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Shifting trends in bloodstream infection-causing microorganisms and their clinical impact in patients with haematologic malignancies in South Korea: A propensity score-matched study

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ABSTRACT

Background: This study aimed to identify recent trends in the epidemiology of bloodstream infection (BSI)-causing microorganisms among patients with haematologic malignancies (HMs) between 2011 and 2021, and to determine their impact on patient outcomes.

Methods: This retrospective study included 6792 patients with HMs, of whom 1308 (19.3%) developed BSI within 1 y of diagnosis. The incidence of BSI-causing microorganisms was determined, and a propensity score-matched study was performed to identify risk factors for 28-d all-cause mortality in patients with HM.

Results: A total of 6792 patients with HMs were enrolled. The cumulative incidence of BSI and neutropenia was significantly higher in the acute myeloid leukaemia and acute lymphoblastic leukaemia groups compared to other groups, and neutropenia and type of HMs were risk factors for the development of BSI. The annual incidence of coagulase-negative staphylococci (CoNS)-BSI decreased significantly ($P < 0.001$), whereas *Klebsiella pneumoniae*-BSI increased ($P = 0.01$). Carbapenem nonsusceptibility rates in *K. pneumoniae* isolates increased from 0.0% to 76.5% ($P < 0.001$). BSI caused by *K. pneumoniae* (adjusted odds ratio 2.17; 95% confidence interval 1.12–4.21) was associated with higher 28-d all-cause mortality compared to that caused by CoNS (adjusted odds ratio 0.86; 95% confidence interval 0.48–1.55).

Conclusion: The pathogenic spectrum of BSI-causing bacteria in patients with HMs gradually shifted from Gram-positive to Gram-negative, especially from CoNS to *K. pneumoniae*. Considering that *K. pneumoniae*-BSI had a significantly higher 28-d mortality rate than CoNS-BSI, this evolving trend could adversely impact the clinical outcomes of patients with HMs.

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1. Introduction

Patients with haematologic malignancies (HMs) are at a high risk of developing hospital-acquired bloodstream infections (BSIs). Prolonged immunosuppression and/or frequent use of intravascular catheters contribute to increased vulnerability to infections and consequently increase patient morbidity and mortality [1–3]. Moreover, The incidence of BSI accounts for 11%–38% of all HM cases, with a crude mortality rate of 12%–42% [4–7]. Despite major improvements in chemotherapeutic treatment, neutropenia remains a common complication in patients with HMs and can lead to BSIs, mainly caused by bacteria or fungi [8].

Between 1980 and 2000, Gram-positive organisms were more frequently isolated from BSIs in patients with HMs than Gram-negative organisms [3,5]. However, with the decline in the use of intravascular catheters and changes in prophylactic antimicrobial regimens, the isolation rates of Gram-negative organisms in the aforementioned patients have been similar to or higher than those of Gram-positive organisms since the 2000s [9–11]. In the last decade, the emergence and explosive spread of carbapenemase-producing *Enterobacteriaceae* strains have become a global concern, posing a serious threat to patients with HMs [12,13]. However, a paucity of data exists analysing whether carbapenem resistance contributes to changes in BSI-causing microorganisms in patients with HMs and the clinical impact of infections with these pathogens.

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This study aimed to identify recent trends in the epidemiologic shift of BSI-causing microorganisms in patients with HM between 2011 and 2021 and to determine the impact of the shift on the prognosis of these patients. Furthermore, we investigated the variance in the pathogenic spectrum and timing of BSIs among the different types of HMs.

2. Methods

2.1. Study population and data collection

This retrospective study included patients who were first diagnosed with HMs between 2011 and 2021 at two university hospitals (tertiary care hospitals in Seoul, South Korea, with more than 2,000 and 800 beds, respectively). Patients under the age of 18, those with a hospital stay of 3 d or less, and those patients with either no demographic data or more than 20% missing variables were excluded.

The incidence of BSIs within 1 y of the initial HM diagnosis for each patient was assessed, considering only the first BSI episode. According to the Centers for Disease Control/National Healthcare Safety Network definitions (2023) [14], BSI was defined as either the presence of recognised bacterial pathogens identified from ≥1 blood culture, excluding skin contaminants (i.e. diphtheroids, *Bacillus* spp., coagulase-negative staphylococci [CoNS], micrococci) or the presence of the same skin contaminants in ≥2 consecutive blood cultures. Neutropenia refers to an absolute neutrophil count of fewer than 500 cells/μL. Additionally, neutropenia was considered severe if the value was fewer than 100 cells/μL [4].

Clinical information such as demographics, underlying comorbidities, Charlson comorbidity index (CCI), and date of blood specimen collection was retrieved using the electronic medical record extraction tool of the institutions. To identify the most abnormal values within 48 h of blood specimen collection, both the minimum and maximum values of laboratory test results and vital signs were extracted to calculate the Sequential Organ Failure Assessment (SOFA) score. We also extracted the use of mechanical ventilators, antimicrobial agents, and vasopressors. The primary outcome of interest was the 28-d all-cause mortality (ACM) rate in patients after the onset of BSI.

2.2. Propensity-score matched analysis

Propensity-score (PS) indicates the assignment probability based on independent factors and is used to adjust the distribution of baseline confounders. Five variables were selected for this assignment: patient age, sex, baseline SOFA score, and CCI. Each group of patients with or without 28-d ACM was matched using the nearest neighbour method (1:3 match). Matching was performed when the logit difference of the PS was <0.2 times the standard deviation score.

2.3. Statistical analysis

Continuous variables were displayed as the means and standard deviations (or medians and interquartile ranges in the case of nonparametric variables), while categorical variables were presented as numbers and percentages. Statistical significance between groups for qualitative data was determined using the chi-square test (or Fisher's exact test in the case of nonparametric variables). For quantitative data, the Student's *t* test (or the Mann-Whitney *U* test) was applied. Univariable and multivariable analyses were performed using logistic/Cox regression and conditional logistic regression, respectively, to assess the risk factors for BSI and 28-d ACM. After excluding factors with multicollinearity, the dependent variables were selected for multivariable analyses based on the statistical significance provided by the univariable analyses. The 1-y cumulative incidence of the first BSI was analysed using the Kaplan-Meier estimator and tested for differences between the various HM groups using the log-rank test. All reported *P*-values were two-sided and were considered statistically significant at $P < 0.05$. R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses and graphic compositions, with the following packages: MatchIt, Survival, and ggplot2.

3. Results

3.1. Baseline characteristics

After applying the exclusion criteria, 6792 adult patients were included from the 11 993 cases diagnosed with HMs. The baseline characteristics of the enrolled patients are displayed in Table 1. Among the study population, 1308 (19.3%) patients had BSI within 1 y of their first diagnosis, which was particularly common in patients diagnosed with acute lymphoblastic leukaemia (ALL) (37.5%) and acute myeloid leukaemia (AML) (37.4%). The mean age at diagnosis was the highest for patients with multiple myeloma (64.4 y ± 11.3) and the lowest in those with ALL (47.8 y ± 18.6). Significant differences existed among the different HM groups in most variables, including baseline SOFA score, CCI, and prevalence of neutropenia (all $P < 0.001$).

3.2. Distribution of BSI-causing microorganisms

A downward trend was observed in the annual number of BSI cases despite the increasing number of patients enrolled each y (Fig. 1 and Table A.1). The annual incidence of BSI caused by CoNS significantly declined from 51.2/million inpatient-days in 2011 to 22.0/million inpatient-days in 2021 (Poisson regression; mean decrease, 11% per year; $P < 0.001$; Fig. A.1). In contrast, BSI caused by *Klebsiella pneumoniae* increased significantly from 11.7/million inpatient-days in 2011–18.9/million inpatient-days in 2021 (mean increase of 7% per year; $P = 0.01$). Consequently, the relative incidences of Gram-positive BSI and CoNS-BSI decreased from 67.2% and 38.4% in 2011 to 39.5% and 18.4% in 2021, respectively, while those of Gram-negative BSI and *K. pneumoniae*-BSI increased from 27.2% and 8.8% in 2011 to 50.9% and 15.8% in 2021, respectively. The mean age and CCI of enrolled patients increased from 56.3 ± 16.0 y and 4.6 ± 2.3 in 2011 to 60.4 ± 15.9 y and 4.9 ± 2.3 in 2021, and carbapenem nonsusceptibility rates in *K. pneumoniae* isolates increased significantly from 0.0% to 76.5% during the same period ($P < 0.001$) (Table A.1). Compared with patients with CoNS-BSI, *K. pneumoniae*-BSI cases were associated with old age and high CCI values (Table A.2).

During the study period, CoNS was the most common BSI-causing microorganism (31.9%), followed by *Escherichia coli* (16.1%), *Enterococcus faecalis* (10.9%), and *K. pneumoniae* (9.8%) (Fig. 1 and Table A.3). The proportion of CoNS-BSIs was particularly prominent in patients diagnosed with AML (45.5%); however, Gram-negative bacteria were the most prevalent pathogens causing BSIs in patients with aplastic anaemia (63.9%), with a relatively high proportion of *K. pneumoniae* infection (14.0%) and fungemia (11.6%). The relative incidence of *E. coli* was notably higher in patients with ALL (26.9%).

3.3. Cumulative incidence and risk factors for BSI

The 1-y cumulative incidences of the first BSI and neutropenia after HM diagnosis are illustrated in Figure 2. A significantly higher cumulative incidence of BSI and neutropenia was observed in the AML and ALL groups than in the other groups (both $P < 0.001$).

Table 1
Baseline characteristics of patients with HMs.

Baseline characteristics	Total (*N* = 6792)	AML (*N* = 916)	ALL (*N* = 427)	Lymphoma (*N* = 3465)	MM (*N* = 1106)	AA (*N* = 354)	Others (*N* = 524)	*P*
Age at diagnosis of HMs	58.6 ± 16.3	57.3 ± 16.5	47.8 ± 18.6	58.7 ± 16.0	64.4 ± 11.3	55.4 ± 19.0	59.2 ± 17.2	<0.001
Female sex	3036 (44.7%)	411 (44.9%)	201 (47.1%)	1502 (43.3%)	505 (45.7%)	193 (54.5%)	224 (42.7%)	0.002
Total length of hospital stays	30 (9–69)	67 (29–109)	69 (20–112)	23 (7–62)	34 (14–51)	15 (6–39)	13 (5–38)	<0.001
ICU admission	895 (13.2%)	204 (22.3%)	62 (14.5%)	393 (11.3%)	128 (11.6%)	50 (14.1%)	58 (11.1%)	<0.001
SOFA score	0 (0–2)	3 (0–5)	0 (0–3)	0 (0–1)	0 (0–2)	2 (0–4)	0 (0–2)	<0.001
Bloodstream infections	1308 (19.3%)	343 (37.4%)	160 (37.5%)	550 (15.9%)	149 (13.5%)	43 (12.1%)	63 (12.0%)	<0.001
Source of bloodstream infection								0.001
Catheter infection	20 (1.5%)	5 (1.5%)	5 (3.1%)	8 (1.5%)	1 (0.7%)	0 (0.0%)	1 (1.6%)	
Pneumonia	107 (8.2%)	51 (14.9%)	11 (6.9%)	30 (5.5%)	6 (4.0%)	5 (11.6%)	4 (6.3%)	
Urinary tract infection	68 (5.2%)	16 (4.7%)	6 (3.8%)	34 (6.2%)	8 (5.4%)	0 (0.0%)	4 (6.3%)	
Abdominal source	10 (0.8%)	3 (0.9%)	0 (0.0%)	6 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	
Other sources	11 (0.9%)	1 (0.3%)	0 (0.0%)	6 (1.1%)	2 (1.3%)	1 (2.3%)	1 (1.6%)	
Multiple sites	7 (0.5%)	1 (0.3%)	0 (0.0%)	5 (0.9%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	
Unknown origin	1085 (83.0%)	266 (77.6%)	138 (86.2%)	461 (83.8%)	132 (88.6%)	36 (83.7%)	52 (82.5%)	
Vascular catheter	2501 (36.8%)	634 (69.2%)	223 (52.2%)	868 (25.1%)	555 (50.2%)	102 (28.8%)	119 (22.7%)	<0.001
Indwelling urinary catheter	1914 (28.2%)	336 (36.7%)	127 (29.7%)	935 (27.0%)	328 (29.7%)	85 (24.0%)	103 (19.7%)	<0.001
Chemoport	2194 (32.3%)	30 (3.3%)	109 (25.5%)	1959 (56.5%)	70 (6.3%)	10 (2.8%)	16 (3.1%)	<0.001
Ventilator	707 (10.4%)	175 (19.1%)	61 (14.3%)	318 (9.2%)	78 (7.1%)	33 (9.3%)	42 (8.0%)	<0.001
Charlson comorbidity index	4.7 ± 2.3	4.9 ± 2.0	4.1 ± 2.1	5.2 ± 2.2	3.9 ± 2.2	3.0 ± 2.4	4.6 ± 2.1	<0.001
Diabetes mellitus	616 (9.1%)	100 (10.9%)	26 (6.1%)	313 (9.0%)	97 (8.8%)	34 (9.6%)	46 (8.8%)	0.122
Congestive heart diseases	301 (4.4%)	47 (5.1%)	13 (3.0%)	93 (2.7%)	93 (8.4%)	23 (6.5%)	32 (6.1%)	<0.001
Chronic obstructive pulmonary diseases	69 (1.0%)	22 (2.4%)	3 (0.7%)	27 (0.8%)	12 (1.1%)	2 (0.6%)	3 (0.6%)	0.001
Severe renal diseases	149 (2.2%)	14 (1.5%)	5 (1.2%)	41 (1.2%)	60 (5.4%)	19 (5.4%)	10 (1.9%)	<0.001
Anticancer chemotherapy	5415 (79.7%)	787 (85.9%)	346 (81.0%)	2846 (82.1%)	917 (82.9%)	141 (39.8%)	378 (72.1%)	<0.001
Initiation date of chemotherapy, median	6 (1–15)	1 (0–5)	3 (0–9)	7 (3–16)	8 (3–21)	27 (1–87.5)	1 (0–14)	<0.001
Neutropenia								
<500 cells/μL	3443 (50.7%)	664 (72.5%)	295 (69.1%)	1787 (51.6%)	403 (36.4%)	143 (40.4%)	151 (28.8%)	<0.001
<100 cells/μL	2616 (38.5%)	595 (65.0%)	270 (63.2%)	1268 (36.6%)	331 (29.9%)	74 (20.9%)	78 (14.9%)	<0.001
Total duration of neutropenia	19 (10–81)	10 (5–18.5)	10 (5–18)	21 (13–75)	142 (94–195)	6 (0–47)	23 (4.5–110)	<0.001
GM-CSF	1070 (15.8%)	316 (34.5%)	154 (36.1%)	469 (13.5%)	61 (5.5%)	42 (11.9%)	28 (5.3%)	<0.001
Clostridioides difficile infection	412 (6.1%)	104 (11.4%)	49 (11.5%)	167 (4.8%)	68 (6.1%)	10 (2.8%)	14 (2.7%)	<0.001
VRE colonisation	475 (7.0%)	127 (13.9%)	47 (11.0%)	200 (5.8%)	65 (5.9%)	15 (4.2%)	21 (4.0%)	<0.001
Antibiotic prophylaxis	2502 (36.8%)	548 (59.8%)	198 (46.4%)	1197 (34.5%)	375 (33.9%)	72 (20.3%)	112 (21.4%)	<0.001
Antifungal prophylaxis	823 (12.1%)	428 (46.7%)	79 (18.5%)	219 (6.3%)	39 (3.5%)	29 (8.2%)	29 (5.5%)	<0.001

Data are presented as number (%), mean ± standard deviation, or median (1st–3rd quartile).
HM: haematologic malignancy; AML: acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; MM: multiple myeloma; AA: aplastic anaemia; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; GM-CSF: granulocyte-macrophage colony-stimulating factor; VRE: vancomycin-resistant *Enterococcus faecium*.

The earliest onset of BSI after the diagnosis of HM was observed in the ALL group but eventually did not differ from the 1-y cumulative incidence of BSI in the AML group. The variables associated with the occurrence of BSI in patients with HMs are displayed in Figure 3. Multivariable analysis with time-dependent Cox regression demonstrated that the type of HMs, total length of hospital stays, intensive care unit admission, and baseline SOFA score were independent risk factors for BSI. After adjusting for other variables, neutropenia remained significantly associated with BSI (adjusted hazard ratio, 3.22; 95% confidence interval [CI], 2.68–3.85).

3.4. Risk factors for 28-d ACM

The 28-d ACM rate in the patients with HMs who developed BSI was 18.6% (Table 2). Furthermore, PS matching was performed to analyse the impact of BSI-causing microorganisms on clinical outcomes by reducing selection bias. After matching, patient age, sex, type of HMs, baseline SOFA score, and CCI were well distributed in the survivor and 28-d ACM groups, with no statistical difference. The type of HMs, source of BSI, and CCI were identified as independent risk factors for 28-d ACM in multivariable analysis using conditional logistic regression. Additionally, BSIs caused by *Enterococcus faecium* (adjusted odds ratio [aOR] 3.23; 95% CI 1.72–6.07), fungus (aOR 3.33; 95% CI 1.44–7.69), *K. pneumoniae* (aOR 2.17; 95% CI 1.12–4.21), and polymicrobial infection (aOR 4.10; 95% CI 1.98–8.50) were all significantly associated with higher 28-d ACM compared to those by *E. coli* (aOR 1.00; reference). Conversely, BSI caused by CoNS (aOR 0.86; 95% CI 0.48–1.55) demonstrated no significant prognostic difference compared with that caused by *E. coli*.

To further analyse patient outcomes based on the antimicrobial resistance phenotypes exhibited by the BSI-causing microorganisms, we compared the survival probability of patients in the subgroups after PS matching (Fig. A.2). Patients with BSI caused by vancomycin-resistant *E. faecium* had a worse prognosis than those with BSI caused by *E. faecium* with a vancomycin-susceptible phenotype ($P = 0.01$). Similarly, in *K. pneumoniae*-BSI, strains with carbapenem-nonsusceptible phenotypes had a significantly lower survival probability of patients compared to third-generation cephalosporin (3GC)-susceptible phenotypes ($P = 0.04$); however, methicillin-resistant *Staphylococcus aureus* and 3GC-nonsusceptible

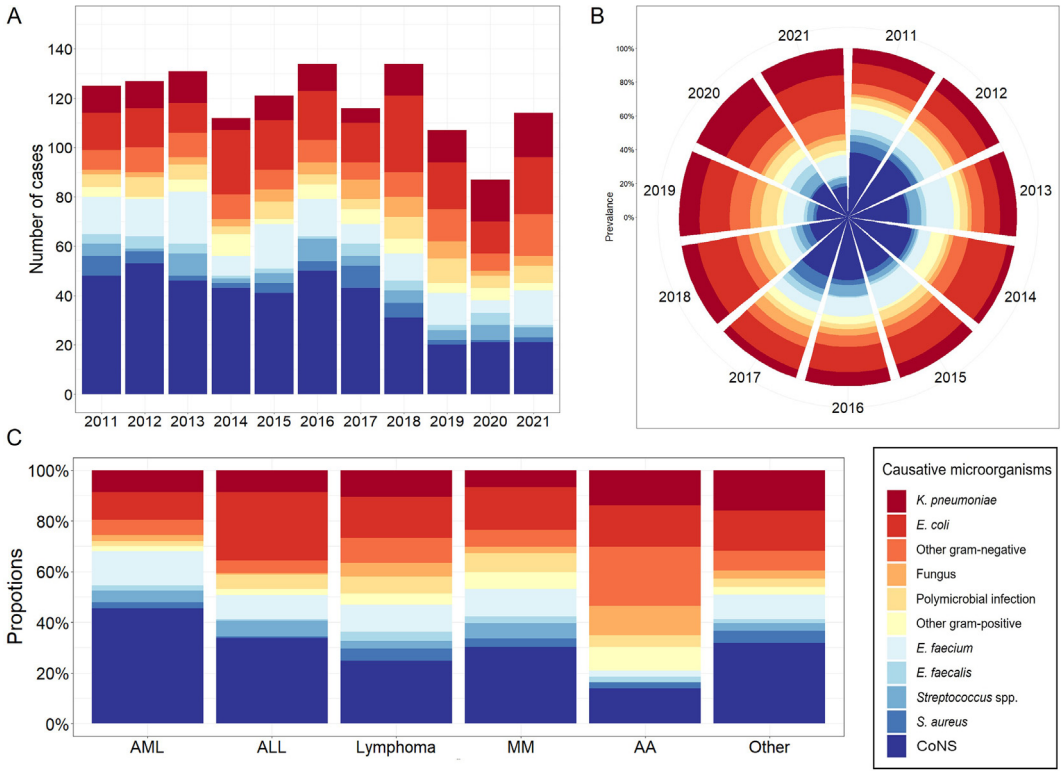

Figure 1. Number (A) and distribution (B) of BSI-causing microorganisms by the year of disease onset, and pathogenic spectrum of different types of HMs (C). Data in each column is expressed as a number or proportion of total BSI cases in patients with HMs, and detailed figures are indicated in Tables A.1 and A.3.

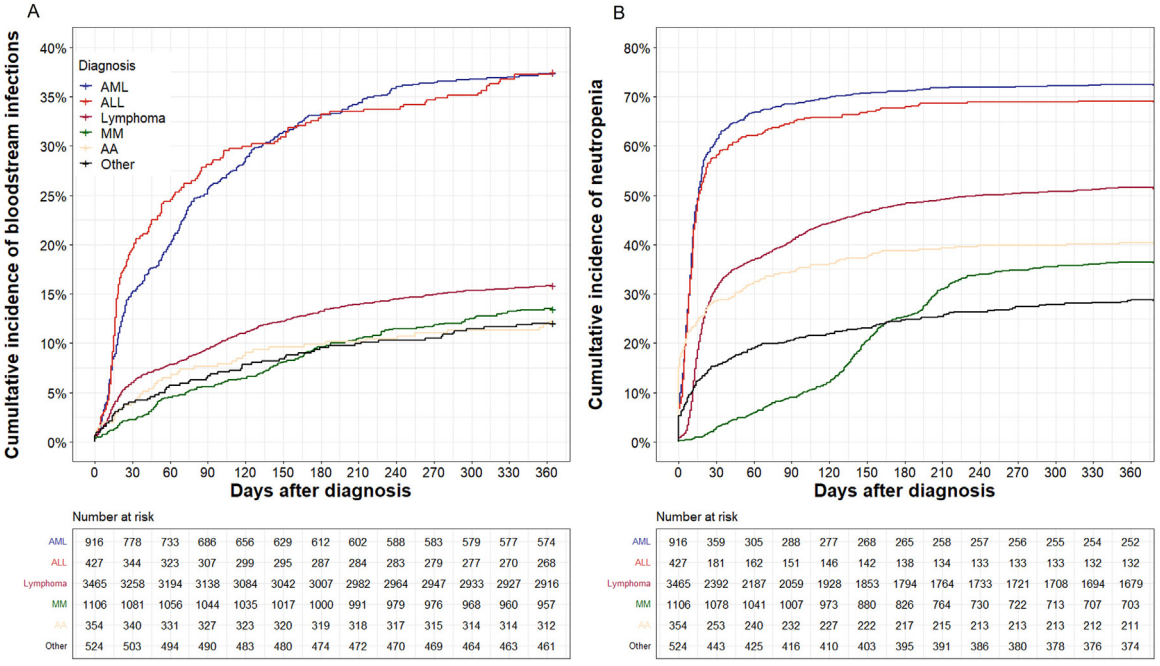

Figure 2. Cumulative incidence of first BSI (A) and neutropenia (B) within 1 y of initial diagnosis of haematologic malignancies. AML: acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; MM: multiple myeloma; AA: aplastic anaemia.

E. coli were not significantly associated with the clinical outcome of patients in subgroup analyses.

4. Discussion

During the study period, 19.3% (1308 of 6792) of the enrolled patients developed BSI, aligning with the reported rates of 11%-38% [1,4,6]. Over the years, an upward trajectory was observed in the number of patients diagnosed with HM, as well as the mean age and CCI values of the associated cases. Nevertheless, the annual incidence of BSI in the aforementioned patients is declining, which is mainly attributed to the decreasing prevalence of CoNS. In this study, the pathogenic spectrum of BSI-causing microorganisms in patients with HMs gradually shifted from Gram-positive to Gram-

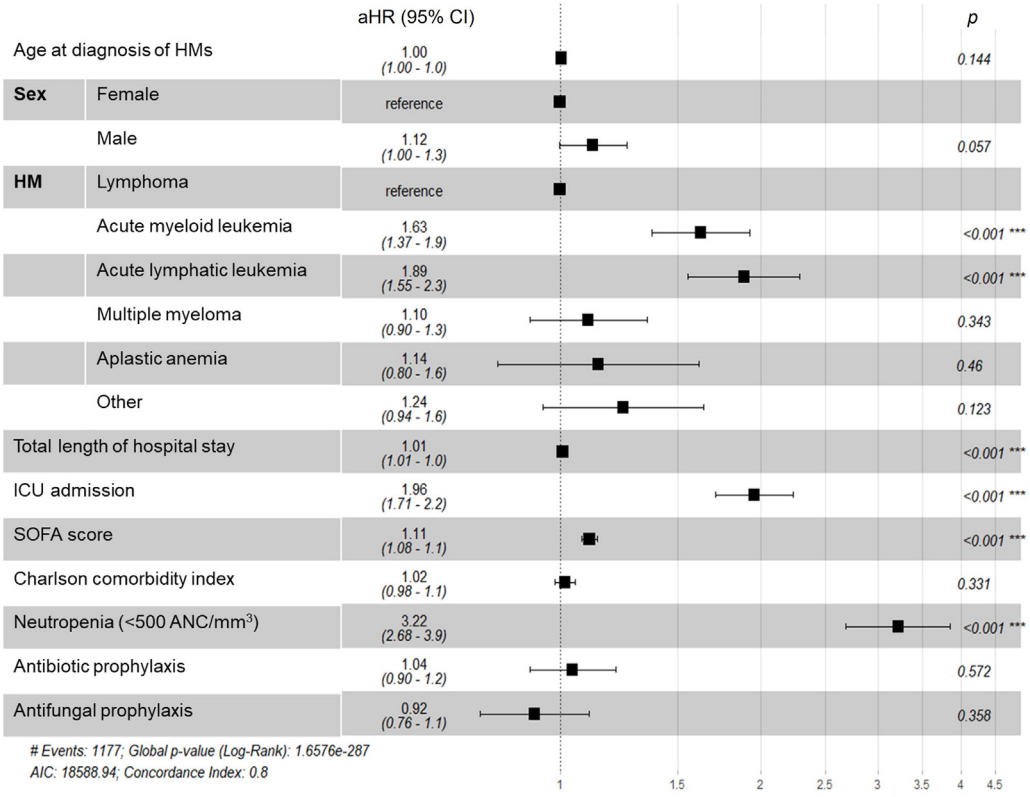

Figure 3. Risk factors for the development of BSI after diagnosis of haematologic malignancies in a multivariable time-dependent Cox proportional hazard model.

negative, especially from CoNS to *K. pneumoniae*. Considering that BSI caused by *K. pneumoniae* had a significantly higher 28-d ACM rate than that caused by CoNS, this evolving trend can adversely impact clinical outcomes and impart an increased medical burden on the management of patients with HMs.

Since the 2000s, a global trend has been observed in which the major BSI-causing microorganisms in patients with HMs have shifted from Gram-positive to Gram-negative bacteria [9–11]. The decrease in the use of prophylactic quinolones has been suggested as the main cause of this trend [10,11,15]. Quinolones, which are widely used to reduce the risk of Gram-negative bacteraemia in patients with neutropenia, have been identified as risk factors for the selection and infection of multidrug-resistant strains and the emergence of hypervirulent *Clostridioides difficile*, leading to a global decline in their use [16,17]. In our institutions, the prescription of quinolones gradually decreased after 2018 [18], at which point the BSI-causing bacteria in HM patients also rapidly shifted from Gram-positive to Gram-negative bacteria. In addition, the nonsusceptibility rates of the antibiotics for *E. coli* and *K. pneumoniae* remained high during the study period, at 84.2% and 78.2%, respectively. The decreasing use of prophylactic quinolones and the high resistance rates to these antimicrobials could have acted as selective pressures for changes in BSI-causing pathogens. Other possible explanations for this shift in the pathogenic spectrum include changes in chemotherapy regimens or patient management [10,16,19]. Low cytotoxicity anticancer agents can reduce infections caused by the viridian group streptococci and enterococci by lowering mucosal toxicity. The increasing rate of antimicrobial resistance in microorganisms may also influence changes in the causative pathogens [20]. Carbapenems remain the last-resort antibiotics for the treatment of Gram-negative bacteria in many countries. We identified that the increase in nonsusceptibility rates to carbapenems in *K. pneumoniae* was accompanied by an increase in BSIs caused by this strain.

Differences were observed in the pathogenic spectrum and cumulative incidence of BSI across different types of HMs. Consistent with previous reports [3,16,21], the proportion of BSIs caused by CoNS was higher in patients with AML than in those with other HMs, likely due to the more frequent use of central venous catheters. In patients with ALL, the occurrence of *E. coli*-BSI was observed to be significantly more common compared to patients with other HMs. Lymphocyte function deficiency induced in patients with ALL may lead to hypogammaglobulinemia and, consequently, susceptibility to infection by encapsulated bacteria such as extraintestinal *E. coli* [22,23]. Patients with AML and ALL have a higher cumulative incidence of BSI after diagnosis than those with other types of HMs. This is probably related to differences in the cumulative incidence of neutropenia, which is the chief risk factor for BSIs. These findings suggest that the management approach for BSI differs depending on the type of HMs. Patients with AML and ALL may require closer monitoring and more aggressive prophylactic antibiotic administration compared to other types of HM. Furthermore, empiric antimicrobial therapy could be tailored based on epidemiological investigations of the incidence of BSI-causing microorganisms [8].

Although previous studies have reported that BSI caused by certain bacteria adversely affect clinical outcomes in patients with HM [1,24], no study has compared patient prognosis according to different causative pathogens after adjusting for other confounding factors. Underlying differences, such as patient demographics and specific types of HMs associated with BSI caused by certain pathogens, could contribute to differences in clinical outcomes. To reduce selection bias due to the fundamental differences and analyse the impact of BSI-causing microorganisms on outcomes, we performed a PS-matching study [25]. PS-matching is an analytical method designed to mimic the characteristics of a randomised controlled trial, ensuring similarity in the distribution of observed baseline confounders between groups of survivors and 28-d ACMs.

Table 2
Univariable and multivariable analysis using conditional logistic regression of risk factors for 28-d all-cause mortality in patients with HMs who developed a BSI after propensity score matching.

Variables	Before the PS match			After the PS match						
	Survivor	28-d ACM	*P*	Survivor	28-d ACM	*P*	Univariable analysis		Multivariable analysis	
	(*N* = 1065)	(*N* = 243)		(*N* = 672)	(*N* = 224)		OR (95% CI)	*P*	aOR (95% CI)	*P*
Age at diagnosis of HMs	55.4 ± 16.0	61.9 ± 14.8	<0.001	60.0 ± 14.1	61.6 ± 14.6	0.136	1.01 (1.00–1.03)	0.058		
Female sex	457 (42.9%)	87 (35.8%)	0.050	264 (39.3%)	83 (37.1%)	0.607	0.9 (0.65–1.25)	0.538		
Haematologic malignancy						0.104				
Acute myeloid leukaemia	295 (27.7%)	48 (19.8%)	0.001	144 (21.4%)	43 (19.2%)		0.95 (0.62–1.44)	0.793	0.99 (0.62–1.57)	0.963
Acute lymphoblastic leukaemia	137 (12.9%)	23 (9.5%)		70 (10.4%)	23 (10.3%)		1.06 (0.62–1.79)	0.841	1.38 (0.76–2.50)	0.293
Lymphoma	443 (41.6%)	107 (44.0%)		322 (47.9%)	98 (43.8%)		Reference (1.00)		Reference (1.00)	
Multiple myeloma	119 (11.2%)	30 (12.3%)		84 (12.5%)	29 (12.9%)		1.12 (0.68–1.82)	0.659	1.43 (0.83–2.48)	0.201
Aplastic anaemia	28 (2.6%)	15 (6.2%)		16 (2.4%)	13 (5.8%)		2.73 (1.26–5.89)	0.011	6.08 (2.34–15.8)	<0.001
Other	43 (4.0%)	20 (8.2%)		36 (5.4%)	18 (8.0%)		1.67 (0.90–3.11)	0.103	2.86 (1.39–5.87)	0.004
SOFA score	1 (0–3)	2 (0–5)	<0.001	2 (0–4)	2 (0–4)	0.087	1.05 (0.99–1.12)	0.102		
Source of BSI										
Catheter infection	15 (1.4%)	5 (2.1%)	0.048	9 (1.3%)	1 (0.4%)	0.057	0.04 (0.00–0.51)	0.014	0.05 (0.00–0.76)	0.031
Pneumonia	83 (7.8%)	24 (9.9%)		53 (7.9%)	21 (9.4%)		0.13 (0.02–0.71)	0.018	0.26 (0.04–1.57)	0.143
Urinary tract infection	56 (5.3%)	12 (4.9%)		36 (5.4%)	9 (4.0%)		0.09 (0.01–0.49)	0.006	0.13 (0.02–0.86)	0.035
Abdominal source	4 (0.4%)	6 (2.5%)		2 (0.3%)	6 (2.7%)		Reference (1.00)		Reference (1.00)	
Other sources	10 (1.0%)	1 (0.4%)		6 (0.8%)	1 (0.4%)		0.06 (0.00–0.82)	0.035	0.09 (0.01–1.50)	0.093
Multiple sites	6 (0.6%)	1 (0.4%)		5 (0.7%)	1 (0.4%)		0.06 (0.00–0.95)	0.048	0.09 (0.01–1.49)	0.093
Unknown origin	891 (83.7%)	194 (79.8%)		561 (83.5%)	185 (82.6%)		0.11 (0.02–0.55)	0.007	0.20 (0.04–1.10)	0.064
Charlson comorbidity index	4.6 ± 2.2	5.6 ± 2.5	<0.001	5.2 ± 2.2	5.5 ± 2.5	0.072	1.09 (1.01–1.18)	0.026	1.19 (1.08–1.31)	<0.001
BSI-causative microorganisms			<0.001			<0.001				
Escherichia coli	187 (17.6%)	24 (9.9%)		120 (17.9%)	23 (10.3%)		Reference (1.00)		Reference (1.00)	
Enterococcus faecium	98 (9.2%)	45 (18.5%)		68 (10.1%)	39 (17.4%)		2.96 (1.64–5.33)	<0.001	3.23 (1.72–6.07)	<0.001
Enterococcus faecalis	26 (2.4%)	8 (3.3%)		19 (2.8%)	7 (3.1%)		1.92 (0.72–5.13)	0.193	1.96 (0.71–5.47)	0.196
Staphylococcus aureus	34 (3.2%)	11 (4.5%)		23 (3.4%)	11 (4.9%)		2.66 (1.14–6.20)	0.024	2.20 (0.90–5.39)	0.085
Coagulase-negative staphylococci	381 (35.8%)	36 (14.8%)		222 (33.0%)	35 (15.6%)		0.83 (0.47–1.47)	0.523	0.86 (0.48–1.55)	0.617
Fungus	34 (3.2%)	15 (6.2%)		23 (3.4%)	15 (6.7%)		3.4 (1.52–7.58)	0.003	3.33 (1.44–7.69)	0.005
Klebsiella pneumoniae	99 (9.3%)	29 (11.9%)		66 (9.8%)	27 (12.1%)		2.22 (1.18–4.21)	0.014	2.17 (1.12–4.21)	0.022
Others	163 (15.3%)	50 (20.6%)		103 (15.3%)	44 (19.6%)		2.3 (1.29–4.10)	0.005	2.36 (1.29–4.33)	0.005
Polymicrobial infection	43 (4.0%)	25 (10.3%)		28 (4.2%)	23 (10.3%)		4.16 (2.06–8.39)	<0.001	4.10 (1.98–8.50)	<0.001

Data are presented as number (%), mean ± standard deviation, or median (1st–3rd quartile).
HM: haematologic malignancy; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; SOFA: Sequential Organ Failure Assessment.

In survival analyses, BSI caused by strains such as vancomycin-resistant *E. faecium* and carbapenem-nonsusceptible *K. pneumoniae* had a worse prognosis than those caused by strains susceptible to the antimicrobials, which is consistent with prior reports [26,27]. However, BSI caused by methicillin-resistant *S. aureus* or 3GC non-susceptible *E. coli* in patients with HMs did not exhibit a difference in survival probability compared to the antibiotic-susceptible group [28,29]. This is probably because our data lacked the statistical power to detect statistical differences.

The retrospective nature of our study, which was conducted in a single country, limits our findings, and the relatively low proportion of patients with AML and ALL at our institution could also have influenced the generalisability of the study. However, the concurrence of the results with previous data on the incidence of BSIs

in patients with HMs and the associated mortality rates substantiates the validity of our data. A hidden bias could be present in patients with false-negative culture results or those lost to follow-up. However, we attempted to minimise bias by employing a large number of cases and conducting PS-matched analyses to assess risk factors for patients with HMs.

5. Conclusions

This study identified a gradual shift in the pathogenic spectrum of BSI-causing microorganisms among patients with HMs, transitioning from Gram-positive to Gram-negative bacteria. The increasing incidence of BSI caused by *K. pneumoniae*, along with the remarkable increase in the carbapenem resistance rate of this strain, negatively affects patient outcomes. With the emergence and spread of multidrug-resistant bacteria, infections in patients with HMs may become an increasingly important public health issue. Prospective and multinational studies would help understand the global epidemiology of BSI-causing microorganisms and support the informed selection of appropriate prophylactic antimicrobial therapy.

Declarations

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Competing interests: None to declare.

Ethical approval: This study was approved by the Institutional Review Board (approval no.: 3-2023-0246) of Yonsei University Gangnam Severance Hospital (Seoul, Republic of Korea).

Sequence information: Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2024.107212.

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