by mean total medical costs and the colour scaling indicates the adjusted hazard ratio (aHR) for 30-day mortality calculated in multivariable analysis models. As expressed in the legend, an HR less than 1 increases the blue tint and greater than 1 darkens the red.

deceased patients during the first 7 days was 10.6 (SD 4.3), which was significantly higher than those during days 8—30 (7.0 $\pm$ 4.2) and after Day 30 (4.0 $\pm$ 3.5) (Fig. S2).

Machine learning-based feature assortment was conducted for all independent variables, and predictors with SHAP analyses were selected from the best performing XGBoost classifiers (Table S7 and Fig. S3). Multivariable analysis models consisting of these variables are presented in Table 2. For all time periods, a high baseline SOFA score, high CCI score, current cancer chemotherapy, high C-reactive protein levels, and low hemoglobin concentrations were significantly associated with a high mortality rate. While catheter or urogenital tract-originated secondary BSI has a favorable prognosis, respiratory tract-originated secondary BSI showed a poor outcome. Appropriate empirical therapy was significantly associated with low mortality rates of patients both during the first 7 days and on days 8—30 (both $p < 0.001$).

Mortality attributed to BSI-causative microorganisms by period of the BSI timeline

The statistical association between BSI-causative microorganisms and patient mortality rate varied by period. *E. coli*-

Table 2 Multivariable analyses using logistic regression of mortality risk factors for patients with BSI.

Variables	7-day mortality		Mortality during days 8—30		In-hospital mortality after Day 30	
	aOR (95 % CI)	p	aOR (95 % CI)	p	aOR (95 % CI)	p
Patient's age	1.01 (1.00—1.01)	<0.001	0.99 (0.99—1.00)	0.004	0.98 (0.98—0.99)	<0.001
Male sex	0.89 (0.80—0.98)	0.02	1.04 (0.94—1.14)	0.49	1.11 (1.03—1.20)	0.01
ICU admission	0.38 (0.33—0.44)	<0.001	1.36 (1.19—1.55)	<0.001	0.95 (0.85—1.07)	0.38
SOFA score	1.41 (1.39—1.44)	<0.001	1.14 (1.12—1.16)	<0.001	1.04 (1.02—1.05)	<0.001
Infection origin (may be multiple)						
Gastrointestinal tract	0.51 (0.42—0.60)	<0.001	1.00 (0.87—1.15)	0.99	1.34 (1.20—1.51)	<0.001
Catheter-related	0.35 (0.27—0.45)	<0.001	0.69 (0.57—0.83)	<0.001	0.97 (0.83—1.13)	0.67
Respiratory tract	1.12 (0.96—1.30)	0.14	1.29 (1.11—1.50)	0.001	1.39 (1.21—1.59)	<0.001
Urogenital tract	0.57 (0.50—0.65)	<0.001	0.75 (0.67—0.85)	<0.001	0.91 (0.83—1.00)	0.05
Charlson comorbidity index	1.12 (1.10—1.14)	<0.001	1.23 (1.21—1.25)	<0.001	1.32 (1.29—1.34)	<0.001
Current cancer chemotherapy	1.90 (1.66—2.16)	<0.001	1.55 (1.37—1.76)	<0.001	1.71 (1.54—1.89)	<0.001
Devices						
Ventilator	1.49 (1.27—1.76)	<0.001	1.25 (1.05—1.49)	0.01	0.91 (0.77—1.09)	0.31
Central venous line	0.88 (0.78—0.98)	0.03	0.66 (0.58—0.75)	<0.001	0.94 (0.84—1.05)	0.27
Indwelling catheter	1.38 (1.24—1.54)	<0.001	1.08 (0.97—1.20)	0.18	0.87 (0.79—0.95)	0.002
Stool CRE/CPE	0.82 (0.60—1.11)	0.20	0.74 (0.54—0.99)	0.05	1.14 (0.88—1.47)	0.31
Clostridioides difficile infection	1.41 (1.06—1.89)	0.02	0.96 (0.71—1.28)	0.77	1.06 (0.82—1.37)	0.64
Stool VRE	1.16 (0.90—1.5)	0.24	1.42 (1.13—1.78)	0.003	1.76 (1.41—2.19)	<0.001
Laboratory tests						
C-reactive protein (mg/L)	1.00 (1.00—1.00)	<0.001	1.00 (1.00—1.00)	<0.001	1.00 (1.00—1.00)	0.01
WBC count (10^9/L)	1.00 (1.00—1.00)	0.70	1.01 (1.01—1.02)	<0.001	1.00 (0.99—1.00)	0.05
Hemoglobin concentration (g/dL)	0.90 (0.88—0.93)	<0.001	0.85 (0.83—0.87)	<0.001	0.81 (0.80—0.83)	<0.001
Appropriate empirical therapy	0.69 (0.62—0.77)	<0.001	0.78 (0.70—0.86)	<0.001	0.95 (0.87—1.03)	0.21
Isolated BSI-causative microorganisms during hospitalization (maybe multiple)						
Staphylococcus aureus	1.21 (1.02—1.43)	0.03	1.25 (1.06—1.46)	0.007	0.95 (0.83—1.09)	0.50
Enterococcus faecalis	0.76 (0.59—0.98)	0.04	0.86 (0.68—1.08)	0.20	1.37 (1.17—1.61)	<0.001
Enterococcus faecium	0.82 (0.71—0.96)	0.01	1.79 (1.58—2.04)	<0.001	1.74 (1.54—1.96)	<0.001
Escherichia coli	0.63 (0.55—0.72)	<0.001	0.68 (0.60—0.78)	<0.001	1.05 (0.95—1.15)	0.35
Klebsiella pneumoniae	0.71 (0.62—0.81)	<0.001	0.90 (0.79—1.02)	0.11	1.26 (1.13—1.39)	<0.001
Acinetobacter baumannii	1.23 (1.00—1.52)	0.05	1.17 (0.94—1.44)	0.15	1.74 (1.42—2.13)	<0.001
Pseudomonas aeruginosa	0.89 (0.71—1.12)	0.32	1.03 (0.83—1.28)	0.78	1.51 (1.26—1.81)	<0.001
Candida albicans	1.73 (1.38—2.17)	<0.001	2.35 (1.93—2.87)	<0.001	1.61 (1.31—1.97)	<0.001

Independent variables included in the multivariable analyses were selected via SHAP analysis through a machine learning model.
BSI, bloodstream infection; ICU, intensive care unit; aOR, adjusted odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; CRE, carbapenem-resistant Enterobacteriaceae; CPE, carbapenemase-producing Enterobacteriaceae; VRE, vancomycin-resistant enterococci; WBC, white blood cell.

BSI resulted in lower mortality rates of patients both during the first 7 days and on days 8—30 compared with BSIs caused by other microorganisms. In contrast, BSIs caused by *A. baumannii* and *C. albicans* were more likely to result in deaths of patients for all time periods. Interestingly, BSIs caused by *Enterococcus faecalis* and *E. faecium*, which had favorable prognoses during the first 7 days with death aORs of 0.76 (95 % CI 0.59—0.98) and 0.82 (95 % CI 0.71—0.96), respectively, were associated with a poor outcome for in-hospital mortality during the period after Day 30 with death aORs of 1.36 (95 % CI 1.16—1.60) and 1.74 (95 % CI 1.55—1.97), respectively. Notably, gut colonization with VRE was a risk factor for both progression to VRE-BSI (OR 9.53; 95 % CI 7.79—11.65) and in-hospital mortality during both days 8—30 and after Day 30.

Mortality attributed to AMR by period of the BSI timeline

Subgroup analyses of AMR phenotypes of major pathogens and mortalities of patients for each period are shown in Fig. 5 and Fig. S4. After adjusting for patient factors, none of the AMR phenotypes of major pathogens was associated with the mortality rate during the first 7 days. However, BSIs caused by *E. coli* with nonsusceptible phenotypes to BLBLIs and by *K. pneumoniae* with nonsusceptible phenotypes to 3GCs, BLBLIs, and/or carbapenems were positively correlated with the mortality rates of patients during both days 8—30 and after Day 30. Moreover, BSI caused by *E. faecium* with a vancomycin-resistance phenotype was associated with a poor prognosis for in-hospital mortality

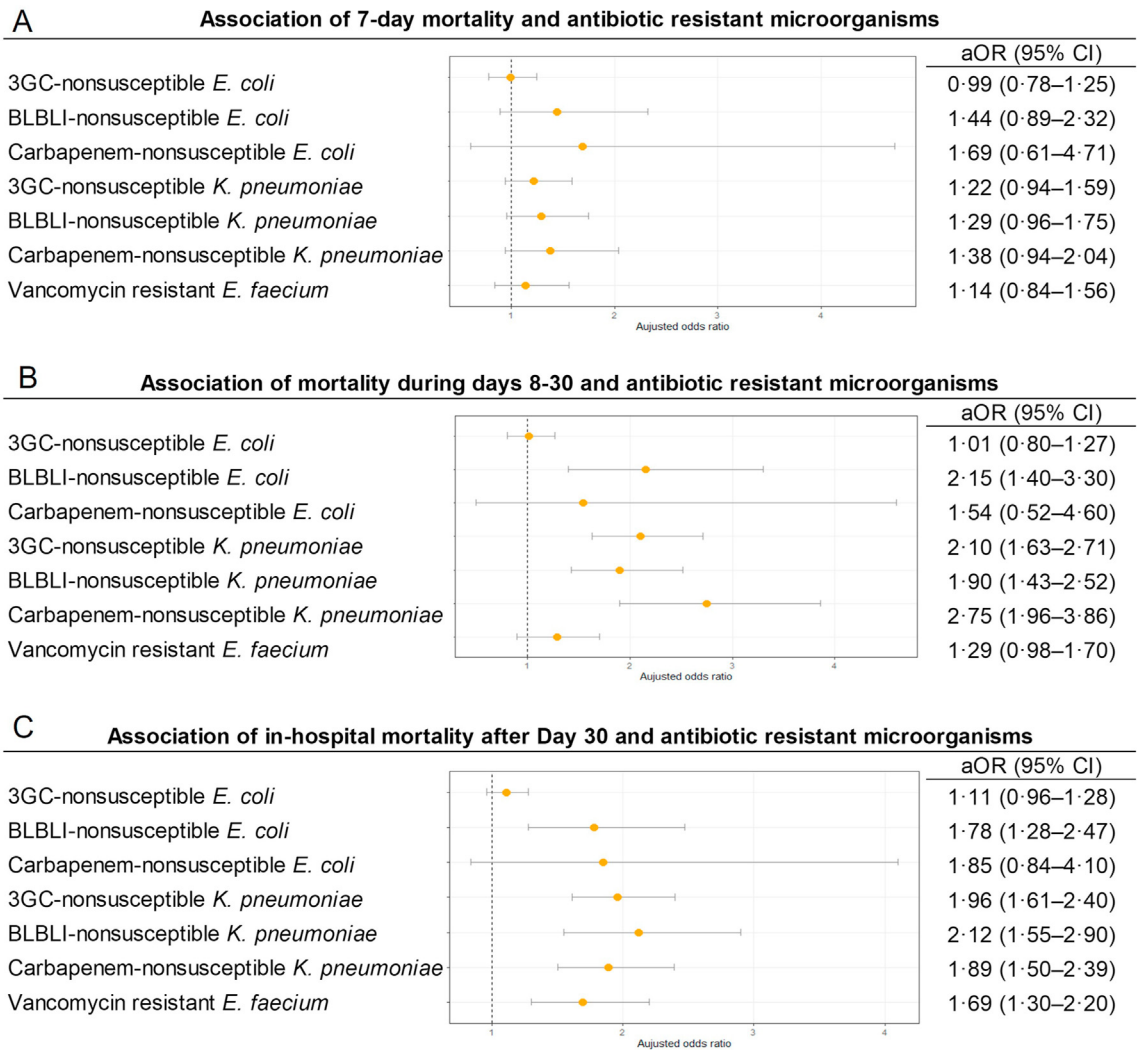

Figure 5. Mortality attributed to antimicrobial resistance or major pathogens by period of the BSI timeline. The death aORs of major antibiotic-resistant bacteria for each period of the BSI timeline are presented in A-C. BSI, bloodstream infection; aOR, adjusted odds ratio; CI, confidence interval; VRE, vancomycin-resistant enterococci; BLBLI, β-lactam/β-lactamase inhibitors; 3 GC, third-generation cephalosporins.

during only the period after Day 30, with a death aOR of 1.69 (95 % CI 1.30—2.20). Poor long-term survival rates of the patients with BSI caused by bacteria with major AMR phenotypes were also observed in the Kaplan—Meier survival analyses (Fig. S4) and Cox proportional hazard model (Fig. S5). We further analyzed the in-hospital mortality of patients according to therapeutic regimens (Fig. S6).

Discussion

Longitudinal follow-up of patients with BSI in this study showed that the effects of baseline risk factors for mortality varied by period of the BSI timeline and that the association of the risk factors with mortality was either strengthened or weakened by period. The risk factor analyses stratified by period of the BSI timeline demonstrated that a patient's baseline severity had a more serious impact on mortality[16,17] during the first 7 days rather than during days 8—30 and after Day 30. In contrast, the impact of microbiological factors, including species of BSI-causative microorganisms and their major AMR, on mortality was emphasized during both days 8—30 and after Day 30 rather than during the first 7 days.

BSIs caused by *E. coli* or *K. pneumoniae* showed favorable short-term outcomes compared with those caused by other microorganisms. However, nonsusceptible phenotypes to extended-spectrum β-lactams of these Enterobacterales influenced the prognoses of patients with BSI in terms of high mortality rates during both days 8—30 and after Day 30. Survival analyses using Kaplan—Meier curves also demonstrated the same results as evidenced by differences in survival slopes. Furthermore, index BSIs caused by microorganisms with AMR phenotypes exhibited a significant association with the occurrence of sBSI by *E. faecium*. Prolonged or unresolved infection due to those AMR of causative microorganisms or patient factors could lead to the depletion of immune cells and cytokines along with

increased myeloid-derived suppressor cell pathways.[18,19] In this regard, severe sepsis that fails to eradicate the index BSI is considered to induce an immunocompromised state in the patient, consequently increasing the risk of subsequent infections and death.[19—21] It has also been reported that both prior use of antibiotics and index BSI caused by *Candida* species or 3 GC-resistant Gram-negative rods were risk factors for the development of sBSI.[3] This study identified additional risk factors, gut colonization by VRE, ICU admission, and current cancer chemotherapy, for the occurrence of sBSI.

The occurrence of *A. baumannii*-BSI and candidemia was significantly related to patients with high baseline SOFA scores and high CCI scores, respectively, consistent with previous studies.[22—24] Even after adjusting for patient factors, BSIs caused by these opportunistic pathogens resulted in a higher mortality rate of patients compared with those caused by other microorganisms for all time periods. The results indicated that *A. baumannii* and *Candida* species were not only more likely to cause BSI in patients with poor underlying conditions but were also risk factors for high mortality rates among patients with BSI. Consequently, there is a vicious synergy between microbiological and patient factors, suggesting that the poor baseline condition of patients predisposes them to serious opportunistic BSIs, aggravating patient outcomes.

Gut colonization by VRE was significantly associated with progression to VRE-BSI, resulting in an increased in-hospital mortality rate of patients. Decreased normal flora in the gut due to the use of antibiotics might mediate an environment susceptible to colonization and cause subsequent infection by VRE.[25,26] Considering both the high mortality rates among immunocompromised patients with VRE-BSI and the difficulty of decolonizing the bacteria from the gut through traditional antimicrobial treatments, further studies on alternative treatment strategies, such as fecal microbiota transplantation, are needed.[27]

Crude mortality after diagnosis of BSI varies widely across previous studies,[1,10] ranging from 8 % to 48 %, and was 38.8 % in our cohort.

BSIs in inpatients tend to prolong LOS in hospitals and increase total medical costs; however, as resource consumption is most concentrated in the early stages of hospitalization, prolonged LOS could lead to a reduction in actual medical costs per day. Therefore, BSI could be a serious burden on both patients and hospitals, for the former in terms of high mortality and economic burden due to prolonged LOS and increased total costs for hospitalization and for the latter in terms of deterioration of hospital finances due to reduced daily income by patients. In particular, BSIs caused by *E. faecium*, *A. baumannii*, *C. albicans*, and *P. aeruginosa* were a risk factor for increased total medical costs even after adjusting for other host factors.

The observational approach of our study is limited by its retrospective nature. Data were derived from two tertiary care institutions in a single country, influencing the generalizability of the results. To increase the specificity of the data extraction, we excluded all cases in which skin commensals were isolated from blood cultures. Additionally, patients who previously received antimicrobial therapy and produced false-negative blood culture results might also have been misclassified in this study. Machine learning techniques have inherent advantages in analyzing big data, including variables with multicollinearity and nonlinear relationships.[28] Thus, we attempted to comprehensively analyze risk factors among patients with BSI by integrating machine learning techniques into conventional multivariable models to minimize bias.

Conclusion

Here, we provided a large amount of evidence to show the impacts of microbiological factors on in-hospital mortality after the first 7 days of the BSI timeline. Furthermore, AMR of major pathogens was also a risk factor for the progression to sBSI, resulting in increased LOS and medical costs. Time-stratified risk factor analysis utilizing medical big data could have a crucial role in understanding the impact of microbiological factors in the field of infectious disease research by correcting for the confounding effect of patient conditions.

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Author contributions

M.H.C. and S.H.J. contributed to study design and research concept. M.H.C. and J.K. collected and analysed data. D.K., J.K., Y.G.S., and S.H.J. reviewed and edited the manuscript. M.H.C. and S.H.J. wrote the original draft of the manuscript.

Declaration of competing interest

All authors: No conflicts.

References

1. Tacconelli E, Göpel S, Gladstone BP, Eisenbeis S, Hölzl F, Buhl M, et al. Development and validation of BLOOMY prediction scores for 14-day and 6-month mortality in hospitalised adults with bloodstream infections: a multicentre, prospective, cohort study. *Lancet Infect Dis* 2022;**22**:731—41.
2. Lee XJ, Stewardson AJ, Worth LJ, Graves N, Wozniak TM. Attributable length of stay, mortality risk, and costs of bacterial health care-associated infections in Australia: a retrospective case-cohort study. *Clin Infect Dis* 2021;**72**:e506—14.
3. Guillamet MCV, Vazquez R, Noe J, Micek ST, Fraser VJ, Kollef MH. Impact of baseline characteristics on future episodes of bloodstream infections: multistate model in septic patients with bloodstream infections. *Clin Infect Dis* 2020;**71**:3103—9.
4. Goto M, Al-Hasan M. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infection* 2013;**19**:501—9.
5. Angus DC, Van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;**369**:840—51.

6. Søgaard M, Nørgaard M, Dethlefsen C, Schønheyder HC. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. *Clin Infect Dis* 2011;**52**:61—9.
7. Boix-Palop L, Dietl B, Calbo E, Di Marco A, Xercavins M, Pérez-Crespo PMM, et al. Risk of cardiac device-related infection in patients with late-onset bloodstream infection. Analysis on a National Cohort. *J Infect* 2022;**85**:123—9.
8. Al-Hasan MN, Eckel-Passow JE, Baddour LM. Recurrent gram-negative bloodstream infection: a 10-year population-based cohort study. *J Infect* 2010;**61**:28—33.
9. Oh HJ, Kim JH, Kim HR, Ahn JY, Jeong SJ, Ku NS, et al. The impact of sarcopenia on short-term and long-term mortality in patients with septic shock. *J Cachexia Sarcopenia Muscle* 2022;**13**:2054—63.
10. McNamara JF, Righi E, Wright H, Hartel GF, Harris PNA, Paterson DL. Long-term morbidity and mortality following bloodstream infection: a systematic literature review. *J Infect* 2018;**77**:1—8.
11. Jang TN, Lee SH, Huang CH, Lee CL, Chen WY. Risk factors and impact of nosocomial Acinetobacter baumannii bloodstream infections in the adult intensive care unit: a case-control study. *J Hosp Infect* 2009;**73**:143—50.
12. Spanik S, Novotny J, Mateicka F, Pichnova E, Sulcova M, Jurga L, et al. Bacteremia due to multiresistant gram-negative bacilli in neutropenic cancer patients: a case-controlled study. *J Infect Chemother* 1999;**5**:180—4.
13. Lye D, Earnest A, Ling M, Lee T-E, Yong H-C, Fisher D, et al. The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay: cohort study. *Clin Microbiol Infection* 2012;**18**:502—8.
14. Huh K, Chung DR, Ha YE, Ko JH, Kim SH, Kim MJ, et al. Impact of difficult-to-treat resistance in gram-negative bacteremia on mortality: retrospective analysis of nationwide surveillance data. *Clin Infect Dis* 2020;**71**:e487—96.
15. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care—associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**:309—32.
16. Ani C, Farshidpanah S, Stewart AB, Nguyen HB. Variations in organism-specific severe sepsis mortality in the United States: 1999—2008. *Crit Care Med* 2015;**43**:65—77.
17. Naucler P, Darenberg J, Morfeldt E, Ortqvist A, Henriques Normark B. Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia. *Thorax* 2013;**68**:571—9.
18. Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton AH, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA* 2011;**306**:2594—605.
19. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol* 2013;**13**:862—74.
20. Leentjens J, Kox M, van der Hoeven JG, Netea MG, Pickkers P. Immunotherapy for the adjunctive treatment of sepsis: from immunosuppression to immunostimulation. Time for a paradigm change? *Am J Respir Crit Care Med* 2013;**187**:1287—93.
21. Hutchins NA, Unsinger J, Hotchkiss RS, Ayala A. The new normal: immunomodulatory agents against sepsis immune suppression. *Trends Mol Med* 2014;**20**:224—33.
22. Smolyakov R, Borer A, Riesenberg K, Schlaeffer F, Alkan M, Porath A, et al. Nosocomial multi-drug resistant Acinetobacter baumannii bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. *J Hosp Infect* 2003;**54**:32—8.
23. Gu Y, Jiang Y, Zhang W, Yu Y, He X, Tao J, et al. Risk factors and outcomes of bloodstream infections caused by Acinetobacter baumannii: a case-control study. *Diagn Microbiol Infect Dis* 2021;**99**:115229.
24. Agnelli C, Valerio M, Bouza E, Guinea J, Sukiennik T, Guimarães T, et al. Prognostic factors of Candida spp. bloodstream infection in adults: a nine-year retrospective cohort study across tertiary hospitals in Brazil and Spain. *The Lancet Regional Health - Americas* 2022;**6**.
25. Brandl K, Plitas G, Mihu CN, Ubeda C, Jia T, Fleisher M, et al. Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. *Nature* 2008;**455**:804—7.
26. Peters BM, Jabra-Rizk MA, O'May GA, Costerton JW, Shirtliff ME. Polymicrobial interactions: impact on pathogenesis and human disease. *Clin Microbiol Rev* 2012;**25**:193—213.
27. Belga S, Chiang D, Kabbani D, Abraldes JG, Cervera C. The direct and indirect effects of vancomycin-resistant enterococci colonization in liver transplant candidates and recipients. *Expert Rev Anti-infect Ther* 2019;**17**:363—73.
28. Baxt WG. Complexity, chaos and human physiology: the justification for non-linear neural computational analysis. *Cancer Lett* 1994;**77**:85—93.

Appendix A. Supplementary data

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