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FULL LENGTH ARTICLE

Impact of urinary tract infection-causative microorganisms on the progression to bloodstream infection: A propensity score-matched analysis

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SUMMARY

Objectives: We aimed to determine the risk factors for the progression of urinary tract infection (UTI) to bloodstream infection (BSI) and to evaluate the mortality-associated factors in patients with urinary tract-related BSI (UT-BSI).

Methods: A propensity score-matched study was conducted using clinical data from all adult patients with UTIs in two South Korean hospitals.

Results: A total of 84,406 patients with UTIs were enrolled. The relative incidence of UTIs caused by *Escherichia coli* decreased along with an increase in the incidence of *Candida* species infections during the study period. UTI caused by *E. coli, Klebsiella pneumoniae, Staphylococcus aureus, and Candida species* had a relatively high rate of progression to BSI. UT-BSI caused by *Candida* species (adjusted odd ratio 5.67; 95% confidence interval 3.97–8.11; $p < 0.001$) was significantly associated with high 30-day mortality.

Conclusions: UTI-causative microorganisms were associated with both progression to UT-BSI and 30-day mortality in patients with UT-BSI. Considering the trend of increasing age of patients and more frequent use of indwelling urologic devices, UT-BSIs caused by other microorganisms than *E. coli* could be a more serious medical burden in the future.

Introduction

Urinary tract infections (UTIs) are the most common infections encountered in clinical settings and are mainly caused by bacteria or fungi.[1-3] In general, *Escherichia coli* is the leading cause of all UTIs, but it has been reported that the relative incidence of UTI-causative organisms varies depending on demographic and clinical factors, including patient age, sex, and the presence of indwelling catheters.[4,5]

Although UTIs are mostly self-limiting and have favourable outcomes,[6] they can also progress to secondary bloodstream infections (BSIs), urosepsis, and death.[7-9] Urosepsis accounts for approximately 10% to 30% of all severe sepsis cases,[10,11] and has a mortality rate of 20% to 40%.[12] Secondary BSIs occur in 4% to 15% of UTI episodes.[13,14] Previous studies have demonstrated the underlying risk factors for progression from UTI to BSI, focusing on host factors such as urinary tract obstruction, functional or congenital anomalies, and urologic interventions.[6] However, the impact of UTI-causative bacterial or fungal species on the progression to BSI has never been demonstrated.

The purposes of this study were to determine the risk factors for the progression of UTI to secondary BSI, including the impact of causative microorganisms, and to evaluate mortality-associated factors in patients with urinary tract-related BSI (UT-BSI).

Methods

Study population and data collection

A retrospective study enrolled all patients with bacteriuria or funguria from two university hospitals (tertiary care hospitals with more than 2000 and 800 beds, respectively) in South Korea during 2011–2021. Both institutions operate an infection control and antimicrobial stewardship committee to make decisions on limited antibiotic management and prevention of the spread of antimicrobial-resistant microorganisms. The major antimicrobial resistance rates and the empirical antibiotics used during the study period are described in table S1. We collected patient-level clinical data using the electronic medical record extraction program

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of the institutions, including demographics, age-adjusted Charlson comorbidity index values, date of blood and urine specimen collection, and date of patient death. To obtain the most abnormal values within 48 h of urine specimen collection, both minimum and maximum values of laboratory test results and vital signs were extracted, and a Sequential Organ Failure Assessment (SOFA) score[15] was calculated. In addition, history of urological intervention and operation within seven days before urine specimen collection was investigated.

Definitions

According to the Centers for Disease Control/National Healthcare Safety Network definitions (2019),[16] the positive results of urine culture included the followings: the presence of $\geq 10^5$ of colony-forming unit (CFU)/mm^3 in urine with no more than two species of microorganisms, $>10^4$ CFU/mm^3 of a single microorganism, or $>10^3$ CFU/mm^3 of a single microorganism isolated from a urine specimen collected via a straight catheter. UT-BSI was defined when the same species of microorganism was isolated from both urine and blood specimens of a patient within three days.[4,8,9,16] Urinalysis was classified as positive if it contained leukocyte esterase, nitrites, or pyuria (the presence of $\geq 10^3$ WBCs/mm^3 or $\geq$3 WBCs/high-power field).[16]

Urinary tract obstruction was considered when an enlarged prostate, urethral stricture, urinary calculi, or urinary tract cancer was diagnosed. Anatomical anomalies (congenital and/or acquired) or functional disorders of the urinary tract due to causes other than urinary tract obstruction were categorized as structural or functional urinary tract abnormalities. Patients with indwelling urologic devices (IUDs) included those with transurethral catheters, percutaneous nephrostomy catheters, suprapubic catheters, or ureteral stents within seven days prior to urine specimen collection. Empirical therapy was considered as inappropriate if the initial treatment regimen did not include an antimicrobial agent susceptible to the infection-causative microorganism. The term "neutropenia" refers to an absolute neutrophil count at $<$ 500 cells/mm^3.

Propensity score (PS)-matched analysis

Differences in host factors can act as confounding factors for the development of UT-BSI. To reduce selection bias and to analyze the impact of UTI-causative organisms on clinical outcomes, a PS-matched study was conducted. The nearest neighbor matching method was used to match each patient with or without UT-BSI (1:3 match) based on three variables: patient age, sex, and presence or absence of IUD. Matching was performed when the difference in logits of the PS was less than 0.2 times the standard deviation (SD) scores.

Statistical analysis

All variables were assessed by the Kolmogorov–Smirnov test to evaluate Gaussian distributions. Descriptive statistics are presented either as the means and SDs for continuous variables or as numbers and percentages for categorical variables. The statistical significance between groups was tested with either the chi-square test (or Fisher's exact test in the case of nonparametric variables) for qualitative data or Student's t-test (or the Mann–Whitney U test) for quantitative data. Conditional and simple logistic regression were used for univariable and multivariable analyses to demonstrate the risk factors for the occurrence of UT-BSI and all-cause 30-day mortality, respectively. For multivariable analyses, dependent variables were selected based on the statistical significance provided by univariable analyses after excluding variables with multicollinearity.

All reported p values were two-tailed, and $p < 0.05$ was assumed to indicate statistical significance. All statistical analyses and graphic compositions were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), and the used packages were: MatchIt, Survival, and ggplot2.

Ethics

The Institutional Review Board at Severance Hospital, affiliated with the Yonsei University Health System (3–2021–0178), approved this study.

Results

Baseline characteristics before ps matching

During the study period, a total of 116,170 patients were classified as having bacteriuria or funguria, excluding duplicate/multiplicate positive urine culture results (Fig. S1). Cases with no demographic information, more than 20% missing values, or under 18 years of age were excluded. Finally, a total of 84,406 patients with bacteriuria or funguria were enrolled in this study, and 5137 (6.09%) of them had UT-BSI. The characteristics of the enrolled patients are described in Table 1. Patients with UT-BSI showed significant differences in most demographic and clinical characteristics compared with UTI patients without UT-BSI. The all-cause 30-day mortality rate (14.3%) of the patients with UT-BSI was significantly higher than that (7.3%) of the UTI patients without UT-BSI ($p < 0.001$). Blood culture and urinalysis were performed in 54,145 (64.1%) and 82,012 (97.2%) of the total cases, respectively (Table S2).

There were significant differences in the pathogen spectrum according to sex, age group, presence of IUDs, and occurrence of UT-BSI (Fig. 1 and Table S3). *E. coli* was the dominant UTI-causative bacterial species, and it was more prominent in females, patients $<$65 years of age, and patients without IUDs. In contrast, *Candida, Pseudomonas, Acinetobacter, Staphylococcus,* and *Enterococcus faecalis* were more frequently isolated from male patients and patients with IUDs. *Candida* species caused UTIs more frequently in the $\geq$65-year-old group than in the $<$65-year-old group.

While the relative incidence of *E. coli* has gradually decreased since 2014 (49.2% of all UTI cases) to 42.1% in 2021, an upward trend in the relative incidence of UTIs caused by *Candida* species was observed, from 2.3% in 2011 to 14.4% in 2021. The annual incidence of candiduria per million inpatient-days increased from 150.4 in 2011 to 1284.2 in 2021 (Poisson regression; mean increase 20.3% per year; $p < 0.001$; Fig. S2). During the study period, the rate of UTI patients with IUDs increased from 39.9% of all UTI cases in 2011 to 45.6% in 2021, and the use of IUDs was significantly associated with candiduria [adjusted odds ratio (aOR) 2.35; 95% confidence interval (CI) 2.10–2.63; Table S4]. The detailed composition of isolated *Candida* species and the clinical characteristics of patients with candiduria are shown in Table S5. Of 7632 patients with candiduria, infection by *C. albicans* (53.8%) accounted for the largest proportion, followed by *C. glabrata* (24.0%), *C. tropicalis* (16.8%), and *C. parapsilosis* (4.0%). *C. auris* isolates were recovered from only two patients during the study period.

After ps matching

To analyze risk factors for the occurrence of UT-BSI, including the impact of UTI-causative microorganisms, PS matching was performed by adjusting the patient's age, sex, and presence of

Table 1
Comparison of UTI patients with and without urinary tract-related BSI.

	Hospital A	Hospital B	*P*	Total	No BSI	Urinary tract-related BSI	*p*
	(*N* = 23,083)	(*N* = 61,323)		(*N* = 84,406)	(*N* = 79,269)	(*N* = 5137)	
Sex			<0.001				<0.001
Female	16,451 (71.3%)	40,188 (65.5%)		56,639 (67.1%)	53,338 (67.3%)	3301 (64.3%)	
Male	6632 (28.7%)	21,135 (34.5%)		27,767 (32.9%)	25,931 (32.7%)	1836 (35.7%)	
Age	64.3 ± 17.4	63.9 ± 16.3	0.001	64.0 ± 16.6	63.8 ± 16.8	67.2 ± 14.4	<0.001
Under 65 years of age	10,134 (43.9%)	27,511 (44.9%)	0.013	37,645 (44.6%)	35,704 (45.0%)	1941 (37.8%)	<0.001
65 years or older	12,949 (56.1%)	33,812 (55.1%)		46,761 (55.4%)	43,565 (55.0%)	3196 (62.2%)	
SOFA score	1 [0–3]	1 [0–4]	<0.001	1 [0–4]	1 [0–3]	4 [2–8]	<0.001
Charlson comorbidity index score	4.0 ± 2.3	4.5 ± 2.4	<0.001	4.3 ± 2.4	4.3 ± 2.4	4.7 ± 2.2	<0.001
Diabetes mellitus	2385 (10.3%)	8677 (14.1%)	<0.001	11,062 (13.1%)	10,313 (13.0%)	749 (14.6%)	0.001
Solid organ cancer	5037 (21.8%)	20,242 (33.0%)	<0.001	25,279 (29.9%)	23,546 (29.7%)	1733 (33.7%)	<0.001
Leukaemia	43 (0.2%)	586 (1.0%)	<0.001	629 (0.7%)	561 (0.7%)	68 (1.3%)	<0.001
Lymphoma	192 (0.8%)	1074 (1.8%)	<0.001	1266 (1.5%)	1162 (1.5%)	104 (2.0%)	0.002
Kidney diseases	852 (3.7%)	2158 (3.5%)	0.238	3010 (3.6%)	2805 (3.5%)	205 (4.0%)	0.098
Liver diseases	560 (2.4%)	1644 (2.7%)	0.041	2204 (2.6%)	1960 (2.5%)	244 (4.7%)	<0.001
Structural or functional urinary tract abnormalities	220 (1.0%)	950 (1.5%)	<0.001	5137 (6.1%)	5102 (6.1%)	35 (3.0%)	<0.001
Prior history of urinary tract obstruction	957 (4.1%)	2283 (3.7%)	0.005	3240 (3.8%)	2997 (3.8%)	243 (4.7%)	<0.001
Prior history of urologic interventions	7529 (32.6%)	21,996 (35.9%)	<0.001	29,525 (35.0%)	27,343 (34.5%)	2182 (42.5%)	<0.001
Indwelling urologic device (maybe multiple)	8396 (36.4%)	26,706 (43.5%)	<0.001	35,102 (41.6%)	31,981 (40.3%)	3121 (60.8%)	<0.001
Transurethral catheter	8138 (35.3%)	25,654 (41.8%)	<0.001	33,792 (40.0%)	30,795 (38.8%)	2997 (58.3%)	<0.001
Percutaneous nephrostomy catheter	243 (1.1%)	959 (1.6%)	<0.001	1202 (1.4%)	982 (1.2%)	220 (4.3%)	<0.001
Suprapubic catheter	101 (0.4%)	445 (0.7%)	<0.001	546 (0.6%)	509 (0.6%)	37 (0.7%)	0.557
Ureteral stent	520 (2.3%)	1886 (3.1%)	<0.001	2406 (2.9%)	2119 (2.7%)	287 (5.6%)	<0.001
Ventilator use	382 (1.7%)	1317 (2.1%)	<0.001	1699 (2.0%)	1534 (1.9%)	165 (3.2%)	<0.001
Neutropenia	211 (0.9%)	1051 (1.7%)	<0.001	1262 (1.5%)	1058 (1.3%)	204 (4.0%)	<0.001
Maximum C-reactive protein level (mg/L)	86.5 ± 85.3	86.3 ± 85.1	0.776	86.3 ± 85.2	80.6 ± 79.8	163.6 ± 104.4	<0.001
All-cause 30-day mortality	1542 (6.7%)	4993 (8.1%)	<0.001	6535 (7.7%)	5800 (7.3%)	735 (14.3%)	<0.001

Data are presented as the number (%), mean ± standard deviation, or median [1st-3rd quartile].
UTI: urinary tract infection; BSI: bloodstream infection; SOFA: Sequential Organ Failure Assessment.

IUDs. After PS matching, these three variables were well balanced in 5137 pairs at a 1:3 ratio and were not significantly different (Table 2).

In multivariable analyses to identify risk factors for the occurrence of UT-BSI, Charlson comorbidity index score (aOR 0.97; 95% CI 0.95–0.99), structural of functional urinary tract abnormalities (aOR 0.57; 95% CI 0.38–0.84), prior history of urinary tract obstruction (aOR 1.75; 95% CI 1.47–2.10), and neutropenia (aOR 3.34; 95% CI 2.68–4.15) were associated with UT-BSI. UTIs caused by *Staphylococcus aureus* (aOR 1.77; 95% CI 1.44–2.16) showed a significantly higher rate of progression to BSI compared with that caused by other microorganisms, whereas *E. faecalis* (aOR 0.11, 95% CI 0.09–0.13) showed a lower rate of progression. In a subgroup analysis of patients infected with *E. coli*, nonsusceptibility to third-generation cephalosporins (3GC) was not significantly associated with progression to UT-BSI (aOR 0.95; 95% 0.87–1.04), whereas in that of patients infected with *K. pneumoniae*, nonsusceptibility to 3GC (aOR 0.52; 95% CI 0.43–0.64) was associated with a lower incidence of UT-BSI.

Mortality risk factors in patients with UT-BSI

The variables associated with all-cause 30-day mortality are described in Table 3. A multivariable analysis with simple logistic regression showed that the baseline SOFA score (aOR 1.29; 95% CI 1.25–1.32), Charlson comorbidity index score (aOR 1.26; 95% CI 1.21–1.32), and neutropenia (aOR 2.88; 95% CI 2.03–4.10) were independent risk factors in terms of all-cause 30-day mortality. UT-BSI caused by *Candida* species (aOR 5.67; 95% CI 3.97–8.11) was significantly associated with higher 30-day mortality, while that caused by *E. coli* (aOR 1.00; reference) showed more favourable outcomes than that caused by other microorganisms. Furthermore, inappropriate empirical therapy (aOR 1.37; 95% CI 1.07–1.76) was also a significant risk factor for the 30-day mortality rate; however, nonsusceptibility to 3GC in both *E. coli* (aOR 1.08; 95% 0.79–1.48) and *K. pneumoniae* (aOR 1.75; 95% CI 0.54–5.56) was not significantly associated with the 30-day mortality rate in subgroup analyses (Table S6). There was no significant difference in the rates of UT-BSI occurrence or 30-day mortality by UTI-causative *Candida* species; however, higher rates of UT-BSI occurrence and 30-day mortality were observed in patients infected with *A. baumannii* than in those infected with non-*baumannii Acinetobacter* (6.06% vs. 0.53% and 15.4% vs. 7.5%, respectively; $p < 0.001$ for both).

The incidence of UTI and its clinical progression stratified by UTI-causative microorganisms are illustrated in Fig. 2. UTIs caused by *E. coli* were the most common cases of BSI progression, but the adjusted mortality risk was relatively low. In contrast, a high adjusted mortality risk was observed in cases with *A. baumannii* UTIs despite a low frequency of progression to BSI. UTIs caused by *S. aureus* and *Candida* species showed high values in both progression rate to BSI and adjusted mortality risk.

Discussion

The prevalence of UTI-causative microorganisms varied depending on host factors and showed differences according to the year of disease onset. *E. coli* was the most common UTI-causative microorganism in all subgroups, but the relative incidence of UTIs caused by other microorganisms than *E. coli* was increased in males, patients ≥65 years of age, and patients with IUDs. Previous reports have stated that the relative incidence of UTIs caused by *E. coli* decreased along with an increase in the incidence of infections caused by *Candida* species,[2,17,18] which is consistent with our study. Similar to previous studies, old age, high Charlson comorbidity index score and SOFA score, and IUD application were risk factors for UTI by *Candida* species in this study.[1,8,9,19-21] Considering the upward trend of underlying disease severity and age

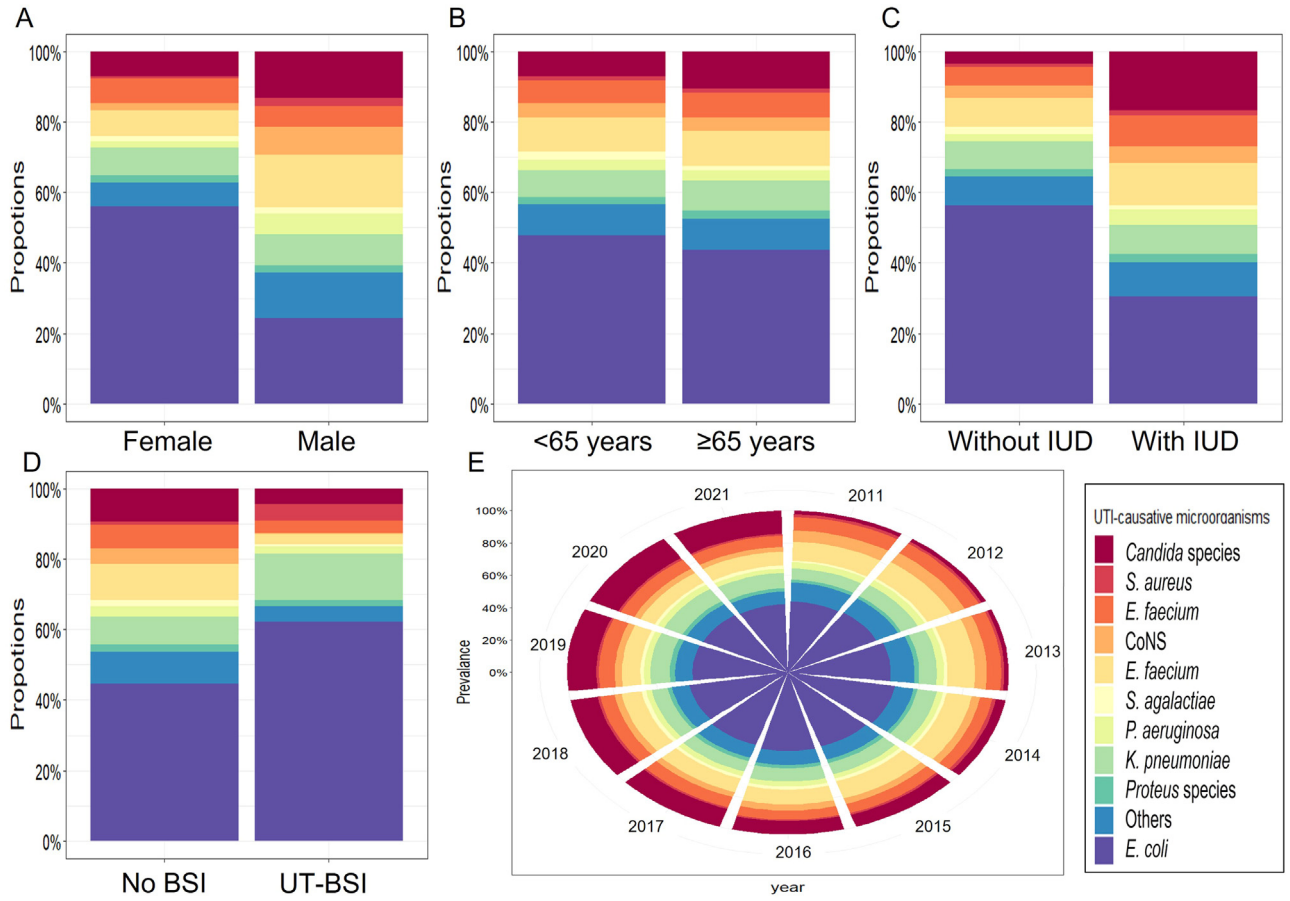

Fig. 1. Distribution of UTI-causative microorganisms by sex (A), age group (B), presence or absence of indwelling urologic device (IUD) (C), progression to urinary tract-related bloodstream infection (UT-BSI) (D), and the year of disease onset
Data in each column is expressed as a proportion of total UTI cases. All microorganisms that accounted for less than 1% of the total cases were clustered together as "Others", and detailed figures are indicated in Table S3. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Univariable and multivariable analysis using conditional logistic regression of risk factors for urinary tract-related BSI in patients with UTI after propensity score matching.

	No BSI	Urinary tract-related BSI		Univariable analysis		Multivariable analysis	
	(N = 15,411)	(N = 5137)	p	OR (95% CI)	p	aOR (95% CI)	p
Male sex	5503 (35.7%)	1836 (35.7%)	0.980	–		–	
Age	67.2 ± 14.4	67.2 ± 14.4	0.998	2.61 (0.42–16.43)	0.306	–	
SOFA score	2 [0–4]	4 [2–8]	<0.001	–		–	
Charlson comorbidity index score	4.9 ± 2.3	4.7 ± 2.2	<0.001	0.95 (0.94–0.97)	<0.001	0.97 (0.95–0.99)	0.004
Structural or functional urinary tract abnormalities	163 (1.1%)	35 (0.7%)	0.021	0.64 (0.44–0.92)	0.018	0.57 (0.38–0.84)	0.004
Prior history of urinary tract obstruction	421 (2.7%)	243 (4.7%)	<0.001	1.77 (1.51–2.08)	<0.001	1.75 (1.47–2.10)	<0.001
Prior history of urologic interventions	6353 (41.2%)	2182 (42.5%)	0.119	1.05 (0.99–1.13)	0.109	1.03 (0.96–1.11)	0.372
Indwelling urologic device	9363 (60.8%)	3121 (60.8%)	>0.999	–		–	
Ventilator use	477 (3.1%)	165 (3.2%)	0.711	1.04 (0.87–1.25)	0.674	1.07 (0.88–1.31)	0.497
Neutropenia	221 (1.4%)	204 (4.0%)	<0.001	2.82 (2.32–3.42)	<0.001	3.34 (2.68–4.15)	<0.001
Maximum C-reactive protein level (mg/L)	80.9 ± 78.7	163.6 ± 104.4	<0.001	–		–	
Microorganism							
E. coli	5818 (37.8%)	3197 (62.2%)	<0.001	1.00 (reference)		1.00 (reference)	
Klebsiella pneumoniae	1230 (8.0%)	679 (13.2%)		0.91 (0.81–1.01)	0.073	0.90 (0.81–1.00)	0.059
Enterococcus faecalis	2220 (14.4%)	149 (2.9%)		0.11 (0.09–0.13)	<0.001	0.11 (0.09–0.13)	<0.001
Enterococcus faecium	1261 (8.2%)	180 (3.5%)		0.24 (0.20–0.28)	<0.001	0.23 (0.19–0.27)	<0.001
Staphylococcus aureus	209 (1.4%)	246 (4.8%)		1.73 (1.42–2.12)	<0.001	1.77 (1.44–2.16)	<0.001
Candida spp.	888 (5.8%)	222 (4.3%)		0.38 (0.32–0.44)	<0.001	0.39 (0.33–0.46)	<0.001
Others	3785 (24.6%)	464 (9.0%)		0.19 (0.17–0.22)	<0.001	0.19 (0.17–0.22)	<0.001

Data are presented as the number (%), mean ± standard deviation, or median [1st-3rd quartile].
UTI: urinary tract infection; BSI: bloodstream infection; SOFA: Sequential Organ Failure Assessment; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; 3GC: third-generation cephalosporins.

Table 3
Univariable and multivariable analysis of risk factors for all-cause 30-day mortality in patients with urinary tract-related BSI.

	Survival	All-cause 30-day mortality		Univariable analysis		Multivariable analysis	
	(N = 4402)	(N = 735)	p	OR (95% CI)	p	aOR (95% CI)	p
Male sex	1472 (33.4%)	364 (49.5%)	<0.001	1.95 (1.67–2.29)	<0.001	1.12 (0.92–1.36)	0.277
Age	67.0 ± 14.5	68.4 ± 13.7	0.011	1.01 (1.00–1.01)	0.012	1.00 (0.99–1.01)	0.682
SOFA score	4.6 ± 3.9	10.3 ± 4.8	<0.001	1.31 (1.29–1.34)	<0.001	1.29 (1.25–1.32)	<0.001
Charlson comorbidity index score	4.5 ± 2.1	5.9 ± 2.3	<0.001	1.31 (1.26–1.35)	<0.001	1.26 (1.21–1.32)	<0.001
Indwelling urologic device	2513 (57.1%)	608 (82.7%)	<0.001	3.60 (2.95–4.40)	<0.001	0.98 (0.77–1.26)	0.901
Microorganism							
E. coli	2939 (66.8%)	258 (35.1%)	<0.001	1.00 (reference)		1.00 (reference)	
Klebsiella pneumoniae	521 (11.8%)	158 (21.5%)		3.45 (2.78–4.30)	<0.001	1.90 (1.46–2.47)	<0.001
Enterococcus faecalis	128 (2.9%)	21 (2.9%)		1.87 (1.16–3.02)	0.011	2.26 (1.31–3.90)	0.003
Enterococcus faecium	122 (2.8%)	58 (7.9%)		5.42 (3.86–7.59)	<0.001	3.29 (2.17–4.98)	<0.001
Staphylococcus aureus	186 (4.2%)	60 (8.2%)		3.67 (2.67–5.05)	<0.001	3.81 (2.60–5.59)	<0.001
Candida spp.	131 (3.0%)	91 (12.4%)		7.91 (5.88–10.64)	<0.001	5.67 (3.97–8.11)	<0.001
Others	375 (8.5%)	89 (12.1%)		2.70 (2.08–3.52)	<0.001	2.15 (1.58–2.93)	<0.001
Inappropriate empirical therapy	713 (16.2%)	153 (20.8%)	0.002	1.36 (1.12–1.65)	0.002	1.37 (1.07–1.76)	0.012
Ventilator use	62 (1.4%)	103 (14.0%)	<0.001	11.41 (8.24–15.8)	<0.001	1.36 (0.92–2.02)	0.120
Neutropenia	114 (2.6%)	90 (12.2%)	<0.001	5.25 (3.93–7.00)	<0.001	2.88 (2.03–4.1)	<0.001

Data are presented as the number (%), mean ± standard deviation, or median [1st-3rd quartile].
BSI: bloodstream infection; SOFA: Sequential Organ Failure Assessment; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

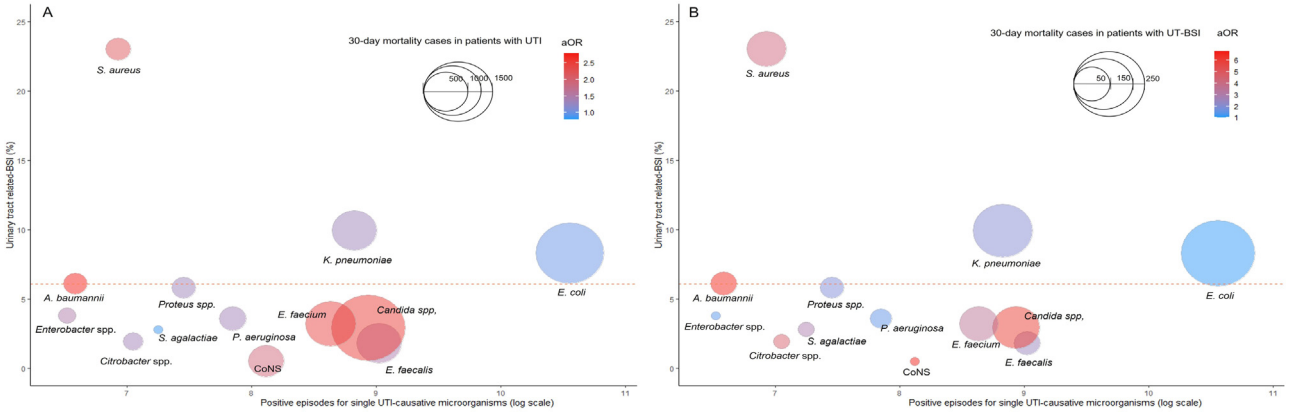

Fig. 2. Incidences of UTI and its clinical progression stratified by UTI-causative microorganisms in patients with UTI (A) and UT-BSI (B)
In this bubble plot, the x-axis represents the total number of cases of each UTI-causative microorganism infection and the y-axis represents the progression rate of UTI to secondary BSI. The red dotted lines indicate the mean incidence of UT-BSI among all cases. Bubble sizes represent the number of 30-day mortality cases and the color scaling indicates the adjusted odds ratio (aOR) for 30-day mortality calculated in multivariable analysis models. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of patients and more frequent use of IUDs, UTIs caused by *Candida* species could be a more serious medical burden in clinical settings in the future.

Host factors of urinary tract obstruction, urological intervention, and IUD use have been reported as risk factors for the occurrence of UT-BSI.[19,22-24] Functional, structural, or iatrogenic urinary retention may cause prolonged exposure to UTI-causative microorganisms and result in an increased risk of their urothelial invasion.[25] After adjusting for host factors and other independent variables, we found that infection caused by *Candida* species is a risk factor for 30-day mortality in patients with UT-BSI. Considering that 46–68% of candidemia patients are associated with previous candiduria,[17,26] prevention and close monitoring of progress to UT-BSI of candiduria are essential to decrease both occurrence of candidemia and deaths by the disease, especially in older patients and/or those with IUDs. *C. albicans, C. glaburata*, and *C. tropicalis* accounted for more than 90% of candiduria cases, and there was no significant difference in the rates of progression to UT-BSI or 30-day mortality among them. *C. auris*, an emerging pathogen with various virulence factors enabling easy adherence and colonization of the fungal host in hospital settings[27], was isolated from only two patients with favourable clinical outcomes in our study.

Although *S. aureus* and *A. baumannii* were not frequent UTI-causing microorganisms, accounting for only 1.2% and 0.9% of all UTI cases, respectively, UTIs caused by both microorganisms showed relatively high rates of progression to UT-BSI. Furthermore, the UT-BSIs were statistically associated with high 30-day mortality rates. Notably, patients with UTIs caused by *A. baumannii* had a higher 30-day mortality rate than those with UTIs caused by non-*baumannii Acinetobacter*. *A. baumannii* has the ability to form biofilms and it is notorious for having a high rate of resistance to last-resort antibiotics, carbapenems, in some parts of the world,[28] making it difficult to treat. More attention and further studies are needed to investigate the impacts of carbapenem resistance of bacterial hosts on progression to UT-BSI and clinical outcomes in patients with UTIs.

UTIs caused by the most frequent pathogens, *E. coli* and *K. pneumoniae*, progressed to BSIs at a high ratio, but they showed favourable outcomes. Interestingly, nonsusceptibility to 3GC was a preventive risk factor for progression to BSI in patients with *K. pneumoniae* UTIs in a subgroup analysis. We previously showed an inverse relationship between the number of genes for virulence factors and those for antimicrobial resistance determinants in *K. pneumoniae* bacterial hosts, i.e., hypervirulent strains of serotypes K1 and K2 rarely had the genes for CTX-M-type

extended-spectrum beta-lactamase, while less virulent strains of other serotypes frequently carried them.[29] This might be a clue to explain the phenomena observed in this study that UTI-causing hypervirulent strains lacking extended-spectrum beta-lactamases penetrated the bloodstream of patients more easily than less virulent strains; however, UT-BSIs caused by hypervirulent strains might be easily treated with extended-spectrum beta-lactams, resulting in favourable outcomes.

Inappropriate empirical therapy was another independent risk factor associated with 30-day mortality in patients with UT-BSI. Although administration of antimicrobials is recommended only for patients with symptomatic UTIs, deciding when to initiate antimicrobial treatment is not easy, especially for immunosuppressed, critically ill, and old patients exhibiting nonspecific symptoms of UTI.[30] The increasing frequency of UTIs caused by antimicrobial-resistant microorganisms is another important cause of this issue. The mortality rate of patients with urosepsis is generally lower than that of patients with sepsis from other sources, but the increased risk of inappropriate empirical treatment due to antimicrobial-resistant microorganisms could be an important consideration in patient management.[9]

Our results are limited by the retrospective and single-country nature of this study, and hidden bias and residual confounders may have influenced the generalizability of the study. Defining UT-BSI as a case in which the same microorganism is isolated in both urine and blood cultures might not be strictly true. In the case of UTIs caused by *S. aureus* and *Candida* species, a positive urine culture might be the first sign of BSI rather than evidence of UTI. Thus, the risk of UTI caused by these microorganisms progressing to BSI could have been overestimated in our data. Moreover, patients who were previously treated with antimicrobial agents and produced false negative culture results or who underwent only blood culture without urine culture may not have been enrolled in this study. However, we tried to analyze the risk factors for patients with UTI by minimizing bias using a large number of cases and a PS-matched study.

We found that UTI-causative bacterial or fungal species were associated with both progression to UT-BSI and 30-day mortality in patients with UT-BSI. Furthermore, inappropriate empirical therapy could increase the mortality rates of patients with UT-BSI. As the life expectancy of the population increases, the number of patients with underlying diseases, including urological comorbidities, increases. Therefore, the prevalence of UT-BSI, especially that caused by other microorganisms than *E. coli*, is likely to become more frequent. Prospective and multinational studies would help identify changes in UTI-causative microorganisms and support the rationale for the selection of appropriate empirical treatments.

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Declaration of competing interest

None to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.08.039.

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