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Article

Clinico-demographic and microbiological profile of acute pyelonephritis in Azadi Teaching Hospital, Duhok province, Iraqi Kurdistan

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Abstract: The aims of this study were to identify the demographic and clinical characteristics of community associated acute pyelonephritis (CA-APN) or healthcare associated APN (HCA-APN), to determine risk factors linked with APN, and to identify the microbiological profile and its susceptibility patterns to antibiotics. A cross-sectional study was conducted from September to November 2022 at the nephrology unit of Azadi Teaching Hospital, Duhok, Iraqi Kurdistan. Urine and blood samples were collected from patients diagnosed with APN. These samples were investigated to identify the microbiologic profile of the infecting organisms and determine their antibiotic susceptibility results. From a total of 97 adult and elderly APN patients, 55 (56.7%) were classified as HCA-APN, while 42 (43.3%) were classified as CA-APN. In the univariate analysis, age ≥ 65, catheterization, chronic kidney disease, hemodialysis, diabetes mellitus (DM), cardiovascular disease (CVD), neurologic disease, chronic pulmonary disease, PCT level, and ANC were identified as significant risk factors for HCA-APN compared to CA-APN. Patients with catheterization and CVD history showed independent association in the multivariate analysis. The overall mortality rate was 11.3%, which was significantly associated with HCA-APN (P = 0.002). Considering the microbiological profile, *Escherichia coli* uropathogen (n=61) was the predominant isolated bacteria followed by *Klebsiella pneumonia*e (n=17). High antibiotic resistance rates were observed in fluoroquinolones and third generation cephalosporin classes among *E. coli* uropathogen in both CA-APN and HCA-APN patients, with a rate of 74.5 % and 63.9%, respectively. In conclusion, there is an increase in mortality rate regarding HCA-APN. The HCA-APN characteristics should be considered when prescribing empiric antibiotics. In our local setting, carbapenems are effective empiric therapies against enterobacteraceae uropathogens, for both HCA-APN and CA-APN. In order to prevent the emergence and spread of antibiotic resistance, implementing surveillance systems, infection prevention and control measures, and antimicrobial stewardship programs within our healthcare setting is crucial.

Keywords: healthcare associated; community associated; microbiological profile; *E. coli*

1. Introduction

Acute pyelonephritis (APN) is a kidney-related ascending urinary tract infection (UTI) that may cause bacteremia. It results in significant short-term morbidity and may cause serious, or occasionally fatal consequences. Young women have the highest incidence of APN, followed by newborns and the elderly (World Health Organization, 2020). Globally, it is estimated that the annual cases of pyelonephritis are between 10.5 million and 25.9 million. In the United States, the number of cases falls within the range of 459,000 to 1,138,000 annually (Johnson and Russo, 2018). APN is attributed to more than 250,000 hospital visits and over 100,000 hospitalizations every year, leading to a high economic impact of 2.14 billion dollars. According to the recent U.S. Department of Health and Human Services National Inpatient Sample Comparison Report, kidney and UTI infections were the second most prevalent inpatient infections and the sixth most frequent overall diagnosis (Rothrock *et al*., 2020).

Adult APN rates in the US are approximately 15–17 cases per 10,000 women and 3–4 cases per 10,000 males annually, with the majority of cases being treated in ambulatory settings, such as the emergency department. International clinical practice guidelines recommend the use of in vitro antibiotic susceptibility testing and microbiologic culture to identify urinary pathogens, which improves the diagnosis and treatment of APN. A correctly obtained, uncontaminated urine culture gives relevant and objective information that can be used not only to guide the patient's treatment with antibiotics but also to monitor local antibiotic resistance rates (Liang and Durkin, 2019).

Pyelonephritis is distinguished from other UTIs by flank pain and tenderness in the presence of pyuria. Usually, fever is present, and in 20% of patients, lower urinary tract symptoms, such as frequency, urgency, and dysuria may not be present. Additional symptoms and indicators of pyelonephritis may include tachycardia or hypotension, nausea, vomiting, abdominal discomfort, abdominal or suprapubic tenderness, and constitutional symptoms, namely chills and malaise (Herness *et al*., 2020). Certain risk factors can increase the likelihood of developing APN. These risk factors include DM, immunosuppression, a history of recurrent urinary tract infections, pregnancy, a compromised immune system, urinary tract abnormalities or obstructions, such as kidney stones or an enlarged prostate, and urinary catheterization (Bosch- Nicolau *et al*., 2017). APN is either a community associated APN (CA-APN) or a healthcare associated APN (HCA-APN). CA-APN is diagnosed in patients who develop symptoms of APN outside of healthcare setting. On the other hand HCA-APN is diagnosed in patients with the following characteristics: those who develop symptoms of APN within 48 hours of hospital admission, those who are on dialysis or have received intravenous antibiotics, and those who have had a urinary catheter within the past 30 days (Buonaiuto *et al*., 2014).

APN was defined by the presence of the following two: (1) axillary temperature equal or more than 38.3 ºC or chills; (2) flank pain, costovertebral angle tenderness, or pain on bimanual palpation of the kidney; and (3) mictional syndrome including two or more of the following: frequency, dysuria, suprapubic pain or urgency, as well as pyuria (a positive leukocyte esterase dipstick test result, later confirmed by a urinalysis with more than 5 leukocytes per high-power field in centrifuged sediment) or positive urine culture (Buonaiuto *et al*., 2014). HCA-APN was defined using the following criteria (Park *et al*., 2014): at least 48 hours of hospitalization within the previous 3 months, invasive urinary procedure, urologic surgery, or urethral catheterization within the 30 days prior to APN, intravenous chemotherapy or hemodialysis clinic attendance. If the patient did not meet any of the mentioned criteria, the episode was classified as CA-APN.

In the majority of APN cases, treatment can be initiated based on clinical and laboratory findings without the need for imaging. Patients with simple kidney infections typically do not undergo radiologic imaging. Moreover, patients with mild symptoms of APN can receive care outside of the hospital. Hospitalization is necessary for patients who are presented with life-threatening complications like septicemia and multi-organ failure (Venkatesh and Hanumegowda, 2017). A wide range of causative organisms can cause APN, chiefly Gram-negative bacilli, *Escherichia coli (E.coli)* being the most prevalent type (Ha *et al*., 2011). The aims of this study were to identify the demographic and clinical characteristics of CA-APN and HCA-APN, to determine risk factors linked with APN, and to identify the microbiological profile and its susceptibility patterns to antibiotics.

2. Materials and Methods

2.1. Ethical approval

This study was approved by the Research Protocol Ethics Committee of the Kurdistan Board of Medical Specialties (number: 4573, date: 28.04.2022).

2.2. Patient consent

All patients willingly provided verbal consent prior to their enrollment in the study.

2.3. Study setting

The study was conducted in nephrology unit at Azadi Teaching Hospital, which is the main tertiary referral hospital in Duhok province (Figure 1), Iraqi Kurdistan. The hospital comprises of 8 floors and houses 480 beds, along with several auxiliary facilities providing a broad range of medical services to over one million individuals in Duhok governorate. The medical laboratory of the hospital maintains a registry for various medical investigations.

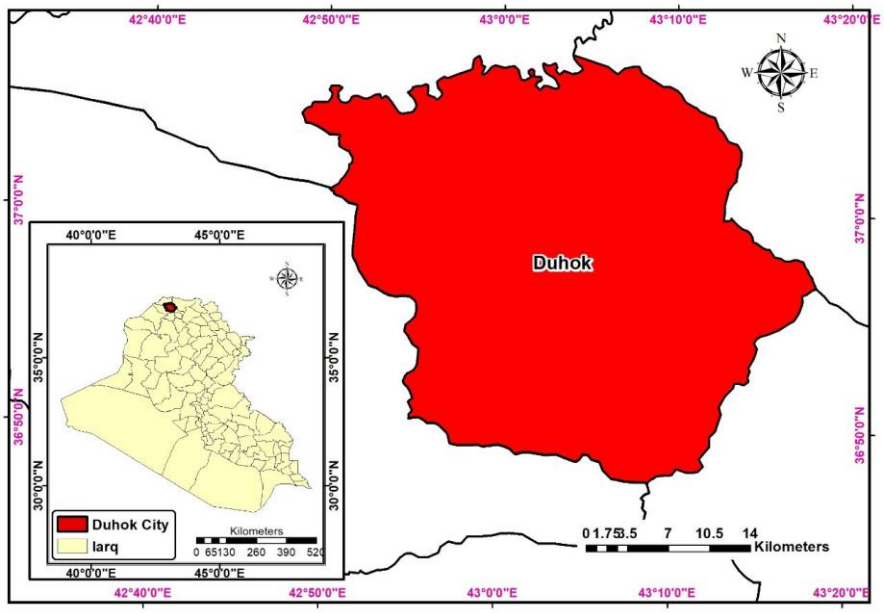

Figure 1. Study area map of Duhok province.

2.4. Study design and subject's enrollment

A cross-sectional study was conducted from September to November 2022. All patients with documented APN were included. Patients who were already on antibiotic treatment were excluded from this study. A standardized questionnaire was used to gather information on socio-demographic and clinical characteristics of the studied population.

2.5. Laboratory investigations

Regarding urine culture, a clean midstream catch or urine obtained from the port of catheter was collected in a sterile disposable (5ml) container, then inoculated on Blood and MacConkey agar (Oxoid, UK) and incubated at 37 °C aerobically. Blood culture was done by obtaining 20 mL of venipuncture blood in which half volume (10 ml) was placed in an anaerobic blood culture bottle first and the other half was put in an aerobic blood culture bottle; afterwards the blood culture was examined manually two or three times daily the first 2 days and thereafter daily for 1 week. Sub culturing of the two-blood culture bottle were done on the days 2 and 7 on Chocolate, Blood and MacConkey agar. All bacterial isolates were first classified by using Gram staining and then identified based on their colony, morphology, culture characteristics, and biochemical reactions according to the standard microbiological procedure (Mahon *et al.*, 2014).

The following antibiotics were used for antibiotic susceptibility: (Aminoglycosides: gentamicin and/or amikacin; Fluoroquinolones: ciprofloxacin and /or levofloxacin; third generation cephalosporin: ceftriaxone or cefotaxime; Carbapenem: imipenem or meropenem; Glycopeptide: vancomycin as appropriate). Complete blood count was analyzed using hematology analyzing system (Swelab alfa, Sweden); White Blood Cells (WBC) with a count of more than 10 $x10^9$/l were considered abnormal, and Absolute Neutrophil Count (ANC) of more than 7 $x10^9$/l were considered abnormal (Bain *et al*., 2016). Serum procalcitonin (PCT) level was determined using (VIDAS® B·R·A·H·M·S PCT™). CRP test was completed by latex agglutination test (Biorex, Antrim, BT41 1QS, UK).

2.6. Statistical analysis

Statistical Package for Social Sciences 27 (SPSS 27; IBM; USA) was used for the statistical analysis. The findings' description was presented in percentages and frequencies. In Univariate analysis Chi Square test or binary logistic regression analysis were used for comparing dichotomous or categorical variables as appropriate.

P of ≤ 0.05 was considered a statistically significant correlation. Multivariate logistic regression was used for candidate analysis of $P < 0.05$ in the univariate analysis.

3. Results

Altogether, 97 adult and elderly APN patients were recruited. A higher percentage (33%) was noticed among age group of 55-64 years; there was a female predominance, accounting for 83.5% (Table 1). Fifteen (15.5 %) were smokers, while 12 (12.4 %) had a history of immunosuppressive therapy. Approximately 42.3 % were on catheterization. Sixty-Nine (71.1 %) were diabetics. Fifty-six (57.7%) displayed a history of cardiovascular disease (CVD), 26 (26.8%) had a history of neurologic disease, and 9 (9.3 %) had a history of chronic pulmonary disease. Out of the total cases, 55 cases (56.7%) were classified as HCA-APN, while 42 cases (43.3%) were classified as CA-APN (Figure 2).

Table 1. Sociodemographic distribution and clinical characteristics of the study population.

Characteristics	**No. (%)**
Age (year)	
25-34	4 (4.1)
35-44	10 (10.3)
45-54	22 (22.7)
55-64	32 (33.0)
≥ 65	29 (29.9)
Gender	
Female	81 (83.5)
Male	16 (16.5)
Smoking	
Yes	15 (15.5)
No	82 (84.5)
Immunosuppressive therapy	
Yes	12 (12.4)
No	85 (87.6)
Catheterization	
Yes	38 (39.2)
No	59 (60.8)
Chronic pulmonary disease	
Yes	28 (28.9)
No	69 (71.1)
Hemodialysis	
Yes	26 (26.8)
No	71 (73.2)
Diabetes mellitus	
Yes	69 (71.1)
No	28 (28.9)
Cardiovascular disease	
Yes	56 (57.7)
No	41 (42.3)
Neurologic disease	
Yes	26 (26,8)
No	71 (73.2)
Solid Tumor	
Yes	11 (11.3)
No	86 (88.7)
Malignancy	
Yes	10 (10.3)
No	87 (89.7)
Chronic Pulmonary disease	
Yes	9 (9.3)
No	88 (90.7)

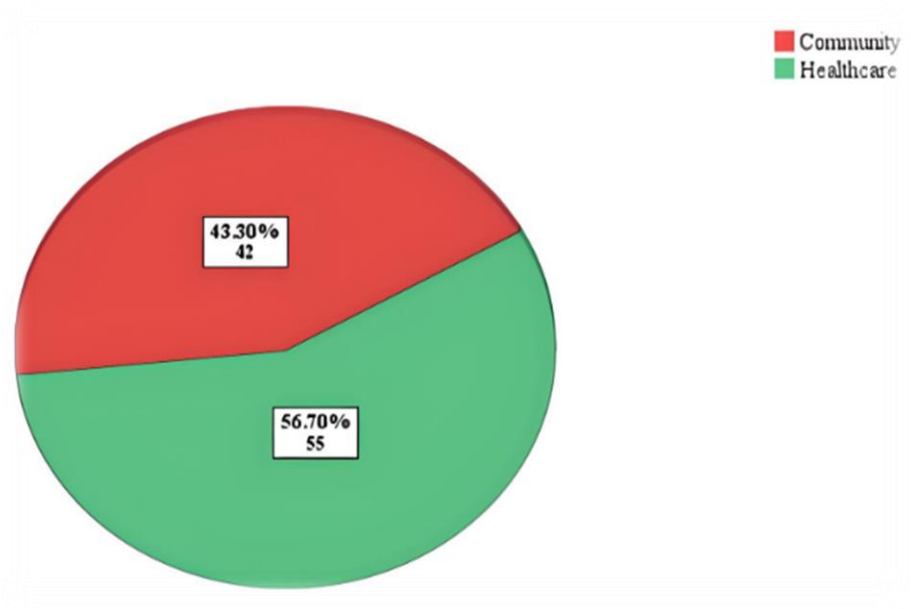

Figure 2. Distribution of community-associated and healthcare-associated acute ayelonephritis in the studied population.

In terms of risk factors, the univariate analysis revealed a significant association between the age group of ≥ 65 years and HCA-APN compared to CA-APN. Other identified risk factors were catheterization, a history of chronic kidney disease, hemodialysis, DM, CVD, neurologic disease, chronic pulmonary disease, PCT levels, and ANC. Among these factors, catheterization and a history of CVD showed independent associations with the development of APN (Table 2).

Table 2. Univariate and multivariate analysis of risk factors associated with Community-Related and Healthcare-Related acute pyelonephritis.

Characteristics		**Univariate analysis**						**Multivariate analysis**	
		APN*							
		CA-APN**		**HCA-APN*****		**P-value**	**OR (95% CI)**	**P- value**	**OR (95% CI)**
		No.	**%**	**No.**	**%**				
Age (year)									
25-34		3	7.1	1	1.8	**Reference**			
35-44		7	16.7	3	5.5	0.85	1.28 (0.09- 17.95)	-	-
45-54		17	40.5	5	9.1	0.92	0.88 (0.07- 10.46)	-	-
55-64		10	23.8	22	40.0	0.12	6.60 (0.60- 71.55)	-	-
≥ 65		5	11.9	24	43.6	0.03	14.40 (1.23- 168.50)	0.82	1.54(0.03-65.45)
Gender	Female	38	90.5	43	78.2	0.106	2.65 (0.78- 8.91)	-	-
	Male	4	9.5	12	21.8				
Smoking	Yes	5	11.9	10	18.2	0.39	0.60 (0.19-1.93)	-	-
	No	37	88.1	45	81.8				
Immunosuppressive therapy	Yes	4	9.5	8	14.5	0.45	0.61 (0.17-2.21)	-	-
	No	38	90.5	47	85.5				
Catheterization	Yes	4	9.5	34	61.8	< 0.01	15.38(4.79.- 49.31)	0.01	8.52(1.68-43.03)
	No	38	90.5	21	38.2				
Chronic Kidney disease	Yes	3	7.1	25	45.5	< 0.01	10.83 (2.98- 39.30)	0.284	0.44(0.001-13.18)
	No	39	92.9	30	54.5				
Hemodialysis	Yes	3	7.1	23	41.8	< 0.01	9.34 (2.57- 33.97)	0.73	0.37(0.001-112.5)
	No	39	92.9	32	58.2				
Malignancy	Yes	2	4.8	8	14.5	0.11	0.29 (0.59- 1.46)	-	-
	No	40	95.2	47	85.5				
Diabetes mellitus	Yes	25	59.5	44	80.0	0.02	2.72 (1.10- 6.71)	0.62	0.67(0.13-3.34)
	No	17	40.5	11	20.0				

Table 2. Contd.

Characteristics		Univariate analysis						Multivariate analysis	
		APN*							
		CA-APN**		HCA-APN***		P-value	OR (95% CI)	P- value	OR (95% CI)
		No.	%	No.	%				
Cardiovascular disease	Yes	12	28.6	44	80.0	< 0.01	10.00 (3.90- 25.61)	0.008	9.84(1.82-53.20)
	No	30	71.4	11	20.0				
Neurologic disease	Yes	4	9.5	22	40.0	0.002	6.33 (1.98- 20.26)	0.1	4.43(0.26-41.69)
	No	38	90.5	33	60.0				
Solid tumor	Yes	2	4.8	9	16.4	0.07	3.91 (0.79- 19.18)	-	-
	No	40	95.2	46	83.6				
Chronic Pulmonary Disease	Yes	1	2.4	8	14.5	0.04	6.97 (0.83- 58.17)	0.35	3.31(0.26-41.69)
	No	41	97.6	47	85.5				
WBC	>10X10^9/L	33	78.6	50	90.9	0.08	2.72 (0.83-8.86)	-	-
	4-10X10^9/L	9	21.4	5	9.1				
PCT	> 0.5 ng/ml	15	35.7	43	78.2	< 0.01	6.45 (2.62- 15.84)	0.83	0.57(0.94-3.53)
	0 - 0.5	27	64.3	12	21.8				
ANC	>7X10^9/L	31	73.8	49	89.1	0.05	2.89 (0.97-8.634)	0.55	0.57(0.09-3.53)
	1.8- 7X10^9/L	11	26.2	6	10.9				
CRP	> 6 mg/L	40	95.2	55	100	0.102	0.95(0.89-1.019)	-	-
	< 6 mg/L	2	4.8	0	0				
Blood culture	Positive	1	2.4	1	1.8	0.84	0.75(0.046-12.503)	-	-
	Negative	41	97.6	54	98.2				

*APN: Acute Pyelonephritis
**CA-APN: Community Associated Acute Pyelonephritis
***HCA-APN: Healthcare Associated Acute Pyelonephritis

Among these 97 patients, the overall mortality rate was 11.3 %, which was significantly associated with HCA-APN (P = 0.002) (Table 3). Considering the microbiological profile, *Escherichia coli* uropathogen (n=61) was the predominant isolated bacteria followed by *Klebsiella pneumonia*e (n=17) (Figure 3). Regarding blood culture, two isolates of *E. coli* and *Klebsiella pneumoniae* were found to be positive, which matched the ones obtained from the urine culture. High antibiotic resistance rates (Table 4) were observed in fluoroquinolones and third generation cephalosporins classes among *E. coli* uropathogen in both CA-APN and HCA-APN patients, with a rate of 74.5 % and 63.9%, respectively, without showing significant differences between CA-APN and HCA-APN. The sensitivity pattern for carbapenem class was found to be high with a rate of 94.1% and 96.6% among CA-APN and HCA-APN patients, respectively. Concerning *Klebsiella pneumoniae*, a higher sensitivity was observed among the aminoglycosides and carbapenems classes with no significant correlation between CA-APN and HCA-APN (P of 0.379 and 0.107, respectively). Fluoroquinolone resistance was high among *Staphylococcus aureus* isolates in HCA-APN patients (83.3%), which was significantly higher compared to those of CA-APN patients (P = 0.01).
Both CA-APN and HCA-APN patients showed high resistance of *pseudomonas aeruginosa* to most antibiotics, except for carbapenem class.

Table 3. Outcome of patients with acute pyelonephritis.

		APN			*P* value
		CA-APN	HCA-APN	Total	
		No. (%)	No. (%)	No. (%)	
Patient Outcome	Recovered	42 (100)	44 (80)	86 (88.7)	0.002
	Died	0 (0)	11(20)	11 (11.3)	

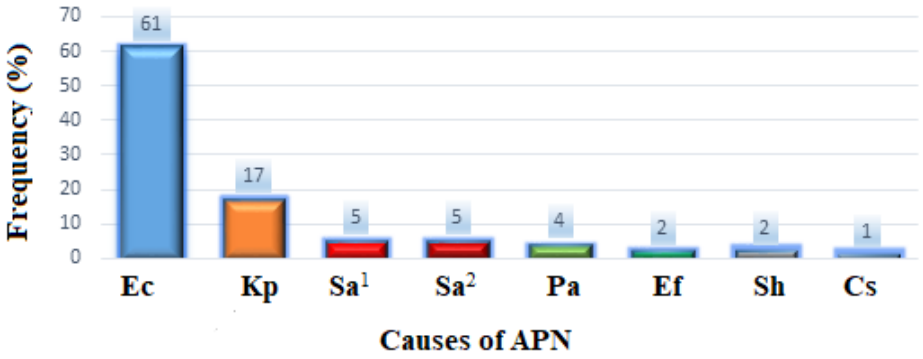

Figure 3. Uropathogens isolated from urine cultures.

(Ec): *Escherichia coli*, (Kp): *Klebsiella pneumonia*, (Sa^1): *Staphylococcus aureus*, (Sa^2): *Streptococcus agalactiae*, (Pa): *Pseudomonas aeruginosa*, (Ef): *Enterococcus faecalis*, (Sh): *Staphylococcus haemolyticus*, (Cs): *Candida* sp.

Table 4. Antibiotic susceptibility patters of acute pyelonephritis patients.

Uropathogens	**Antibiotics**	**APN**			***P* value**
		CA-APN (%)**		**HCA-APN*** (%)**	
E. coli	Aminoglycosides	R	7 (13.7)	14 (23.7)	0.183
		S	44 (86.3)	45 (76.3)	
	Fluoroquinolones	R	41 (74.5)	39 (63.9)	0.217
		S	14 (25.5)	22 (36.1)	
	3rd generation Cephalosporin	R	17 (70.8)	24 (70.6)	0.984
		S	7 (29.2)	10 (29.4)	
	Carbapenem	R	2 (5.9)	1 (3.4)	0.651
		S	32 (94.1)	28 (96.6)	
Klebsiella pneumoniae	Aminoglycosides	R	0 (0)	2 (11.8)	0.379
		S	6 (100)	15 (88.2)	
	Fluoroquinolones	R	7 (58.3)	17 (77.3)	0.247
		S	5 (41.7)	5 (22.7)	
	3rd generation Cephalosporin	R	2 (50)	3 (60)	0.764
		S	2 (50)	2 (40)	
	Carbapenem	R	0	4 (22.2)	0.107
		S	10 (100)	14 (77.8)	
Staphylococcus aureus	Aminoglycosides	R	2 (50)	2 (50)	1.0
		S	3 (50)	3 (50)	
	Fluoroquinolones	R	0	5 (83.3)	0.01
		S	4 (100)	1 (16.7)	
	3rd generation Cephalosporin	R	0	4 (100)	-
		S	0	0	
	Carbapenem	R	0	0	-
		S	0	4	
	Penicillin	R	0	2 (100)	-
		S	0	0	
	Bactrim	R	2 (100)	1 (33.3)	0.136
		S	0	2 (66.7)	
Pseudomonas aeruginosa	Aminoglycosides	R	4 (100)	4 (100)	-
		S	0	0	
	Fluoroquinolones	R	2 (100)	2 (100)	-
		S	0	0	
	3rd generation Cephalosporin	R	3 (100)	3 (100)	
		S	0	0	
	Carbapenem	R	1 (25)	1 (25)	1.0
		S	3 (75)	3 (75)	

Table 4. Contd.

Uropathogens	Antibiotics	APN			*P* value
		CA-APN** (%)		HCA-APN*** (%)	
Streptococcus agalactiae	Aminoglycosides	R	0	0	-
		S	1 (100)	4 (100)	
	Fluoroquinolones	R	0	4 (66.7)	0.102
		S	2 (100)	2 (33.3)	
	3rd generation Cephalosporin	R	1	3 (50)	-
		S	0	3 (50)	
	Carbapenem	R	0	1 (33.3)	-
		S	0	2 (66.7)	
	Penicillin	R	1 (100)	2 (50)	0.361
		S	0	2 (50)	
	Bactrim	R	1 (100)	2 (50)	1
		S	0	2 (50)	
Staphylococcus haemolyticus	Aminoglycosides	R	-	2 (50))	-
		S	-	2 (50)	
	Fluoroquinolones	R	-	4 (100)	-
		S	-	-	
	3rd generation Cephalosporin	R	-	4 (100)	
		S	-	0	
	Carbapenem	R	-	0	-
		S	-	4 (100)	
	Bactrim	R	-	2 (100)	-
		S	-	0	
Enterococcus faecalis	Aminoglycosides	R	2 (66.7)	-	-
		S	1 (33.3)	-	
	Fluoroquinolones	R	1 (33.3)	-	-
		S	2 (66.7)	-	
	3rd generation Cephalosporin	R	3 (75)	-	-
		S	1 (25)	-	
	Bactrim	R	1 (50)	-	-
		S	1 (50)	-	
	Vancomycin	R	2 (100)	-	-
		S	0	-	

*APN: Acute Pyelonephritis
**CA-APN: Community Associated Acute Pyelonephritis
***HCA-APN: Healthcare Associated Acute Pyelonephritis

4. Discussion

In the current study, the clinical and microbiological characteristics of patients with HCA-APN versus HCA-APN were investigated. Among a total of 97 patients, the prevalence of HCA-APN was 56.7 %, while that CA-APN was 43.30%. Our finding was consistent with a study from Republic of Korea that investigated 319 cases of APN, where 118 (37.0%) were CA-APN and 201 (63%) were HCA-APN (Ha *et al*., 2011). On the contrary, another study from Spain investigating 607 APN patients, revealed a reversed percentage pattern of CA-APN (17.1%) compared to HCA-APN (82.9%) (Bosch-Nicolau *et al*., 2017). These varying percentages of HCA-APN and CA-APN observed across the aforementioned studies could be attributed to diverse populations and healthcare settings. Additional factors along the lines of geographical location, population demographics, healthcare practices, and antibiotic usage patterns might contribute to these differences.

In the univariate analysis, patients aged ≥ 65 were significantly associated with an increased HCA-APN incidence ($P = 0.03$, OR 14.40, 95% CI 1.23-168.50). This could be related to several conditions associated with an increased risk of APN among elderly patients, such as reduced immunity, higher rates of colonization with Gram-negative organisms, multiple co-morbidities, structural changes like benign prostatic hypertrophy in men and atrophic vaginitis in women, and increased post-void residual urine (Matsumoto, 2001).

In the present study, the frequency APN was higher among females, with 38 (90.5%) of CA-APN and 43 (78.2%) of HCA-APN cases occurring in female patients. This finding is concordant with several previously conducted studies in Iraq and Iran (Naqid *et al*., 2020, Vakilzadeh *et al*., 2020, Ibrahim *et al*., 2021, Alfetlawi

and Jasim, 2022). This can be justified by an increased number of women being susceptibility to UTIs due to several factors including basic anatomy of shorter urethra, hormone fluctuations across the menstrual cycle, and genetic factors (Alfetlawi and Jasim, 2022).

Catheterization was a HCA-APN risk factor when compared to CA-APN (*P* of < 0.01, OR 15.38, 95% CI 4.79-49.31) and remained a potential risk factor in the multivariate analysis (*P* of 0.01, OR 8.52) (95 % CI 1.68-43.03). In fact, bacteriuria is extremely ubiquitous in catheterized individuals, and a blinded autopsy by Warren *et al*. (1988) concluded that 38% of elderly nursing home patients with a urinary catheter at the time of death had acute inflammation of the renal parenchyma, compared to 5% of non-catheterized patients (*P* 0.004). Another study documented that a prolonged catheterization duration was found to be significantly associated with polymicrobial bacteriuria, chronic renal inflammation, and chronic pyelonephritis, and a death rate of 10% was observed in patients who were catheterized for more than 90 days during their last year of life (Warren *et al*., 1994). In our study, chronic kidney disease was a significant risk factor for HCA-APN in the univariate analysis (*P* of 0.01, OR 10.83, 95% CI 2.98-39.30), but not in the multivariate analysis. Similarly, a study from Hong Kong found that deranged renal function is a death predicator (Chung *et al*., 2014). Additionally, a study from Spain indicated that chronic kidney disease was a significant risk factor of HCA-APN (Bosch-Nicolau *et al*., 2017). In this study, hemodialysis was also found to be risk factor for HCA-APN with a *P* of <0.01, OR 9.34 (95 % CI 2.57- 33.97). The risk of UTI among patients undergoing dialysis depends on the frequency per week. It is well documented that frequent dialysis may lead to lower immunity, hence increasing susceptibility to APN (Haider *et al*., 2016).

In the present study, DM was found to be significantly linked with HCA-APN (*P* 0.02, OR 2.72,95 % CI 1.10-6.71) in the univariate analysis, which was in line with the findings of (Bosch-Nicolau *et al*., 2017). Diabetic patients tend to have an increased risk of developing emphysematous pyelonephritis and papillary necrosis, leading to shock and renal failure (Kumar *et al.,* 2014). DM impairs the urinary tract's immunological defenses, increasing the risk of UTI progression to pyelonephritis, renal abscess, and necrotizing papillitis. Traditionally, glycosuria has been identified as the most likely cause, with glucose providing a more conducive environment for bacterial growth (Zasloff, 2018). The mortality rate for APN patients has been reported to be 1.2% to 33 % (Lee *et al.,* 2012, Yoshimura *et al*., 2005). In our study, none of CA-APN died, while mortality rate among HCA-APN was 20 %, accounting for 11.3 % of the total population, with a significant association (*P* of 0.002) when compared to CA-APN. A study by Efstathiou *et al*. (2003) has recognized age>65 years, bedridden status, septic shock, immunosuppression, and recent use of antibiotics as independent predictors of death.

Furthermore, in our study, patients with CVD history were risk factors for HCA-APN in univariate analysis (*P* < 0.01) and a predicator in multivariate analysis (*P* 0.008). An explanation for this finding could be linked to the connection between acute systemic infections including UTI and significant increases in inflammatory cells in the atherosclerotic coronary arteries (Madjid *et al*., 2007). In this study, a history of neurologic diseases and chronic pulmonary diseases were significant additional risk factors for HCA-APN (*P* = 0.002 and 0.04, respectively), while the multivariate analysis did not show this association. Even though some studies did not show increased risk of extra- pulmonary infections in patients with chronic lung diseases such as chronic obstructive pulmonary diseases (Lange, 2009), it has been documented that prolonged steroid use in chronic lung diseases like bronchial asthma can lead to immune suppression, which in turn increases susceptibility to bacterial and viral infections (Oehling *et al*., 1997). However, further researches are warranted to better understand the mechanisms underlying this association.

The predominant isolated etiologic agent in our study was *E. coli* uropathogen (62.8%). Correspondingly, in almost all studies, *E. coli* was the most frequent isolated bacteria (47.2% to 90%), followed by other Gram-negative bacilli including: *Klebsiella pneumoniae, Pseudomonas aeruginosa*. Nonetheless, there is a significant range of variation in the prevalence of different bacteria depending on age, site of acquisition, and comorbid conditions (Czaja *et al*., 2007, Bouchillon *et al*., 2013). The common cause of APN is *E.coli* due to its distinctive ability to adhere and colonize the urinary tract and kidneys through adhesive molecules (P-fimbriae), which interact with uroepithelial cell surface receptors (Bien *et al*., 2012). In the current study, Candida albicans was isolated at a low rate (1%). The fungal pyelonephritis prevalence is substantially lower than that of bacterial pyelonephritis. Candida albicans is the most prevalent genitourinary fungal pathogen implicated in APN (Bien *et al*., 2012).

To treat APN, selecting an appropriate empiric antibiotic is challenging. In our study, high antibiotic resistance were observed among *E. coli* isolates, specifically to fluoroquinolones, third generation cephalosporin. In view of the fact that fluoroquinolone is a common empirically prescribed APN antibiotic, it is rather alarming that it's resistance has increased in recent years. The proportion of *E. coli* isolates resistant to fluoroquinolones has increased globally, exceeding 50% in some parts of the world, particularly Asia (Dalhoff, 2012). The high rate of third generation cephalosporins resistance is attributed to their irrational various bacterial diseases.

Consequently, their overuse and misuse can lead to the emergence of such resistance. Generally, the emergence of antibiotic resistance perplexed managing the APN (Al-Assil *et al*., 2013). Hence, implementing appropriate antibiotic stewardship programs in management of UTI is fundamental to prevent the development and spread of antibiotic-resistant infections.

The main limitations of this study were: its retrospective nature, single hospital-based study, and small sample size. Therefore, further prospective studies with larger sample sizes are warranted to better understand the microbiological profile and antibiotic resistance pattern of APN.

5. Conclusions

In conclusion, our study addresses that there is a rise in the mortality rate regarding HCA-APN. Several risk factors, including age ≥ 65 years, catheterization, chronic kidney disease, hemodialysis, DM, CVD, neurologic disease, chronic pulmonary disease, PCT level, and ANC were predictors for HCA-APN when compared to CA-APN. The predominant isolated etiologic agent was *E. coli* uropathogens, which recorded high resistance rates against fluoroquinolones and third generation cephalosporins. The HCA-APN characteristics should be considered when prescribing empiric antibiotics. In our local setting, carbapenems are effective empiric therapies against enterobacteraceae uropathogens, for both HCA-APN and CA-APN. In order to prevent the emergence and spread of antibiotic resistance, implementing surveillance systems, infection prevention and control measures, and antimicrobial stewardship programs within our healthcare setting is crucial.

Data availability

All relevant data are within the manuscript.

Conflict of interest

None to declare.

Authors' contribution

Conceptualization: Muayad A. Merza; methodology: Sagvan Kareem Taha, Muayad A. Merza, Zana Sidiq Mohammaed Saleem, Safa EizAldein Almukhtar; formal analysis: Muayad A. Merza, Fatima Nawaf Abdulkareem, Kais Hasan Abd; writing—original draft preparation: Fatima Nawaf Abdulkareem; writing—review and editing: Muayad A. Merza. All authors have read and approved the final manuscript.

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