

ORIGINAL ARTICLE

Gender has no influence on VUR rates after renal transplantation

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Conflicts of interest

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Summary

The influence of recipient gender on urological complications including vesicoureteral reflux (VUR) after renal transplantation has not yet been established. In this study, post-transplantation voiding cystourethrography and ultrasonography were used to evaluate the upper and lower urinary tract in 598 consecutive renal transplant recipients. Our cohort included 209 females and 389 males, respectively. Gender-specific urological complications and potential confounders were analyzed in relation to long-term allograft outcomes. Postoperative urinary retention occurred more frequently in men ($P = 0.004$). Urinary tract infections (UTIs) were diagnosed more frequently in women after transplantation ($P = 0.05$). In a multivariate analysis, gender was not a risk factor for VUR [HR, 1.35 (CI, 0.90–1.96); $P = 0.14$]. VUR rates were influenced by the surgeon's experience level at the time of transplantation [HR, 0.59 (CI, 0.40–0.87); $P = 0.008$]. No gender-specific differences were seen for ureteral stenosis, leakage, hydronephrosis, death-censored graft or patient survival, and long-term allograft function. Donor/recipient gender mismatch had no impact on postoperative complication rates. In conclusion, male transplant recipients are at risk for developing postoperative urinary retention, whereas female patients more likely develop UTIs. Surgeon's experience level is a risk factor for developing VUR.

Introduction

Renal transplantation is the renal replacement therapy of choice for many patients with end-stage renal disease. Although short-term survival rates have significantly improved over the last decades, a variety of immunological and nonimmunological factors were shown to considerably shorten graft survival in the long term [1]. Among nonimmunological factors, urological complications following renal transplantation may cause significant morbidity, with studies reporting vesicoureteral reflux (VUR) rates up to 86% on voiding cystourethrography (VCUG) in asymptomatic transplant recipients [2,3]. In addition to VUR,

ureteral leakage and stenosis are frequent postoperative complications that increase the risk of impaired graft function or even graft loss. Both may present as hydronephrosis or pelvic fluid collection on ultrasonography [4]. Another common complication is the occurrence of urinary tract infections (UTIs) facilitated by immunosuppressive treatment and exposure to nosocomial pathogens [5,6].

Regarding potential gender differences, it is known for the general population that women and men are individually susceptible to specific urological complications. Men more likely develop voiding symptoms, whereas women are more susceptible to UTIs due to the gender-specific anatomy of the lower urinary tract [7–9]. The incidence

of voiding symptoms and urinary retention is presumably higher in men due to a higher rate of bladder outlet obstructions [10,11]. In the transplant cohort, urological complications such as VUR, UTI, and urinary retention represent potential risk factors for poorer graft outcome [12]. Thus far, studies analyzing post-transplant gender issues have focused merely on the influence of donor/recipient gender mismatch [13]. Gender-specific complication rates have not yet been described in post-transplant patients. In particular, the impact of gender on upper and lower urinary tract complications remains unclear.

To our knowledge, this is the first study evaluating gender-specific differences in urological complications after renal transplantation.

Patients and methods

Study patients

In the present study, we retrospectively analyzed 598 of 1167 consecutive adult patients who underwent renal transplantation between January 2001 and December 2007 (follow-up until December 2013) at our tertiary referral center. Criteria for study inclusion were (i) age ≥ 18 years, (ii) availability of per-protocol VCUG within 60 days of transplantation and before first discharge, and (iii) availability of ultrasonography within 24 h of the VCUG. Of 1167 patients, 569 were excluded due to incomplete data. Comparing study patients with excluded subjects, who were transplanted during the same time period, we found small but significant differences regarding donor age [median 51 (IQR 41–61) vs. 49 (IQR 39–59) $P = 0.03$] and proportion of living donor transplantation [57 (10%) vs. 69 (17%), $P = 0.001$], respectively. There were, however, no significant differences regarding other baseline variables, such as recipient age, gender, donor/recipient gender mismatch, HLA mismatch, cold ischemia time, prior kidney transplantation, and surgeon experience level.

Surgical and urological procedures and evaluation

Ureteral implantation was routinely performed in an anti-reflux manner using extravesical submucosal tunneling. Ureteral anastomosis was performed using running absorbable sutures [14,15]. Our protocol did not include the routine placement of ureteral stents. Foley catheter removal was routinely scheduled 5 days after transplantation. Indications for reinsertion of Foley catheter were urinary retention or postvoid residual urine volumes exceeding 150 ml. As part of our routine protocol, all patients underwent VCUG prior to their first discharge after transplantation. The median interval between renal transplantation and VCUG was 18 (IQR 13–27) days.

Within 24 h of the VCUG, all patients underwent renal transplant ultrasonography. VCUG and ultrasonography results were reviewed and graded by both a radiologist and an urologist. Hydronephrosis was graded using the Society for Fetal Urology grading system [16]. VUR severity was graded according to the International Reflux Committee Study [17]. The level of training and experience of the surgeon in each case was analyzed. Surgeons who had performed less than 30 transplantations were considered inexperienced regarding their level of training, whereas surgeons with more than 30 transplantations were categorized as experienced.

Within the first year after transplantation, patients were routinely evaluated for the presence of UTI by urine analysis and urine culture obtained at follow-up visits, as well as upon admission for presentation of clinical symptoms. UTIs were diagnosed based on positive urine cultures with $>10^5$ colony-forming units of pathogenic organism per milliliter of urine. Recurrent infections were defined as UTIs with two or more episodes during a follow-up period of 12 months. Following the KDIGO Guidelines [18], transplant recipients received UTI prophylaxis with daily trimethoprim-sulfamethoxazole for 6 months. Patients with asymptomatic UTIs did not routinely receive antibiotic treatment.

Study endpoints

Study endpoints included gender-specific differences in urological complications after renal transplantation, such as VUR, hydronephrosis, urinary retention, and UTI; graft survival, overall survival, and eGFR rate calculated according to the Mayo Clinic equation (patients receiving dialysis were considered as having an eGFR of 5 ml/min/1.73 m²) [19].

Statistical analysis

Continuous data are given as median and interquartile range (IQR; range from the 25th to the 75th percentile). Discrete data are presented as counts (N) and percentage (%). Chi-square tests or Fisher's exact tests were used to compare groups of categorical data. For comparisons of continuous data, the nonparametric Mann-Whitney U -test was used. Kaplan-Meier analysis was used to calculate graft and patient survival, and the Mantel Cox Log-rank test was used to compare survival between groups. Multivariate analysis (logistic regression) was used to determine the independent effect of gender on transplant complications. Multivariate models included confounding variables unequally distributed between groups or confounders considered to have an impact on the end point. A two-sided P value <0.05 was considered statistically significant.

Statistical calculations were performed using spss for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA). The study was approved by the ethics committee of the Medical University Vienna.

Results

Demographics

Of 598 renal transplant recipients, 209 were women (34.9%) and 389 were men (65.1%). A total of 301 patients (50.3%) received a donor/recipient gender match, whereas 297 patients (49.7%) received a gender mismatch. Median age was 54 (IQR 40–63) years and 54 (IQR 44–64) years in women and men, respectively ($P = 0.26$). Patient baseline characteristics are shown in Table 1.

Complication rates and graft outcome

In our study cohort, rates for ureteral stenosis, ureteral leakage, and postoperative urinary retention were 8.9% (53 patients), 4.7% (28 patients), and 4.8% (29 patients), respectively. Overall, 237 (39.6%) of the 598 studied transplant recipients were diagnosed with post-transplantation VUR before discharge. Forty-six (7.7%), 120 (20.1%), 54 (9.0%), and 17 (2.8%) patients had grade I, II, III, and IV VUR, respectively. Hydronephrosis was found in 88 patients (14.7%), of whom 59 (9.8%), 25 (4.2%), and 4 (0.7%) had grade I, II, and III hydronephrosis, respectively. Lymphoceles occurred in 49 (8.2%) patients. Median eGFR (ml/min/1.73 m²) levels at 1, 3, and 5 years after transplantation were 56 (IQR 39–76), 55 (IQR 33–76), and 50 (IQR 28–72), respectively.

Over the entire period, 377 transplantations (63%) were performed by experienced surgeons and 221 (37%) were carried out by inexperienced surgeons. The presence or absence of VUR was significantly influenced by the surgeon's experience level at the time of transplantation. VUR

was less common in transplantations performed by experienced as compared to inexperienced surgeons (34% vs. 50%, $P = 0.001$). However, the level of expertise of the surgeon did not influence the incidence of other urological complications.

Gender and complication rates

Our study cohort included 209 women and 389 men with upper and lower urinary tract evaluation. Bivariate analysis showed lower VUR rates in women (70 patients, 33.5%) compared to men (167 patients, 42.9%; $P = 0.03$). However, in a multivariate model including all potential confounders [donor and recipient age, recipient gender, donor/recipient gender mismatch, experience level of surgeon, living donor, re-transplantation, HLA mismatch, cold ischemic time (CIT)], recipient gender was not a risk factor for VUR [HR, 1.35 (CI, 0.90–1.96); $P = 0.14$]. The presence or absence of VUR was still influenced by the surgeon's experience level at the time of transplantation (Table 2). Gender mismatch had no impact on urological complication rates. Detailed results of the gender-specific analysis are demonstrated in Table 3.

Gender and UTI

Women were more susceptible to UTIs (74 patients, 35.4%) than men (111 patients, 28.5%; $P = 0.05$). Recurring UTIs occurred in 13 women (6.2%) and 12 men (3.1%), respectively ($P = 0.03$). The overall rate of febrile UTIs was 7.7% for women (16 patients) and 5.4% for men (21 patients; $P = 0.29$). In patients with VUR, the rate of febrile UTIs was 7.6%, including seven women (10%) and 11 men (6.6%; $P = 0.42$). In multivariate logistic regression analysis including all relevant confounders, male gender still predicted lower rates of UTI [HR, 0.69 (CI, 0.47–1.01) $P = 0.05$].

Table 1. Baseline characteristics of 598 transplant recipients.

Variables	All (N = 598)	Female (N = 209)	Male (N = 389)	P value
Recipient age (years), median (IQR)	54 (43–64)	54 (40–63)	54 (44–64)	0.26
Prior kidney transplantation, N (%)	105 (18)	38 (18)	67 (17)	0.77
Living donor transplantation, N (%)	57 (9)	18 (9)	39 (10)	0.58
Donor age (years), median (IQR)	51 (41–61)	52 (43–62)	49 (40–61)	0.16
Cold ischemia time > 14 h, N (%)	250 (42)	94 (45)	156 (40)	0.32
HLA mismatch (A, B, and DR), median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.40
Donor/recipient gender mismatch	297 (50)	113 (54)	184 (47)	0.12
Surgeon experience level				
>30 transplantations performed (%)	377 (63)	142 (68)	237 (61)	0.10
<30 transplantations performed (%)	221 (37)	67 (32)	152 (39)	

IQR, interquartile range; N, number.

Table 2. Multivariate analysis of risk factors for VUR in 598 transplant recipients.

Variable	HR	95% CI	P value
Donor age	1.24	0.78–1.96	0.36
Recipient age	1.03	0.68–1.57	0.88
Recipient gender	1.35	0.90–1.96	0.14
D/R gender mismatch	0.74	0.51–1.08	0.12
Surgeon experience level	0.59	0.40–0.87	0.008
Living donor transplantation	0.53	0.21–1.33	0.18
Prior kidney transplantation	0.44	0.17–1.14	0.09
HLA mismatch (A, B, and DR)	1.02	0.89–1.17	0.76
Cold ischemia time >14 h	1.02	0.69–1.50	0.92

HR, hazard ratio; CI, confidence interval.

Gender and lower urinary tract

Three women (1.4%) and 26 men (6.7%) required reinsertion of a Foley catheter due to postoperative urinary retention ($P = 0.004$). Of the 26 men, 16 (61.5%) had benign prostatic enlargement (BPE). The median prostate volume in these patients was 45 (35–50) ml. VUR occurred in nine of the 16 men (56.3%) with BPE. The median residual diuresis before transplantation was 300 (20–500) ml/24 h. All women who required reinsertion of a Foley catheter had a residual diuresis before transplantation of <150 ml/24 h. The median postvoid residual urine volumes after renal transplantation were 57 (0–120) ml and 30 (0–220) ml in women and men ($P = 0.15$), respectively.

Gender and graft outcome

We found no gender-specific differences in eGFR levels at 1, 3, and 5 years after transplantation ($P = 0.14$, $P = 0.68$, $P = 0.30$, respectively). In women, median eGFR (ml/min/1.73 m²) at 1, 3, and 5 years after transplantation was 61 (IQR 40–83), 55 (IQR 29–79), and 45 (IQR 25–72), respec-

tively. In men, median eGFR (ml/min/1.73 m²) at 1, 3, and 5 years after transplantation was 54 (IQR 38–73), 55 (IQR 35–75), and 51 (IQR 34–72), respectively. Kaplan–Meier analysis showed no significant difference in death-censored graft survival ($P = 0.53$) and patient survival ($P = 0.38$) between women and men (Fig. 1).

Discussion

In this study, we have investigated whether recipient gender has an impact on urological complications following renal transplantation. Urological complications represent an important cause of morbidity in patients following renal transplantation [20,21]. However, the evidence available is currently poor, and studies analyzing post-transplant gender issues have focused on the mismatch of donor/recipient gender [13]. A major finding of our study was that male transplant recipients had a significantly higher incidence of postoperative urinary retention, whereas women experienced UTIs more often. On bivariate analysis, the incidences of VUR were higher in men and in transplantations performed by experienced as compared to inexperienced surgeons. However, after adjusting for potential confounders, only the surgeon's experience level remained a significant risk factor.

In our cohort of 598 transplant recipients, who underwent per-protocol VCUG, we found a 39.6% overall VUR rate. This stands in accordance with previously published data reporting an incidence of reflux as high as 86% in asymptomatic patients after renal transplantation [22,23]. There is still an ongoing debate on the actual impact of VUR on graft survival. Studies evaluating VCUGs in asymptomatic renal transplant recipients have revealed relatively high VUR rates [24]. Even though antireflux ureteroneocystostomy technique was used in all of our patients, we found higher rates of VUR in men ($P = 0.03$). Moreover, our analysis demonstrated that the surgeon's

Table 3. Gender-specific analysis of complication rates in 598 transplant recipients.

Complication	All (N = 598)		Female (N = 209)		Male (N = 389)		P-value
	N	%	N	%	N	%	
Vesico-ureteral reflux	237	39.6	70	33.5	167	42.9	0.03
Hydronephrosis	88	14.7	34	16.3	54	13.9	0.54
Single urinary tract infection	185	30.9	74	35.4	111	28.5	0.05
Recurrent urinary tract infection	25	4.2	13	6.2	12	3.1	0.03
Febrile urinary tract infection	37	6.2	16	7.7	21	5.4	0.29
Urinary retention	29	4.8	3	1.4	26	6.7	0.004
Ureteral leakage	28	4.7	7	3.3	21	5.4	0.31
Ureteral stenosis	53	8.9	19	9.1	34	8.7	0.88
Lymphocele	49	8.2	17	8.1	32	8.2	1.00
Delayed graft function	61	10.2	19	9.1	42	10.8	0.53

N, number.

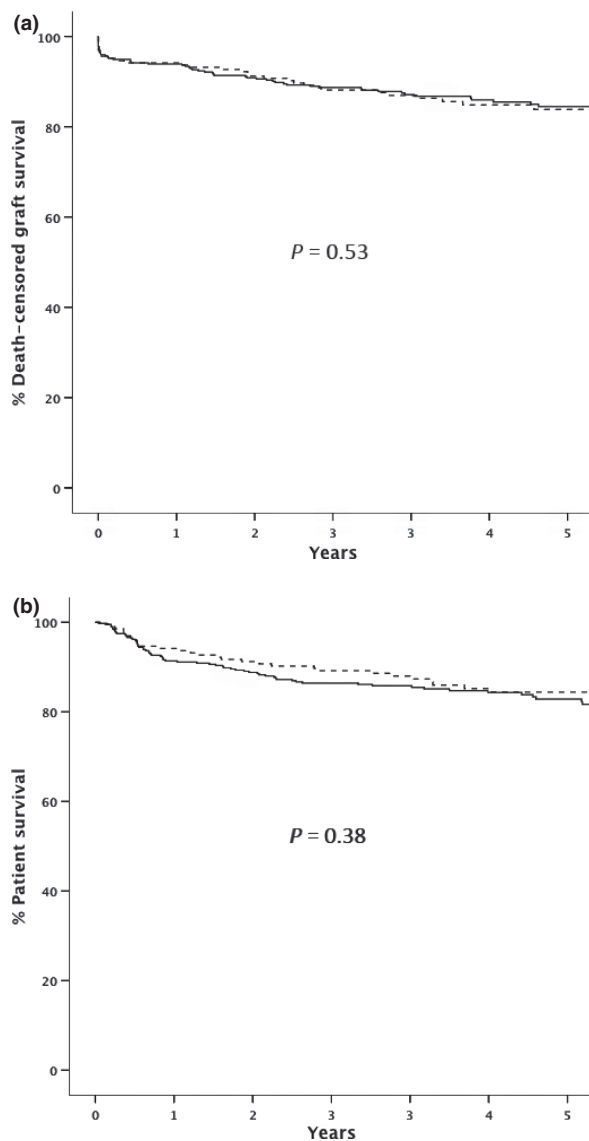


Figure 1 Kaplan–Meier survival estimated for gender-specific death-censored graft survival (a) and gender-specific overall patient survival (b). Females – dashed line; Males – solid line.

experience level significantly influenced VUR rates ($P = 0.001$). In multivariate analysis, the surgeon's experience level predicted the presence or absence of VUR. Cash *et al.* [25] evaluated the impact of surgeons' experience level on functional outcomes after renal transplantation and found no significant difference between experienced and inexperienced surgeons. However, their analysis did not include an evaluation of VUR.

The mechanism of gender-specific differences in VUR rates after transplantation remains unclear. We believe that in men, elevated reflux rates are associated with higher rates of postoperative voiding dysfunctions and urinary retention ($P = 0.004$). Tsaur *et al.* [26] reported incidences

of voiding dysfunctions in male transplant recipients of up to 27%. Hurst *et al.* [27] showed that acute urinary retention, recurrent UTIs, and the necessity of a transurethral resection of the prostate up to 3 years following transplantation were significantly associated with the presence of postoperative voiding dysfunctions.

As transplantation in the elderly has become part of the routine practice, rates of preoperative voiding symptoms particularly in male patients are also thereby increasing [28]. A trend toward an increased risk for VUR in male recipients might derive from increased intravesical pressure due to bladder outlet obstruction. In our cohort of patients with postoperative urinary retention, increased VUR rates in men with BPE were found (56.3% vs. 42.9% in general male cohort). As men are more likely to develop bladder outlet obstruction due to BPE, adequate evaluation and treatment of lower urinary tract symptoms prior to renal transplantation should be considered.

In our study, gender-mismatched transplant recipients did not show significantly different incidence rates of postoperative complications, including urinary leakage and stenosis, urinary retention, hydronephrosis, and UTIs. Nevertheless, it has been reported that graft survival can be improved by appropriate donor/recipient gender matching. Female recipients are known to show worse short-term but better long-term graft survival. According to the literature, male recipients of female donors have the poorest graft survival, which should be taken into account during clinical routine [29].

In female transplant recipients, UTIs represent frequent complications [12,30,31]. For infections, an adverse impact on renal allograft function has been postulated even in the absence of VUR [32,33]. Our data showed that the incidence of infections, both solitary ($P = 0.05$) and recurrent ($P = 0.03$), was more frequent in women, whereas the rate of febrile UTIs was not influenced by gender. Previous studies reporting higher rates of UTIs in transplant recipients compared with the nontransplanted cohort widely differ on the patient characteristics that increase the risk for developing post-transplant UTIs [12]. Erturk *et al.* [34] reported a high incidence of UTIs over a mean period of 54 months among transplant recipients with VUR history, but did not focus on gender aspects. Studies analyzing VUR into the transplanted kidney found no increased risk for UTI [20,35,36]. Our data are consistent with these data showing no association of the presence or absence of VUR with UTIs in both men and women. Furthermore, no potential negative effect of UTIs on long-term graft outcome or patient survival was found.

In contrast to the lower urinary tract, complications of the upper urinary tract were not influenced by recipient gender in our cohort of patients. No difference was seen in the incidence of ureteral leakage or stenosis, and

hydronephrosis rates were comparable in both genders ($P = 0.54$). The overall incidences of ureteral stenosis and leakage were 8.9% and 4.7%, respectively. These data are consistent with previous studies reporting incidence rates of 0–20% after renal transplantation [21]. Evaluation of long-term patient and graft survival revealed no gender-specific differences. The 1-, 3-, and 5-year renal function analysis showed equal results for both genders.

To the best of our knowledge, this study is the largest gender-specific evaluation of urological complication rates in renal transplant recipients. Nevertheless, we are aware that our study has some inherent limitations. These limitations include the retrospective character and that VUCG and ultrasonography were performed early after transplantation without the availability of follow-up exams.

In conclusion, men are at risk for developing postoperative urinary retention, whereas female patients are more likely to develop single and recurrent UTIs. In a multivariate model, gender was not a risk factor for VUR. However, VUR rates were significantly influenced by the surgeon's experience level, even though all patients underwent antireflux procedures for ureteral implantation. Upper urinary tract complications remain unaffected by recipient gender. Thus, male transplant recipients should undergo thorough evaluation of the lower urinary tract, whereas female patients should be routinely screened and consequently treated for UTIs to prevent recurrent infections and prolong graft longevity.

Authorship

AF: designed study, analyzed data, wrote the paper. GG: collected/analyzed data. FM: performed research, reviewed the paper. PH: performed research, reviewed the paper. GAB: collected/analyzed data, reviewed the paper. MM: designed study, collected/analyzed data, wrote the paper.

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