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

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Directed by Professor Seok Hoon Jeong

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This certifies that the Doctoral Dissertation of
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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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Background: The impact of microbiological factors on the prognosis of patients with bloodstream infection (BSI) could be masked by host factors when only comparing short-term outcomes. This study was designed to determine shifts in risk factors on the prognosis of patients during each period of the BSI timeline by dividing it into three periods as the first 7 days, days 8-30, and after Day 30.

Methods: Through an integrated study of multivariable regressions with machine learning techniques, the risk factors for mortality during each period of BSI were analysed using clinical data from all adult patients with BSIs from two South Korean hospitals.

Results: During 2011-2021, a total of 302303 inpatients who underwent blood cultures were enrolled. 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 during days 8-30 (7.0 ± 4.2) and after Day 30 (4.0 ± 3.5). BSIs caused by A. baumannii and C. albicans were more likely to result in deaths of patients for all time periods (all, $p<0.001$). BSIs caused by E. faecalis and E. faecium, which had favourable prognoses during the first 7 days with death adjusted odd ratio (aOR) of 0.76 (95%

CI 0.59−0.98) and 0.82 (0.71−0.96), were associated with a poor outcome for in-hospital mortality during the period after Day 30 with aORs of 1.36 (1.16−1.60) and 1.74 (1.55−1.97). BSI caused by E. faecium with a vancomycin-resistant phenotype was associated with a poor prognosis for in-hospital mortality during only the period after Day 30, with aOR of 1.69 (1.30−2.20).

Conclusions: A patient's baseline severity had a more serious impact on mortality in the first 7 days. In contrast, the influence of microbiological factors on mortality, including BSI-causative microorganisms and their major antimicrobial resistance, was emphasized during both days 8-30 and after Day 30. Furthermore, antimicrobial resistance of major pathogens was also a risk factor for the progression to subsequent BSI, resulting in increased hospital length of stay 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.

Key words:
bloodstream infection, subsequent bloodstream infection, antimicrobial resistance, mortality, long-term mortality, machine learning

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I. 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 potentially be confounded 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.

II. MATERIALS AND METHODS

1. 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 2,000 and 800 beds, respectively) during 2011–2021 were retrospectively collected. The exclusion criteria were patients with no demographic information, ≥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 hours 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 hours, and the subsequent BSI (sBSI) was defined as additional isolation of microorganisms other than those identified in index blood cultures from subsequent blood cultures.[3] Total medical costs were presented in euros and US dollars by applying exchange rates of 1127.26:1 and 1360.50:1 (average of the study period) to Korean won, respectively.

The primary outcome was patient mortality during each period of the BSI timeline. To compare very short-term, short-term, and long-term prognostic risk factors, the 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.

2. Propensity score (PS)-matching

To reduce selection bias in imbalanced data and to analyze the impact of BSI on clinical outcomes, 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, 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).

3. 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.

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 of 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 neighbour, 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 find optimal model while preventing overfitting. Each model with the highest area under the receiver operator characteristic curve were generated for model comparison. 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 analyse 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).

4. Ethics

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

III. RESULTS

1. 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). PS matched analyses showed that positive

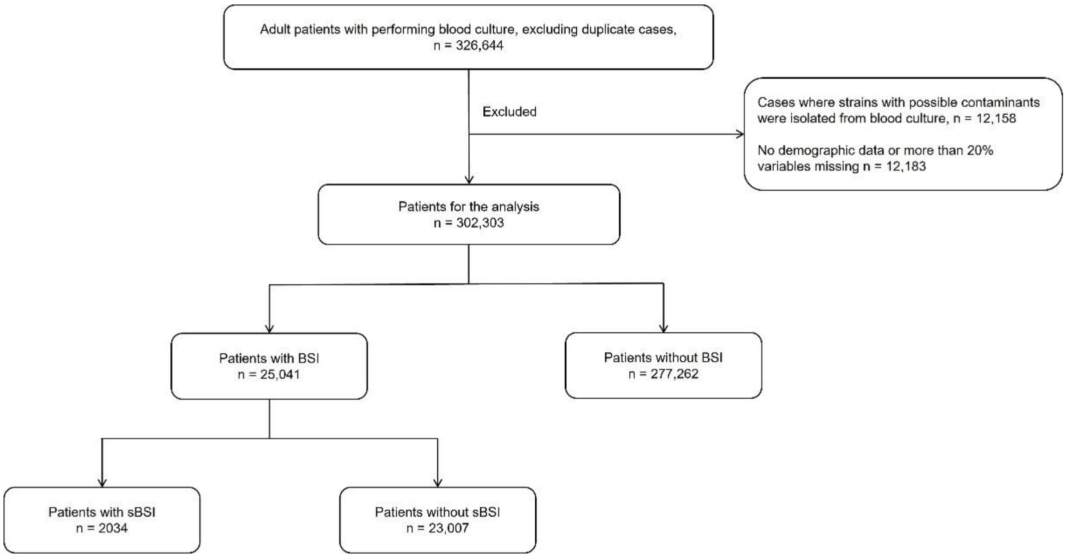

Figure 1. Flowchart of patient selection process

BSI, bloodstream infection; sBSI, subsequent BSI

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).

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, Table 2). *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. 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

Table 1. Baseline characteristics of development and external validation cohort

	Hospital A	Hospital B	p	Total	No BSI	BSI	p
	(N=231035)	(N=71268)		(N=302303)	(N=277262)	(N=25041)	
Patient's age	60.7±16.7	59.7±18.8	<0.001	60.5±17.2	60.0±17.4	65.5±14.4	<0.001
Female sex	106082 (45.9%)	34056 (47.8%)	<0.001	140138 (46.4%)	128793 (46.5%)	11345 (45.3%)	0.001
ICU admission	28305 (12.3%)	10355 (14.5%)	<0.001	38660 (12.8%)	33005 (11.9%)	5655 (22.6%)	<0.001
Hospital length of stay	8 [3-17]	6 [2-15]	<0.001	8 [3-17]	7 [3-15]	16 [7-34]	<0.001
7-day mortality	7818 (3.4%)	2308 (3.2%)	<0.001	10126 (3.3%)	7324 (2.6%)	2802 (11.2%)	<0.001
Mortality date	3.0 ± 2.2	3.0 ± 2.2	0.629	3.0 ± 2.2	3.1 ± 2.2	2.6 ± 2.1	<0.001
Mortality during days 8-30	10737 (4.6%)	2487 (3.5%)	<0.001	13224 (4.4%)	10870 (3.9%)	2354 (9.4%)	<0.001
Mortality date	17.6 ± 6.6	17.1 ± 6.5	<0.001	17.5 ± 6.6	17.7 ± 6.6	17.0 ± 6.6	<0.001
In-hospital mortality after Day 30	32915 (14.2%)	5402 (7.6%)	<0.001	38317 (12.7%)	33748 (12.2%)	4569 (18.2%)	<0.001
Mortality date	141.4 ± 93.9	137.1 ± 101.3	0.003	140.8 ± 95.0	142.0 ± 92.4	131.9 ± 111.9	<0.001
Total medical costs (USD $)	3994.6 [1661.8-9399.5]	2960.8 [1050.0-7697.1]	<0.001	3736.8 [1488.6-9033.0]	3502.9 [1389.0-8408.5]	7725.4 [3389.4-19266.7]	<0.001
Total medical costs (euro €;)	4821.2 [2005.7-11344.3]	3573.5 [1267.3-9289.6]	<0.001	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]	<0.001	1 [0-4]	1 [0-3]	4 [2-8]	<0.001
Infection origin (may be multiple)							
Abdomen	2201 (1.0%)	472 (0.7%)	<0.001	-	-	2673 (10.7%)	-
Catheter-related	1291 (0.6%)	139 (0.2%)	<0.001			1430 (5.7%)	
Pneumonia	2201 (1.0%)	819 (1.1%)	<0.001			3020 (12.1%)	
Urogenital tract	4951 (2.1%)	1331 (1.9%)	<0.001			6282 (25.1%)	
Skin and soft tissue	922 (0.4%)	206 (0.3%)	<0.001			1128 (4.5%)	
Other sites	55 (0.0%)	49 (0.1%)	<0.001			104 (0.4%)	
Charlson comorbidity index score	4.7±2.7	3.9±2.7	<0.001	4.5±2.7	4.4±2.7	5.6±2.6	<0.001
Solid cancer	97858 (42.4%)	19691 (27.6%)	<0.001	117549 (38.9%)	105748 (38.1%)	11801 (47.1%)	<0.001
Diabetes mellitus	32631 (14.1%)	7418 (10.4%)	<0.001	40049 (13.2%)	35203 (12.7%)	4846 (19.4%)	<0.001
Chronic obstructive pulmonary disease	8325 (3.6%)	1595 (2.2%)	<0.001	9920 (3.3%)	9167 (3.3%)	753 (3.0%)	0.012
Leukaemia	4090 (1.8%)	269 (0.4%)	<0.001	4359 (1.4%)	3685 (1.3%)	674 (2.7%)	<0.001
Liver disease	21198 (9.2%)	3747 (5.3%)	<0.001	24945 (8.3%)	21317 (7.7%)	3628 (14.5%)	<0.001
Kidney disease	14982 (6.5%)	1961 (2.8%)	<0.001	16943 (5.6%)	14956 (5.4%)	1987 (7.9%)	<0.001
Devices							
Ventilator	10927 (4.7%)	4410 (6.2%)	<0.001	15337 (5.1%)	12233 (4.4%)	3104 (12.4%)	<0.001
Arterial line	13468 (5.8%)	3073 (4.3%)	<0.001	16541 (5.5%)	14261 (5.1%)	2280 (9.1%)	<0.001
Central venous line	28510 (12.3%)	6573 (9.2%)	<0.001	35083 (11.6%)	29161 (10.5%)	5922 (23.6%)	<0.001
Indwelling catheter	63263 (27.4%)	15531 (21.8%)	<0.001	78794 (26.1%)	68749 (24.8%)	10045 (40.1%)	<0.001
CRE/CPE colonization	954 (0.4%)	295 (0.4%)	0.997	1249 (0.4%)	750 (0.3%)	499 (2.0%)	<0.001
Clostridioides difficile infection	1857 (0.8%)	479 (0.7%)	<0.001	2336 (0.8%)	1827 (0.7%)	509 (2.0%)	<0.001
VRE colonization	1528 (0.7%)	392 (0.6%)	0.001	1920 (0.6%)	1194 (0.4%)	726 (2.9%)	<0.001

Data are presented as number (%), mean ± standard deviation, or median [1st-3rd quartile]

BSI, bloodstream infection; SOFA: sequential organ failure assessment; CRE, carbapenem-resistant Enterobacteriaceae; CPE, carbapenemase-producing Enterobacteriaceae; VRE, vancomycin-resistant enterococci

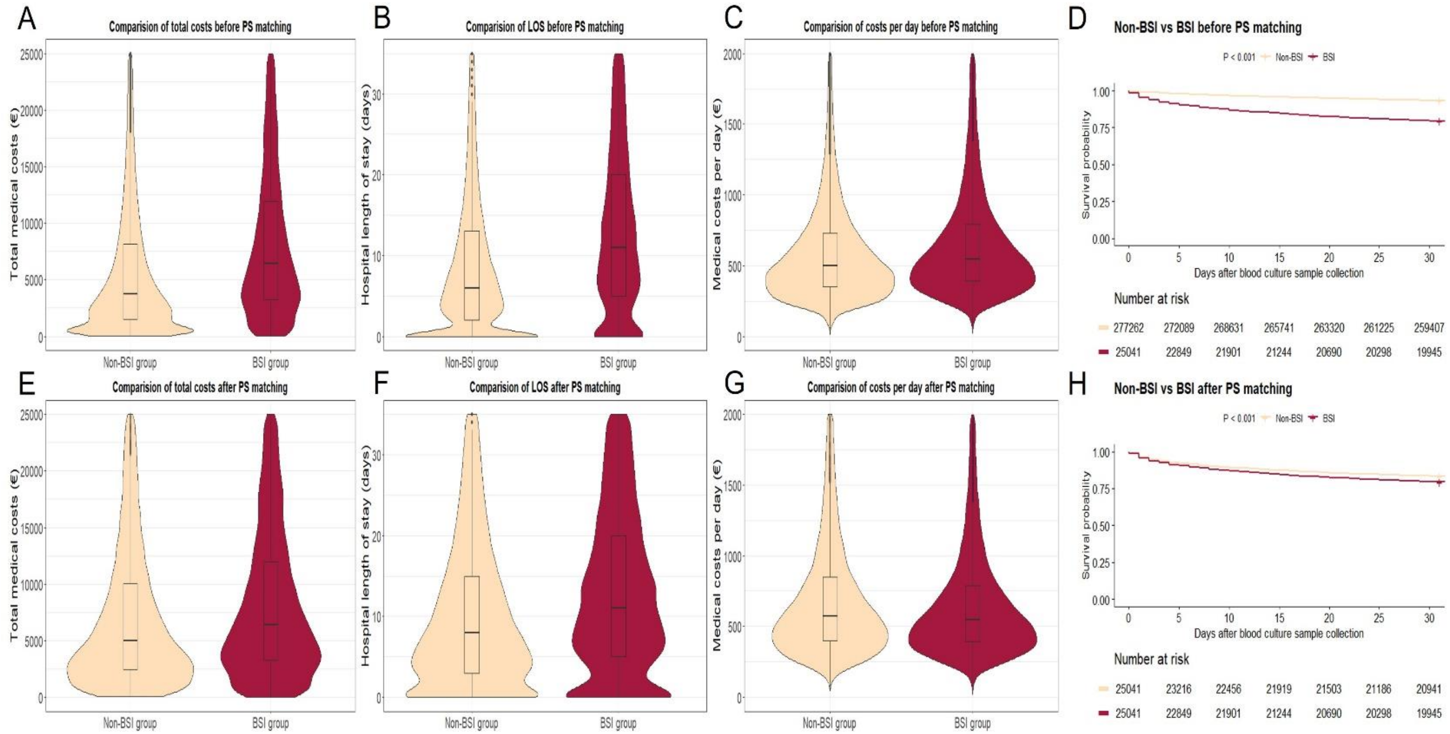

Figure 2. Comparison of medical costs, hospital length of stay and 30-day mortality between patients with and without BSI

Comparison of medical costs and 30-day mortality between patients with and without BSI, before the propensity-score matching (A-D) and after the propensity-score matching (E-H).

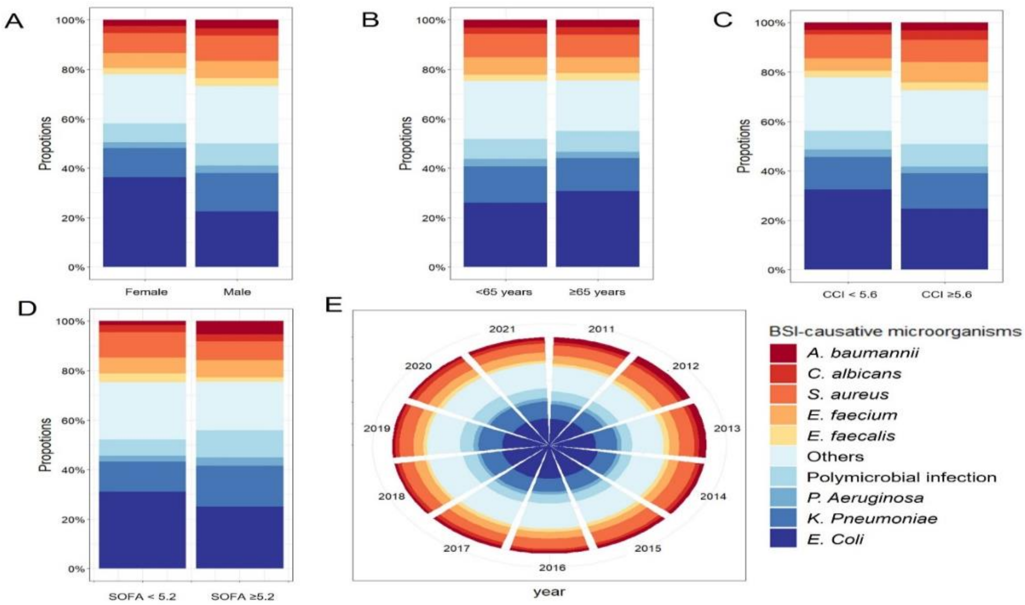

Figure 3. Distribution of BSI-causative microorganisms by sex (A), age group (B), groups above and below the mean Charlson comorbidity index score (C), SOFA score (D), and the year of disease onset

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 2.

identified among patients with high baseline SOFA scores. BSIs showed discriminatory clinical outcomes by causative microorganism (Fig. 4 and Table 3). 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.

3. Subsequent BSI

Of 25,041 patients with BSI, 2,034 (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

Table 2. Detailed number of distributions of BSI-causative microorganisms by sex, age group, Charlson comorbidity index scores, and SOFA scores

	Femail	Male	<65 years	≥65 years	CCI score<5.6	CCI score≥5.6	SOFA score<5.2	SOFA score≥5.2
	(N=11345)	(N=13696)	(N=10722)	(N=14319)	(N=13230)	(N=11811)	(N=15123)	(N=9918)
Gram positive								
Staphylococcus aureus	922 (9.0%)	1395 (11.6%)	1009 (10.7%)	1308 (10.1%)	1264 (10.8%)	1053 (9.9%)	1557 (11.7%)	760 (8.5%)
Enterococcus faecium	701 (6.9%)	956 (7.9%)	759 (8.1%)	898 (7.0%)	686 (5.9%)	971 (9.2%)	970 (7.3%)	687 (7.7%)
Enterococcus faecalis	285 (2.8%)	442 (3.7%)	280 (3.0%)	447 (3.5%)	350 (3.0%)	377 (3.6%)	540 (4.1%)	187 (2.1%)
Streptococcus agalactiae	135 (1.3%)	156 (1.3%)	131 (1.4%)	160 (1.2%)	173 (1.5%)	118 (1.1%)	209 (1.6%)	82 (0.9%)
Streptococcus pneumoniae	58 (0.6%)	113 (0.9%)	83 (0.9%)	88 (0.7%)	110 (0.9%)	61 (0.6%)	106 (0.8%)	65 (0.7%)
Other Gram positive	232 (2.0%)	289 (2.1%)	259 (2.4%)	262 (1.8%)	300 (2.3%)	221 (1.9%)	366 (2.4%)	155 (1.6%)
Gram negative								
Escherichia coli	4125 (40.4%)	3069 (25.4%)	2790 (29.7%)	4404 (34.2%)	4284 (36.7%)	2910 (27.5%)	4709 (35.4%)	2485 (27.7%)
Klebsiella pneumoniae	1338 (13.1%)	2124 (17.6%)	1565 (16.7%)	1897 (14.7%)	1756 (15.0%)	1706 (16.1%)	1835 (13.8%)	1627 (18.2%)
Klebsiella oxytoca	79 (0.8%)	123 (1.0%)	72 (0.8%)	130 (1.0%)	95 (0.8%)	107 (1.0%)	130 (1.0%)	72 (0.8%)
Acinetobacter baumannii	279 (2.7%)	480 (4.0%)	334 (3.6%)	425 (3.3%)	398 (3.4%)	361 (3.4%)	232 (1.7%)	527 (5.9%)
Pseudomonas aeruginosa	261 (2.6%)	437 (3.6%)	336 (3.6%)	362 (2.8%)	386 (3.3%)	312 (2.9%)	350 (2.6%)	348 (3.9%)
Enterobacter species	218 (1.9%)	359 (2.6%)	290 (2.7%)	287 (2.0%)	297 (2.2%)	280 (2.4%)	378 (2.5%)	199 (2.0%)
Citrobacter species	85 (0.7%)	149 (1.1%)	105 (1.0%)	129 (0.9%)	128 (1.0%)	106 (0.9%)	131 (0.9%)	103 (1.0%)
Proteus species	139 (1.2%)	82 (0.6%)	53 (0.5%)	168 (1.2%)	119 (0.9%)	102 (0.9%)	123 (0.8%)	98 (1.0%)
Serratia species	43 (0.4%)	88 (0.6%)	64 (0.6%)	67 (0.5%)	68 (0.5%)	63 (0.5%)	70 (0.5%)	61 (0.6%)
Stenotrophomonas maltophilia	61 (0.6%)	86 (0.7%)	62 (0.7%)	85 (0.7%)	71 (0.6%)	76 (0.7%)	88 (0.7%)	59 (0.7%)
Bacteroides fragilis	123 (1.2%)	209 (1.7%)	163 (1.7%)	169 (1.3%)	175 (1.5%)	157 (1.5%)	249 (1.9%)	83 (0.9%)
Other Gram negative	367 (3.2%)	537 (3.9%)	459 (4.3%)	445 (3.1%)	551 (4.2%)	353 (3.0%)	616 (4.1%)	288 (2.9%)
Fungus								
Candida albicans	317 (3.1%)	396 (3.3%)	274 (2.9%)	439 (3.4%)	237 (2.0%)	476 (4.5%)	436 (3.3%)	277 (3.1%)
Candida glabrata	132 (1.3%)	142 (1.2%)	105 (1.1%)	169 (1.3%)	90 (0.8%)	184 (1.7%)	146 (1.1%)	128 (1.4%)
Candida parapsilosis	96 (0.9%)	163 (1.4%)	121 (1.3%)	138 (1.1%)	118 (1.0%)	141 (1.3%)	170 (1.3%)	89 (1.0%)
Candida tropicalis	99 (1.0%)	173 (1.4%)	122 (1.3%)	150 (1.2%)	93 (0.8%)	179 (1.7%)	136 (1.0%)	136 (1.5%)
Other fungus	20 (0.2%)	23 (0.2%)	22 (0.2%)	21 (0.1%)	18 (0.1%)	25 (0.2%)	25 (0.2%)	18 (0.2%)
Polymicrobial infections	867 (7.6%)	1216 (8.9%)	870 (8.1%)	1213 (8.5%)	1004 (7.6%)	1079 (9.1%)	998 (6.6%)	1085 (10.9%)

CCI, Charlson comorbidity index; SOFA, Sequential Organ Failure Assessment

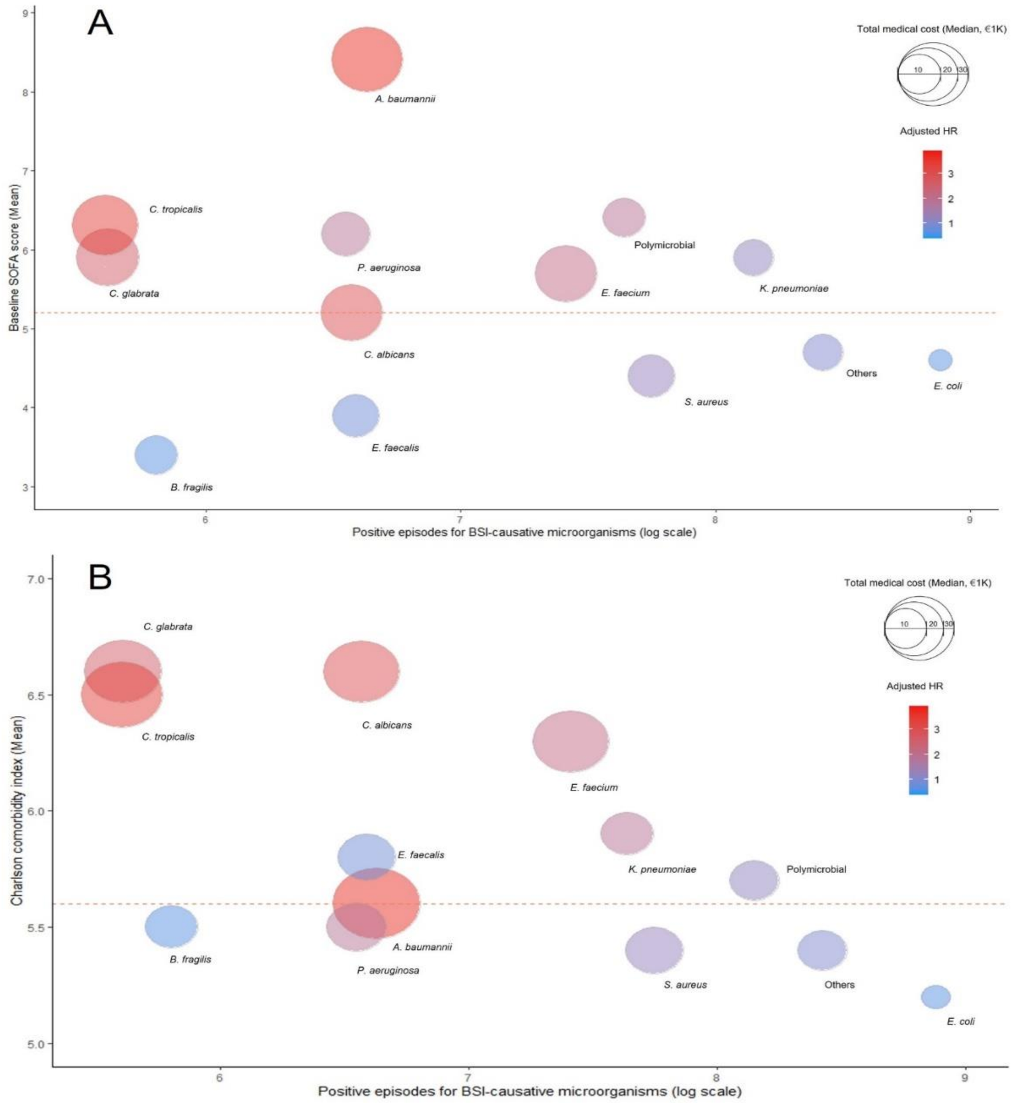

Figure 4. Incidences of BSI and its clinical progression stratified by BSI-causative microorganisms

In these bubble plots, the x axis expresses the total number 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.

Table 3. Multivariable analyses using linear regression of risk factors for total medical costs (euros)

	ß coefficient	Standard error	p
ICU admission	14986.5	586.800	<0.001
Ventilator	15209.1	811.700	<0.001
WBC count	-104.4	20.100	<0.001
Hospital length of stay	514.1	2.700	<0.001
CRE/CPE colonization	25523.6	1408.600	<0.001
Immunocompromised status	25621.7	901.300	<0.001
Liver diseases	4730.5	568.200	<0.001
Hospital A	1658.6	483.000	<0.001
C-reactive protein level	-8.6	2.000	<0.001
Catheter-related bloodstream infection	11166.6	878.700	<0.001
Patient's age	-64.8	14.000	<0.001
Blood urea nitrogen	25.5	9.600	0.008
Staphylococcus aureus	-740.1	685.200	0.280
Enterococcus faecalis	878.8	948.900	0.354
Enterococcus faecium	9157.9	652.400	<0.001
Escherichia coli	-706.7	470.500	0.133
Klebsiella pneumoniae	768.4	552.200	0.164
Acinetobacter baumannii	6455.9	987.500	<0.001
Pseudomonas aeruginosa	3439.1	994.200	0.001
Candida albicans	3454.4	1037.300	0.001
SOFA score	320.7	65.400	<0.001

ICU, intensive care unit; WBC, white blood cell; CRE, carbapenem-resistant Enterobacteriaceae; CPE, carbapenemase-producing Enterobacteriaceae; SOFA, Sequential Organ Failure Assessment

colonization with vancomycin-resistant enterococci (VRE) [adjusted odds ratio (aOR) 1.82; 95% confidence interval (CI) 1.47–2.24], ICU admission (aOR 3.79; 95% CI 3.35–4.28), and current cancer chemotherapy (aOR 1.54; 95% CI 1.36–1.74) (Table 4).

Table 4. Multivariable analysis using logistic regression of mortality risk factors for patients with subsequent BSI

	No subsequent BSI	Subsequent BSI	p	Univariate analysis			Multivariate analysis		
	(N=23007)	(N=2034)		OR	95% CI	p	aOR	95% CI	p
Sex			0.001						
Female	10498 (45.6%)	847 (41.6%)							
Male	12509 (54.4%)	1187 (58.4%)		1.18	(1.07-1.29)	<0.001	1.08	(0.97-1.19)	0.1547
Patient's age	65.6 ± 14.4	64.2 ± 13.9	<0.001	0.99	(0.99-1)	<0.001	0.99	(0.98-0.99)	<0.001
Hospital length of stay	15 [7-31]	46 [25-88]	<0.001						
ICU admission	4596 (20.0%)	1059 (52.1%)	<0.001	4.35	(3.97-4.77)	<0.001	3.79	(3.35-4.28)	<0.001
SOFA score	5 [1-17]	19 [6-44]	<0.001						
Charlson comorbidity index score	3834 (16.7%)	735 (36.1%)							
Solid cancer	935.2 [429.4-2215.7]	4466.0 [2079.8-10270.6]	<0.001						
Current chemotherapy	5.1 ± 4.2	6.8 ± 4.4	<0.001	1.09	(1.08-1.1)	<0.001	0.99	(0.98-1.01)	0.4743
Devices	5.5 ± 2.5	6.2 ± 2.6	<0.001	1.12	(1.1-1.14)	<0.001	1.11	(1.09-1.14)	<0.001
Ventilator	10806 (47.0%)	995 (48.9%)	0.096	1.08	(0.99-1.18)	0.0913			
Arterial line	3314 (14.4%)	482 (23.7%)	<0.001	1.85	(1.66-2.06)	<0.001	1.54	(1.36-1.74)	<0.001
Central venous line									
Indwelling catheter	2544 (11.1%)	560 (27.5%)	<0.001	3.06	(2.75-3.40)	<0.001	1.05	(0.89-1.23)	0.5859
COVID-19	1950 (8.5%)	330 (16.2%)	<0.001	2.09	(1.84-2.37)	<0.001	0.87	(0.74-1.02)	0.0847
CRE/CPE colonization	5293 (23.0%)	629 (30.9%)	<0.001	1.50	(1.36-1.65)	<0.001	0.90	(0.79-1.02)	0.0916
Clostridioides difficile infection	9075 (39.4%)	970 (47.7%)	<0.001	1.40	(1.28-1.53)	<0.001	0.97	(0.86-1.08)	0.5517
VRE colonization	178 (0.8%)	12 (0.6%)	0.434	0.76	(0.42-1.37)	0.3616			
C-reactive protein (mg/L)									
Serum albumin (g/dL)	48 (0.2%)	11 (0.5%)	0.006	2.60	(1.35-5.02)	0.0043	3.68	(1.84-7.35)	0.0002
Sex	389 (1.7%)	110 (5.4%)	<0.001	3.32	(2.68-4.13)	<0.001	1.71	(1.34-2.18)	<0.001
Female	423 (1.8%)	86 (4.2%)	<0.001	2.36	(1.86-2.99)	<0.001	1.33	(1.01-1.73)	0.0386
Male	571 (2.5%)	155 (7.6%)	<0.001	3.24	(2.7-3.89)	<0.001	1.82	(1.47-2.24)	<0.001
Patient's age									
Hospital length of stay	128.2 ± 99.9	135.0 ± 99.7	0.004	1.00	(1.00-1.01)	0.0042	1.00	(1.00-1.00)	0.0789
ICU admission	2.9 ± 0.7	2.6 ± 0.5	<0.001	0.48	(0.44-0.51)	<0.001	0.63	(0.58-0.70)	<0.001

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

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 5). 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. 5). It was noteworthy that the index BSI caused by *E. coli* nonsusceptible to third-generation cephalosporins (3GCs) and *K. pneumoniae*

Table 5. Number of distributions of causative microorganisms by index and subsequent BSI

	Index BSI	**Subsequent BSI**
	(N=25,041)	(N=2034)
Gram positive		
Staphylococcus aureus	2317 (10.4%)	92 (4.5%)
Enterococcus faecium	1657 (7.4%)	412 (20.3%)
Enterococcus faecalis	727 (3.3%)	58 (2.9%)
Streptococcus agalactiae	291 (1.3%)	0 (0.0%)
Streptococcus pneumoniae	171 (0.8%)	2 (0.1%)
Other gram positive	521 (2.1%)	44 (2.2%)
Gram negative		
Escherichia coli	7194 (32.3%)	88 (4.3%)
Klebsiella pneumoniae	3462 (15.5%)	194 (9.5%)
Klebsiella oxytoca	202 (0.9%)	6 (0.3%)
Acinetobacter baumannii	759 (3.4%)	175 (8.6%)
Pseudomonas aeruginosa	698 (3.1%)	102 (5.0%)
Enterobacter species	577 (2.3%)	32 (1.6%)
Citrobacter species	234 (0.9%)	11 (0.5%)
Proteus species	221 (0.9%)	5 (0.2%)
Serratia species	131 (0.5%)	15 (0.7%)
Stenotrophomonas maltophilia	147 (0.7%)	77 (3.8%)
Bacteroides fragilis	332 (1.5%)	12 (0.6%)
Other gram negative	904 (3.6%)	111 (5.5%)
Fungus		
Candida albicans	713 (3.2%)	153 (7.5%)
Candida glabrata	274 (1.2%)	112 (5.5%)
Candida parapsilosis	259 (1.2%)	67 (3.3%)
Candida tropicalis	272 (1.2%)	61 (3.0%)
Other fungus	43 (0.2%)	36 (1.8%)
Polymicrobial infections	2083 (8.3%)	168 (8.3%)

BSI, bloodstream infection

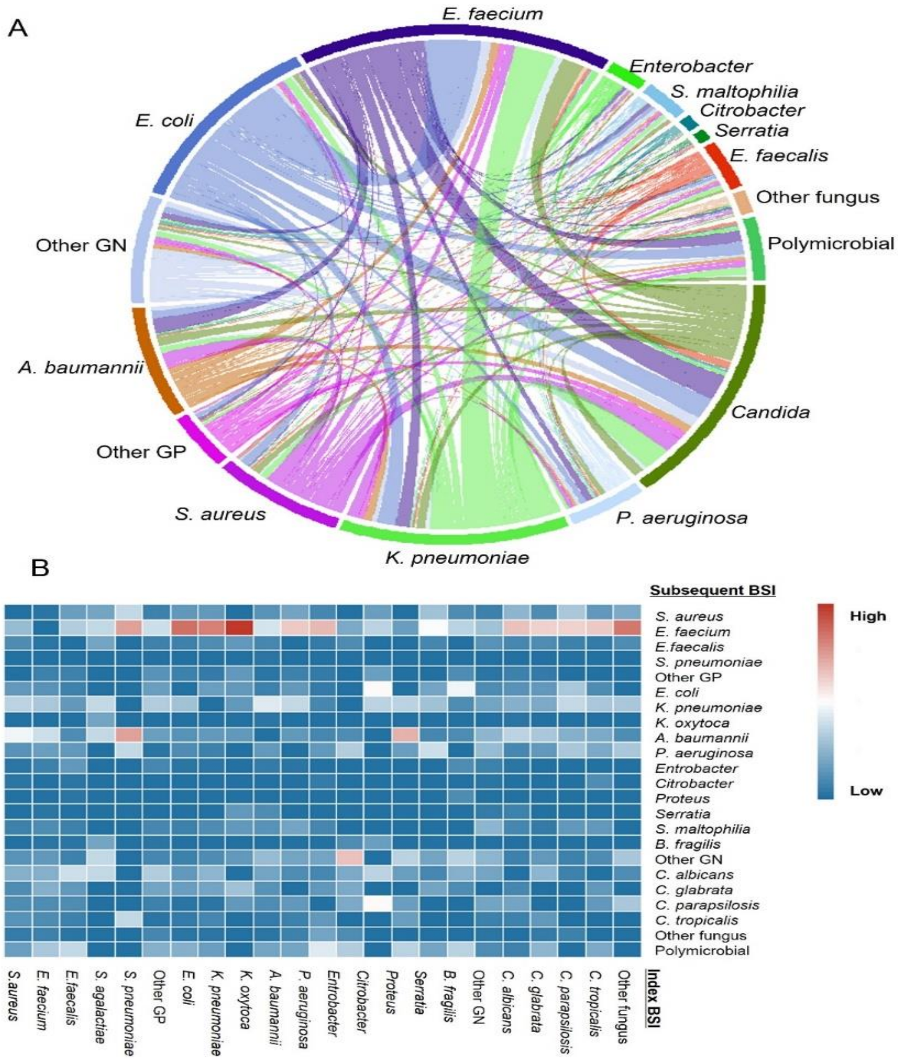

Figure 5. Circular plot and correlation heatmap for infection shifts in index and subsequent BSI-causative microorganisms.

The circular plot (A) and correlation heatmap (B) present the infection shift between index and subsequent BSI-causative microorganisms. Larger areas in the circular plot and darker reds in the heatmap indicate a stronger correlation of infection shift.
BSI, bloodstream infection; GP, gram positive; GN, gram negative

Table 6. Correlation analysis between major antibiotic resistant bacteria and the occurrence of *E. faecium*-sBSI

	E. feacium-sBSI	Non *E. feacium*-sBSI	p	OR	95% CI	p
3GC-nonsusceptible *E. coli*	59 (14.3%)	2502 (10.2%)	0.007	1.48	(1.12-1.95)	0.006
BLBLI-nonsusceptible *E. coli*	10 (2.4%)	317 (1.3%)	0.071	1.91	(1.01-3.61)	0.0469
Carbapenem-nonsusceptible *E. coli*	0 (0.0%)	67 (0.3%)	0.562	0.01	(0.01-2.31)	0.949
3GC-nonsusceptible *K. pneumoniae*	51 (12.4%)	1122 (4.6%)	<0.001	2.96	(2.19-3.99)	<0.001
BLBLI-nonsusceptible *K. pneumoniae*	35 (8.5%)	688 (2.8%)	<0.001	3.23	(2.27-4.61)	<0.001
Carbapenem-nonsusceptible *K. pneumoniae*	18 (4.4%)	356 (1.4%)	<0.001	3.11	(1.92-5.05)	<0.001

sBSI, subsequent bloodstream infection; OR, odds ratio; CI, confidence interval; 3GC, third-generation cephalosporins; BLBLI, ß-lactam/ß-lactamase inhibitors

nonsusceptible to 3GCs, β-lactam/β-lactamase inhibitors (BLBLIs), and/or carbapenems showed a positive correlation with the occurrence of *E. faecium*-sBSI (Table 6).

4. Mortality attributed to patient factors by period of the BSI timeline

The 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 (Fig. 6). In particular, 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 during days 8-30 (7.0±4.2) and after Day 30 (4.0±3.5).

Machine learning-based feature assortment was conducted for all independent variables, and predictors with SHAP analyses were selected from the best performing XGBoost classifier (Fig. 7). 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 haemoglobin concentrations were significantly associated with a high mortality rate.

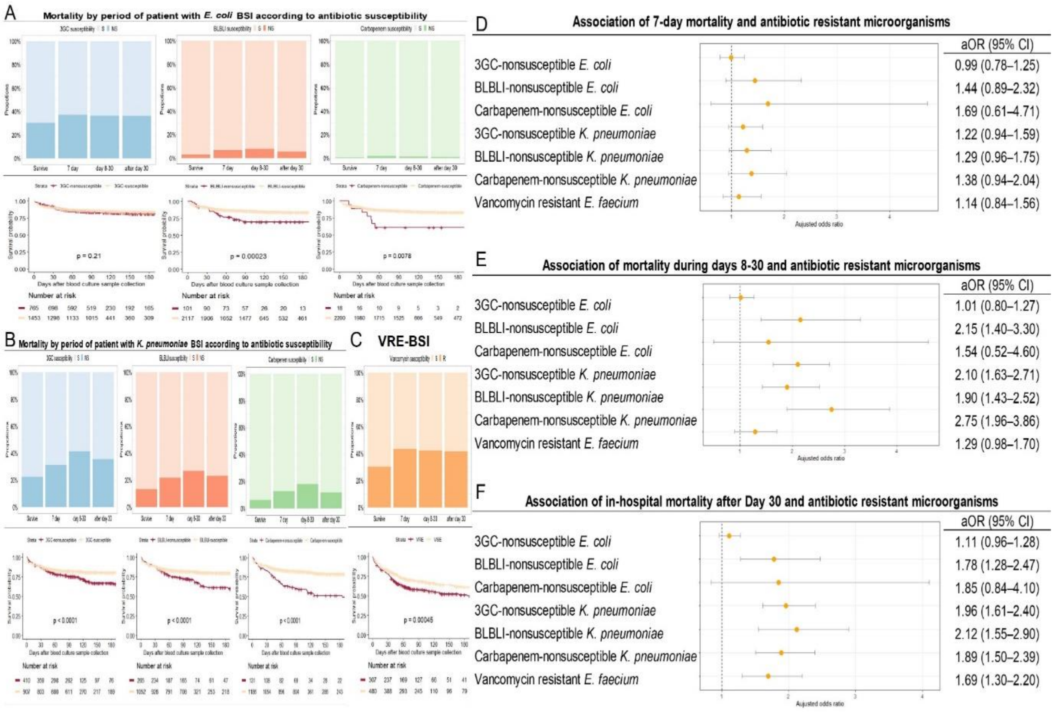

Figure 6. Mortality attributed to antimicrobial resistance or major pathogens by period of the BSI timeline

Bar charts represent mortality rates for each period of the BSI timeline, and Kaplan–Meier survival analyses show differences in long-term mortality between the major antimicrobial resistance phenotypes of *E. coli* (A), *K. pneumoniae* (B), and *E. faecium* (C). The death aORs of major antibiotic-resistant bacteria for each period of the BSI timeline are presented in E-F.

BSI, bloodstream infection; aOR, adjusted odds ratio; CI, confidence interval; VRE, vancomycin-resistant enterococci; BLBLI, ß-lactam/ß-lactamase inhibitors; 3GC, third-generation cephalosporins

Machine learning-based feature assortment was conducted for all independent variables, and predictors were selected from the best performing XGBoost classifier with SHAP analyses (Fig. 7). Multivariable analysis models consisting of these variables are presented in Table 7. For all time periods, high baseline SOFA score, high CCI, current

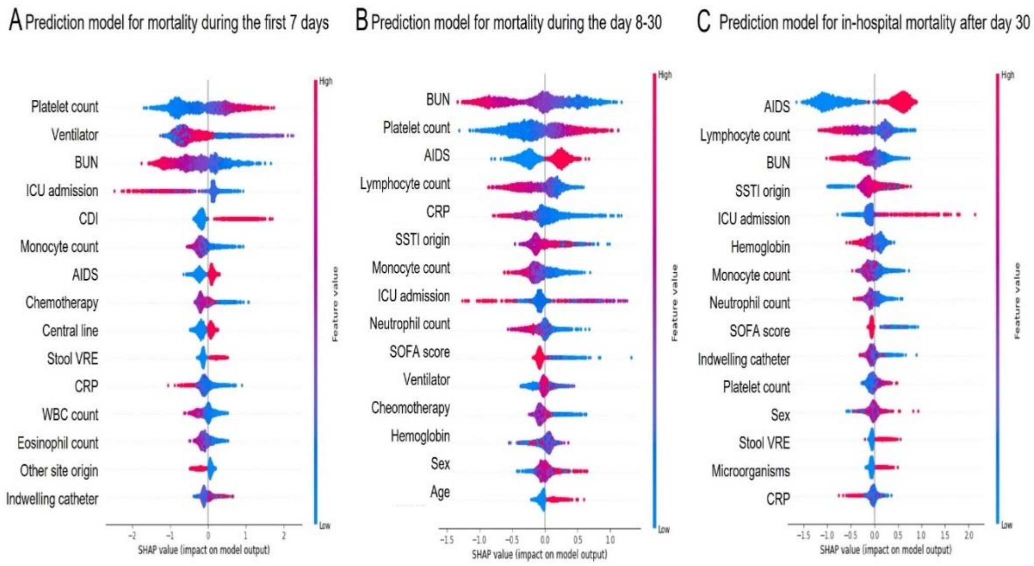

Figure 7. Critical variables with SHAP analyses to predict mortality for each period of the BSI timeline

A SHAP value summary dot plot of the XGBoost model.

The colour of the SHAP dot represents the value of the independent variable, and the location of the dot on the x axis indicates its SHAP value. A positive value indicates that the variable increases the likelihood of mortality.

cancer chemotherapy, high C-reactive protein levels, and low hemoglobin concentrations were significantly associated with high mortality rate.

5. 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*-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 *E. faecalis* and *E. faecium*, which had favourable prognoses during the first 7 days with death aORs of 0.76 (95% CI

Table 7. Univariable and multivariable analyses using logistic regression of risk factors of BSI

	Mortality during the first 7 days			Mortality between day 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
Female sex	0.90	(0.81-0.99)	0.033	1.04	(0.94-1.15)	0.439	1.11	(1.03-1.20)	0.009
ICU admission	0.38	(0.33-0.44)	<0.001	1.35	(1.18-1.54)	<0.001	0.95	(0.85-1.06)	0.370
SOFA score	1.41	(1.39-1.43)	<0.001	1.14	(1.12-1.16)	<0.001	1.04	(1.02-1.05)	<0.001
Infection origin (may be multiple)									
Abdomen	0.50	(0.42-0.60)	<0.001	1.00	(0.87-1.15)	0.998	1.34	(1.20-1.51)	<0.001
Catheter-related	0.37	(0.29-0.47)	<0.001	0.71	(0.59-0.85)	<0.001	0.97	(0.83-1.13)	0.709
Pneumonia	1.14	(0.98-1.32)	0.095	1.31	(1.13-1.52)	0.001	1.39	(1.21-1.59)	<0.001
Urogenital tract	0.58	(0.51-0.66)	<0.001	0.76	(0.68-0.86)	<0.001	0.91	(0.83-1.00)	0.051
Charlson comorbidity index	1.12	(1.11-1.14)	<0.001	1.23	(1.21-1.25)	<0.001	1.32	(1.29-1.34)	<0.001
Current chemotherapy	1.93	(1.69-2.21)	<0.001	1.57	(1.39-1.77)	<0.001	1.71	(1.54-1.89)	<0.001
Devices									
Ventilator	1.50	(1.28-1.77)	<0.001	1.26	(1.06-1.50)	0.008	0.92	(0.77-1.09)	0.321
Central venous line	0.87	(0.78-0.98)	0.020	0.66	(0.58-0.75)	<0.001	0.94	(0.84-1.05)	0.266
Indwelling catheter	1.37	(1.22-1.52)	<0.001	1.07	(0.96-1.2)	0.193	0.87	(0.79-0.95)	0.002
Surveilllance study									
Stool CRE/CPE	0.90	(0.66-1.21)	0.480	0.77	(0.57-1.04)	0.090	1.16	(0.90-1.49)	0.264
Clostridioides difficile infection	1.41	(1.06-1.89)	0.020	0.96	(0.71-1.28)	0.763	1.06	(0.83-1.37)	0.628
Stool VRE	1.19	(0.92-1.53)	0.182	1.44	(1.14-1.81)	0.002	1.76	(1.42-2.20)	<0.001
Laboratory tests									
C-reactive protein (mg/L)	1.01	(1.00-1.01)	<0.001	1.01	(1.00-1.01)	<0.001	1.01	(1.00-1.01)	0.012
WBC count	1.00	(0.99-1.01)	0.685	1.01	(1.01-1.02)	<0.001	1.00	(0.99-1.00)	0.047
Hb	0.90	(0.87-0.92)	<0.001	0.85	(0.82-0.87)	<0.001	0.81	(0.80-0.83)	<0.001
Isolated BSI-causative microorganisms during hospitalization (maybe multiple)									
Staphylococcus aureus	1.11	(0.94-1.32)	0.230	1.18	(1.01-1.38)	0.040	0.94	(0.82-1.08)	0.414
Enterococcus faecalis	0.76	(0.59-0.98)	0.038	0.83	(0.66-1.04)	0.105	1.36	(1.16-1.60)	<0.001
Enterococcus faecium	0.82	(0.71-0.96)	0.015	1.80	(1.58-2.05)	<0.001	1.74	(1.55-1.97)	<0.001
Escherichia coli	0.59	(0.52-0.68)	<0.001	0.66	(0.58-0.75)	<0.001	1.04	(0.95-1.14)	0.411
Klebsiella pneumoniae	0.68	(0.59-0.77)	<0.001	0.87	(0.76-0.99)	0.038	1.25	(1.13-1.38)	<0.001
Acinetobacter baumannii	1.40	(1.14-1.72)	0.001	1.26	(1.02-1.55)	0.032	1.78	(1.46-2.17)	<0.001
Pseudomonas aeruginosa	0.88	(0.70-1.10)	0.245	1.02	(0.82-1.27)	0.862	1.51	(1.26-1.81)	<0.001
Candida albicans	2.02	(1.62-2.51)	<0.001	2.59	(2.14-3.15)	<0.001	1.65	(1.35-2.01)	<0.001

Independent variables included in the multivariable analysis were selected via SHAP analysis through machine learning model.

BSI, bloodstream infection; OR, odd ratio; CI, confidence interval; SOFA, sequential organ failure assessment; CRE, carbapenem-resistant Enterobacteriaceae; CPE, carbapenemase-producing Enterobacteriaceae; VRE, vancomycin-resistant enterococci

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.

6. 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. 6. 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-resistant phenotype was associated with a poor prognosis for in-hospital mortality 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.

IV. 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 [17,18] 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 favourable 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 the 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.[19,20] In this regard, severe sepsis that fails to eradicate the index BSI is considered to induce an immunocompromised state in the patient, increasing the risk of subsequent infections and death.[20-22] It has also been reported that both prior use of antibiotics and index BSI caused by *Candida* species or 3GC-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.[23-25] 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.[26,27] 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 faecal microbiota transplantation, are needed.[28]

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 tertiary care institutions in a single country, influencing the generalizability of the results. Patients who previously received antimicrobial therapy and produced false-negative blood culture results might have been misclassified in this study. Machine learning techniques have inherent advantages in analysing big data, including variables with multicollinearity and nonlinear relationships.[29] Thus, we attempted to comprehensively analyse risk factors among patients with BSI by integrating machine learning techniques into conventional multivariable models to minimize bias.

V. 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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ABSTRACT (IN KOREAN)

혈류감염 기간별 환자 사망 위험인자 변화

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내용
배경: 단기 예후만을 비교할 경우, 미생물학적 요인이 혈류감염환자의 예후에 미치는 영향은 숙주요인에 의해 가려질 수 있다. 본 연구는 혈류감염의 각 기간을 처음 7일, 8-30일, 30일 이후의 세 구간으로 나누어 환자의 예후에 영향을 미치는 위험인자의 변화를 알아보고자 하였다.
방법: 다변수 회귀분석과 머신러닝 기법의 통합 연구를 통해 국내 2개 병원의 모든 성인 혈류감염 환자의 임상데이터를 이용하여 혈류감염 기간별 사망 위험인자를 분석하였다.
결과: 2011-2021년 동안 혈액 배양을 받은 총 302,303명의 입원 환자가 등록되었다. 사망한 환자의 첫 7일 동안의 평균 SOFA 점수는 10.6 (SD 4.3)으로 8-30일 동안의 7.0±4.2과 30일 이후의 4.0±3.5 보다 유의미하게 높았다. *A. baumannii* 및 *C. albicans*에 의해 유발된 혈류감염은 모든 기간 동안 환자의 사망의 위험을 높였다 (전부, p<0.001). *E. faecalis* 및 *E. faecium*에 의해 유발된 혈류감염은 처음 7일 동안 0.76 (95% CI 0.59–0.98) 및 0.82(0.71 –0.96)의 사망 odd ratio (OR)로 좋은 예후를 보인 반면, 30일 이후의 예후는 1.36(1.16–1.60) 및 1.74(1.55–1.97)의 OR로 좋지 않은 결과와 관련이 있었다. 반코마이신 내성 표현형을 가진 *E. faecium*에 의해 유발된 혈류감염은 30일 이후의 기간에서 1.69 (1.30-2.20)의 OR로 병원 내 사망률에 대한 불량한 예후와 관련이 있었다.
결론: 환자의 기준 중증도는 처음 7일 동안 사망률에 더 심각한 영향을 미쳤다. 이에 반해 혈류감염 원인균과 이들의 주요 항균제 내성을 포함한

미생물학적 요인이 사망률에 미치는 영향은 8-30일과 30일 이후에 더 강조되었다. 또한, 주요 병원체의 항균제 내성은 후속 혈류감염으로의 진행에 대한 위험 요소였으며, 그 결과 입원 기간 및 의료 비용을 증가시켰다. 의료 빅데이터를 활용한 시간 계층적 위험인자 분석은 환자 상태의 교란효과를 보정함으로써 감염병 연구 분야에서 미생물학적 요인의 영향을 이해하는 데 중요한 역할을 할 수 있다.

핵심되는 말 : 혈류감염, 후속혈류감염, 항균제 내성, 사망률, 장기 사망률, 기계학습

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