Journal of Infection and Public Health 17 (2024) 349–358

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: www.elsevier.com/locate/jiph

Original article

Clinical and microbiological characteristics of female patients with acute pyelonephritis who experienced urinary tract infections within the previous year

Choseok Yoon [a], Jeoungyeon Kim [a], Wooyoung Jang [a], Ji Won Ko [b], Jinnam Kim [a], Hyunjoo Pai [a,c], Yangsoon Lee [d], Bongyoung Kim [a,c,*]

[a] Division of Infectious Diseases, Department of Internal Medicine, Hanyang University Seoul Hospital, Seoul, South Korea
[b] School of Medicine, Hanyang University College of Medicine, Seoul, South Korea
[c] Department of Internal Medicine, Hanyang University College of Medicine, Seoul, South Korea
[d] Department of Laboratory Medicine, Hanyang University College of Medicine, Seoul, South Korea

ARTICLE INFO

Article history:
Received 7 June 2023
Received in revised form 26 November 2023
Accepted 14 December 2023

Keywords:
Acute pyelonephritis
Recurrent
Urinary tract infection
South Korea
Escherichia coli

ABSTRACT

Background: This study aimed to examine the clinical and microbiological characteristics of female patients with recurrent acute pyelonephritis (APN).

Methods: A retrospective cohort study was conducted at a tertiary care hospital in South Korea from July 2019 to December 2021. All female patients aged ≥ 19 years who were diagnosed with community-acquired APN on admission were enrolled. The recurrent group included patients with APN who experienced urinary tract infections within the previous year. The clinical characteristics, types of causative organisms, major antibiotic resistance, and molecular characteristics of *Escherichia coli* strains were compared between the recurrent and non-recurrent groups.

Results: A total of 285 patients with APN were analyzed, including 41 (14.4%) in the recurrent group. Compared to the non-recurrent group, the recurrent group had a higher Charlson Comorbidity Index (1.8 ± 2.1 *vs.* 1.1 ± 1.5; $P = 0.01$) and a higher proportion of bladder abnormalities, such as neurogenic bladder (12.2% *vs.* 2.0%; $P = 0.001$) and urinary catheterization (12.2% *vs.* 1.6%; $P < 0.001$). *Escherichia coli* was the most common causative organism in both groups. The proportion of *Klebsiella pneumoniae* (17.1% *vs.* 4.7%; $P = 0.007$) and *Pseudomonas aeruginosa* (5.7% *vs.* 0.5%; $P = 0.014$) as a causative organism was higher in the recurrent group. Regarding the microbiological characteristics of *Escherichia coli*, there were no significant differences in the proportion of antibiotic resistance, phylogenetic groups, resistance genes, and virulence factors between the two groups. Multivariable analysis showed that neurogenic bladder and a history of admission or antibiotic use during 1 year prior to inclusion were significantly associated with recurrent APN.

Conclusions: The proportion of causative organisms except *Escherichia coli* was higher in the recurrent group than in the non-recurrent group. Neurogenic bladder and a history of admission or antibiotic use during 1 year prior to inclusion were risk factors for recurrent APN.

Introduction

Acute pyelonephritis (APN), one of the most common community-acquired bacterial infections, is an upper urinary tract infection (UTI) commonly caused by *Escherichia coli* [1]. In the United States, the annual incidence of APN is 15–17 cases per 10, 000 adults, with women accounting for 80% of cases [2]. This higher incidence in women is due to anatomical differences in the urinary tract, such as a shorter urethra in women than in men [3]. In South Korea, the

Abbreviations: APN, acute pyelonephritis; CA-APN, community-acquired acute pyelonephritis; UTI, urinary tract infection; MLST, multilocus sequence typing; ESC, extended spectrum cephalosporin; BL/BLI, beta-lactam/beta-lactam inhibitor; PMQR, plasmid-mediated quinolone resistance; OR, odds ratio; CI, confidence interval

* Correspondence to: Department of Internal Medicine, Hanyang University College of Medicine, 222-1 Wangsimni-ro, Seongdong-gu, Seoul 04763, South Korea.
E-mail address: sobakas@hanyang.ac.kr (B. Kim).

https://doi.org/10.1016/j.jiph.2023.12.011

annual incidence of APN is 39.1 per 10,000 adults, with women being 11 times more likely to be diagnosed and treated for APN than men [4]. It is usually treated well with antibiotics [5], but can sometimes cause severe symptoms or even death, with a mortality rate of 5–20% when bacteremia is present [6].

APN tends to recur in approximately 10% of patients [7]. In South Korea, approximately 15% of patients with APN experience recurrence within 1 year, and the recurrence rate increases with the number of previous recurrences [4]. Understanding recurrent APN is important because they affect the quality of life of the patient, increase medical costs, and increase the risk of antibiotic resistance [8].

Some studies have attempted to understand the characteristics of recurrent UTI, and many risk factors have been identified [9]. In a retrospective study conducted in the US, the risk factors for recurrence were neurogenic bladder, history of UTI, and fluoroquinolone nonsusceptibility of the index UTI [10]. However, because these studies focused on UTI and not APN, it remains questionable whether the study results can be applied to patients with APN. Studies on recurrent UTI in South Korea are limited. The aim of this study was to examine the clinical and microbiological characteristics of patients with APN who experienced UTIs within the previous year, in South Korea.

Material and methods

Patients and study design

A single-center cohort study was conducted at a 855-bed university-affiliated tertiary care hospital in South Korea from July 2019 to December 2021. All female patients aged ≥ 19 years who were diagnosed with community-acquired APN (CA-APN) on admission were prospectively screened and enrolled through a retrospective medical record review. Male patients were not included because their clinical features of APN are significantly different from those in female patients [3,4].

The inclusion criteria of CA-APN were fever (body temperature ≥38 ℃) and ≥ 3 of the followings: (1) back pain, (2) costovertebral angle tenderness, (3) symptoms of lower UTI (dysuria, urgency, frequency, and suprapubic pain), (4) pyuria (≥5–9 white blood cells per high-power field), or (5) leukocytosis (white blood cell count > 11,600 /mm^3 with bands > 65%) [11]. Patients diagnosed with APN 48 h after admission, those transferred from other hospitals, those without follow-up, and those with insufficient data were excluded. Patients with prolonged hospitalization of > 28 days owing to medical problems not associated with APN treatment were also excluded.

The clinical characteristics of patients with APN and a history of UTI within 1 year were compared with those of patients without UTI. Additionally, the microbiological characteristics of *E. coli*, the causative pathogen of APN isolated from those patients, were compared.

Clinical data and definitions

Data on demographic characteristics (age and sex), risk factors, initial clinical features, antibiotic prescriptions, and clinical outcomes were collected through a retrospective review of medical records. Risk factors included comorbidities, structural and functional abnormalities of the urinary tract, and histories associated with the development of APN.

Comorbidities included components of the Charlson Comorbidity Index and bedridden status [12]. Urinary tract conditions included neurogenic bladder, urinary catheterization, and intermittent catheterization. Patients with structural and functional abnormalities of the urinary tract were defined as those with ≥ 1 urinary tract condition. Histories associated with the development of recurrent UTIs included a history of admission and antibiotic use within 1 year prior to inclusion, a history of antibiotic use within 1 month prior to inclusion, the use of chemotherapeutic agents and immunosuppressants, and a history of urinary catheterization within 1 month prior to inclusion.

The initial clinical features included Pitt bacteremia score [13], symptoms of UTI, costovertebral angle tenderness, back pain, vomiting/diarrhea, hematuria (≥5–9 red blood cells per high-power field), and azotemia (serum blood urea nitrogen ≥20 mg/dL and/or serum creatinine ≥1.4 mg/dL). The clinical failure rate, hospitalization days, febrile days, and total antibiotic duration were evaluated to assess clinical outcomes. Clinical failure was defined as death or APN recurrence within 14 days of therapy.

Data on antibiotic prescriptions for APN were also collected. The antibiotics prescribed within 48 h of admission and those continued for 48 h or more were considered 'initial empirical antibiotics,' and antibiotics prescribed used within 48 h after report of culture result and continued for 48 h or more were considered 'definitive antibiotics'. Any antibiotics used at least once during the treatment of APN were considered 'total antibiotics'. If the susceptibility results of the identified pathogen showed 'I' (intermediate) or 'R' (resistant) to the initially empirical antibiotics, it was regarded as 'discordant empirical antibiotic therapy' [14]. Third- and fourth-generation cephalosporins were considered to be extended-spectrum cephalosporins [15].

In this study, we defined the 'recurrent group' as APN patients with a history of UTI (APN or cystitis) within the previous year [16,17].

Microbiological analyses

At the study hospital, blood and/or urine cultures were routinely obtained upon admission to evaluate the causative organisms and their antibiotic susceptibility. Among the causative pathogens, *E. coli* was subcultured, and additional microbiological and molecular analyses were performed.

Antibiotic susceptibility testing

Etiological agents were identified when urinary pathogens were isolated from blood and/or microorganisms at a concentration of ≥ 10^5 CFU/mL were isolated from urine. When the results of the blood and urine tests differed, the results of the blood tests were adopted. Bacterial species were identified and their antibiotic susceptibility was determined using a semi-automated system (bioMérieux Vitek, Hazelwood, MO, USA or MicroScan Dade Behring, West Sacramento, CA, USA). The breakpoints of each compound were defined with reference to the Clinical and Laboratory Standards Institute [18], and R (resistance) or I (intermediate) were defined as resistance [15].

Additional *in vitro* antibiotic susceptibility testing was performed using the agar dilution or broth microdilution method according to the Clinical and Laboratory Standards Institute guidelines for the following antibiotics [18]: amikacin (8–512 μg/mL), cefepime (1–512 μg/mL), ciprofloxacin (0.5–512 μg/mL), fosfomycin (32–512 μg/mL), imipenem (1–512 μg/mL), nitrofurantoin (0.5–512 μg/mL), piperacillin/tazobactam (8–512 μg/mL), and trimethoprim/sulfamethoxazole (2–512 μg/mL).

DNA extraction

Bacterial lysates were prepared by suspending 5–10 *E.coli* colonies in 500 μL of purified water, heating at 100 ℃ for 10 min, and centrifuging at 13,000 ×*g* for 5 min. Supernatants were stored at −20 ℃ until PCR was performed.

Phylogenetic typing

For phylogenetic analysis of the isolated *E. coli* strains, *chuA*, *yjaA*, *arpA*, and *TspE4. C2* genes were amplified by multiplex PCR and classified as previously described [19].

Multilocus sequence typing (MLST) and analysis

Seven housekeeping genes (*adk*, *fumC*, *gyrB*, *icd*, *mdh*, *purA*, and *recA*) were amplified using specific primers. Sequence analysis was performed and ST was obtained (https://pubmlst.org/). PCR was performed using AccuPower® Taq Master Mix (Bioneer, Daejeon, Korea) in a total reaction volume of 20 μL, using the following conditions: initial denaturation for 2 min at 95 ℃, followed by 30 cycles of 60 s at 95 ℃, 60 s at 54–60 ℃, and 2 min at 72 ℃, and a final extension for 5 min at 72 ℃.

Purified PCR products were bidirectionally sequenced by Bioneer. Multiple sequence alignments were performed using the BLAST program of the National Center for Biotechnology Information and concatenated using MEGA 6.0 [20]. Phylogenetic trees were constructed using the maximum likelihood method with 1000 bootstrap replicates.

Resistance genes and virulence factors

Extended-spectrum β-lactamase ($bla_{CTX\text{-}M}$), plasmid-mediated AmpC β-lactamase (bla_{CMY}), and plasmid-mediated quinolone resistance encoding genes (*qnr* and *aac(6′)-Ib-cr*) were amplified using AccuPower® PCR Premix (Bioneer). PCR was performed in a 20-μL reaction volume containing 2 μL of DNA template, 0.5 μL of forward and reverse primers, and 17 μL of sterile distilled water. The target genes were amplified using specific primers [21,22]. The PCR conditions were as follows: initial denaturation at 95 ℃ for 3 min followed by 30 cycles of denaturation at 95 ℃ for 45 s, annealing at primer-specific temperatures (58 ℃ for $bla_{CTX\text{-}M}$, 52 ℃ for bla_{CMY}, 53 ℃ for *qnr*, and 55 ℃ for *aac(6′)-Ib-cr*) for 45 s, elongation at 72 ℃ for 50 s, and a final extension step at 72 ℃ for 5 min.

Multiplex PCR was performed to screen for 11 virulence factors: *fimH*, *papA*, *papEF*, *sfa/foc*, *ompT*, *hlyA*, *sat*, *fyu*, *iutA*, *kpsMTII*, and *usp* [23,24].

Statistical analysis

All statistical analyses were conducted using SPSS for Windows (version 21; IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using Fisher's exact test and continuous variables were analyzed using independent *t*-tests. Multivariable logistic regression analysis was performed to determine the risk factors for APN in patients with a history of UTI within the previous year. To avoid collinearity, we adopted a stepwise regression method with backward elimination. Statistical significance was defined as a two-tailed *P*-value < 0.05.

Ethics statement

The study protocol was approved by the Institutional Review Board of Hanyang University Seoul Hospital (approval number: 2022–04-007). The requirement for written informed consent was waived.

Results

Comparison of demographic characteristics and risk factors

A flowchart of the patient selection process is shown in Fig. 1. A total of 285 patients were included in this study, of whom 41 (14.4%) were included in the recurrent group. The demographic characteristics and risk factors of female patients with community-acquired APN are summarized in Table 1. The mean age of the recurrent group was 61.7 ± 18.5 years, which was not significantly different from that of the non-recurrent group (62.4 ± 18.7 years) ($P = 0.817$). The recurrent group had a significantly higher Charlson Comorbidity Index than the non-recurrent group (1.8 ± 2.1 *vs.* 1.1 ± 1.5; $P = 0.010$). Regarding factors associated with the Charlson Comorbidity Index, the proportion of patients with

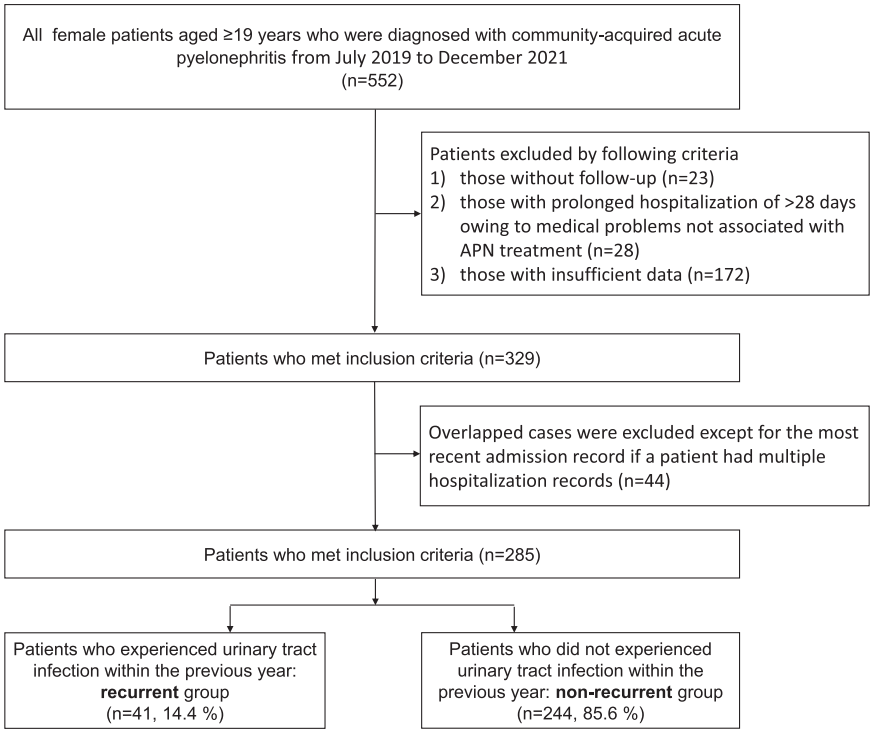

Fig. 1. Flowchart describing patient inclusion criteria.

Table 1
Comparison of demographic data and risk factors of community-acquired acute pyelonephritis between the patients of recurrent group and that of non-recurrent group.

	Recurrent (n=41)	Non-recurrent (n=244)	*P*
Demographic data			
Age (years), mean ± SD	61.7 ± 18.5	62.4 ± 18.7	0.817
Underlying co-morbidities			
Charlson comorbidity index, mean ± SD	1.8 ± 2.1	1.1 ± 1.5	0.010 *
Diabetes mellitus	17 (41.5)	88 (36.1)	0.507
Renal disease	10 (24.4)	19 (7.8)	0.001 *
Connective tissue disease	6 (14.6)	21 (8.6)	0.223
Congestive heart failure	4 (9.8)	19 (7.8)	0.668
Cerebrovascular accident	4 (9.8)	18 (7.4)	0.597
Tumor without metastases	4 (9.8)	10 (4.1)	0.121
Dementia	3 (7.3)	11 (4.5)	0.441
Chronic pulmonary disease	2 (4.9)	2 (0.8)	0.041 *
Myocardial infarction	1 (2.4)	7 (2.9)	0.877
Liver disease	0 (0)	6 (2.5)	0.310
Hemiplegia	0 (0)	3 (1.2)	0.475
Metastatic solid tumor	0 (0)	2 (0.8)	0.561
Bedridden state	4 (9.8)		0.004 *
Underlying urinary tract conditions		4 (1.6)	
Urinary structural or functional abnormality	12 (29.3)	58 (23.8)	0.449
Neurogenic bladder	5 (12.2)	5 (2.0)	0.001 *
Urinary catheterization	5 (12.2)	4 (1.6)	< 0.001 *
Urolithiasis	4 (9.8)	40 (16.4)	0.276
Intermittent catheterization	3 (7.3)	0 (0)	< 0.001 *
Urinary retention	2 (4.9)	2 (0.8)	0.041 *
Bladder diverticulum	1 (2.4)	3 (1.2)	0.542
Surgically reconstructed bladder	1 (2.4)	0 (0)	0.015 *
Polycystic kidney	0 (0)	1 (0.4)	0.681
Renal tumor or fibrosis	0 (0)	2 (0.8)	0.561
Past history			
History of admission during 1 year prior to inclusion	21 (51.2)	29 (11.9)	< 0.001 *
History of antibiotic usage during 1 year prior to inclusion	37 (90.2)	70 (28.7)	< 0.001 *
History of antibiotic usage during 1 month prior to inclusion	17 (41.5)	57 (23.4)	0.014 *
Use of chemotheraputic agents	1 (2.4)	3 (1.2)	0.542
Use of immunosuppressants	8 (19.5)	19 (7.8)	0.018 *
History of urinary catheterization during 1 month prior to inclusion	2 (4.9)	4 (1.6)	0.181

Note: Data are numbers (%) of patients, unless otherwise indicated.
Abbreviations: SD, standard deviation.
* *P value* < 0.05

chronic pulmonary (4.9% *vs.* 0.8%; *P* = 0.041) and renal (24.4% *vs.* 7.8%; *P* = 0.001) disease was significantly higher in the recurrent group than in the non-recurrent group. The proportion of bedridden patients was also higher in the recurrent group than in the non-recurrent group (9.8% *vs.* 1.6%; *P* = 0.004).

Several urinary tract conditions were more prevalent in the recurrent group than in the non-recurrent group, including neurogenic bladder (12.2% *vs.* 2.0%; *P* = 0.001), urinary retention (4.9% *vs.* 0.8%; *P* = 0.041), intermittent catheterization (7.3% *vs.* 0.0%; *P* < 0.001), urinary catheterization (12.2% *vs.* 1.6%; *P* < 0.001), and surgically reconstructed bladder (2.4% *vs.* 0.0%; *P* = 0.015). The proportion of patients with a history of admission (51.2% *vs.* 11.9%; *P* < 0.001) or antibiotic use (90.2% *vs.* 28.7%; *P* < 0.001) during 1 year prior to inclusion and immunosuppressant use (19.5% *vs.* 7.8%; *P* = 0.018) was also higher in the recurrent group than in the non-recurrent group.

Comparison of clinical characteristics and outcomes

Table 2 shows that there were no significant differences in clinical characteristics between the two groups. ESC was the most common empirical and definitive antibiotic regimen in both groups followed by BL/BLI, although the proportions were not significantly different. The proportion of discordant empirical antibiotic therapy did not show a significant difference between two groups (25.7% *vs.* 17.9%, *P* = 0.348). Clinical outcomes, including the clinical failure rate (4.9% *vs.* 4.5%; P = 0.916), hospitalization days (7 *vs.* 8 days; P = 0.412), febrile days (1 *vs.* 2 days; P = 0.345), and total antibiotic duration (15.8 ± 6.4 *vs.* 18.1 ± 8.2 days; P = 0.081), were also not significantly different between the two groups.

Comparison of causative organisms of community-acquired APN

Etiologic agents were detected in 35 and 190 patients in the recurrent and non-recurrent groups, respectively. *E. coli* was the most common causative organism in both groups. However, the proportion of *E. coli* as a causative organism was significantly lower in the recurrent group than in the non-recurrent group (68.6% *vs.* 91.9%; P < 0.001). Conversely, the proportion of *Klebsiella pneumoniae* (17.1% *vs.* 4.7%; P = 0.007), *Pseudomonas aeruginosa* (5.7% *vs.* 0.5%; P = 0.014), *Enterococcus* spp. (5.7% *vs.* 0.5%; P = 0.014), and

Table 2
Comparison of clinical characteristics of community-acquired acute pyelonephritis between the patients of recurrent group and that of non-recurrent group.

	Recurrent (n=41)	Non-recurrent (n=244)	*P*
Clinical characteristics			
Pitt's score, mean ± SD	0.9 ± 1.0	1.0 ± 1.1	0.445
Costovertebral angle tenderness	35 (85.4)	212 (86.9)	0.791
Urinary tract infection symptoms	26 (63.4)	151 (61.9)	0.852
Back pain	21 (51.2)	127 (52.0)	0.922
Azotemia	20 (48.8)	110 (45.1)	0.660
Hematuria	19 (46.3)	147 (60.2)	0.095
Vomiting/diarrhea	10 (24.4)	68 (27.9)	0.644
Initial empirical antibiotics			
ESC	30 (73.2)	169 (69.3)	0.614
BL/BLI	11 (26.8)	55 (22.5)	0.547
FQ	0 (0)	16 (6.6)	0.091
Carbapenem	2 (4.9)	11 (4.5)	0.916
Aminoglycoside	0 (0)	0 (0)	-
Trimethoprim/sulfamethoxazole	0 (0)	1 (0.4)	1.000
Others	1 (2.4)	2 (0.8)	0.374
Definitive antibiotics			
ESC	18/35 (51.4)	101/190 (53.2)	0.856
BL/BLI	7/35 (20.0)	40/190 (21.1)	1.000
FQ	12/35 (34.3)	49/190 (25.8)	0.306
Carbapenem	2/35 (5.7)	17/190 (8.9)	0.745
Aminoglycoside	1/35 (2.9)	2/190 (1.1)	0.399
Trimethoprim/sulfamethoxazole	0/35 (0)	0/190 (0)	-
Others	0/35 (0)	1/190 (0.5)	1.000
Total antibiotics			
ESC	37 (90.2)	210 (86.1)	0.466
BL/BLI	20 (48.8)	121 (49.6)	0.924
FQ	15 (36.6)	89 (36.5)	0.989
Carbapenem	5 (12.2)	39 (16.0)	0.534
Aminoglycoside	1 (2.4)	5 (2.0)	1.000
Trimethoprim/sulfamethoxazole	0 (0)	6 (2.5)	0.598
Others	2 (4.9)	8 (3.3)	0.641
Discordant empirical antibiotic therapy	9/35 (25.7)	34/190 (17.9)	0.348
Clinical outcomes			
Clinical failure	2 (4.9)	11 (4.5)	0.916
Hospitalization days, median (IQR)	7 (6-8.5)	8 (7-11)	0.412
Febrile days, median (IQR)	1 (1-3)	2 (1-3)	0.345
Duration of total antibiotics, days, mean ± SD	15.8 ± 6.4	18.1 ± 8.2	0.081
Causative pathogen of APN			
Escherichia coli	24/35 (68.6)	173/190 (91.9)	< 0.001 *
Klebsiella pneumonia	6/35 (17.1)	9/190 (4.7)	0.007 *
Proteus spp.	0/35 (0)	4/190 (2.1)	0.386
Enterobacter spp.	0/35 (0)	0/190 (0)	-
Citrobacter spp.	0/35 (0)	0/190 (0)	-
Pseudomonas aeruginosa	2/35 (5.7)	1/190 (0.5)	0.014 *
Acinetobacter baumanii	0/35 (0)	0/190 (0)	-
Enterococcus spp.	2/35 (5.7)	1/190 (0.5)	0.014 *
Staphylococcus aureus	1/35 (2.9)	0/190 (0)	0.020 *
Others	0/35 (0)	2/190 (1.1)	0.542
Surgical procedure or intervetion related to APN	6/35 (14.6)	28/190 (11.5)	0.564

Note: Data are numbers (%) of patients, unless otherwise indicated.
Abbreviations: SD, standard deviation; ESC, extended-spectrum cephalosporin; FQ, fluoroquinolone; BL/BLI, beta-lactam/beta-lactamase inhibitor; IQR, interquartile range.
* *P value* < 0.05

Staphylococcus aureus as a causative organism (2.9% *vs.* 0.0%; P = 0.020) was significantly higher in the recurrent group than in the non-recurrent group (Table 2).

Antibiotic resistance of E. coli isolates

The antibiotic resistance of *E. coli* isolates from patients with CA-APN is shown in Table 3. There were no significant differences in the proportion of *E. coli* isolates with resistance to antibiotics such as amikacin (0.0% *vs.* 0.8%; P = 1.000), cefotaxime (25.0% *vs.* 22.5%; P = 0.788), ciprofloxacin (22.2% *vs.* 24.6%; P = 1.000), piperacillin/tazobactam (0.0% *vs.* 5.4%; P = 0.598), and trimethoprim/sulfamethoxazole (44.4% *vs.* 38.5%; P = 0.618) between the two groups.

Molecular epidemiology and virulence factors

Table 4 shows the molecular epidemiology and distribution of virulence factors in *E. coli* isolated from CA-APN. Group B2 (77.8% *vs.*

Table 3
Comparison of antimicrobial resistance of *E.coli* isolates in the patients of recurrent group and those in non-recurrent group.

Antibiotics	Recurrent (n = 24)			Non-recurrent (n = 173)			*P* [a]
	Resistance (%)	MIC_{50} (μg/Mℓ)	MIC_{90} (μg/Mℓ)	Resistance (%)	MIC_{50} (μg/Mℓ)	MIC_{90} (μg/Mℓ)	
Amikacin[b]	0 (0)	8	16	1 (0.8)	4	8	1.000
Amoxicillin/clavulanate	4 (16.7)	≤8/4	16/8	34 (19.7)	≤8/4	16/8	0.728
Ampicillin	18 (75.0)	> 16	> 16	116 (67.1)	> 16	> 16	0.434
Ampicillin/sulbactam	18 (75.0)	16/8	> 16/8	97 (56.1)	16/8	> 16/8	0.078
Aztreonam	5 (20.8)	≤1	> 16	38 (22.0)	≤1	> 16	0.900
Cefepime[b]	5 (27.8)	32	32	23 (17.7)	32	32	0.337
Cefotaxime	6 (25.0)	≤1	> 16	39 (22.5)	≤1	> 32	0.788
Cefoxitin	2 (8.3)	≤8	≤8	9 (5.2)	≤8	≤8	0.531
Ceftazidime	5 (20.8)	≤1	> 16	38 (22.0)	≤1	16	0.900
Cefuroxime	6 (25.0)	≤4	> 16	45 (26.0)	≤4	> 16	0.916
Ciprofloxacin[b]	4 (22.2)	≤0.5	1	32 (24.6)	≤0.5	1	1.000
Levofloxacin	5 (20.8)	≤1	> 4	50 (28.9)	≤1	> 4	0.476
Colistin	0 (0)	≤2	≤2	0 (0)	≤2	≤2	-
Gentamicin	7 (29.2)	≤2	> 8	45 (26.0)	≤2	> 8	0.742
Imipenem[b]	0 (0)	≤1	≤1	0 (0)	0.5	≤1	-
Meropenem	0 (0)	≤1	≤1	0 (0)	≤1	≤1	-
Fosfomycin[b]	0 (0)	≤32	128	1 (0.8)	≤32	128	1.000
Nitrofurantoin[b]	2 (11.1)	16	32	12 (9.2)	16	32	0.680
Piperacillin	16 (66.7)	> 64	> 64	112 (64.7)	> 64	> 64	0.853
Piperacillin/tazobactam[b]	0 (0)	8	8	7 (5.4)	2	8	0.598
Trimethoprim/sulfamethoxazole[b]	8 (44.4)	≤4/76	8/152	50 (38.5)	2/38	8/152	0.618
Tobramycin	6 (25.0)	≤2	> 8	42 (24.3)	≤2	> 8	0.938
Tigecycline	0 (0)	≤1	≤1	0 (0)	≤1	≤1	-

Note: Data are numbers (%) of patients, unless otherwise indicated.
[a] Comparison of resistance rate between recurrent and non-recurrent groups.
[b] In vitro antimicrobial susceptibility tests, using agar dilution or broth microdilution method, were performed for 18 and 130 *E. coli* isolates from the recurrent and non-recurrent groups, respectively.

60.0%; P = 0.197) was the most prevalent group on the phylogenetic tree for both groups followed by group D (22.2% *vs*. 34.6%; P = 0.424).

The most prevalent β-lactamase and plasmid-mediated quinolone resistance (PMQR) genes were CTX-M-1 G (44.4% *vs*. 60.0%; P = 0.308) and *aac(6′)-lb-cr* (50.0% *vs*. 36.2%; P = 0.303), respectively. *Sfa/foc* (83.3% *vs*. 82.3%; P = 1.000) was the most common virulence factor, followed by *kpsMTII* (70.0% *vs*. 62.3%; P = 1.000) and *fimH* (66.7% *vs*. 58.5%; P = 0.613).

The predominant clone identified by multilocus sequence typing (MLST) was ST131 (22.2% *vs*. 17.8%; P = 0.744) followed by ST95 (16.2% *vs*. 16.7%; P = 1.000) and ST69 (0.0% *vs*. 13.8%; *P* = 0.130) (Supplementary Table S1).

There was no significant difference in the molecular epidemiology between the recurrent and non-recurrent groups. The clonal clusters and phylogenetic trees for *E.coli* isolates from patients in both groups are shown in Fig. 2.

Risk factors for APN with a history of UTI within the previous year

Multivariable analysis showed that neurogenic bladder (odds ratio [OR], 18.97; 95% confidence interval [CI]: 2.75–130.97; P = 0.003) and a history of admission (OR, 2.51; 95% CI: 1.10–5.73; P = 0.029) or antibiotic use (OR, 21.68; 95% CI: 6.13–76.66; P < 0.001) during 1 year prior to inclusion were significantly associated with APN with a history of UTI within the previous year (Table 5).

Discussion

Several studies have shown that recurrent UTIs, including APN, is associated with structural and functional abnormalities of the urinary tract, chronic intermittent catheterization or urinary catheterization, neurological disorders, chronic hospitalization, immunodeficiency, and behavioral factors, such as sexual activity [25,26]. Similar to previous studies, we showed that patients with recurrent group had more comorbidities and structural and functional abnormalities of the urinary tract than those with non-recurrent group.

In our study, the Charlson Comorbidity Index was higher in the recurrent group than in the non-recurrent group. In particular, patients with chronic pulmonary or renal disease were more likely to experience recurrence. A Spanish multicenter retrospective study found that the incidence of UTIs increased over time in patients with chronic obstructive pulmonary disease (COPD), possibly because of the adverse effects of inhaled anticholinergics [27]. Further research is required to elucidate the exact mechanisms.

Table 4
Comparison of molecular epidemiology and distribution of virulence factors of *E.coli* isolated from community-acquired acute pyelonephritis between the patients of recurrent group and that of non-recurrent group.

	Recurrent (n=18)	Non-recurrent (n=130)	*P*
Phylogenic groups			
A	0 (0)	1 (0.8)	1.000
B1	0 (0)	6 (4.6)	1.000
B2	14 (77.8)	78 (60.0)	0.197
D	4 (22.2)	45 (34.6)	0.424
Resistance genes			
β-lactamases			
SHV	2 (11.1)	17 (13.1)	1.000
TEM	9 (50.0)	70 (53.8)	0.805
OXA	6 (33.3)	28 (21.5)	0.368
CTX-M			
CTX-M-1G	8 (44.4)	78 (60.0)	0.308
CTX-M-9G	3 (16.7)	44 (33.8)	0.182
PABL			
CMY-1	3 (16.7)	19 (14.6)	0.733
CMY-2	10 (55.6)	43 (33.1)	0.071
DHA	10 (55.6)	62 (47.7)	0.619
ACT	6 (33.3)	46 (35.4)	1.000
PMQR			
qnr A	3 (16.7)	18 (13.8)	0.722
qnr B	4 (22.2)	27 (20.8)	1.000
qnr D	2 (11.1)	12 (9.2)	0.680
qnr S	0 (0)	14 (10.8)	0.219
qep A	6 (33.3)	50 (38.5)	0.798
aac(6')-lb-cr	9 (50.0)	47 (36.2)	0.303
Virulence factors			
Adhesins			
sfa/foc	15 (83.3)	107 (82.3)	1.000
fimH	12 (66.7)	76 (58.5)	0.613
papEF	9 (50.0)	51 (39.2)	0.446
ompT	6 (33.3)	36 (27.7)	0.589
papA	1 (5.6)	10 (7.7)	1.000
Toxins			
sat	9 (50.0)	61 (46.9)	0.808
hlyA	2 (11.1)	5 (3.8)	0.203
Siderophores			
iutA	12 (66.7)	64 (49.2)	0.211
fyuA	3 (16.7)	31 (23.8)	0.765
Capsules			
kpsMTII	7 (70.0)	81 (62.3)	1.000
usp	6 (33.3)	41 (31.5)	1.000
Major clones by MLST			
ST131	4 (22.2)	23 (17.7)	0.744
ST95	3 (16.7)	21 (16.2)	1.000
ST73	3 (16.7)	9 (6.9)	0.164
ST69	0 (0)	18 (13.8)	0.130
ST1193	0 (0)	9 (6.9)	0.601
Others	8 (44.4)	50 (38.5)	0.618

Note: Data are numbers (%) of patients, unless otherwise indicated.
Abbreviations: PABL, Plasmid-Mediated AmpC β-Lactamases; PMQR, Plasmid-Mediated Quinolone Resistance; MLST, Multilocus Sequence Typing.

E. coli was the most common causative organism in both the recurrent and non-recurrent groups. However, the proportion of causative organisms, except *E. coli* (*e.g.*, *K. pneumoniae* and *P. aeruginosa*), was higher in the recurrent group than in the non-recurrent group, in our study. This may be due to the high proportion of patients with structural and functional abnormalities of the urinary tract (*e.g.*, neurogenic bladder and urinary catheterization) in the recurrent group. It is well known that pseudomonas infection is prevalent in patients with urinary catheters [26,28]. A Taiwanese prospective single-center study suggested that strongly adherent *K. pneumoniae* strains may cause relapse of UTI owing to their ability to invade and survive in human urinary epithelial cells after antibiotic treatment [29]. This may explain why the proportion of *K. pneumoniae* was higher in the recurrent group than in the non-recurrent group.

A recent prospective multicenter study in South Korea showed that group B2 was predominant over group D [30]. Similar to a previous study, group B2 was the predominant group followed by group D. Furthermore, there was no significant difference in the distribution of phylogenetic groups between recurrent and non-recurrent groups. A study conducted in Denmark did not identify any significantly associated genetic factors or exhibited any distinct phylogenetic clustering between the recurrent and non-recurrent UTI groups, similar to our study [31].

A multicenter prospective study conducted in Denmark found no significant differences in the virulence profiles of *E. coli* isolates between recurrent and non-recurrent UTI [32]. The results of that study support those of the present study.

In our study, neurogenic bladder and a history of admission or antibiotic use during 1 year prior to inclusion were identified as independent risk factors for APN, in patients with a history of UTI within the previous year, in multivariable analysis. Neurogenic bladder has been identified as a major contributing factor for the recurrence of UTIs [10]. A retrospective study conducted in the United States also showed that independent risk factors for UTI recurrence included neurogenic bladder, history of UTI within the previous year, and fluoroquinolone non-susceptibility [10]. Furthermore, a retrospective multicenter study conducted in South Korea reported that the independent risk factor for recurrent APN was a history of APN within the previous year [33]. Why a history of admission or antibiotic use during 1 year prior to inclusion s associated with recurrent UTI, including APN, is unknown. One possible explanation is that changes in the intestinal or vaginal microbiome due to a history of hospitalization or antibiotic use can cause recurrent UTIs. A prospective single-center study conducted in the United States reported a decrease in the number of Lactobacillus colonies in the vagina of patients with recurrent UTIs compared to that in those with non-recurrent UTIs [34]. In a randomized controlled trial of female patients treated with antibiotics in the United States, the recurrence rate of UTI was significantly lower in the group receiving intravaginal lactobacilli compared with the placebo group [35]. Further studies with larger sample sizes are needed to obtain more reliable results.

There are several limitations of this single-center study. First, because of the small sample size and limited number of patients who met the inclusion criteria, our cohort may not represent the general population. Second, because we only recruited patients from

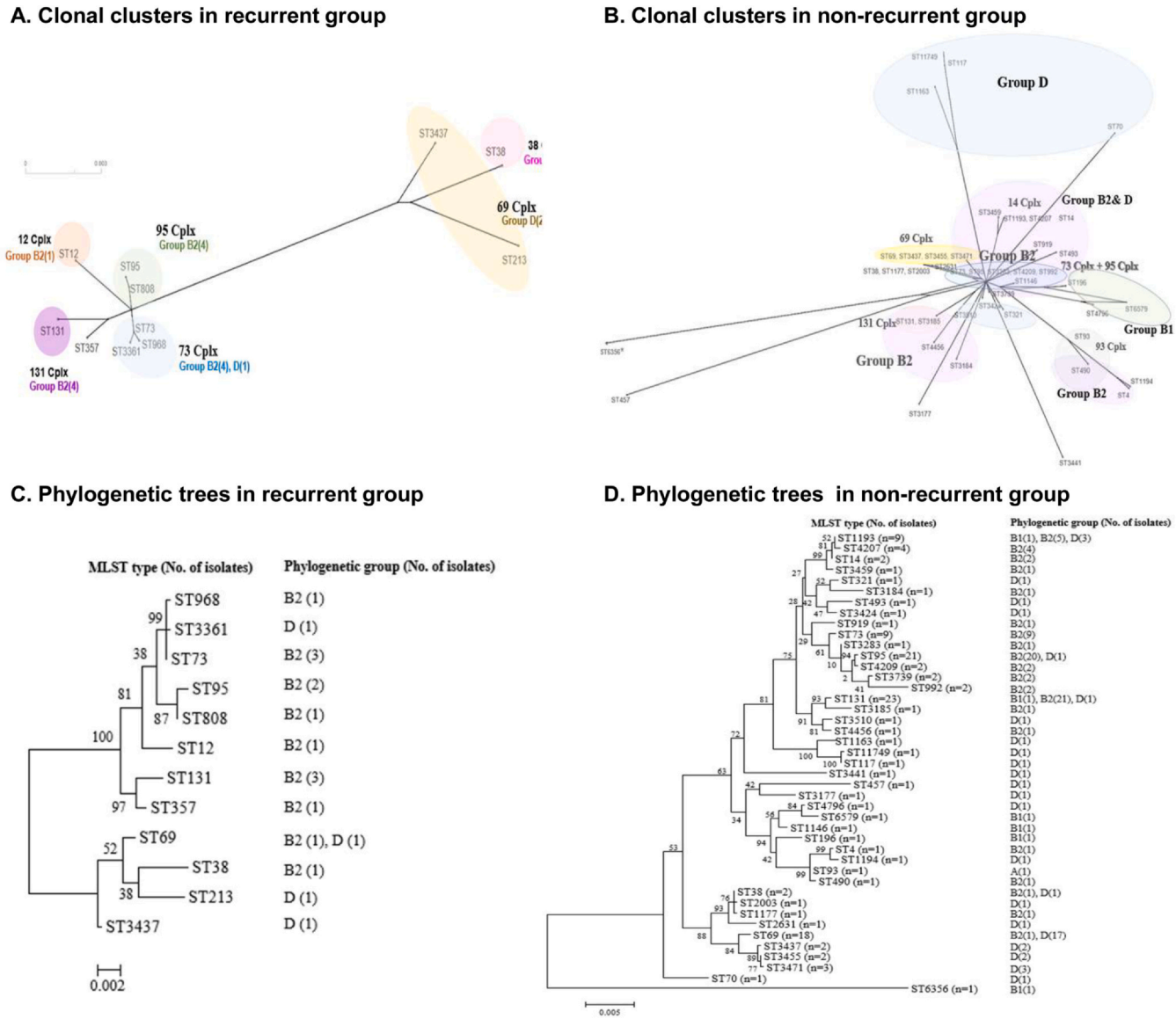

Fig. 2. The clonal clusters and phylogenetic trees for *E.coli* isolates. A. Clonal clusters in recurrent group; B. Clonal clusters in non-recurrent group; C. Phylogenetic trees in recurrent group; D. Phylogenetic trees in non-recurrent group. Abbreviations: MLST, multilocus sequence typing.

a tertiary hospital, these patients may have a higher number of co-morbidities than the general population of patients with UTIs. Third, although recurrent UTIs are internationally defined as ≥ 2 episodes in the last 6 months or ≥ 3 episodes in the last 12 months [36], we defined the 'recurrent group' as APN patients with history of UTI in the last 12 months due to the limitations of the data. Finally, we did not strictly classify recurrent UTIs as reinfections and relapses [36]. However, there were only three cases of relapse that occurred within 14 days of the previous UTI, so they likely had a minimal impact on the overall results (data not shown).

Table 5
Risk factors for the recurrent community-acquired acute pyelonephritis.

Variables	N	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P*-value	OR (95% CI)	*P* value
Age ≥ 65					
No	134	*1*			
Yes	151	0.82 (0.42-1.59)	0.561		
Renal disease					
No	256	1			
Yes	29	3.82 (1.63-8.96)	0.002		
Chronic pulmonary disease					
No	281	1			
Yes	4	6.21 (0.85-45.35)	0.072		
Bedridden state					
No	277	1			
Yes	8	6.65 (1.56-27.06)	0.010		
Neurogenic bladder					
No	185	1		1	
Yes	10	6.64 (1.83-24.07)	0.004	18.97 (2.75-130.97)	0.003 *
Urinary catheterization					
No	276	1			
Yes	9	8.33 (2.14-32.49)	0.002		
History of admission during 1 year prior to inclusion					
No	235	1		1	
Yes	50	7.78 (3.77-16.07)	< 0.001	2.51 (1.10-5.73)	0.029 *
History of antibiotic usage during 1 year prior to inclusion					
No	178	1		1	
Yes	107	22.99 (7.90-66.92)	< 0.001	21.68 (6.13-76.66)	< 0.001 *
Use of immunosuppressants					
No	258	1			
Yes	27	2.87 (1.16-7.08)	0.022		

Abbreviations: OR, odds ratio; CI, confidence interval
* *P* value < 0.05

Conclusions

The proportion of causative organisms except *E.coli* was higher in the recurrent group than in the non-recurrent group. There were no significant differences in the clinical characteristics and outcomes, genetic characteristics, or antibiotic resistance rates of *E.coli* between the two groups. Neurogenic bladder and a history of admission or antibiotic use during 1 year prior to inclusion were risk factors for APN in patients with a history of UTI within the previous year. Further studies involving a larger number of patients from multiple centers or exploring other potential underlying mechanisms, such as the microbiome, will be undertaken for a more detailed understanding.

Funding

This work was supported by the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT [grant number NRF-2021R1C1C1004577]. The funding sources had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

CRediT authorship contribution statement

Conceptualization: BK; Data Curation: CY, JK, WJ, and JWK; Formal Analysis: CY; Investigation: CY, JK, WJ, JWK, JK, HP, YL, and BK; Methodology: JK and BK; Project Administration: BK; Resources: YL and BK; Software: CY; Validation: BK; Visualization: JK; Writing – Original Draft: CY; Writing – Review & Editing: BK. All authors have approved the final article.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

Acknowledgments

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.12.011.

References

[1] Jang W, Jo H, Kim B, Kwon KT, Ryu S, Wie SH, et al. Comparison of the clinical characteristics of community-acquired acute pyelonephritis between male and female patients. J Infect Chemother 2021;27:1013–9.
[2] Czaja CA, Scholes D, Hooton TM, Stamm WE. Population-based epidemiologic analysis of acute pyelonephritis. Clin Infect Dis 2007;45:273–80.
[3] Bergeron MC. Treatment of pyelonephritis in adults. Med Clin North Am 1995;79:619–49.
[4] Kim B, Myung R, Kim J, Lee MJ, Pai H. Descriptive epidemiology of acute pyelonephritis in Korea, 2010-2014: population-based study. J Korean Med Sci 2018;33:e310.
[5] Foxman B, Klemstine KL, Brown PD. Acute pyelonephritis in US hospitals in 1997. Hosp -Hosp Mortal Ann Epidemiol 2003;13:144–50.
[6] Peralta G, Sanchez MB, Garrido JC, De Benito I, Cano ME, Martinez-Martinez L, et al. Impact of antibiotic resistance and of adequate empirical antibiotic treatment in the prognosis of patients with *Escherichia coli* bacteraemia. J Antimicrob Chemother 2007;60:855–63.
[7] Johnson JR, Russo TA. Acute pyelonephritis in adults. N Engl J Med 2018;378:48–59.
[8] Jhang JF, Kuo HC. Recent advances in recurrent urinary tract infection from pathogenesis and biomarkers to prevention. Tzu Chi Med J 2017;29:131–7.
[9] Lee SJ, Choe HS, Na YG, Kim KH, Kim JH, Chung H, et al. 2017 guidelines of the Korean Association of Urogenital Tract Infection and Inflammation: recurrent urinary tract infection. Urogenit Trac Infect 2017;12:7–14.
[10] Zhang HL, Perez R, Krishnan J, Lautenbach E, Anderson DJ. Risk factors for recurrence of community-onset urinary tract infections caused by extended spectrum cephalosporin-resistant Enterobacterales. Open Forum Infect Dis 2023. https://doi.org/10.1093/ofid/ofad561
[11] Calbo E, Romani V, Xercavins M, Gomez L, Vidal CG, Quintana S, et al. Risk factors for community-onset urinary tract infections due to *Escherichia coli* harbouring extended-spectrum beta-lactamases. J Antimicrob Chemother 2006;57:780–3.

[12] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[13] Rhee JY, Kwon KT, Ki HK, Shin SY, Jung DS, Chung DR, et al. Scoring systems for prediction of mortality in patients with intensive care unit-acquired sepsis: a comparison of the Pitt bacteremia score and the Acute Physiology and Chronic Health Evaluation II scoring systems. Shock 2009;31:146–50.
[14] Wie SH, Ki M, Kim J, Cho YK, Lim SK, Lee JS, et al. Clinical characteristics predicting early clinical failure after 72h of antibiotic treatment in women with community-onset acute pyelonephritis: a prospective multicentre study. Clin Microbiol Infect 2014;20:O721–9.
[15] Yoon C, Park SY, Kim B, Kwon KT, Ryu S, Wie SH, et al. Relationship between the appropriateness of antibiotic treatment and clinical outcomes/medical costs of patients with community-acquired acute pyelonephritis: a multicenter prospective cohort study. BMC Infect Dis 2022;22:112.
[16] Ki M, Park T, Choi BY, Foxman B. The epidemiology of acute pyelonephritis in South Korea, 1997–1999. Am J Epidemiol 2004;160:985–93.
[17] Vasudevan R. Urinary tract infection: an overview of the infection and the associated risk factors. J Microbiol Exp 2014;1:42–54.
[18] Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; 30th informational supplement. CLSI document M100-S15. Wayne: CLSI; 2020.
[19] Clermont O, Christenson JK, Denamur E, Gordon DM. The Clermont *Escherichia coli* phylo-typing method revisited: improvement of specificity and detection of new phylo-groups. Environ Microbiol Rep 2013;5. 58e65.
[20] Tamura K, Stecher G, Peterson D, Filipski A, Kumar S. Molecular evolutionary genetics analysis version 6.0. Mol Biol Evol 2013;30. 2725e9.
[21] Barguigua A, El Otmani F, Talmi M, Bourjilat F, Haouzane F, Zerouali K, et al. Characterization of extended-spectrum betalactamase-producing *Escherichia coli* and *Klebsiella pneumonia* isolates from the community in Morocco. J Med Microbiol 2011;60. 1344e52.
[22] Yang HY, Nam YS, Lee HJ. Prevalence of plasmid-mediated quinolone resistance genes among ciprofloxacin-nonsusceptible *Escherichia coli* and *Klebsiella pneumoniae* isolated from blood cultures in Korea. Can J Infect Dis Med Microbiol 2014;25. 163e9.
[23] Li B, Lu Y, Lan F, He Q, Li C, Cao Y. Prevalence and characteristics of ST131 clone among unselected clinical *Escherichia coli* in a Chinese university hospital. Antimicrob Resist Infect Control 2017;6(1):9.
[24] Lee MY, Choi HJ, Choi JY, Song M, Song Y, Kim SW, et al. Dissemination of ST131 and ST393 community-onset, ciprofloxacin-resistant *Escherichia coli* clones causing urinary tract infections in Korea. J Infect 2010;60. 146e53.
[25] Guglietta A. Recurrent urinary tract infections in women: risk factors, etiology, pathogenesis and prophylaxis. Future Microbiol 2017;12:239–46.
[26] Kodner C, Thomas E. Recurrent urinary tract infections in women: diagnosis and management. Am Fam Physician 2010;82:638–43.
[27] Miguel-Diez J, Albaladejo-Vicente R, Palacios-Ceña D, Carabantes-Alarcon D, Zamorano-Leon JJ, Lopez-Herranz M, et al. The impact of COPD in trends of urinary tract infection hospitalizations in Spain, 2001–2018: a population-based study using administrative data. J Clin Med 2020;9:3979.
[28] Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. Dis Mon 2003;49:71–82.
[29] Lin WH, Kao CY, Yang DC, Tseng CC, Wu AB, Teng CH, et al. Clinical and microbiological characteristics of *Klebsiella pneumoniae* from community-acquired recurrent urinary tract infections. Eur J Clin Microbiol Infect Dis 2014;33:1533–9.
[30] Kim B, Kim J, Jo HU, Kwon KT, Ryu SY, Wie SH, et al. Changes in the characteristics of community-onset fluoroquinolone-resistant *Escherichia coli* isolates causing community-acquired acute pyelonephritis in South Korea. J Microbiol Immunol Infect 2022;55:678–85.
[31] Nielsen KL, Stegger M, Kiil K, Lilje B, Ejrnæs K, Leihof RF, et al. *Escherichia coli* causing recurrent urinary tract infections: comparison to non-recurrent isolates and genomic adaptation in recurrent infections. Microorganisms 2021;9:1416.
[32] Ejrnæs K. Bacterial characteristics of importance for recurrent urinary tract infections caused by *Escherichia coli*.. Dan Med Bull 2011;58:B4187.
[33] Kim SH, Huh K, Cho SY, Kang CI, Chung DR, Peck KR. Factors associated with the recurrence of acute pyelonephritis caused by extended-spectrum β-lactamase–producing *Escherichia coli*: the importance of infectious disease consultation. Diagn Microbiol Infect Dis 2019;94:55–9.
[34] Gupta K, Stapleton AE, Hooton TM, Roberts PL, Fennell CL, Stamm WE. Inverse association of H2O2-producing lactobacilli and vaginal *Escherichia coli* colonization in women with recurrent urinary tract infections. J Infect Dis 1998;178:446–50.
[35] Stapleton AE, Au-Yeung M, Hooton TM, Fredricks DN, Roberts PL, Czaja CA, et al. Randomized, placebo-controlled phase 2 trial of a *Lactobacillus crispatus* probiotic given intravaginally for prevention of recurrent urinary tract infection. Clin Infect Dis 2011;52:1212–7.
[36] Epp A, Larochelle A, Lovatsis D, Walter JE, Easton W, Farrell SA, et al. Recurrent urinary tract infection. J Obstet Gynaecol Can 2010;32:1082–90.