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Original Article

Urinary Tract Infections after Kidney Transplantation and their Associated Factors

Bahareh Ghiasi[1], Maryam Kheiry[2], Saeed Shafieian[2], Hossein Seidkhani[3], Aliashraf Mozafari[4]*

[1]Nephrology Ward, Shahid Mostafa Khomeini Hospital, Ilam University of Medical Sciences, Ilam, Iran
[2]Non-Communicable Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran
[3]Department of Biostatistics, Faculty of Health, Ilam University of Medical Sciences, Ilam, Iran
[4]Department of Epidemiology, Faculty of Health, Ilam University of Medical Sciences, Ilam, Iran

ABSTRACT

Background: Many of the patients undergoing kidney transplantation (KT) are prone to urinary tract infections (UTIs) due to reasons such as ureter manipulation and damage during surgery, prolonged insertion of urinary catheters, and developing neurogenic bladder. Despite notable progress in surgical techniques and immunosuppression methods after kidney transplantation, UTIs persist as an important conundrum in these patients, predisposing them to morbidities and mortality.

Objective: Therefore, this study aimed to investigate the factors associated with UTIs in patients undergoing kidney transplantation.

Methods: In this follow-up analysis, 69 patients receiving KT under the supervision of the nephrology clinic of Shahid Mostafa Khomeini Hospital of Ilam city, Iran, from 2016 to 2018 were followed up in terms of developing post-transplant UTIs. All patients were examined for underlying diseases, renal failure, post-transplant UTI and its frequency, asymptomatic or symptomatic UTI, post-UTI renal function, type of organism, and drug resistance. The data gathered were analyzed using the firth logistic regression by STATA software version 12.

Results: In this study, the first signs of UTIs appeared within one-month post-transplantation in 15.4% of the patients and within 12 months in 42.3% of them. No drug resistance was observed in 50% of the patients. Recurrent UTIs after transplantation was noticed in 57.6%. During the follow-up, all patients experienced at least one symptomatic UTI, and 38.5% of them developed asymptomatic UTIs at least once. In addition, kidney function decreased in 38.5% of the patients developing UTIs, and this rate was 25% among those who had symptomatic infections and 60% in individuals experiencing both symptomatic and asymptomatic UTIs. In multivariate analysis, advanced age (OR= 1.07, 95% CI: 1.02-1.13, P= 0.01) and female gender (OR= 13.10, 95% CI: 2.75-64.74, P= 0.002) were identified as independent risk factors for UTIs, while vitamin D level (OR= 0.94, 95% CI: 0.89-1.00, P= 0.05) was found to be a protective factor for UTIs after KT.

Conclusion: According to our results, the incidence of UTIs in patients receiving renal grafts was higher in women than in men. Vitamin D level was identified as a protective factor against post-transplant UTI. All patients undergoing KT experienced symptomatic UTIs at least once, 38.5% of whom also revealed a decrease in renal function. Therefore, it is recommended to educate health professionals regarding the early signs of UTIs and their risk factors so that effective preventive measures can be implemented to avoid UTIs, subsequent dysfunction of the transplanted kidney, and patient death.

KEYWORDS: Kidney transplantation; Urinary tract infections; Risk factors; Vitamin D

INTRODUCTION

Organ transplantation is one of the most advantageous ways to treat patients with single or multiple organ failures [1]. Kidney transplantation is among the most frequent organ transplantation procedures in the world as this organ can be transferred from a living person to the patient, enabling the donor to continue living with only one kidney. The number of kidney transplantation surgeries is soaring globally, and the United States, where more than 15,000 kidney transplantations are performed annually, claims the highest number of KT in the world [2]. Despite the fact that the survival of the trans-

*Correspondence: Aliashraf Mozafari, PhD
Department of Epidemiology, Faculty of Health, Ilam University of Medical Sciences, Ilam, Iran
ORCID: 0000-0002-9962-3130
E-mail: amozafari99@yahoo.com

planted kidney after KT has improved in recent time, the long-term outcomes of KT has not improved considerably due to a number of reasons. Among the post-transplant complications of KT are diabetes, drug-associated hyperlipidemia, urinary tract infections (UTIs), and post-transplant bone abnormalities [3, 4]. Urinary tract infections comprise the most common infectious disease following KT, with a prevalence varying from 17% to 95% among KT patients. Urinary tract infections are an important contributor to morbidities and mortality in these patients and are one of the most important causes of the transplanted kidney's functional inadequacy. The most common source of infection in KT patients is the urinary system. A study reported a prevalence of 40% for UTIs after KT, which was associated with increased mortality in patients [5]. The main risk factors for UTIs in KT patients include gender, age, insertion of urinary catheters, manipulation of or damage to sexual organs during surgery, structural or functional defects in the transplanted kidney (such as vesicoureteral reflux, stones, etc.), and neurogenic bladder [6-8]. Since UTIs are usually asymptomatic in the first three months after transplantation, they often can present with pyelonephritis, bacteremia, graft dysfunction, and a high risk of recurrent bacterial infections [9, 10]. Most deaths caused by UTIs after KT occur within the first few days after disease presentation due to either delayed onset or lack of treatment. Therefore, it is critical to identify the factors associated with the incidence of UTIs following KT in order to provide immediate care and prevent graft rejection and, subsequently, death and disabilities in patients. Therefore, we here aimed to investigate the risk factors associated with UTIs and the impacts of UTIs on the function of renal grafts in patients referred to a specialized nephrology clinic.

MATERIALS AND METHODS

In this follow-up study, 69 patients undergoing KT receiving care at the nephrology clinic of the Shahid Mostafa Khomeini Hospital of Ilam city were followed up for two years to record post-transplant UTI episodes. Patients' demographic characteristics, including age and sex, were gathered, and then patients who experienced UTIs were identified. All patients were examined for history of underlying diseases (hypertension, renal stone, reflux, ADPKD, diabetes), vitamin D level, GFR, type of renal graft (i.e., deceased or living donor), UTIs associated with immunosuppressants (tacrolimus, sirolimus, cyclosporine), post-UTI renal function, and drug resistance and type of the causative agent. Also, asymptomatic and symptomatic UTIs were determined. Urine samples were transferred to the laboratory for analysis and culture within two hours of collection. MacConkey Agar and Blood Agar media were used for urine culture, and the plates were incubated at 97°C for 42 hours. Diagnostic urine analysis strips (Behering, Germany) were used to check for the presence of erythrocytes, leukocytes, and nitrate. Five mL of the urine sample was poured into a tube and centrifuged at 2500 rpm for five minutes. Then one drop of the sediment was placed on a glass slide and observed under a light microscope to check for the presence of red blood cells, white blood cells, and bacteria. Urine culture samples obtained from symptomatic patients that contained equal to or more than 103 colonies/mL were regarded as pure and possibly positive cultures since these patients were under treatment with immunosuppressive drugs. For asymptomatic patients, equal to or more than 105 colonies/mL was considered a positive culture. Next, the bacteria isolated were characterized by Gram staining and biochemical tests. The antibiotic sensitivity test was performed according to the Kirby-Bauer method on Mueller Hinton agar following standard laboratory protocols. The sensitivity of Gram-negative bacteria was checked against antibiotics such as ciprofloxacin, imipenem, gentamicin, cotrimoxazole, piperacillin, chloramphenicol, tetracycline, and nitrofurantoin and the sensitivity of Gram-positive bacteria against antibiotics such as ciprofloxacin, imipenem, gentamicin, cotrimoxazole, chloramphenicol, tetracycline, nitrofurantoin, linezolid, oxacillin, and vancomycin.

Ethical Considerations

The ethical clearance was approved by Ilam University of Medical Sciences Ethics Committee (IR.MEDILAM.REC.1400.028).

Statistical Analysis

In this study, 69 KT patients were followed up for two to determine events such as graft rejection and post-transplant UTIs. These data were presented using descriptive statistics (frequency, mean, and standard deviation) and analyzed by inferential statistics, including univariate and multivariate firth logistic regression in stata software version 12 (STATA Corporation, College Station, TX). Variables with a P value of less than 0.2 in univariate analysis were considered statistically significant and entered into the multivariate model. The Akaike information criterion (AIC) was used to determine the best-fit model for the data.

RESULTS

Patients' descriptive information has been noted in Table 1. Out of 69 patients who were followed up, 26 experienced UTIs after KT. The average age of patients with UTI was 53.27±14.61 years, and the average age of patients without UTI was 43.74±14.52 years. Out of 69 patients, 22 were women, 14 of whom (63.6%) developed UTIs after transplantation. However, 12 out of 47 men (25.5%) were diagnosed with UTIs after KT.

Of 26 patients experiencing post-transplant UTIs, four (15.4%) and 11 (42.3%) patients presented the first signs of the infection within one- and 12-month post-transplantation, respectively. No drug resistance was observed in 13 patients (50%), and 15 (57.6%) patients experienced recurrent UTIs after transplantation. During the follow-up, all patients (n=26, 100%) suffered at least one episode of symptomatic UTI, and 10 patients (38.5%) encountered at least one episode of asymptomatic UTI. The most frequently encountered causative agent of UTIs in our patients was *Escherichia coli* (n=24, 92.2%). Overall, 38.5% of patients with UTIs had decreased kidney function. Out of 16 patients with symptomatic UTIs, four (25%) individuals experienced a decrease in renal function, and this rate was 60% (6 out of 10) in the patients who experienced both symptomatic and asymptomatic UTIs.

The model including the variables of age, gender, glomerulonephritis, autosomal dominant polycystic kidney disease, vitamin D level, and glomerular filtration rate (GFR) revealed the smallest AIC and the best fit into the data (Table 2). All possible interactions between the variables were examined, none of which was found to have a significant relationship with UTIs. In multivariate regression analysis, advanced age and female gender were recognized as risk factors for post-transplant UTIs, while vitamin D level contributed as a protective factor. In the univariate regression model, ADPKD was recognized to be an important risk factor for UTIs after KT. In the final model, the odds ratio (OR) of UTI for patients with a history of ADPKD was obtained as 10.5 compared to patients without a history of ADPKD. However, this relationship did not trespass the statistical significance threshold at the 5% level, probably because of a small sample size. Our results showed for each year increase in age, the OR of UTIs after KT increased by 0.07%. Also, the likelihood of developing UTIs after KT in women was 13 times that of men. Finally, for each unit increase in serum vitamin D level, the odds of developing post-transplant UTI decreased by 6%, which was statistically significant.

DISCUSSION

The present study aimed to examine the impacts of post-transplant UTIs on the function of the transplanted kidney and determine the risk factors associated with this complication. Overall, 69 patients who underwent KT referred to our nephrology clinic were assessed. The results of our study showed that the prevalence of UTI after KT was higher in women (63.6%) than in men (25.5%). Also, the likelihood of developing post-transplant UTI increased with age. Urinary tract infections comprise more than 30% of all infec

Table 1: Distribution of clinical qualitative and quantities variables associated with UTI after kidney transplant[a].

Variables	UTI after kidney transplant		P-value
	Yes (N=26)	No (N=43)	
Age (years), (mean ± SD)	53.27 (14.61)	43.74 (14.52)	0.01
Sex (%)			
Female	14 (53.85)	8 (18.60)	0.002
Male	12 (46.15)	35 (81.40)	
BMI (kg/m^2), (mean ± SD)	24.72 (4.37)	24.12 (3.40)	0.53
Renal stone (%)			
No	22 (84.62)	39 (90.70)	0.44
Yes	4 (15.38)	4 (9.30)	
Hypertension (%)			
No	24 (92.31)	38 (88.37)	0.71
Yes	2 (7.69)	5 (11.63)	
Reflux (%)			
No	1 (100)	42 (61.76)	0.98
Yes	0 (0.00)	26 (38.24)	
Diabetes (%)			
No	2 (4.65)	41 (95.35)	0.36
Yes	3 (11.54)	23 (88.46)	
Glomerulonephritis (%)			
No	10 (23.26)	33 (76.74)	0.12
Yes	2 (7.69)	24 (92.31)	
ADPKD (%)			
No	1 (2.33)	42 (97.67)	0.04
Yes	5 (19.23)	21 (80.77)	
Serum Vitamin D (mg/dL), (mean ± SD)	19.71 (10.88)	24.99 (14.51)	0.12
Immunosuppressive drug (%)			
Tacrolimus	12 (35.29)	22 (64.71)	0.93
Sirolimus	12 (40.00)	18 (60.00)	
Cyclosporine	2 (40.00)	3 (60.00)	
Types of Kidney Transplants (%)			
Deceased donor	5 (35.71)	9 (64.29)	0.87
Living donor	21 (38.18)	34 (61.82)	
GFR (mL/min), (mean ± SD)	55.97 (20.42)	64.74 (17.76)	0.07

[a]Quantitative and qualitative variables were presented as mean ± SD and number (percent), respectively. Quantitative and qualitative variables were compared between two groups using T-test, Chi-Square and Fischer exact tests.
Abbreviations: UTI: urinary tract infection, BMI: body mass index, ADPKD: Autosomal dominant polycystic kidney disease, GFR: glomerular filtration rate

tious complications in patients receiving renal grafts [11]. The study of Curns *et al.* demonstrated that UTIs accounted for one of the most common reasons for hospitalization in the elderly [12]. Consistent with our observation, Olenski *et al.* in 2019 reported that age and female gender (OR=4.93) were risk factors for UTIs [13]. Likewise, UTIs were encoun

Table 2: Firth regression logistic models of factors for UTI after kidney transplant in univariate and multivariate analysis.

Variables	Crude OR, (95% CI)	P-value[a]	Adjusted OR, (95% CI)	P-value[b]
Age (years)	1.04 (1.01 – 1.08)	0.01**	1.07 (1.02 – 1.13)	0.01**
Sex				
Female	1*			
Male	5.11 (1.71 – 15.16)	0.003**	13.10 (2.75 – 64.74)	0.002**
BMI (kg/m^2)	1.04 (0.92 – 1.19)	0.52		
Renal stone				
No	1			
Yes	1.77 (0.40 – 7.80)	0.45		
Hypertension				
No	1	–		
Yes	0.63 (0.11 – 3.53)	0.60		
Reflux				
No	1	–		
Yes	0.53 (0.02 – 13.61)	0.71		
Diabetes				
No	1	–		
Yes	2.67 (0.42 – 17.19)	0.30		
Glomerulonephritis				
No	1	–		
Yes	0.28 (0.06 – 1.37)	0.12**	0.82 (0.12 – 5.62)	0.84
ADPKD				
No	1	–		
Yes	10.00 (1.10 – 91.16)	0.04**	10.58 (0.85 – 131.95)	0.06
Serum Vitamin D (mg/dL)	0.97 (0.93 – 1.01)	0.12**	0.94 (0.89 – 1.00)	0.05**
Immunosuppressive drug				
Tacrolimus	1	–		
Sirolimus	1.22 (0.18 – 8.36)	0.84		
Cyclosporine	1.22 (0.44 – 3.37)	0.70		
Types of Kidney Transplants				
Deceased donor	1	–		
Living donor	1.11 (0.33 – 3.77)	0.87		
GFR (mL/min)	0.97 (0.95 – 1.00)	0.07**	0.98 (0.94- 1.02)	0.26
AIC			74.55	

*Reference category; ** Significant; AIC = -2LogLikelihood+2P, where p is the number of parameters in the model; Final model include Age, sex, BMI, GN disease, ADPKD, Serum Vit D and GFR was the best fitted model because it has the smallest (AIC= 74.55); Crude OR: HR for variables in univariate analysis; Adjusted OR: HR for variables in multivariate analysis; [a]P-value for crude OR; [b]P-value for adjusted OR.
Abbreviations: UTI: urinary tract infection, BMI: body mass index, ADPKD: Autosomal dominant polycystic kidney disease, GFR: glomerular filtration rate, AIC: Akaike information criterion

tered more commonly in women than in men receiving kidney transplants [14-16].

In the present study, the incidence of post-transplant UTIs did not show a significant relationship with the variables of glomerulone-

phritis, autosomal dominant polycystic kidney disease, GFR, history of underlying diseases (hypertension, renal stone, reflux, and diabetes), and type of renal graft (deceased or living donor). In a study conducted in the US and Spain, allografts were reported to have longer durability in non-diabetic recipients than in diabetic recipients [17]. Also, other studies have identified diabetes mellitus [18] and hypertension [19] as predictors for UTI in patients undergoing KT. The incidence of UTI was shown to be higher among the recipients of renal grafts of deceased donors than those receiving grafts from living donors. Taminato et al. also declared that the patients receiving allografts from deceased donors were more likely to develop UTIs compared to the patients transplanted with grafts from living donors (OR= 2.65) [20]. Studies have shown that structural abnormalities in native or transplanted kidneys can increase the risk of UTIs [21]. Differences observed between our results and those of similar studies may be related to the baseline features of patients undergoing transplantation, as well as varying protocols used for delivering immunosuppressive treatments in different clinics.

The results of the present study revealed that half of the patients developing UTIs had no drug resistance, and 57.6% of the patients experienced recurrent UTIs after KT. Moreover, all of our patients who experienced post-transplant UTIs presented with at least one symptomatic episode, and 38.5% of the patients encountered at least one asymptomatic UTI. Studies have shown that most cases of UTIs occur within the first year after KT (74%) and, particularly, the first three months after the surgery (81.9%) [14].

According to the results of the present study, *E. coli* was the most frequent causative agent of UTIs (92.2%) encountered in our patients, which is in line with previous reports underlining *E. coli* as the main pathogen causing UTIs in KT subjects [16, 22]. In their study, Ozawa *et al.* (2022) investigated the role of diabetes mellitus as a predictive factor for UTIs in patients undergoing KT and reported that 34 patients developed post-transplant UTIs, and the most frequently encountered pathogen was *E. coli* [18]. Yuan *et al.* (2018) also identified *E. coli* as the most common Gram-negative organism (62.5%) isolated from patients with UTIs [23]. Bacterial infections can exaggerate the risk of graft rejection as they activate both innate and adaptive immunity [24].

According to the results of the present study, 38.5% of all patients with UTIs experienced decreased renal function, while this rate was 25% in patients with symptomatic UTIs and 60% among those with both symptomatic and asymptomatic UTIs. Coulthard *et al.* studied therapeutic approaches for UTIs and the risk of renal scars in children and declared that the sooner starting of treatment for UTIs could alleviate kidney injury and decreased renal function [25]. Based on our results, vitamin D seems to have a protective role against UTIs. In another study, Aslan *et al.* compared the polymorphisms of the vitamin D receptor (VDR) gene between children without a history of UTI (n=105) and their peers with a positive history of UTI (n=92) and found that VDR gene polymorphisms played a key role in increasing susceptibility to UTIs and renal scarring, highlighting the essential role of vitamin D in directing immune responses against infectious agents [26]. The recent study's findings agreed with our results. Vitamin D has also been reported to share an important role in the pathogenesis of infectious diseases and in preventing the emergence of drug-resistant pathogens [27]. Shalaby *et al.* announced a significant association between the risk of UTI and vitamin D deficiency, evidenced by a significant correlation between the serum levels of vitamin D and the incidence of lower and upper UTIs [28].

In conclusion, according to our findings, women were more likely to develop UTIs after KT compared to men, and each year increase in age boosted the odds of developing post-transplant UTIs by 0.07%. Serum level of vitamin D was identified as a protective factor against post-transplant UTI, so it is recommended to monitor the level of vitamin D in KT patients developing UTIs. All patients receiving renal grafts experienced at least one

episode of symptomatic UTIs, in 38.5% of whom the renal function was found to decline. Therefore, it is advisable to provide KT patients with the necessary training on the early signs and symptoms of UTIs and regularly monitor their risk factors so that appropriate preventive measures can be implemented to avoid UTIs and, subsequently, renal graft dysfunction, associated morbidities, and death.

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