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Impacts of population ageing on bloodstream infection epidemiology and outcomes: A machine learning and statistical modelling study

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ABSTRACT

Objectives: To investigate the effect of population ageing on pathogen distribution and clinical outcomes in bloodstream infections (BSIs).
Methods: We analysed 37,100 adult patients with BSI from two university hospitals in South Korea (2006-2023) and used statistical and machine learning (ML) approaches to assess temporal trends, age-related changes in causative pathogens, and 30-day mortality.
Results: The mean age of patients was 64.6 years (standard deviation 15.0), with 55.7% aged ≥65. Advanced age was independently associated with a high 30-day mortality via a shift in pathogen distribution. ML models predicted an increasing proportion of BSIs caused by *Escherichia coli, Enterococcus faecalis*, coagulase-negative staphylococci and fungi with ageing and a decreasing proportion of those caused by *Staphylococcus aureus*, streptococci, *Pseudomonas aeruginosa* and *Acinetobacter* spp. Fungaemia contributed to the highest adjusted mortality rate. The advantage of *E. coli*-BSI being associated with low 30-day mortality was diminished in strains not susceptible to third-generation cephalosporins.
Conclusion: Population ageing is associated with shifts in BSI epidemiology and outcomes. Our findings suggest that tailored antimicrobial stewardship and infection management are necessary to address the burden of BSIs in ageing populations.

Introduction

The incidence of bloodstream infections (BSIs), critical and growing healthcare concerns [1–6], in Europe and North America ranges from 167 to 307 cases per 100,000 person-years, with a 30-day mortality rate ranging from 15% to 30% [7–9]. More than half of all reported BSI cases occur in individuals aged ≥65 years [3,10]. As global population ageing continues, the medical burden associated with BSIs intensifies.

Advanced age has been linked to a higher infection susceptibility due to immunosenescence, multiple comorbidities and increased exposure to healthcare environments, among other factors [10,11]. Previous studies have shown that elderly patients with BSIs have higher mortality rates than younger adults, along with differences in the spectrum of causative pathogens [1,12]. In this population, the urinary tract is the leading source of infection; therefore, Gram-negative bacteria are a more frequent cause of BSIs in that population than in younger patients [10,13]. However, data on the correlation between patient age and BSI-causing microorganisms remain limited, and so are studies that analyse the impact of population ageing on pathogen distribution and clinical outcomes.

South Korea, a country with the lowest fertility rate and one of the highest life expectancies among the Organization for Economic Co-operation and Development countries [14], is undergoing one of the most rapid demographic changes globally, potentially providing insight into how population ageing affects the trends in infectious diseases in other countries. This study analysed BSI cases from two university hospitals in South Korea, focusing on temporal and age-related differences in pathogen distribution and their association with clinical outcomes. In addition, machine learning (ML) techniques were used to predict shifts in the proportion of BSI-causing microorganisms with continued population ageing.

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Methods

Study population and data collection

This retrospective study included all adult patients (≥18 years) with at least one blood culture performed during hospitalization and admitted between June 2006 and December 2023 to two tertiary-care hospitals in South Korea: Hospitals A and B, with more than 2000 and 700 beds, respectively. To avoid duplication, only the index episode of BSI per patient was included in the analysis. In total, 50,823 patients met the inclusion criteria, of which 4188 were excluded due to a length of hospital stay of ≤2 days, lack of demographic data, or >20% missing clinical variables.

BSIs were defined according to the criteria established by the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) [15,16], which refers to the isolation of recognized pathogenic organisms from at least one blood culture, excluding common skin commensals, such as diphtheroids (*Corynebacterium* spp., not *Corynebacterium diphtheriae*), *Bacillus* spp. (not *Bacillus anthracis*), coagulase-negative staphylococci (CoNS), *Propionibacterium* spp., *Aerococcus* spp., *Micrococcus* spp., *Rothia* spp., *viridans* group streptococci. These commensals were considered true BSIs only when the same organism was isolated from ≥2 consecutive blood cultures. Polymicrobial infection was defined as the isolation of ≥2 microorganisms from blood cultures within 24 hours [17]. The presumed source of BSI was classified according to the CDC/NHSN surveillance definitions of specific infection sites. Due to potential species-level misidentification prior to implementation of the updated MALDI-TOF MS library, all isolates identified as *Acinetobacter baumannii* were classified as *Acinetobacter* spp. [18]. Based on these criteria, 9535 patients were classified as having contaminated cultures and excluded, resulting in a final cohort of 37,100 patients with BSIs included in the analysis.

Demographic characteristics, underlying comorbidities, Charlson comorbidity index (CCI) and date of blood culture collection were retrieved using electronic medical record (EMR) data extraction tools. BSI was categorized as community-onset if the first positive culture was obtained within 48 hours of admission, and as hospital-onset if after 48 hours [19]. Time to blood culture clearance was defined as the number of days from the index positive blood culture to the first recorded negative follow-up blood culture. The Sequential Organ Failure Assessment (SOFA) score was calculated using the most abnormal laboratory values and vital signs obtained within 24 hours of blood sample collection to assess baseline severity. Information regarding the use of medical devices (e.g. mechanical ventilation, urinary catheters and central venous catheters) and medications (e.g. antibiotics, vasopressors and corticosteroids) was also collected. Antibiotic susceptibility data were available from January 2010 onwards, when consistent reporting began in the EMR system. A summary of the proportion of missing values for each variable is provided in Supplementary Table S1. The primary outcome was all-cause mortality (ACM) within 30 days of BSI onset.

Statistical analysis

Continuous variables were assessed for normality using the Kolmogorov–Smirnov test. Descriptive statistics are presented as means ± standard deviation (SD) for continuous variables and counts with percentages for categorical variables. Group comparisons were performed using the chi-squared test (or Fisher's exact test for nonparametric variables) for categorical variables. Student's *t*-test (or Mann–Whitney *U* test) was used for continuous variables.

To assess the associations among host-related factors, empirical antibiotic use, BSI-causing organisms and isolation of major resistant pathogens, a correlation matrix was constructed using Spearman's rank correlation coefficient, and the results were visualized via a heatmap. Univariable and multivariable logistic regression analyses were conducted to identify the risk factors associated with 30-day ACM. After excluding those with substantial multicollinearity, variables with statistical significance on univariable analysis were selected for inclusion in the multivariable model.

Structural equation modelling was used to evaluate the direct effects of patient age on the distribution of BSI-causing pathogens and 30-day ACM and the indirect effects on 30-day ACM through changes in pathogen distribution. The model was fitted using the weighted least-squares mean and variance-adjusted estimator [20].

All *P*-values were two-sided, and a *P*-value <0.05 was considered statistically significant. All statistical analyses and visualizations were performed using the R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

ML analysis

To estimate how the distribution of BSI pathogens changes with increasing patient age, an ML approach was developed to predict the likelihood of each pathogen using a multiclass classification model. Data from Hospital A were used for model development, with an 80:20 random split into internal training and internal test sets, while data from Hospital B served as an external validation cohort. Missing values were imputed using median or mode imputation, and model-based imputation using Extreme Gradient Boosting (XGBoost). The model performance was evaluated using 5- and 10-fold cross-validation.

Multiple classification algorithms were compared using the PyCaret library in Python (Supplementary Tables S2-S5). Among these, the CatBoost classifier trained with 10-fold cross-validation and XGBoost-based imputation yielded the best performance and was selected as the final model. The hyperparameters were optimized via a random search.

Model performance was assessed using the area under the receiver operating characteristic curve (AUROC) with 95% confidence intervals (CIs) generated through bootstrapping. Additional performance metrics included the F1 score, sensitivity and accuracy. To interpret the model, SHapley Additive exPlanations (SHAP) were used to compute feature importance and visualize contributions [21]. SHAP-dependence plots were used to show age- and SOFA score-related variations in pathogen prediction. The potential impact of population ageing on the distribution of BSI-causing pathogens was explored using SHAP values corresponding to age variables across all observations and pathogen categories. The age input was systematically varied from 5 to 10 years above the mean value, while holding all other variables constant. The corresponding SHAP values were added to the expected log-odds of the model and transformed into probabilities using a logistic function. These predicted probabilities were averaged across the entire cohort to estimate the changes in pathogen distribution as a function of age.

All ML analyses were conducted using Python version 3.9.21 (Python Software Foundation, Wilmington, DE, USA).

Results

Baseline characteristics of the study population

Over the 17-year study period, 37,100 adult patients with BSIs were included, of whom 7438 (20.0%) died within 30 days of BSI onset (Table 1). The mean age of all patients was 64.6 years (SD 15.0), and 55.7% were aged ≥65 years. Most demographic and clinical characteristics significantly differed between the survivors and non-survivors. Patients who died within 30 days were older, more likely to be male, had a higher proportion of hospital-onset BSI,

Table 1
Baseline characteristics of patents with BSI.

Variables	Total (N = 37,100)	Survival (N = 29,662)	30-day all-cause mortality (N = 7438)	P
Age	64.6 ± 15.0	64.2 ± 15.2	66.5 ± 13.8	<0.001
<65 years	16,429 (44.3%)	13,414 (45.2%)	3015 (40.5%)	<0.001
≥65 years	20,671 (55.7%)	16,248 (54.8%)	4423 (59.5%)	
Sex				<0.001
Female	16,581 (44.7%)	13,635 (46.0%)	2946 (39.6%)	
Male	20,519 (55.3%)	16,027 (54.0%)	4492 (60.4%)	
Institutes				0.141
Hospital A (internal training dataset)	28,695 (77.3%)	22,894 (77.2%)	5801 (78.0%)	
Hospital B (external validation dataset)	8405 (22.7%)	6768 (22.8%)	1637 (22.0%)	
Length of hospital stay	19 [9-39]	19 [9-41]	17 [6-31]	<0.001
ICU admission prior to blood culture	3560 (9.6%)	2672 (9.0%)	888 (11.9%)	<0.001
Length of ICU stay	5 [1-16]	4 [1-16]	6 [2-15]	<0.001
Ward at time of blood culture				
Emergency room	15,931 (42.9%)	13,405 (45.2%)	2526 (34.0%)	<0.001
ICU	4079 (11.0%)	2371 (8.0%)	1708 (23.0%)	
General ward	17,090 (46.1%)	13,886 (46.8%)	3204 (43.1%)	
Surgical history within 90 days	3514 (9.5%)	2758 (9.3%)	756 (10.2%)	0.024
Time to blood culture clearance (days)	3 [2-5]	3 [2-5]	3 [2-5]	0.222
Hospital-onset BSIs	26,879 (72.5%)	20,065 (67.6%)	6814 (91.6%)	<0.001
Presumed source of BSI				<0.001
Primary/unidentified	15,330 (41.3%)	13,961 (47.1%)	1369 (18.4%)	
Catheter-related	13,486 (36.4%)	9652 (32.5%)	3834 (51.5%)	
Genitourinary tract	4872 (13.1%)	3845 (13.0%)	1027 (13.8%)	
Respiratory tract	2461 (6.6%)	1496 (5.0%)	965 (13.0%)	
Intra-abdominal	590 (1.6%)	436 (1.5%)	154 (2.1%)	
Skin and soft tissue	253 (0.7%)	202 (0.7%)	51 (0.7%)	
Others	108 (0.3%)	70 (0.2%)	38 (0.5%)	
SOFA score	3 [1-6]	2 [0-4]	6 [3-9]	<0.001
CCI	10.8 ± 2.3	10.5 ± 2.2	11.8 ± 2.4	<0.001
Solid organ cancer	14,870 (40.1%)	10,881 (36.7%)	3989 (53.6%)	<0.001
Diabetes mellitus	3974 (10.7%)	3081 (10.4%)	893 (12.0%)	<0.001
Congestive heart diseases	3071 (8.3%)	2181 (7.4%)	890 (12.0%)	<0.001
Kidney diseases	964 (2.6%)	728 (2.5%)	236 (3.2%)	0.001
Liver diseases	2274 (6.1%)	1845 (6.2%)	429 (5.8%)	0.153
Glucocorticoid use	9716 (26.2%)	6498 (21.9%)	3218 (43.3%)	<0.001
Central venous catheter use	15,600 (42.0%)	10,862 (36.6%)	4738 (63.7%)	<0.001
Indwelling urinary catheter use	10,633 (28.7%)	7471 (25.2%)	3162 (42.5%)	<0.001
Ventilator use	4561 (12.3%)	2348 (7.9%)	2213 (29.8%)	<0.001
Appropriateness of antimicrobial therapy				
Appropriate empirical treatment	19,029 (51.3%)	14,961 (50.4%)	4068 (54.7%)	<0.001
Appropriate definitive treatment	29,451 (79.4%)	23,969 (80.8%)	5482 (73.7%)	<0.001

Continuous variables are presented as mean ± standard deviation or median [1st-3rd quartile], as appropriate. Categorical variables are presented as numbers (%).
BSI, bloodstream infection; CCI, Charlson comorbidity index; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

and had higher baseline SOFA and CCI scores (all $P < 0.001$). The distributions of BSI-causing microorganisms and antimicrobial resistance (AMR) rates between the two groups were also compared (Supplementary Table S6).

Temporal changes in patient characteristics and distribution of BSI-causing pathogens by year and age group are illustrated in Figure 1 and Supplementary Table S7. In hospitals A and B, the mean age of the patients with BSIs steadily increased over the study period (Figure 1a). The 30-day ACM rate decreased until 2019 but increased during the COVID-19 pandemic period (2020-2022), with a subsequent decline in 2023. The baseline SOFA scores exhibited a similar trend (Figure 1b). The proportion of BSIs caused by Gram-positive bacteria increased from 38.1% in 2006 to 43.9% in 2010, followed by a gradual decline to 32.1% by 2023 (Supplementary Table S7). Conversely, the proportion of Gram-negative bacteraemia increased from 43.2% to 52.1% over the same period. The proportion of fungaemia also increased from 4.8% in 2009 to 6.8% in 2023. Across all age groups, *Escherichia coli* was the most common BSI-causing microorganism (Figure 1e, f), and the proportion of fungaemia was significantly higher among patients aged ≥70 years than those that are younger ($P = 0.003$). The annual trends in the major AMR rates are presented in Supplementary Figure S1.

Correlation between patient features and BSI-causing microorganisms

The association between BSI-causing pathogens and clinical characteristics or underlying comorbidities are illustrated in Figure 2. BSIs caused by *Enterococcus faecium*, glucose-nonfermenting Gram-negative bacilli (GNFB), such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. and fungi positively correlated with 30-day ACM, hospital-onset BSI, prior ICU admission, high SOFA scores and CCI and increased use of central venous catheters, mechanical ventilation and glucocorticoids (Figure 2a). In contrast, BSIs due to CoNS, *Enterococcus faecalis, Streptococcus* spp. and *E. coli* negatively correlated with the 30-day ACM and SOFA scores. Positive correlations with age were observed for BSIs caused by *E. coli, Candida albicans, Nakaseomyces glabrata* (formerly *Candida glabrata*) and polymicrobial infections, whereas those caused by CoNS, *Streptococcus* spp. and *P. aeruginosa* showed inverse trends. BSIs caused by major resistant pathogens were related to hospital-

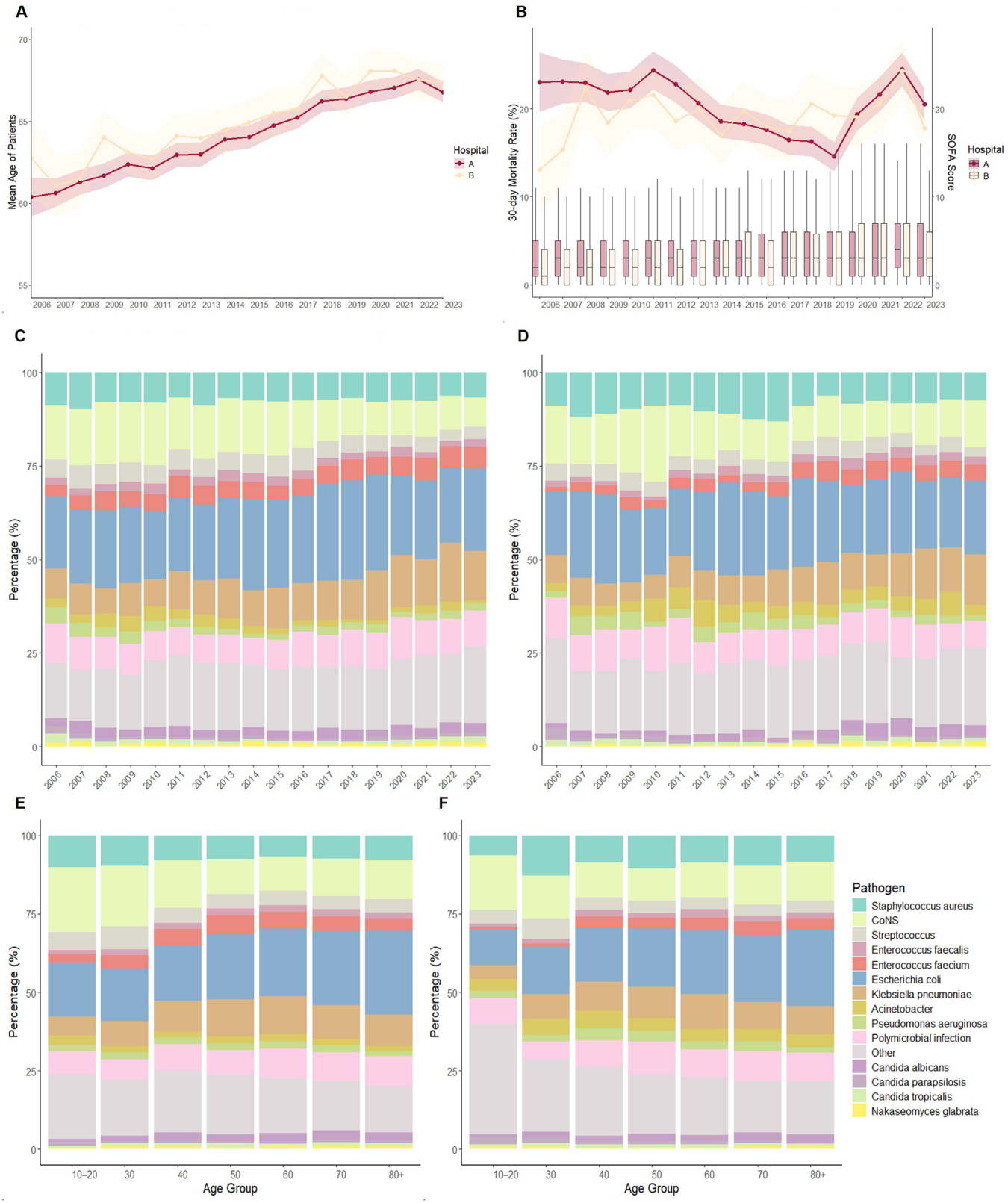

Figure 1. Temporal trends in patient characteristics and distribution of BSI-causing pathogens by year and age group. (a) Mean age of enrolled patients over time, shown by year with 95% confidence intervals. (b) Comparison of 30-day mortality rate (line graph) and SOFA scores (boxplots) by year. (c) Proportion of major bloodstream infection pathogens by year at Hospital A. (d) Proportion of major bloodstream infection pathogens by year at Hospital B. (e) Proportion of major pathogens by patient age group at Hospital A. (f) Proportion of major pathogens by patient age group at Hospital B.

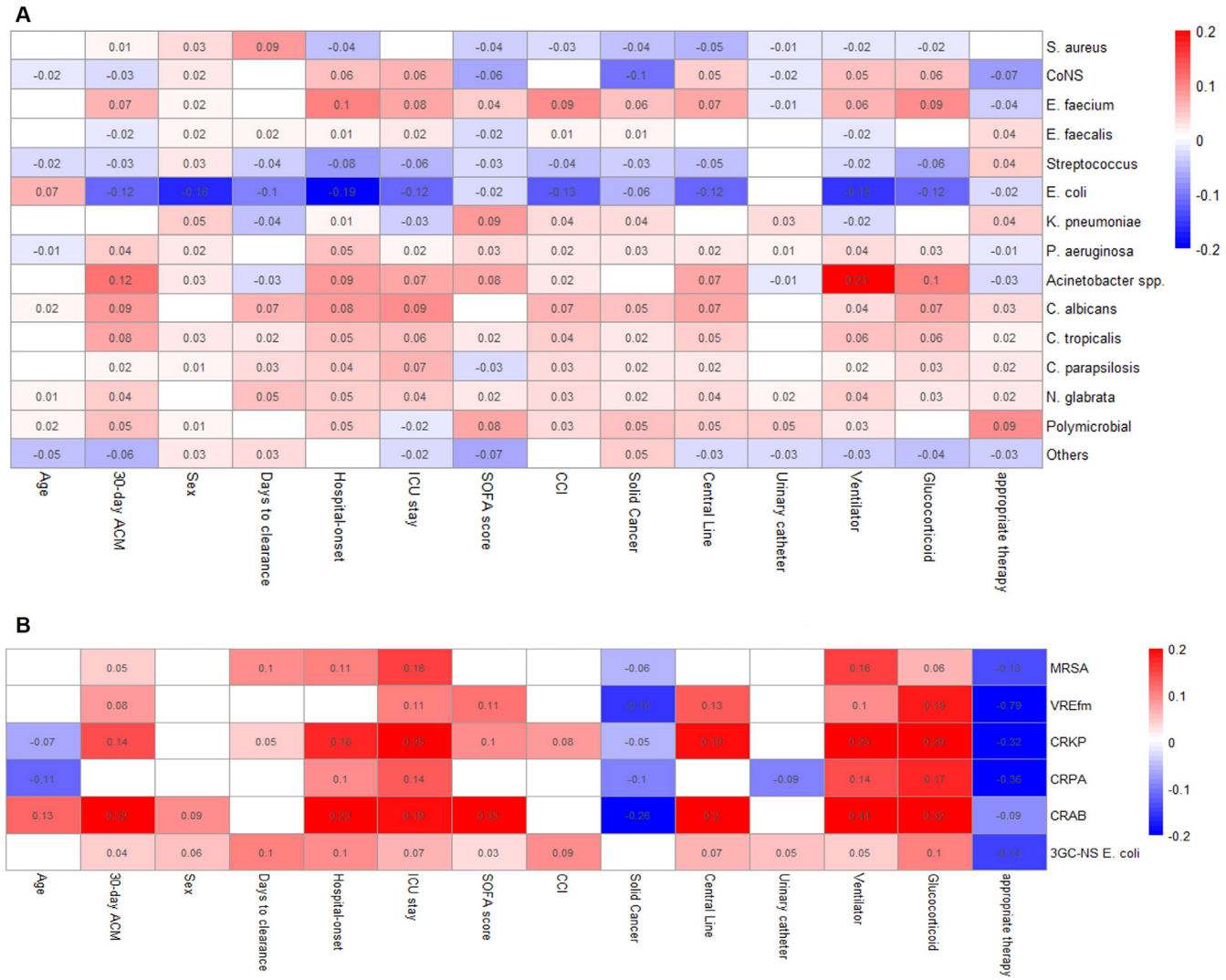

Figure 2. Spearman correlation between BSI-causing pathogens and patient clinical variables. (A) Correlation between causative microorganisms of bloodstream infection and clinical characteristics. (B) Correlation between major resistant pathogens and clinical characteristics.

onset BSI and prior ICU stays, with all but carbapenem-non-susceptible *P. aeruginosa* being associated with increased 30-day ACM (Figure 2b).

Among the comorbidities, *E. coli*-BSI positively correlated with kidney disease and *Klebsiella pneumoniae*-BSI with liver disease (Supplementary Figure S2A). Fungaemia was related to solid organ cancer, whereas CoNS-BSI demonstrated strongest positive correlation with leukaemia. The use of broad-spectrum empirical antibiotics, such as glycopeptides and carbapenems, positively correlated with BSI caused by *E. faecium, Acinetobacter* spp. and *C. albicans* (Supplementary Figure S2B).

Mortality risk factors in patients with BSIs

The features associated with the 30-day ACM are listed in Table 2. Multivariable analysis identified patient age, high illness severity (SOFA score and CCI), immunosuppression (solid cancer, glucocorticoid use) and the use of ventilator as independent risk factors for 30-day ACM. Using *Staphylococcus aureus* as the reference microorganism, BSIs caused by *E. faecium* (adjusted odds ratio 1.22; 95% CI 1.00-1.48), *C. albicans* (1.59; 1.25-2.01) and *Candida tropicalis* (1.74; 1.25-2.41) were associated with increased 30-day ACM, whereas BSIs caused by *Streptococcus* spp., *E. faecalis, E. coli* and *K. pneumoniae* showed favourable outcomes. Pathogen-specific resistance profiles were also evaluated (Supplementary Table S8), but their association with 30-day ACM were not statistically significant after adjustment for other covariates.

Predicted impact of population ageing on the distribution of BSI-causing pathogen and clinical outcome

In our cohort, the best-performing ML model for predicting BSI-causing pathogens yielded an AUROC of 80.6% (95% CI 79.5%-81.6%) and an F1-score of 0.338 on the internal test dataset (Hospital A) and 79.0% (95% CI 78.1%-79.9%) and 0.328 on the external validation dataset (Hospital B) (Supplementary Table S9). SHAP analysis was conducted to interpret the ML model (Supplementary Figure S3). Among all variables, days from admission to blood culture collection was the primary indicator on model predictions, followed by body temperature, and empirical use of β-lactam/β-lactamase inhibitor (Supplementary Figure S3).

Patient age also contributed to the model, having a nonlinear relationship with SHAP values (Supplementary Figure S4A). Based on SHAP-derived age contributions, we simulated age-dependent changes in the predicted distribution of BSI-causing pathogens. With increasing patient age, the predicted relative proportions of

Table 2
Univariable and multivariable analysis using logistic regression of risk factors for 30-day ACM in patients with BSI.

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.011 (1.009-1.013)	<0.001	1.017 (1.014-1.02)	<0.001
Male sex	1.297 (1.232-1.366)	<0.001	1.029 (0.951-1.114)	0.473
ICU admission prior to blood culture	1.369 (1.263-1.484)	<0.001	0.698 (0.616-0.792)	<0.001
Length of ICU stay	0.994 (0.992-0.997)	<0.001	-	
Ward at time of blood culture			-	
Emergency room	Reference			
ICU	3.823 (3.546-4.122)	<0.001		
General ward	1.224 (1.156-1.297)	<0.001		
Surgical history within 90 days	1.104 (1.014-1.201)	0.023	-	
Time to blood culture clearance (days)	0.972 (0.964-0.980)	<0.001	0.967 (0.958-0.976)	<0.001
Hospital-onset BSIs	5.223 (4.795-5.689)	<0.001	1.435 (1.234-1.668)	<0.001
Presumed source of BSI				
Catheter-related	Reference		Reference	
Primary/unidentified	0.247 (0.231-0.264)	<0.001	0.770 (0.632-0.939)	0.010
Genitourinary tract	0.672 (0.621-0.727)	<0.001	1.349 (1.123-1.621)	0.001
Respiratory tract	1.624 (1.485-1.775)	<0.001	1.551 (1.306-1.843)	<0.001
Intra-abdominal	0.889 (0.737-1.073)	0.220	0.895 (0.665-1.205)	0.465
Skin and soft tissue	0.636 (0.467-0.866)	0.004	0.718 (0.439-1.175)	0.188
Others	1.367 (0.919-2.032)	0.123	1.742 (1.020-2.973)	0.042
SOFA score	1.294 (1.285-1.304)	<0.001	1.155 (1.141-1.170)	<0.001
Charlson comorbidity index	1.295 (1.280-1.311)	<0.001	1.174 (1.148-1.200)	<0.001
Solid organ cancer	1.996 (1.896-2.101)	<0.001	1.459 (1.318-1.615)	<0.001
Diabetes mellitus	1.177 (1.087-1.274)	0.000		
Kidney diseases	1.302 (1.122-1.512)	0.001		
Liver diseases	0.923 (0.828-1.028)	0.146		
Glucocorticoid use	2.718 (2.577-2.868)	<0.001	1.536 (1.410-1.674)	<0.001
Central venous catheter use	3.037 (2.881-3.202)	<0.001	0.980 (0.827-1.161)	0.815
Indwelling urinary catheter use	2.197 (2.083-2.316)	<0.001	0.883 (0.800-0.974)	0.013
Ventilator use	4.927 (4.616-5.259)	<0.001	1.452 (1.289-1.636)	<0.001
Appropriate antimicrobial treatment	0.666 (0.627-0.706)	<0.001	0.966 (0.864-1.079)	0.539
BSI-causing microorganisms				
Staphylococcus aureus	Reference		Reference	
CoNS	0.716 (0.638-0.805)	<0.001	0.896 (0.758-1.060)	0.200
Streptococcus spp.	0.626 (0.533-0.735)	<0.001	0.781 (0.618-0.986)	0.038
Enterococcus faecium	1.690 (1.479-1.931)	<0.001	1.216 (1.003-1.475)	0.047
Enterococcus faecalis	0.648 (0.524-0.801)	0.000	0.627 (0.461-0.852)	0.003
Escherichia coli	0.441 (0.395-0.493)	<0.001	0.437 (0.369-0.518)	<0.001
Klebsiella pneumoniae	0.946 (0.842-1.062)	0.345	0.584 (0.489-0.699)	<0.001
Acinetobacter spp.	3.361 (2.884-3.917)	<0.001	1.239 (0.973-1.577)	0.082
Pseudomonas aeruginosa	1.638 (1.383-1.939)	<0.001	0.974 (0.75-1.265)	0.843

(*continued on next page*)

Table 2 (*continued*)

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Candida albicans	2.593 (2.209-3.044)	<0.001	1.587 (1.253-2.011)	0.000
Candida tropicalis	3.514 (2.820-4.377)	<0.001	1.738 (1.252-2.413)	0.001
Candida parapsilosis	1.308 (1.012-1.692)	0.041	1.070 (0.738-1.552)	0.720
Nakaseomyces glabrata	2.280 (1.787-2.909)	<0.001	1.232 (0.862-1.76)	0.253
Polymicrobial infection	1.295 (1.153-1.455)	<0.001	0.748 (0.624-0.896)	0.002
Others	0.633 (0.567-0.707)	<0.001	0.665 (0.565-0.784)	<0.001

ACM, all-cause mortality; aOR, adjusted odds ratio; BSI, bloodstream infection; CI, confidence interval; CoNS, coagulase-negative staphylococci; ICU, intensive care unit; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

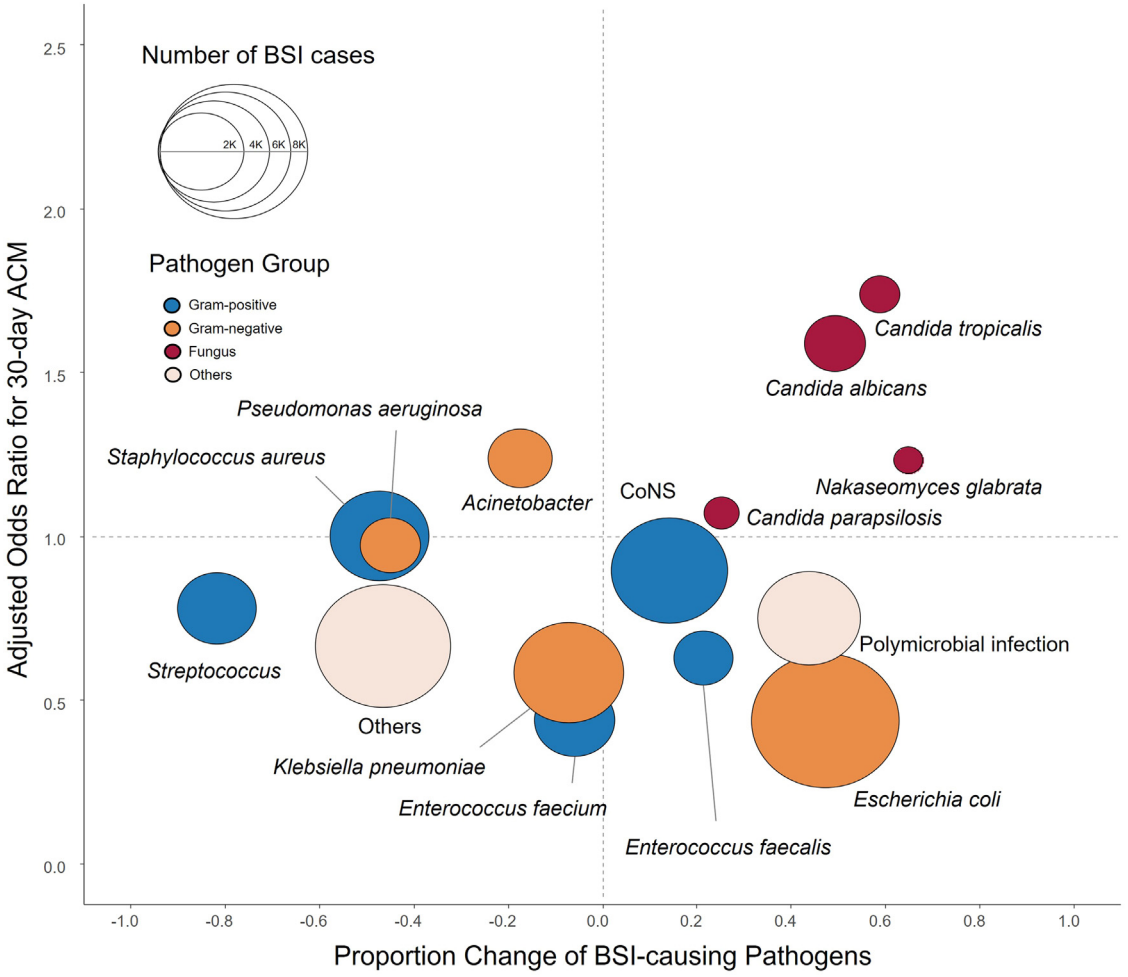

Figure 3. Distribution of BSI-causing pathogens according to case number, mortality risk and age-related shifts.

BSI caused by *E. faecalis*, CoNS, *E. coli, Candida* spp., *N. glabrata* and polymicrobial infections gradually increased, whereas the relative proportions attributed to other pathogens decreased (Supplementary Figure S4B).

Figure 3 summarizes pathogen-specific characteristics in terms of the number of cases, adjusted mortality risk and age-related changes in distribution. *E. coli* was the most common BSI-causing organism and predicted to further increase with population ageing, while being associated with relatively favourable outcomes. In comparison, BSIs due to *Candida* spp. and *N. glabrata* were also projected to become more frequent with advancing age; however, they were associated with high baseline severity and adjusted mortality risk. *Streptococcus* spp. showed a low adjusted mortality risk, and their relative frequency was predicted to decline with age.

Structural equation modelling was used to evaluate the effect of ageing on the 30-day ACM, accounting for the direct and indirect effects mediated by shifts in pathogen distribution (Supplementary Table S10). The predicted increase in *E. coli*-BSI, which is associated with low mortality, contributed to risk reduction. However, a decline in *Streptococcus* spp. and an increase in fungaemia were associated with poor clinical outcomes. In addition to these pathogen-mediated effects, age was di-

rectly associated with the risk of death (standardized $\beta = 0.103$, $P < 0.001$).

Discussion

This study investigated the effects of population ageing on the epidemiology of BSIs and associated clinical outcomes. Over the 17-year study period, the mean age of the inpatients steadily increased. Age was identified as a direct risk factor for 30-day ACM and an indirect mortality risk through shifts in pathogen distribution. Statistical and ML analyses indicated that the relative proportion of BSIs caused by *E. coli, E. faecalis* and fungi increased with ageing. In contrast, those caused by *Streptococcus* spp. and GNFB decreased. Fungaemia is associated with a higher adjusted 30-day ACM than bacteraemia and expected to become more prevalent among patients with BSIs. This shift in pathogen distribution may contribute to an overall increase in BSI-related mortality, whereas the increasing proportion of *E. coli*-BSI, generally associated with favourable outcomes, may partially offset this adverse trend.

The epidemiology of BSI has gradually changed over the past two decades. Indeed, a global survey from 1997 to 2016 reported that *E. coli* and *S. aureus* were the leading causes of BSIs worldwide, accounting for approximately 40% of all reported cases [4]. Before the mid-2000s, *S. aureus* was the most common BSI-causing pathogen; however, *E. coli* has since become predominant, primarily owing to high prevalence in the elderly population. Recent European data from 2023 further support this shift, showing that *E. coli* accounts for 43% of BSIs compared with only 18% for *S. aureus* [22]. In this study, our data reflected a similar trend, with the ratio of *E. coli* to *S. aureus* rising from 2.1 in 2006 to 3.1 in 2023. Additionally, the proportion of Gram-negative bacteraemia increased from approximately one-third to over half, while that of Gram-positive bacteraemia decreased [4,22]. In particular, the decline in pneumococcal BSI was remarkable, consistent with our data, and is thought to be attributed to vaccination programs [23]. Although regional differences persist in the prevalence of specific pathogens such as *S. aureus*, which tends to be more frequently isolated in North American than in East Asian hospitals, the overall trends appear to converge globally [4].

In our cohort, the relative proportions of BSIs caused by *C. albicans, C. tropicalis, Candida parapsilosis* and *N. glabrata* were predicted to increase with ageing. Elderly patients are at high risk of healthcare-associated infections owing to prolonged hospitalization, underlying comorbidities and increased exposure to invasive procedures [10,11], promoting colonization and subsequent fungal infections, especially in immunocompromised hosts [24,25]. Invasive candidiasis has become a major challenge in the ageing population, with more than half of all reported cases occurring in patients >65 years old [24–26]. However, most previous studies on BSI epidemiology focused on bacteraemia, and few comprehensively analysing bacterial and fungal pathogens in an integrated manner [4,6,22,26,27]. To better reflect real-world clinical practice, where blood cultures simultaneously detect bacteria and fungi, our study incorporated the temporal trends of these organisms.

Furthermore, the statistical and ML models consistently indicated that population ageing may lead to a disproportionately greater increase in the proportion of fungaemia relative to bacteraemia, exacerbating the overall prognosis of patients with BSIs. In contrast to traditional regression, the ML model identified nonlinear relationships and facilitated the prediction of age-related changes in pathogen distribution through simulation [21,28]. This approach provides an interpretable and data-driven framework for predicting epidemiological changes in an ageing population.

The adjusted mortality risk was highest for BSIs caused by fungi and *E. faecium* [6]. These infections have the characteristics of hospital-onset infections, including male sex, prior ICU stay, glucocorticoid administration and medical device use. Even after adjusting for these variables, they remained significant predictors of 30-day ACM, suggesting that opportunistic infections in immunocompromised patients perpetuate poor clinical outcomes. In contrast, *E. coli*-BSI showed community-onset characteristics, such as female sex, early onset post-hospitalization and favourable prognosis [10]; however, cases caused by third-generation cephalosporin non-susceptible *strains* showed opposite features. Third-generation cephalosporins are the core antibiotics for managing *E. coli*-BSI; global surveillance data indicated resistance rates approaching 42% [29]. Although BSI caused by *E. coli* has significantly lower mortality rates than that caused by fungaemia, the increasing prevalence of antibiotic-resistant strains may diminish this relative prognostic advantage. These findings highlight the need to control healthcare-associated infections and AMR in elderly patients.

This study has some limitations. First, since the data were collected from two tertiary hospitals in South Korea, the generalizability of the findings to other countries, smaller institutions and community-based settings is restricted. In particular, differences in the healthcare infrastructure, population demographics, infection control practices and AMR patterns may limit the applicability of our results [22,29]. Second, owing to the retrospective design, unmeasured confounders could not be excluded. For example, temporal changes in diagnostic methods, blood culture protocols and institutional policies can influence pathogen detection. Furthermore, we were unable to reliably assess certain important factors such as the total duration of antimicrobial therapy, adherence to source control procedures or long-term microbiological eradication based on serial cultures. Nevertheless, given the consistency between our findings and the global trends in BSI epidemiology, the patterns observed and predicted in this cohort may be relevant to ageing populations beyond the regional context [4]. While the ML model performed well in our cohort, further external validation in diverse healthcare settings remains warranted to assess its generalizability.

In conclusion, this study demonstrates that the epidemiology of BSIs will likely shift with population ageing, potentially influencing patient outcomes. Using large-scale clinical data, we applied statistical and ML-based modelling approaches that consistently predicted an increased proportion of BSIs caused by fungi and *E. coli*. The integration of ML techniques enables the prediction of pathogen distribution trends, providing insights into the evolving dynamics of infectious diseases. As the global population ages, the development of tailored antimicrobial stewardship and infection management strategies for older adults remains necessary to mitigate the growing burden of BSIs.

Ethical approval

This study was approved by the Institutional Review Board at Severance Hospital, Yonsei University Health System (No. 3-2024-0159).

Declaration of competing interest

No author has a conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107998.

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