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ORIGINAL RESEARCH

Clinical Characteristics of Uncomplicated Acute Pyelonephritis Caused by *Escherichia coli* and *Klebsiella pneumoniae*

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ABSTRACT

***Introduction*:** This study compared the clinical characteristics and antimicrobial susceptibility of uncomplicated acute pyelonephritis (APN) caused by *Escherichia coli* and *Klebsiella pneumoniae*.

***Methods*:** We retrospectively reviewed the medical records of patients with uncomplicated APNs caused by *E. coli* and *K. pneumoniae* admitted to Keimyung University Dongsan Hospital between February 2014 and December 2021.

***Results*:** We enrolled 497 patients (372 with *E. coli* infection, 125 with *K. pneumoniae* infection). Male, healthcare-associated infection, solid tumors, liver cirrhosis, chronic renal disease, solid organ transplantation, and antibiotic usage within the last 3 months were more strongly associated with *K. pneumoniae* uncomplicated APNs than with *E. coli*. Bacteremia and fever occurred more frequently in *E. coli* uncomplicated APNs. Antimicrobial resistance rates to piperacillin/tazobactam and carbapenem were higher in *K. pneumoniae*. Antimicrobial resistance rates to aztreonam and ciprofloxacin were lower in *K. pneumoniae*. Thirty-day mortality was more observed in *K. pneumoniae* group in univariate analysis, but this difference was not observed after adjustment. Male sex, ultimately fatal disease in McCabe, and prior antibiotic use within 3 months were more associated with *K. pneumoniae*.

***Conclusions*:** Male, underlying diseases, and prior antibiotic use was more associated with *K. pneumoniae*. Further study will be needed that microbiome of each situation and the related with the distribution of the strains.

Keywords: Uncomplicated; Acute pyelonephritis; Urinary tract infection; *Escherichia coli*; *Klebsiella pneumoniae*

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Key Summary Points

The unique characteristics of *K. pneumoniae* in uncomplicated acute pyelonephritis (APNs) were retrospectively analyzed.

Uncomplicated APNs of *K. pneumoniae* demonstrates a greater association with men, underlying diseases.

Uncomplicated APNs of *K. pneumoniae* exhibits a lower proportion of bacteremia.

The thirty-day mortality rate is significantly higher in *K. pneumoniae* uncomplicated APN.

Antimicrobial resistance is counterintuitively lower in *K. pneumoniae* infection.

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common bacterial infections [1]. *Escherichia coli* is the most common bacterium causing UTIs, followed by *Klebsiella pneumoniae* [2]. Most studies on UTIs have been conducted on uropathogenic *E. coli* [3]; thus, the clinical and microbiological characteristics of uropathogenic *E. coli* are well known [4–7]. Compared with the information on *E. coli*, comprehensive knowledge about the clinical characteristics of *K. pneumoniae* is limited. Researchers have analyzed the microbiological and genotypic characteristics of *K. pneumoniae* in UTIs [8–10].

A few studies compared the clinical characteristics of *E. coli* and *K. pneumoniae* strains in UTIs and most research has focused on the antimicrobial resistance of these two species [11–15]. A Danish study compared community-acquired bacteremias and urinary tract infections focusing ESBL producing, caused by *E. coli* and *K. pneumoniae* based on treatment outcomes such as mortality and length of stay rather than the clinical characteristics of *E. coli* and *K. pneumoniae* [14]. We previously compared UTIs including complicated UTIs, caused by *E. coli* and *K. pneumoniae*, and identified differences in the clinical characteristics and antibiotic resistance proportions between the two species in South Korea. We found that *K. pneumoniae* was more associated with a urinary catheter, whereas *E. coli* was more associated with urogenital problems [15]. In the previous study, both uncomplicated acute pyelonephritis (APN) and complicated UTIs were included. However, it was determined that anatomical, functional factors and differences of the bacteria were complexively involved, so complicated UTI was excluded from this study. Therefore, this is the first study to compare *E. coli* and *K. pneumoniae*, the causative agent of uncomplicated APNs, and is a study that can focus more on the differences between the strains.

The aim of this research was to identify the clinical characteristics of *K. pneumoniae* compared to *E. coli* in uncomplicated APN in Koreans. Therefore, we compared the predisposing factors, clinical presentations, treatment outcomes, and antimicrobial susceptibility profiles of *E. coli* and *K. pneumoniae* in uncomplicated acute pyelonephritis requiring hospitalization in South Korea.

METHODS

Study Participants

Patients with uncomplicated APN who were admitted to Keimyung University Dongsan Hospital between January 2014 and December 2021 and who had *E. coli* or *K. pneumoniae* isolated from blood or urine were enrolled in this study. Patients with asymptomatic bacteriuria or polymicrobial infections were excluded from this study. Patients under 18 years of age and those transferred to other hospitals during treatment were also excluded.

Definitions and Criteria for UTIs

APN was diagnosed in participants exhibiting at least one of the following: (1) fever (body temperature above 38 °C), pyuria, and bacteriuria with urinary symptoms, flank pain, and tenderness of the costovertebral angle; (2) no specific symptoms or signs of UTI, but APN was

identified in the radiologic findings with fever or leukocytosis, with no other focus of infection [16]. Uncomplicated APN was defined as APN without structural and functional abnormalities within the urinary tract. Therefore, the exclusion criteria of this study were those that met urinary catheter, intermittent urinary catheterization, hydronephrosis, urinary tract stone, renal abscess, prostatic abscess, and pregnancy. Community-acquired infections were defined as those in which symptoms occurred within 48 h after visiting the hospital. Patients with community-acquired infections who had healthcare-associated risk factors were categorized under healthcare-associated infections. Healthcare-associated risk factors included hospitalization within 90 days, hemodialysis, intravenous medication in outpatient clinics, or residency in long-term care facilities. Nosocomial infections were defined as those in which symptoms occurred 48 h after hospital admission. Severe UTI was defined as severe sepsis or shock owing to the UTI. Recurrent UTI was defined as three or more microbiologically documented episodes of symptomatic UTI during the previous year or two episodes during the last 6 months [17]. Treatment outcomes were evaluated by defervescence within 72 h after empirical antibiotic administration, 30-day mortality, infection-related 30-day mortality, acute kidney injury, the need for invasive procedures, and recurrence of UTI within 3 months. Infection-related 30-day mortality was defined as death owing to UTI or complications of UTI within 30 days. Acute kidney injury was defined as an increase in serum creatinine by > 0.3 mg/dl within 48 h, an increase in serum creatinine to > 1.5 times the baseline, or urine volume < 0.5 ml/kg/h for 6 h [18].

Study Design

The study design was a single-center, retrospective observational study based on medical records. We reviewed medical charts about baseline characteristics including age, sex, underlying diseases, predisposing factors, previous antibiotic use, history of UTI, clinical presentations, empirical antibiotic treatment, and clinical outcomes. Previous antibiotic use was confirmed through the previous prescription of the antibiotics at our hospital or medical charts recorded the patients' statements. We also reviewed concomitant bacteremia, antimicrobial susceptibility profile, antibiotic adequacy through laboratory tests, and microbiological results. The severity of comorbidities was classified based on the McCabe–Jackson comorbid classification as nonfatal underlying disease, ultimately fatal disease, and rapidly fatal disease [19]. Diabetes, genitourinary, and gastrointestinal diseases were considered as nonfatal diseases. The Pitt bacteremia score was calculated based on temperature (35.1–36 °C or 39.0–39.9 °C: one point; ≤ 35–40 °C or ≥ 40 °C: two points), blood pressure (hypotension, two points), mental status (disorientation: one point; stupor: two points; coma: four points), respiratory status (mechanical ventilation: two points), and cardiac status (cardiac arrest: four points). The worst reading was recorded when obtaining the first positive blood culture or the day before blood culture [20, 21]. Patients discharged from the hospital within 30 days of admission were followed up for over 1 month at the outpatient clinic. The participants were divided into *E. coli* and *K. pneumoniae* groups.

This study was approved by the Institutional Review Board of Dongsan Medical Center (IRB 2019-07-007) and followed the STROBE guidelines for observational studies. The need for informed consent was waived owing to the retrospective nature of the study.

Antimicrobial Susceptibility Testing

E. coli and *K. pneumoniae* were identified using the Vitek system (bioMérieux, Lyon, France). Antimicrobial susceptibility profiles were determined by interpreting the breakpoints recommended by the Clinical and Laboratory Standards Institute (2014–2017, 2012 CLSI; 2018-2019, 2015 CLSI; 2020-2021, 2017). Before February 2020, the Vitek 2 AST system (bioMérieux, Lyon, France) with N224 and N225 cards was used for susceptibility testing. After February 2020, antimicrobial susceptibility tests

were performed using Phoenix GN Combo Panel 448,541 (PD Diagnostic Systems, Sparks, MD, USA).

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using Pearson's chi-square or Fisher's exact test. Continuous variables were compared using the Mann–Whitney *U* test or Student's *t* test. Logistic regression was used to identify the variables that were significantly associated with 30-day mortality and *K. pneumoniae* infection. Variables with statistical significance in the univariate analysis, along with those considered potentially meaningful, were included in the binary logistic regression model. Statistical significance was defined as $p<0.05$.

RESULTS

Among the 531 patients diagnosed with uncomplicated APNs, 394 and 137 patients were infected with *E. coli* and *K. pneumoniae*, respectively. Twenty-two patients with *E. coli* and 12 patients with *K. pneumoniae* infections were excluded because they were transferred to another hospital during treatment or were under 18 years of age, leaving a total of 497 patients with uncomplicated APNs, among which 372 (74.85%) were infected with *E. coli* and 125 (25.15%) with *K. pneumoniae* (Fig. 1).

Baseline Characteristics and Clinical Presentations Between *E. coli* and *K. pneumoniae* in Uncomplicated APNs

The demographics, underlying diseases, and predisposing factors of the two groups are presented in Table 1. Mean age was higher in the *E. coli* group than in the *K. pneumoniae* group; however, the difference was not significant. *K. pneumoniae* were more frequently observed among men ($p=0.001$). In underlying diseases, solid tumors ($p=0.002$), cardiovascular disease ($p=0.015$), liver cirrhosis ($p=0.002$), chronic renal disease ($p<0.001$), and solid organ transplantation ($p<0.001$) were more frequently associated with *K. pneumoniae*. McCabe–Jackson classification indicated that ultimately fatal disease was more frequently associated with *K. pneumoniae* ($p<0.001$). In predisposing factors, use of antibiotics within the last 3 months ($p<0.001$) was more associated with *K. pneumoniae*. Recurrent UTI was observed in

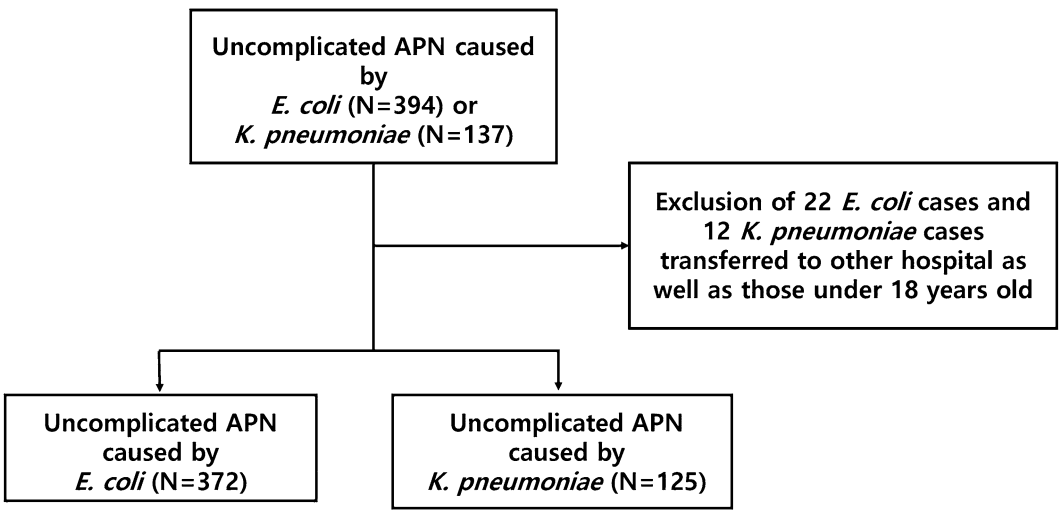

Fig. 1 Flow chart of patient enrollment in this study

Table 1 Comparison of baseline characteristics and clinical presentations of uncomplicated acute pyelonephritis caused by *E. coli* and *K. pneumoniae*

Variable	*E. coli* (*n* = 372), *N* (%)	*K. pneumoniae* (*n* = 125), *N* (%)	*p* value
Age (years)	69.24 ± 15.28	66.89 ± 14.42	0.131
Male	17 (4.6%)	17 (13.6%)	0.001
Underlying diseases			
Solid tumor	44 (11.8%)	29 (23.2%)	0.002
Diabetes mellitus	149 (40.1%)	45 (36.0%)	0.422
Chronic liver disease	46 (12.4%)	15 (12.0%)	0.914
Liver cirrhosis	11 (3.0%)	11 (11.1%)	0.002*
Cardiovascular disease	108 (29.0%)	51 (40.8%)	0.015
Chronic renal disease	16 (4.3%)	28 (22.4%)	< 0.001
Chronic lung disease	32 (8.6%)	5 (4.0%)	0.090
Neurologic disease	102 (27.4%)	35 (28.0%)	0.900
Solid organ transplantation	2 (0.5%)	18 (14.4%)	< 0.001
McCabe–Jackson classification			
Nonfatal	362 (97.6%)	103 (82.4%)	< 0.001
Ultimately fatal	9 (2.4%)	22 (17.6%)	
Predisposing factors			
Neurogenic bladder	8 (2.2%)	3 (2.4%)	0.999
Benign prostate hypertrophy or uterine prolapse	1 (0.3%)	0 (0.0%)	0.999
Recurrent UTI	46 (12.4%)	12 (9.6%)	0.405
Prior antibiotic within 3 months	75 (20.2%)	54 (43.2%)	< 0.001
Category of infection			
Community-acquired infection	278 (74.7%)	57 (45.6%)	< 0.001
Healthcare-associated infection	7 (1.9%)	33 (26.4%)	< 0.001
Nosocomial infection	87 (23.4%)	35 (28.0%)	0.300
Clinical presentations			
Fever	352 (94.6%)	108 (86.4%)	0.002
Dysuria	89 (23.9%)	22 (17.6%)	0.142
Urinary frequency	77 (20.7%)	27 (21.6%)	0.830
CVA tenderness	160 (43.0%)	13 (10.4%)	< 0.001
Severe UTI	94 (25.3%)	24 (19.2%)	0.168

Table 1 continued

Variable	*E. coli* (*n* = 372), *N* (%)	*K. pneumoniae* (*n* = 125), *N* (%)	*p* value
Bacteremic UTI	225 (60.5%)	33 (26.4%)	< 0.001
Pitt bacteremia score	0.92 ± 1.09	0.94 ± 1.39	0.919
30-day mortality	2 (0.5%)	4 (4.1%)	0.019*
Relapse of UTI within 3 months	20 (5.4%)	7 (5.6%)	0.909

*Fisher's exact test

UTI urinary tract infection

12.4% of *E. coli* group and 9.6% of *K. pneumoniae* group, without significance.

Clinical presentations of the two groups are presented in Table 1. Healthcare-associated infection was more associated with *K. pneumoniae* ($p < 0.001$). Community-acquired infection was observed more in *E. coli* ($p < 0.001$). Fever ($p = 0.002$) and costovertebral angle tenderness ($p < 0.001$) were observed more frequently in the patients belonging to the *E. coli*. Urinary frequency and dysuria were found in 20.7%, 23.9% of *E. coli* group and 21.6%, 17.6% in *K. pneumoniae*, respectively. Bacteremia was observed more frequently in the *E. coli* ($p < 0.001$). Pitt bacteremia scores for cases with bacteremia were 0.92 and 0.94 in the *E. coli* and *K. pneumoniae* groups, respectively. The incidence of systemic inflammatory response syndrome was 82.3% and 49.6% in the *E. coli* and *K. pneumoniae*, respectively ($p < 0.001$). Severe UTI did not differ significantly between the groups.

Comparison of Antimicrobial Resistance and ESBL Production Between *E. coli* and *K. pneumoniae* in Uncomplicated APNs

Antimicrobial resistance of the two groups is presented in Table 2. The rates of antimicrobial resistance to piperacillin/tazobactam ($p < 0.001$), and imipenem ($p = 0.004$) were higher in the *K. pneumoniae* group. Among four cases of carbapenem-resistant *K. pneumoniae*, two cases were categorized as healthcare-associated infection (in 2019 and 2021) and two cases were categorized as nosocomial infection (in 2018 and 2021). All of four cases were used prior antibiotics within 3 months. The rates of antimicrobial resistance to aztreonam ($p = 0.005$) and ciprofloxacin ($p = 0.034$) were higher in the *E. coli* group than in the *K. pneumoniae* group. The proportion of ESBL-producing isolates was higher in the *E. coli* group than in the *K. pneumoniae* group, without significance. The antimicrobial resistant rate to amikacin was higher in the *K. pneumoniae* group, without significance. The antimicrobial-resistant rate to trimethoprim/sulfamethoxazole was higher in *E. coli* group, without significance.

Comparisons of Empirical Antibiotics, Antibiotic Adequacy, and Treatment Outcomes Between *E. coli* and *K. pneumoniae* in Uncomplicated APNs

Empirical antibiotics, concordance of antibiotics to antimicrobial susceptibility, antibiotic modification and duration of total antibiotics are listed in Supplementary Table 1. Third-generation cephalosporins were the most commonly used empirical antibiotics in both groups ($p < 0.001$). In the *E. coli* group, 10.4, 4.8, 1.9% cases used carbapenem, piperacillin/tazobactam, fluoroquinolones as empirical antibiotics, respectively. In the *K. pneumoniae* group, 12.4, 12.3, 15.7% cases used carbapenem, piperacillin/tazobactam, fluoroquinolones, respectively. A total of 282 cases of *E. coli* uncomplicated APNs and 95 cases of *K. pneumoniae* uncomplicated APNs were treated with concordant antibiotics. During the hospitalization, antibiotic treatments were

Table 2 Comparison of antimicrobial resistance between *E. coli* and *K. pneumoniae* uncomplicated APNs

	E. coli (*n* = 372), *N* (%)	*K. pneumoniae* (*n* = 125), *N* (%)	*p* value
Amikacin	1 (0.3%)	2 (1.6%)	0.155
Amoxicillin/clavulanate	72 (29.1%)	17 (22.6%)	0.147
Aztreonam	127 (34.3%)	39 (31.7%)	0.005
Cefazolin	190 (51.2%)	55 (44.7%)	0.171
Cefepime	128 (34.5%)	39 (31.7%)	0.547
Cefoxitin	27 (6.0%)	4 (3.3%)	0.257
Ceftazidime	127 (34.2%)	41 (33.3%)	0.855
Ciprofloxacin	162 (43.7%)	41 (33.3%)	0.034
Ertapenem	0 (0.0%)	4 (3.3%)	0.004*
Gentamicin	111 (29.9%)	27 (21.9%)	0.075
Imipenem	0 (0.0%)	4 (3.3%)	0.004*
Piperacillin/tazobactam	19 (5.1%)	19 (15.4%)	< 0.001
TMP/SMX	151 (40.7%)	40 (32.5%)	0.106
ESBL	127 (34.2%)	35 (28.5%)	0.237

*Fisher's exact test

TMP/SMX trimethoprim/sulfamethoxazole, *ESBL* extended-spectrum beta-lactamase

modified in 351 patients in the *E. coli* group and 71 patients in the *K. pneumoniae* group ($p < 0.001$). This modification was performed to adjust the concordant antibiotic treatment after antibiotic-susceptibility testing, aggravation of symptoms or persistent fever, the occurrence of side effects from the initial antibiotics, or to switch to oral antibiotics. The mean duration of antibiotic treatment corresponding to *E. coli* and *K. pneumoniae* groups was 19.36 and 17.20 days, respectively. Defervescence within 72 h were 83.0% of *E. coli* group and 89.6% of *K. pneumoniae* group ($p = 0.196$). Thirty-day mortality was higher in the *K. pneumoniae* group than in the *E. coli* group ($p = 0.019$). Rates of relapse of UTI within 3 months were similar between the two groups (5.4 vs. 5.6%, $p = 0.909$) (Table 1).

Factors Related to *K. pneumoniae* Uncomplicated APNs According to a Comparison of the Two Species

According to univariate analysis, male sex, ultimately fatal disease, and prior antibiotic use within 3 months were more strongly associated with *K. pneumoniae* uncomplicated APNs. Fever, costovertebral angle tenderness, and bacteremia were more strongly associated with *E. coli* uncomplicated APNs. In the multivariate analysis, male sex (odds ratio [OR] 4.124, 95% confidence interval [95% CI] 1.744–9.752, $p = 0.001$), ultimately fatal disease (OR 7.851, 95% CI 3.035–20.307, $p < 0.001$), and prior antibiotic use within 3 months (OR 1.850, 95% CI 1.112–3.079, $p = 0.018$) were more strongly associated with *K. pneumoniae* uncomplicated APNs. Fever (OR 0.434, 95% 0.194–0.971, $p = 0.042$), costovertebral angle tenderness (OR 0.213, 95% CI 0.112–0.408, $p < 0.001$), and

Table 3 Factors related to *K. pneumoniae* in uncomplicated APN

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Male sex	3.287	1.623–6.659	0.001	4.124	1.744–9.752	0.001
Fever	0.361	0.183–0.714	0.003	0.434	0.194–0.971	0.042
CVA tenderness	0.154	0.084–0.283	< 0.001	0.213	0.112–0.408	< 0.001
McCabe Classification (ultimately fatal)	8.591	3.838–19.232	0.0001	7.851	3.035–20.307	< 0.001
Recurrent UTI	0.753	0.385–1.471	0.406			
Prior antibiotics within 3 months	3.012	1.949–4.654	< 0.001	1.850	1.112–3.079	0.018
Concomitant bacteremia	0.234	0.150–0.367	< 0.001	0.246	0.147–0.413	< 0.001
Pitt bacteremia score	1.022	0.688–1.565	0.919			
Severe UTI	0.703	0.425–1.162	0.169			

APN acute pyelonephritis, *CVA* costovertebral angle, *UTI* urinary tract infection, *OR* odds ratio, *95% CI* 95% confidence interval

bacteremia (OR 0.246, 95% CI 0.147–0.413, $p<0.001$) were less associated with *K. pneumoniae* uncomplicated APNs (Table 3).

Risk Factors for 30-Day Mortality

Thirty-day mortality was selected as the clinical outcomes to identify the associated variables via logistic regression analysis. Univariate analysis revealed that *K. pneumoniae* infection, ultimately fatal disease in the McCabe–Jackson comorbid classification, and antibiotic modification were significantly associated with 30-day mortality. Multivariate analysis indicated that no significant variables

Table 4 Variables associated with 30-day mortality

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	0.990	0.942–1.041	0.702			
K. pneumoniae	7.872	1.420–46.631	0.018	6.244	0.745–52.338	0.091
ESBL	1.010	0.183–5.574	0.991			
McCabe–Jackson comorbid classification (ultimately fatal)	10.524	1.823–60.737	0.008	5.511	0.772–39.324	0.089
Concomitant bacteremia	0.879	0.175–4.398	0.875	2.604	0.366–18.553	0.339
Severe UTI	1.731	0.313–9.582	0.530			
Concordance of initial antibiotics	1.501	0.174–12.993	0.712	2.189	0.146–32.865	0.571
Not modified antibiotics	7.070	1.393–35.875	0.018	2.612	0.373–18.266	0.333

UTI urinary tract infection, *ESBL* extended-spectrum beta-lactamase, *OR* odds ratio, *95% CI* 95% confidence interval

were associated with 30-day mortality (Table 4).

DISCUSSION

Male sex, healthcare-associated infection, patients with underlying diseases, and higher antimicrobial-resistant rates to piperacillin/tazobactam, carbapenem were more observed in *K. pneumoniae* uncomplicated APNs. Fever, community-acquired infection, higher antimicrobial-resistant rates to aztreonam, ciprofloxacin, and bacteremia were more observed in *E. coli* uncomplicated APNs. *K. pneumoniae* was more associated with male sex, ultimately fatal disease, prior antibiotics within 3 months while *E. coli* tended to be more associated with bacteremia, fever, and costovertebral angle tenderness.

Sex-related differences between *E. coli* and *K. pneumoniae* UTIs have also been reported [6, 15, 22–24]. A descriptive study in Iran reported that *E. coli* and *K. pneumoniae* were the two most common uropathogens regardless of the season; UTIs caused by these two species were more frequently observed in women [24]. In a UTI study conducted in Gabon, *K. pneumoniae* was more frequent than *E. coli* in males [23], and this result was similar to the sex distribution observed in the present study. Several factors exist regarding the prevalence of UTIs in women, such as the "fecal–perineal-urethral hypothesis" and genitourinary anatomy [25]. *E. coli* was the most common bacteria in distribution of colon [26]. This might be the reason of more common *E. coli* in female APNs. On the other side of aspect, UTIs tend to occur and improve easily in females, whereas in males, the pathogen is more likely to have colonized the urinary mucosa for a long time under the influence of androgens [27–29]. Further research is required to determine whether these hypotheses can explain sex-related differences in the strain distributions of UTIs.

In our study, *K. pneumoniae* was more frequently associated with underlying diseases, such as solid tumor, liver cirrhosis, and solid organ transplantation, especially kidney transplantation. In a study conducted in Egypt, *E. coli* and *K. pneumoniae* were mainly gram-negative bacteria causing UTI in both leukemic and solid-tumor patients [30]. In a study conducted in Japan, the proportions of pediatric patients with cancer were higher in the *K. pneumoniae* group than in the *E. coli* group, among symptomatic bacteriuria [31]. In another study conducted in Japan, malignancy was observed in over 50% of *K. pneumoniae* UTIs [32]. *K. pneumoniae* was the most common gram-negative bacteria of clinical isolates in a cancer center in India [33]. Microbiomes of cancer patients and healthy controls were different [34]. UTI is one of the most common causes of infections in patient with liver cirrhosis. *E. coli* and *K. pneumoniae* were two of the most common uropathogens in cirrhotic patients [35]. Patients with *K. pneumoniae* bacteremia had more comorbidities and higher treatment failure rates than *E. coli* bacteremia in liver cirrhosis [36]. In a study conducted in Taiwan, ESBL-producing *Enterobacterales* bacteremia were more associated with liver cirrhosis [37]. In the present study, proportions of ESBL-producers were higher in *E. coli*. Microbiomes in cirrhotic patients were different because of antibiotic (ex. Rifaximin) prophylaxis, portal circulation and intestinal permeability. Differences of uropathogens in liver cirrhosis may be due to various causes, such as susceptibility to prophylactic antibiotic of the strains [38]. Kidney transplant recipients are at risk of developing UTIs [39]. In kidney transplant recipients, urine flow alterations, such as ureteral stenosis, vesicoureteral reflux, or underlying urogenital anatomic abnormalities, may occur during transplantation surgery [40]. In addition, immunosuppression increases the risk of infection [41]. The frequency of *K. pneumoniae* UTIs in kidney transplant recipients has been well investigated [42]; the possibility that this is related to the microbiological characteristics of *K. pneumoniae*, such as adhesion molecules, has been raised in several reports [43, 44]. Also, the microbiome of recurrent UTI was different from healthy controls in kidney transplantation patients [45]. There were more underlying diseases in the *K. pneumoniae* group in the present study, similar to the previous

studies. In the present study, it was found through multivariate analysis that male sex and underlying diseases were more significant factors in *K. pneumoniae* uncomplicated APNs, and more research will be needed to determine whether this is related to differences in the gut microbiome or urine microbiome due to the underlying diseases.

In the present study, 94.6% of *E. coli* group and 86.4% of *K. pneumoniae* group had fever at admission. Studies about febrile UTIs included complicated UTIs or ESBL producers mostly. In a study conducted in Thailand, ESBL-producing *Enterobacterales* were more observed in fever [46]. However, the distributions of ESBL-producers were similar in about 30% of both strains in the present study. Fever was presented in 25–29% cases of spinal cord injury-associated UTI [47, 48]. In a study of febrile UTIs, older aged men were more observed fever and bacteremia [49]. In studies regarding UTIs, there have been reported clinical features such as fever, but there have been few papers comparing the clinical differences including fever of uncomplicated APNs between the two strains of *E. coli* and *K. pneumoniae*. There was a report comparing cytokines of the two strains. Cytokine concentrations of umbilical cord mononuclear cells stimulated with lipopolysaccharides of *E. coli* and *K. pneumoniae* were similar [50]. Research into other inflammatory response mechanisms responsible for the fever patterns of the two strains will be needed.

Bacteremic UTIs were more strongly associated with *E. coli* in the present study. Intracellular bacterial communities of uropathogenic *E. coli* play a key role in the mechanism of UTI occurrence [51]. Several studies have reported that the risk factors for bacteremia in *E. coli* UTIs may be related to virulence factors and sequence type 131 clones [52, 53]. In a UTI study conducted in Turkey, the proportion of bacteremic UTI was higher for *E. coli* than for *K. pneumoniae* [12]. In another study in Korea, proportions of urinary tract-related bloodstream infection were 62.2% in *E. coli* and 13.2% in *K. pneumoniae*. Risk factors of bloodstream infection were Charlson Comorbidity Index score, structural urinary tract abnormalities, prior history of urinary tract obstruction, and neutropenia [54]. However, in the present study, we excluded complicated APNs, and comorbidities were more associated with the *K. pneumoniae* group. Research on the microbiological characteristics of the two strains will be needed.

In present study, the antibiotic-resistant rate, except for piperacillin/tazobactam and carbapenem in the *K. pneumoniae* group, was lower than that in the *E. coli* group despite more cases of previous antibiotic use. The antimicrobial-resistant proportions of *E. coli* and *K. pneumoniae* vary according to the region and study period [11, 13, 14, 23]. A study of community-acquired uropathogens conducted in Gabon in 2018–2019 reported that the antimicrobial-resistant rates to ceftriaxone, levofloxacin, and aztreonam were higher in *E. coli* than *K. pneumoniae* and those to trimethoprim/sulfamethoxazole, piperacillin, cefepime were higher in *K. pneumoniae* [23]. A study conducted in Iraq in 2020–2021 revealed that *E. coli* was found to be more resistant to ceftriaxone, ceftazidime, ampicillin, aztreonam, and levofloxacin and less resistant to imipenem, than *K. pneumoniae* [55]. Antibiotic-resistant *E. coli* causing community-onset APNs has diverse mechanisms of drug resistance including ESBL, plasmid-mediated AmpC-lactamase, or plasmid-mediated quinolone resistance [56]. Extensively drug-resistant *K. pneumoniae* exhibits biofilm-forming ability, which confers it with drug resistance [57]. Previous studies on the antimicrobial resistance of bacteria isolated from the feces of community-dwelling people have reported colonization by antimicrobial-resistant *E. coli* [58]. Many *E. coli* sequence type 131 strains producing ESBL have been identified in stools collected from local communities, including those from infants [59]. Gómez et al. conducted a study on the fecal *Klebsiella* species colonization and observed that the antibiotic-resistance rate of *Klebsiella* species in healthy adults in the community was low [60]. Although *E. coli* and *K. pneumoniae* are both gram-negative *Enterobacterales*, their antibiotic resistance patterns or proportions may vary depending on the type of antibiotic exposure or susceptibility of the bacteria to antibiotic resistance. Further studies are required to determine whether the

antimicrobial resistant pattern was unique to this study or caused by the antimicrobial resistance acquisition mechanism of the *E. coli* and *K. pneumoniae* strains themselves. In the present study, amikacin was not used, although nearly all strains showed susceptibility to it. As a result of the present study, it is recommended to use amikacin as an empirical antibiotic in uncomplicated APNs.

Thirty-day mortality was higher in *K. pneumoniae* uncomplicated APNs in univariate analysis, but this difference was not observed after adjustment. There were no significant risk factors of 30-day mortality including *K. pneumoniae*. Anemia, HbA1c%, and immunosuppression were risk factors of multiple organ dysfunction and death with APNs [61]. Although there was no significance in the present study, it is thought that the 30-day mortality rate was higher in the *K. pneumoniae* group because there were more underlying diseases.

This study had several limitations. First, this was a retrospective study and relied on microbiological culture results, which may have introduced bias in data interpretation. Second, this study was conducted at a single center. These factors can significantly influence the results and their generalizability. Third, the patients included in this study were admitted to a tertiary hospital and may have exhibited more severe symptoms than those admitted to a primary medical center. Furthermore, as we included patients transferred to a tertiary hospital after treatment at a primary medical center, the presence of bacteremia or the initial severity scale may not have been accurate. Because of excluding patients who were transferred to other hospitals, in addition, there was a limitation in determining the overall condition of patients with uncomplicated APNs caused by *E. coli* and *K. pneumoniae* who visited our hospital.

Despite these limitations, our findings elucidate the predisposing factors, clinical manifestations, and antimicrobial susceptibility of *E. coli* and *K. pneumoniae* uncomplicated APNs in a tertiary hospital setting in South Korea. Considering the differences in underlying diseases and predisposing factors for *E. coli* and *K. pneumoniae* uncomplicated APNs, it would be helpful to determine whether there are differences in the gut microbiome and urine microbiome in the two groups. The microbiological characteristics related to bacteremia and antimicrobial resistance of these two species warrant further investigation. Additionally, a multicenter study from primary-care clinics to tertiary hospitals should be conducted.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Miri Hyun, Ji Yeon Lee, Kyong Ree Lim, and Hyun ah Kim declare no conflicts of interest.

Ethical Approval. This study was approved by the Institutional Review Board of Dongsan Medical Center (IRB 2019-07-007) and followed the STROBE guidelines for observational studies. The need for informed consent was waived owing to the retrospective nature of the study.

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