Ureteral strictures post-kidney transplantation: Trends, impact on patient outcomes, and clinical management

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Abstract

Introduction: Ureteral strictures post-kidney transplantation (KT) can be a significant morbidity to the patient, often requiring surgical intervention and impacting graft function. We sought to investigate the incidence, clinical management, and outcomes of ureteral strictures among kidney transplant recipients (KTRs) at a large, multiorgan transplant center.

Methods: We conducted a single-center cohort study looking at KTRs who had transplant surgery from January 1, 2005 to March 31, 2017 with at least one-year followup (n=1742). Any KTRs done outside of our center or simultaneous multiorgan transplants were excluded. The Kaplan-Meier product-limit method was used to determine the incidence of ureteral strictures. Risk factors for ureteric strictures and clinical outcomes among patients with vs. without ureteric strictures were analyzed using Cox proportional hazards models.

Results: The incidence of ureteral strictures was 1.31 (95% confidence interval [CI] 0.85, 2.01) per 100 person-years or a cumulative incidence of 1.2%. We did not find any donor or recipient demographic variables that were independently associated with an increased risk of ureteral stricture development. A large proportion was managed successfully with radiological intervention alone (47.6%). Ureteral strictures were associated with death-censored graft failure (hazard ratio [HR] 7.17, 95% CI 2.81, 18.30), total graft failure (HR 3.04, 95% CI 1.41, 6.59), and hospital re-admission (HR 2.52, 95% CI 1.58, 4.00).

Conclusions: Although uncommon, ureteral strictures can significantly impact patient outcomes after KT. A better understanding of risk factors and clinical management will be important to ensure optimal graft outcomes.

Introduction

Kidney transplantation (KT) is the treatment of choice for most patients with end-stage renal disease (ESRD), providing improved quality of life and increased life expectancy for most patients. Nevertheless, KT is a complex surgical procedure associated with postoperative complications that can reduce the intended benefits. Urological complications, such as obstruction and urine leaks, typically range in incidence from 3.4–10%,[1-6] with some studies reporting an incidence as high as 14–20%.[7,8] Aside from urinary tract infections, ureteral strictures are the most common urological complication following KT.[9] Reported incidences range from 0.5–6.8%,[2-5,9-19] and the majority of cases occur within three months post-KT.[14,17,20] Early cases are thought to be related to surgical technique of KT or ischemic fibrosis, whereas later cases are attributed to ureteral fibrosis or compression by the surrounding fibrotic tissue.[6]

Some reported risk factors for ureteral strictures include older donor age (>65 years), male recipient, kidneys with more than two arteries, delayed graft function, prolonged cold ischemia, fluid collections around the ureter, and BK virus infections.[11,16,17,21,22] There is disagreement regarding the role of surgical technique as a risk factor, with some studies reporting a link,[6,16,17,21] while others do not,[23] and this may be related to whether a refluxing or non-refluxing anastomosis technique is used.

There is also a lack of consensus regarding the best clinical management for these complications. Some studies report immediate open surgical repair (surgical reimplantation of the ureter) as the gold standard and optimal first line of treatment,[5,10,17,19,20] whereas other cohorts benefited more from minimally invasive treatments, such as percutaneous nephrostomy (PN) with balloon dilation.[11,14,24] Yet others report no significant differences in the success or negative outcomes between the two types of interventions, calling for a case-by-case approach.[16,25] Success rates of radiological interventions and surgical interventions seem to be comparable at 71–86% and 80%, respectively.[26] For ureteral strictures occurring after the first three months of KT, however, some studies show a reduced long-term success rate of radiological interventions — as low as 29%[21,26] to 50%.[6] A recent systematic review revealed success rates of 85.4% for open surgery, and 64.3% for radiological interventions, as primary treatments.[7] Among secondary treatments, open surgeries had a success rate of 93.1% vs. 75.5% of radiological interventions.[7] Moreover, among patients receiving surgical repair, 19% require additional intervention,[5] and there does not seem to be a significant difference in graft survival post-radiological or surgical treatment.[5]

Urological complications post-KT, such as ureteral strictures, can be associated with graft dysfunction and graft loss.[4] Ureteral strictures also have direct impacts on patient outcomes, particularly when surgical interventions are required,[27] putting patients at risk for postoperative complications. That said, timely detection and appropriate management of ureteral strictures may prevent graft loss.[16] Thus, it is imperative to improve the understanding and treatment of ureteral strictures post-KT. Importantly, there remains a lack of consensus surrounding important information, such as risk factors and best management practices, which warrant further investigation. We sought to address these gaps by determining the incidence and trends of ureteral strictures, as well as examining the risk factors, clinical management, and patient outcomes of ureteral strictures in a large, single-center cohort of kidney transplant recipients (KTRs).

Methods

Study design and population

A single-center, observational cohort study was conducted on adult KTRs (aged 18 and older) transplanted between January 1, 2005 and March 31, 2017 with a minimum followup of one year. Eight surgeons were involved in the program during the study dates and ureteric stents were routinely used for all cases during the study period. Patients were excluded if they had prior non-kidney transplants, simultaneous multiorgan transplants, or if their transplants were performed at other centers.

Data sources

Patient electronic medical records were reviewed for data abstraction from our institution's Organ Transplant Tracking Record and Electronic Patient Record systems and the Comprehensive Renal Transplant Research Information System.[28] This study received approval from our institution's research ethics board. Data was abstracted from clinical text documents and relevant diagnostic reports, such as Doppler ultrasound and biopsy reports. Adjudication of all suspected cases of ureteric strictures was performed by a transplant urologist (JYL).

Data analyses

In the first part of the analysis, ureteral strictures were examined as an outcome variable. Descriptive statistics were used to determine the incidence of ureteral strictures and trends over time. Baseline recipient, donor, and transplant factors were summarized as mean values (± standard deviation [SD]) for continuous variables. Categorical variables were reported as frequencies and percentages. The incidence of ureteral strictures within one-year post-transplant was reported as a person-time incidence rate and as a cumulative probability using the Kaplan-Meier (KM) product limit estimator.

The analysis of risk factor analysis for ureteral strictures was conducted using univariable and multivariable Cox proportional hazards models. Some risk factors examined include recipient age and sex, medical history (such as history of diabetes and vascular disease), number of arteries, delayed graft function, and induction type. An additional exploratory analysis was conducted to determine the effects of our center's trends in stent removal times on ureteral strictures, using univariable Cox models.

Trends in time to resolution of ureteral strictures were examined and reported as the median number of days, with interquartile ranges at the 25th and 75th percentiles. Time to resolution of ureteral strictures was separated by treatment type, i.e., radiological intervention alone vs. surgery after failed radiological intervention.

Clinical management of ureteral strictures was reported as percentages, stratified by donor type (living vs. deceased). Treatments typically employed at our center include standard ultrasound-guided PN, PN and balloon dilation (range 5–7 mm/15–21 Fr), and open surgical repair (either ureteral re-implantation or ureteroureterostomy using ipsilateral native ureter)

Ureteral strictures were also examined as an exposure variable in their relationship to clinical outcomes post-transplant. Clinical outcomes included death-censored graft failure, death with graft function, total graft failure (defined as a composite of the first two outcomes) and hospital readmissions within one-year post-transplant (defined as at least one overnight stay). The cumulative probabilities of the aforementioned clinical outcomes were examined using the KM product limit method. For univariable and multivariable analyses, Cox proportional hazards models were fitted to determine the association of ureteral strictures on post-transplant outcomes. Violations of the proportionality assumption were checked using log(-log(S(t))) plots and the interactions between the risk factors with time and Schoenfeld residuals. No important departures from proportionality were detected.

Missing values in the Cox proportional hazard models were imputed using multiple imputation.

All analyses were performed using Stata/MP, version 12.0.[29] A two-tailed p-value of <0.05 was considered statistically significant.

Results

Study population

After the application of the inclusion and exclusion criteria, the final study sample size was 1742 KTRs (Supplementary Fig. 1). Over half of the population was male (60.5%), white (61.2%), and a little less than half (46.3%) had a living donor. The mean recipient age was 51.3±13.4 years. The median followup time of KTR was one year. Of the KTRs with a deceased donor, 33.8% were expanded criteria donors (ECD). Table 1 shows the distribution of participant baseline characteristics.

Incidence and trends of ureteral strictures

The incidence rate of ureteral strictures within the first year post-KT among our cohort was 1.31 (95% confidence interval [CI] 0.85, 2.01) per 100 person years, with a cumulative probability of ureteral strictures over the first-year post-transplant of 1.2% (Supplementary Fig. 2). The total number of incident ureteral stricture cases was 21, the majority of which (61.9%) occurred within 3–6 months of KT (Supplementary Table 1). The vast majority of cases developed after KTRs were discharged from their transplant admission (95.2%). Incident cases were evenly distributed over the study cohort period, with five new cases (23.8%) occurring in 2016 (as compared to 1–3 cases per year during other years) (Supplementary Fig. 3).

An exploratory analysis examined proportions of ureteral strictures among the total number of transplants performed by each of our institution's surgeons. Proportions ranged from 0.0–0.5, with no significant trends across different surgeons (Supplementary Table 2).

Risk factors for ureteral strictures

Variables reported to be associated with greater risk for ureteral strictures in the literature, such as recipient age, male sex, number of arteries, and induction type, were not significantly associated with ureteral strictures among our cohort. Other risk factors explored, such as recipient race, body mass index, and history of diabetes or vascular disease, did not yield any associations (Supplementary Tables 3, 4). An exploratory univariable analysis on the effect of length of stents post transplant on the incidence of first ureteral strictures revealed a significant association (hazard ratio [HR] 1.06, 95% CI 1.05, 1.07).

Table 1. Baseline characteristics of study population at time of transplant

Variables	Number of transplants (n=1742)	Characteristics n (%)
Mean KTR age at transplant (years)	1742	51.3±13.4
Recipient sex		
Female	1053	689 (39.5%)
Recipient race		
Non-white	591	591 (38.8%)
White	931	931 (61.2%)
Recipient history of vascular disease		
No	1250	1250 (72.0%)
Peak PRA		
0%	840	840 (48.3%)
>0%	899	899 (51.7%)
Mean donor age at donation (years)	1733	47.4±14.5
Donor type		
Deceased (non-ECD)	619	619 (35.5%)
Deceased (ECD)	316	316 (18.1%)
Living	807	807 (46.3%)
Delayed graft function		
No	1363	1363 (78.2%)
Number of veins		
1	1604	1604 (94.0%)
>1	103	103 (6.0%)
Number of arteries		
1	1356	1356 (79.3%)
>1	355	355 (20.7%)
Mean cold ischemic time (deceased only) (hours)	867	10.9 (14.8, 7.9)
Induction type		
Non-depleting agent, e.g., basilixumab	424	424 (24.3%)
Depleting agent, e.g., ATG	1308	1308 (75.1%)

ATG: antithymocyte globulin; ECD: expanded criteria donors; KTR: kidney transplant recipients; PRA: panel-reactive antibodies.

Table 2. Treatment of ureteral strictures, separated by donor type

Donor type	Treatment categories				
	Perc nephrostomy only	Perc nephrostomy + balloon dilation only	Perc nephrostomy + surgery	Perc nephrostomy + balloon dilation + surgery	Total
Deceased	1 (9.09%)	5 (45.45%)	4 (36.36%)	1 (9.09%)	11 (100%)
Living	0 (0%)	4 (40.00%)	2 (20.00%)	4 (40.00%)	10 (100%)
Total	1 (4.76%)	9 (42.86%)	6 (28.57%)	5 (23.81%)	21 (100%)

Clinical management of ureteral strictures

While one patient had complete resolution of their stricture with nephrostomy tube (NT) alone, nine (43%) required a balloon dilation. Of these patients, four patients required two dilations. All five patients that had open surgical repair following NT only all had ureteral re-implantations, while two of the five patients that required open surgical repair following attempted interventional radiology management required ureteroureterostomy using the ipsilateral native ureter. Both patients requiring ureteroureterostomy had living donors. One patient that went on to have surgical repair following balloon dilation had only one attempted dilation, while the other four patients each had two attempts.

Among deceased donor KTRs with ureteral strictures (11), six cases (54.4%) were managed successfully with radiological intervention alone, whereas 45.4% required open surgery following unsuccessful radiological interventions. In contrast, 40% of living donor KTRs with ureteral strictures (10) were managed successfully with radiological intervention, while 60% needed surgery (Table 2).

Time to resolution of ureteral strictures

The median number of days to resolution of ureteral strictures with radiological intervention, which included multiple radiological interventions alone and multiple radiological attempts before going to surgery, was 128 (interquartile range [IQR] 90, 262). In contrast, the median number of days to resolution of cases resolved with open surgery after NT alone (i.e., no attempted balloon dilations) was 63 (IQR 43, 65). This difference in time to resolution was significant (p=0.003).

Clinical outcomes of ureteral strictures

Ureteral strictures were significantly associated with death-censored graft failure (HR 7.17, 95% CI 2.81, 18.30), total graft failure (HR 3.04, 95% CI 1.41, 6.59), and hospital re-admissions (HR 2.52, 95% CI 1.58, 4.00). Death with graft failure showed no associations with ureteral strictures in univariable (Figs. 1A–D) or multivariable (Table 3) models.

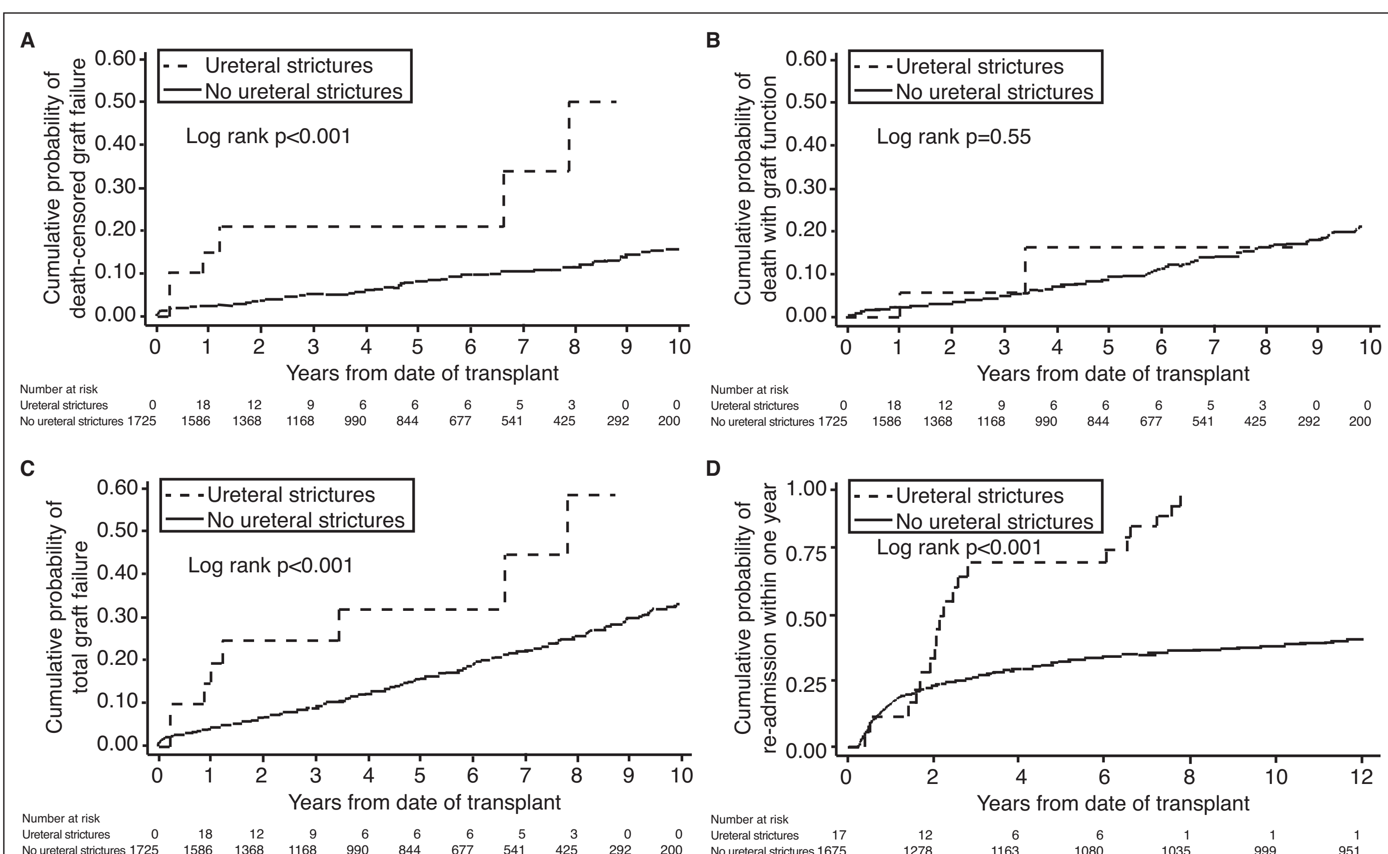

Fig. 1. Cumulative probability of ***(A)*** death-censored graft failure; ***(B)*** death with graft function; ***(C)*** total graft failure; and ***(D)*** hospital re-admissions; separated by presence/absence of ureteral strictures.

Table 3. Multivariable Cox proportional hazard models for the effects of ureteral strictures on clinical outcomes post-transplantation

	Transplant outcomes							
	Death-censored graft failure		Death with graft function		Total graft failure		Hospital re-admission	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Ureteral strictures (yes vs. no)	7.17 (2.81, 18.30)	<0.001	1.21 (0.29, 5.00)	0.79	3.04 (1.41, 6.59)	0.001	2.52 (1.58, 4.00)	<0.001

CI: confidence interval; HR: hazard ratio.

Discussion

Our center's incidence rate of ureteral strictures of 1.31 (95% CI 0.85, 2.01) per 100 person years (1.2% of all KTRs in the first year of followup), is comparable to that reported in the literature, which ranges from 0.5–6.8%. Most cases occurred within the first 3–6 months post-KT. Interestingly, commonly reported risk factors, such as the number of arteries and induction type, were not significantly associated with ureteral strictures in our cohort. Other baseline variables, such as recipient body mass index or medical history, did not show any associations either. This may suggest that surgical technique-related factors may play a bigger role. However, exploratory analysis showed no significant differences in the proportions of KTRs with ureteral strictures across our institution's KT surgeons.

There may exist variables that are either not well-captured or without the granularity required to discern risk factors associated with stricture development in our cohort of KTRs, such as length of ureter used, tissue handling technique, etc. In addition, other factors related to institutional practices may have contributed to the incidence. For instance, an exploratory analysis revealed a significant, positive association between the length of stent dwelling and the risk of ureteral strictures, with a 6% increase in risk per day post-transplant. This finding, while on univariable modelling only, may have implications for practice at our center.

Some studies do report lower rates of urological complications for earlier stent removal times of two weeks post-transplant.[4] At our center, it is standard for KTRs to have their stents removed at 4–6 weeks based upon availability of cystoscopy clinic time. Other factors that impacted this timeframe, however, include reasons such as missed appointments, development of urinary tract infection, or patient illness. We were unable to capture this granular data for each case in a valid manner, so could not provide analysis.

Descriptive statistics of clinical management practices at our center suggest almost half of all KTRs that develop ureteral strictures were successfully managed with interventional radiology (IR) alone. Given the lower morbidity of this management approach compared to surgical ureteric reimplantation, this likely represents a reasonable first option. This seems particularly true for deceased donor KTRs. Though the data is limited by the low overall event rate, the rate of successful IR intervention alone was 54.5% for deceased KTRs vs. 40% for living donor KTRs. In addition, while the event rate was too low to perform statistical analysis, both patients that required ureteroureterostomy repair after attempted balloon dilation (due to increased length of stricture that made simple ureteral reimplantation unfeasible) had living donors. These findings may relate to the increased dissection of the ureter that often occurs during living donor nephrectomy, due to the need for mobilization of the gonadal vessels.[3] This suggests that perhaps living donor KTRs that develop ureteral strictures might be best managed with early surgical repair. However, the small number of events among living donor KTRs do not permit definitive conclusions.

Another finding from our study was that the time to resolution was significantly different between cases requiring multiple IR interventions (including those that eventually proceeded to open surgery) compared to those resolved with open surgery after only one failed radiological intervention. This finding suggests using a more refined treatment algorithm whereby proceeding immediately to open reimplantation after only one failed IR intervention as opposed to multiple attempts at IR management of these strictures. However, given our low incidence, it is difficult to discern which patients would benefit most from an open vs. an IR intervention upfront.

Ureteral strictures post-KT were significantly associated with death-censored graft failure, total graft failure, and hospital re-admissions. There was no association between ureteral strictures and death with graft failure. These findings emphasize the opportunity for improved surveillance and more timely management of ureteral strictures. Importantly, a ureteral stricture could potentially be a marker of a poor-quality graft; whether it is inherent to the graft or the recipient, it is crucial to gain a better understanding of its development and possible prevention. Though the incidence is low, the development of ureteral strictures, and perhaps the approach to management, seem to impact patient outcomes.

Some limitations of our study include its single-center, retrospective design and the varied documentation of ureteral strictures in patients' medical records. However, our transplant patient population is one of the largest and most diverse cohorts in North America, allowing for generalizability of results. To combat the latter limitation, consultations were held with our center's transplant urologist to adjudicate cases. Another major limitation is the lack of granularity with respect to certain variables of interest. For patients managed with balloon dilations, various sizes of balloon dilators were used (15–21 Fr) but we did not have details on why these variations existed, as it was at the discretion of the interventional radiologist of the day. Also, while all surgeons used a refluxing technique for ureteral anastomosis during KT, granular details on length of ureter used, degree of tissue handling, and trauma were not available. These details could play a significant role in ureteral stricture formation.

Our study also only included one-year of post-KT followup for the outcome of ureteral strictures. KTRs that developed ureteral strictures more than one year from the time of KT were not captured in our analysis and so we are unable to characterize the incidence, risk factors, and management outcomes for those delayed presentations. Some of our analyses could not be done with multivariate models due to lack of events or data, warranting further research.

Recommendations for future research include more closely examining the effects of surgical technique on ureteral strictures. A comprehensive cost analysis of ureteral strictures may provide insight as to which interventions should be the first line of treatment and for which patient population. Finally, some studies have explored alternative forms of treatment, such as the thermo-expandable Memokath stent,[30] and surgical interventions using an artificial ureter.[26] It would be worthwhile to further explore these options in larger populations.

Conclusions

This large, single-center cohort of KTRs demonstrated that the incidence of ureteral strictures is low but that it can significantly impact patient and graft outcomes post-KT. While no clear risk factors were found in our cohort, surgical technique may have played a significant factor. While a large proportion of patients can be managed successfully with minimally invasive radiological procedures, a better understanding of which patients will ultimately require definitive open surgical repair is also imperative. Our data suggests living donor KTRs might be better managed with open repair, but further study is required.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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