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ORIGINAL ARTICLE

Trifecta outcome of ureteral reconstruction in iatrogenic injury and non-iatrogenic ureteral lesions: a 10-year experience at a tertiary referral center

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Abstract

Purpose To analyze the trifecta outcome (functional, anatomical, and surgical aspects) of surgical reconstruction for ureteral lesions and investigate the factors affecting the success rate of such reconstruction.

Methods We retrospectively reviewed the data of patients who underwent ureteral reconstruction at our institute between March 2007 and November 2016. Patient profiles, surgical methods, complications, ureteral stenting, laboratory data, and image studies were collected. The trifecta outcome was defined as preserved renal function, no progression of hydronephrosis, and no long-term stenting. The primary endpoint was the percentage of patients who achieved the trifecta outcome. The secondary endpoint was risk factors for trifecta outcome failure.

Results We retrospectively reviewed 178 adult patients who had undergone ureteral reconstruction. The median follow-up period was 37.4 months. In total, 70 (39.3%) patients had iatrogenic ureteral injuries and 108 (60.7%) patients had non-iatrogenic ureteral lesions. Overall, 70% of the patients achieved the trifecta outcome after ureteral reconstruction. A multivariate analysis revealed that risk factors for trifecta failure were malignant diseases [odds ratio (OR) 2.93, $p=0.005$], a history of pelvic radiation (OR 3.08, $p=0.032$), preoperative estimated glomerular filtration rate < 60 (OR 2.52, $p=0.039$), and a type of reconstruction ureteroureterostomy (OR 2.99, $p=0.014$).

Conclusions Trifecta outcome could be used to evaluate the ureteral reconstruction in iatrogenic injury and non-iatrogenic ureteral lesions. This study revealed several risk factors that affected the trifecta outcome.

Keywords Ureter · Iatrogenic injury · Reconstruction · Ureteroureterostomy · Ureteroneocystostomy

Ting-En Tai and Chung-Hung Hong contributed equally to this study.

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Abbreviations

CCr	Creatinine clearance
eGFR	Estimated glomerular filtration rate
IQR	Interquartile range
OR	Odds ratio
sCr	Serum creatinine
UU	Ureteroureterostomy
UNC	Ureteroneocystostomy

Introduction

Ureteral reconstruction is required under various circumstances. Benign ureteral disorders such as ureteral obstruction, ureteral stricture, retrocaval ureter, ureterocele, ureteral fistula, and vesicoureteral reflux require transection or resection of the ureter with further reconstruction or

reimplantation [1]. Surgeries for malignant diseases, such as urothelial carcinoma, gynecologic (e.g., ovarian, endometrial, or vaginal) cancers, huge pelvic tumors (e.g., sarcoma or gastrointestinal stromal tumors), and colorectal cancer invasion require en bloc tumor excision with segmental resection of the ureter. Sometimes, unintentional ureteral injuries resulting from surgical procedures such as gynecologic, colorectal, or even endoscopic urological procedures require reconstruction within 1 week or delayed repair after 12 months [2–5].

The type of ureteral reconstruction required largely depends on the location and length of defects. Short simple ureteral defects are treated with direct tension-free repair through ureteroureterostomy (UU), so long as the ureter is sufficiently long [1]. For distal ureteral injuries, ureteral reimplantation to the bladder is usually performed through ureteroneocystostomy (UNC) technique such as Politano–Leadbetter, Lich–Gregoir, or Cohen ureteral reimplantation. For longer distal and mid-ureteral defects, the bladder may be mobilized using an additional psoas hitch or Boari flap. In rare cases of long ureteral defects, ileal ureteral substitution or auto-transplantation is used for complex reconstructions. Although these techniques have been developed for decades, data from studies with large cohorts and comprehensive outcome assessments are scarce. Several studies havereported high success rates of 79%–95.8% with various surgical indications and outcome definitions [6–11].

The present study reviewed all patients who underwent ureteral reconstruction surgery at our institution between March 2007 and November 2016 with respect to the novel criteria of the trifecta outcome. In addition, we attempted to identify risk factors that affect the outcomes of ureteral reconstruction surgeries.

Patients and methods

The Institutional Review Board of National Taiwan University Hospital approved this study (IRB #201804005RIN). We retrospectively searched the electronic medical records at our institution for patients who underwent ureteral reconstruction between March 1, 2007 and November 31, 2016. The types of surgery included UU, UNC (Politano–Leadbetter, Lich–Gregoir, or Cohen ureteral reimplantation), and Boari flap. Follow-up data were obtained on December 1, 2017. We collected patient data, including clinical characteristics, underlying non-urological condition, causes of ureteral injury or obstruction, surgical methods, complications, ureteral stenting, perioperative laboratory data, and imaging studies. Accidental ureteral damage that required surgical repair was defined as iatrogenic injury, including complete ureteric transection, ureteral ligation, and total loss of a ureteral segment. Ureteral diseases that required a planned surgical intervention were defined as non-iatrogenic lesions, including stricture, tumor obstruction, and other ureteral diseases. Patients with incomplete data and those from the pediatrics department (< 18 years old) were excluded. The surgical principles and techniques were described in the Supplementary Material (Surgical Procedures).

Definition of the Trifecta Outcome

We analyzed the aforementioned data based on our definition of the trifecta outcome. First, functional outcomes were assessed based on perioperative serum creatinine (sCr) levels. Deterioration of renal function was defined as sCr >1.3 mg/dL and 20% elevation after surgery. Second, successful anatomical outcomes were those with no progression of hydronephrosis or kidney atrophy. Third, successful surgical outcomes were those with no redo surgical intervention, no internal stenting more than three months, and no external drainage. The primary endpoint was the percentage of patients who achieved the trifecta outcome. The secondary endpoint was to evaluate the independent factors for trifecta failure in ureteral reconstruction.

Statistical methods

All statistical analyzes were performed using SPSS version 22.0 (IBM Corp, SPSS Inc., Chicago, IL, USA). The Mann–Whitney *U* test and Student's *t* test were conducted to compare medians and means, respectively, between the patient groups. Contingency tables were constructed for comparisons by chi-squared test. A univariate and multivariate logistic regression was used for analyzing risk factors; factors with statistical significance ($p < 0.05$ in the univariate analysis) or clinical importance were selected for the multivariate model. All tests were two tailed. A $p < 0.05$ was considered significant.

Results

We retrospectively reviewed 187 adult patients who underwent ureteral reconstruction surgeries at our institution during the aforementioned study period. Nine patients were excluded because of incomplete follow-up. In total, 178 patients who had undergone ureteral reconstruction surgeries were enrolled in this study with a median follow-up period of 37.4 months [interquartile range (IQR) 13.4–56.9 months]. We observed 78 cases of UU, 75 cases of UNC with or without psoas hitch, and 25 cases of Boari flap.

In total, 70 (39.3%) patients had iatrogenic ureteral injuries, and 108 (60.7%) patients underwent non-iatrogenic ureteral reconstruction surgery. All patients in the iatrogenic group had severe ureteral damage that required surgical

repair, comprising cases of complete ureteric transection, ureteral ligation, and total loss of a ureteral segment. In the non-iatrogenic group, indications for ureteral reconstructions were ureteral stricture or obstructive uropathy in 61 (56.5%) patients, gynecologic or colorectal cancer invasion in 22 (20.4%) patients, ureteral urothelial carcinoma in 15 (13.9%) patients, retrocaval ureter in 4 (3.7%) patients, ureteral fistula in 4 (3.7%) patients, ureterocele in 1 (0.9%) patient, and vesicoureteral reflux in 1 (0.9%) patient.

Table 1 lists the clinical characteristics of 178 patients who underwent ureteral reconstruction in iatrogenic and non-iatrogenic conditions. Female patients were more predominant in the iatrogenic group than in the non-iatrogenic group (80% vs 51.8%, $p < 0.001$). Differences between the two groups were statistically nonsignificant in terms of laterality, length of injury, underlying diseases, or double-J stenting days. The iatrogenic ureteral injuries occurred mainly during gynecological and colorectal procedures, which accounted for 44 (62.9%) and 20 (28.6%) cases, respectively. The iatrogenic ureteric injuries involved more cases in lower ureter (84.3%) than non-iatrogenic injuries (64.8%).

Table 1 Clinical characteristics of 178 patients who underwent ureteral reconstruction in a single tertiary referral center between 2007 and 2016

	Type of ureteral disorders		*p* value
	Iatrogenic	Non-iatrogenic	
No. of patients	70	108	
Age at surgery (year, IQR)	53.6 (46.1–62.6)	52.1 (41.6–63.5)	0.186
Gender (no., %)			< 0.001
Male	14 (20%)	52 (48.2%)	
Female	56 (80%)	56 (51.8%)	
Laterality (no., %)			0.676
Left	29 (41.4%)	47 (43.6%)	
Right	37 (52.9%)	52 (48.2%)	
Bilateral	2 (2.9%)	2 (1.9%)	
Graft	2 (2.9%)	7 (6.5%)	
Sites of injury (no., %)			0.003
Upper	3 (4.3%)	24 (22.2%)	
Middle	8 (11.4%)	14 (13.0%)	
Lower	59 (84.3%)	70 (64.8%)	
Length of the injury (cm)	3.14	3.16	
Procedure (no., %)			0.824
Ureteroneocystostomy (UNC)	41 (58.6%)	64 (59.3%)	
Psoas hitch	16 (22.9%)	13 (12.1%)	
Boari flap	11 (15.7%)	14 (13.0%)	
Ureteroureterostomy (UU)	31 (44.3%)	46 (42.6%)	
Oncologic surgeries (no., %)			0.014
Benign	29 (41.4%)	65 (60.2%)	
Malignancy	41 (58.6%)	43 (39.8%)	
Underlying (no., %)			
Hypertension	11 (15.7%)	26 (24.1%)	0.179
Diabetes mellitus	4 (5.71%)	12 (11.1%)	0.219
Surgical specialty (no., %)			0.001
Urology	6 (8.6%)	75 (69.4%)	
Gynecology	44 (62.9%)	9 (8.3%)	
Colorectal	20 (28.6%)	23 (21.3%)	
Preoperative CKD stage			0.018
eGFR > 60 (mL/min/1.73m2)	63 (90%)	82 (75.9%)	
eGFR ≤ 60 (mL/min/1.73m2)	7 (10%)	26 (24.1%)	
DJ stenting (day, range)	69 (22–450)	61 (20–520)	0.112
Median hospital stay (day, range)	17 (7–88)	11 (3–87)	0.004

DJ double-J, *eGFR* estimated glomerular filtration rate, *UNC* ureteroneocystostomy, *UU* ureteroureterostomy, *N/A* not applicable

Table 2 lists the perioperative functional, surgical, and anatomical outcomes. No significant differences were found between the iatrogenic and non-iatrogenic groups in terms of renal function deterioration (7.1% vs 5.6%, $p = 0.667$), hydronephrosis progression (15.7% vs 8.3%, $p = 0.128$), or long-term stenosis rate (15.7% vs 24.1%, $p = 0.179$). The median sCr levels for presurgery and post-surgery in 1- to 2-year follow-up were within normal limits in both groups (Supplementary Table 1). Moreover, the perioperative trends of sCr were stable in the iatrogenic group (Fig. 1) and non-iatrogenic group (Fig. 2).

In the study cohort, 167 (93.8%) patients had stable or improved renal function, 158 (88.8%) had stable or improved hydronephrosis without kidney atrophy, and 141 (79.2%) were free from long-term ureteral stenting. Overall, 123 (70%) patients achieved the trifecta outcome after ureteric reconstruction surgeries. The detailed success rate of the trifecta, functional, anatomic, and surgical outcomes to all the individual categories are listed in Supplementary Table 2.

Table 2 Peri-operative surgical and functional outcomes of 178 patients

	Type of ureteral disorders		*p* value
	Iatrogenic	Non-iatrogenic	
No. of patients	70	108	
Follow-up months	41.4 (20.6–63.2)	34.9 (12.5–55.6)	0.163
Renal function deterioration			
No deterioration (no., %)	65 (92.9%)	102 (94.4%)	0.667
Deterioration (no., %)	5 (7.1%)	6 (5.6%)	
Hydronephrosis			
Stable or improved hydronephrosis (no., %)	59 (84.3%)	99 (88.8%)	0.128
Hydronephrosis progression (no., %)	11 (15.7%)	9 (11.2%)	
DJ stenting			
Free of stenting (no., %)	59 (84.3%)	82 (75.9%)	0.179
Long-term stenting (no., %)	11 (15.7%)	26 (24.1%)	
Trifecta outcome			
Failure	20 (28.6%)	35 (32.4%)	0.588
Success	50 (71.4%)	73 (67.6%)	

Trifecta outcome no renal function deterioration, no hydronephrosis progression, and free of stenting

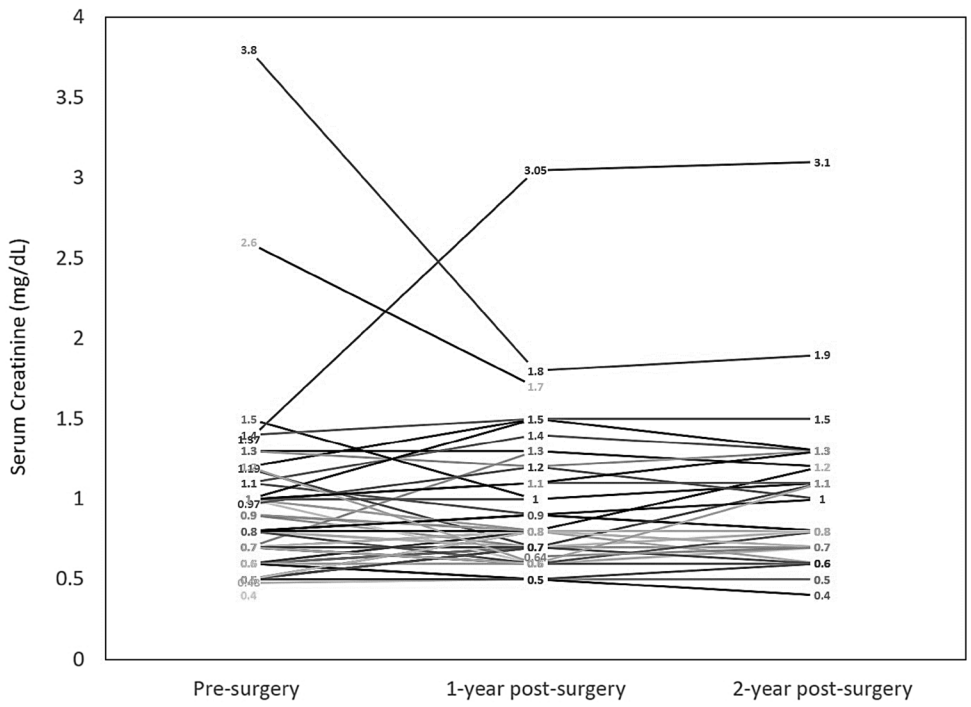

Fig. 1 Changes in sCr (mg/dL) from pre-surgery to 1 year post-surgery and then 2 years post-surgery in the iatrogenic ureteral injury group

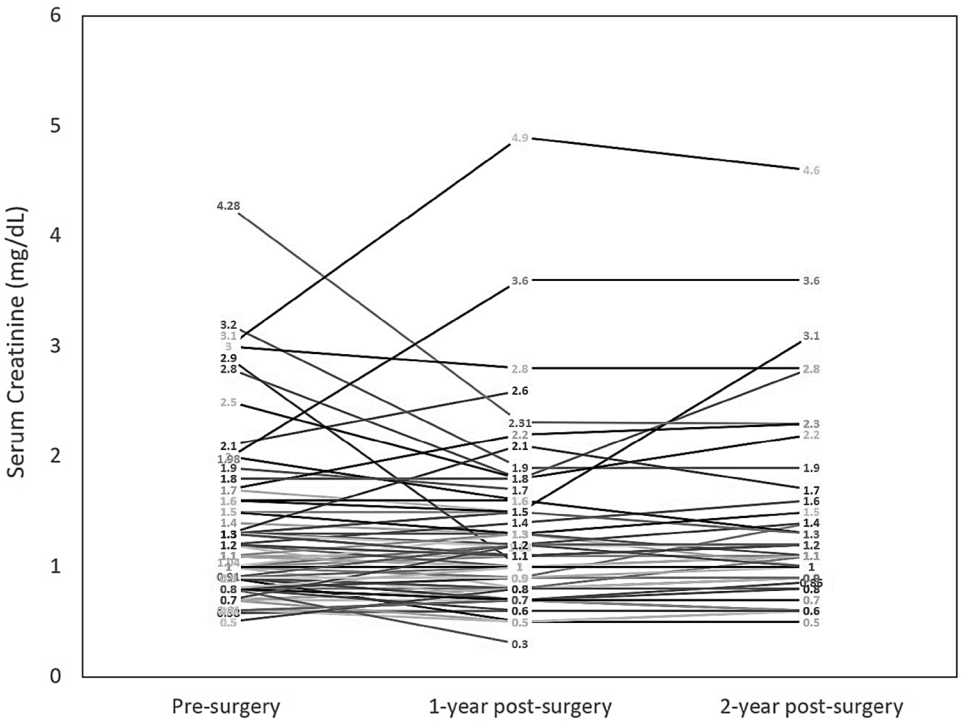

Fig. 2 Changes in sCr (mg/dL) from pre-surgery to 1 year post-surgery and then 2 years post-surgery in the non-iatrogenic planned ureteral surgery group

In the multivariate logistic regression analysis (Table 3), the risk factors for trifecta failure were malignant diseases [odds ratio (OR) 2.93, $p=0.005$], pelvic radiation (OR 3.08, $p=0.032$), preoperative estimated glomerular filtration rate (eGFR) < 60 mL/min/m^2 (OR 2.52, $p=0.039$), and UU (OR 2.99, $p=0.014$). Patients' age, laterality, length of defect, and sites of injury revealed no significant associations with treatment failure.

Discussion

This was one of the largest studies involving patients who had undergone ureteral reconstruction for iatrogenic ureteral injury or non-iatrogenic ureteral lesions. With the novel criteria of the trifecta outcome, the overall success rate for ureteral reconstruction was approximately 70%. Although many studies have reported higher success rates of 79–95.8%, the definition of success has varied among these studies, usually based on the assessment of hydronephrosis [6–10]. In our study, the percentage of patients without hydronephrosis progression was up to 88.8%, and that of patients without renal function deterioration was 93.8%. Achievement of the trifecta outcome was primarily affected by the surgical outcome, namely whether a long-term ureteral stent or external drainage was required, which accounted for 20.8% (37 of 178) of all patients.

The "trifecta" analysis was first mentioned to evaluate the outcomes of patients who had undergone radical prostatectomy [12]. The appreciation of attaining optimal three aspects has become more general, including long-term cancer control, recovery of sexual function, and continence of urinary bladder as an aggregate outcome. Similarly, we assumed that the success of ureteral reconstruction acknowledges three-pronged results, including preserved renal function, no progression of hydronephrosis, and no long-term stents placing. Each factor alone owned its limitations from a single aspect. A stable sCr might be the contribution of a contralateral kidney; the morphological change in hydronephrosis could only reflect a longer extent of obstruction in most cases. Thus, functional and anatomical failures were relatively insensitive. Although surgical success (free from re-intervention) had the most similar result to the trifecta, whether to take re-intervention was largely influenced by patient and physician preference, regardless of the actual outcome. Therefore, all these factors should be taken into consideration when evaluating the success of ureteral reconstruction. Missing any of these factors could result in an overestimation in the success rate (Supplementary Table 2).

Of the patients who had iatrogenic ureteral injury in our study, 71.4% achieved the trifecta outcome. Iatrogenic ureteric injuries have various causes such as ligation, partial or complete transection, thermal injury, and ischemia from devascularization of the ureter [13]. We noted that gynecological surgeries were the most common source of iatrogenic ureteral injuries; this finding was similar to that of previous studies [14] which have found that the lower third of the ureter is the most common site of injury [15].

Table 3 Univariate and multivariate logistic regression analyzes of trifecta failure

Variables	Case number	Failure events	Univariable analysis			Multivariable analysis		
						Model		
			OR	Range	*p* value	OR	Range	*p* value
Age	178	55	1.017	0.99–1.04	0.12	0.999	0.97–1.03	0.949
Gender								
Male	66	20	Ref.	–	–	–	–	-
Female	112	35	0.957	0.50–1.85	0.895	–	–	–
Laterality								
Right	89	28	Ref.	–	–	–	–	–
Left	76	25	3.672	0.43–30.8	0.231	–	–	–
Bilateral	4	1	3.922	0.46–33.1	0.209	–	–	–
Graft	9	1	2.667	0.12–57.6	0.532	–	–	–
Pelvic radiation								
No	159	45	Ref.	–	–	Ref.	–	–
Yes	19	10	2.815	1.07–7.38	0.035	3.082	1.11–8.59	0.032
Etiology								
Iatrogenic	70	20	Ref.	–	–	–	–	–
Non-iatrogenic	108	35	1.199	0.62–2.31	0.589	–	–	–
Underlying								
Benign	94	19	Ref.	–	–	Ref.	–	–
Malignancy	84	36	2.961	1.53–5.75	0.001	2.927	1.37–6.25	0.005
Preop renal function								
> 60 mL/min/m^2	145	40	Ref.	–	–	Ref.	–	–
≤ 60 mL/min/m^2	33	15	2.187	1.01–4.75	0.048	2.519	1.06–6.07	0.039
Length of the injury								
≤ 5 cm	143	42	Ref.	–	–	–	–	–
> 5 cm	35	13	1.421	0.66–3.08	0.374	–	–	–
Sites of injury								
Lower	93	36	Ref.	–	–	–	–	–
Middle	13	9	1.788	0.70–4.55	0.222	–	–	–
Upper	17	10	1.52	0.64–3.63	0.346	–	–	–
Type of surgery								
Lich–Gregoir	49	11	Ref.	–	–	Ref.	–	–
Politano–Leadbetter	28	7	1.152	0.39–3.42	0.799	1.646	0.52–5.22	0.397
Boari flap	26	7	1.273	0.43–3.81	0.666	1.499	0.46–4.90	0.502
Ureteroureterostomy	75	30	2.303	1.02–5.20	0.045	2.985	1.25–7.14	0.014

All patients in our non-iatrogenic group underwent transection and reconstruction of the ureter; 67.6% of these patients achieved the trifecta outcome. Resection of the ureter is essential in many situations, particularly in oncologic surgery and functional ureteral diseases. In oncologic surgery, direct ureteral invasion by gastrointestinal or gynecological cancer requires en bloc ureteral resection to avoid positive margin from the tumor. In patients with low-grade mid-ureteral or distal ureteral urothelial carcinomas, nephron-sparing treatments are available by segmental ureterectomy [16]. Occasionally, benign lesions located inside the ureter such as endometriosis [17], strictures [9], or fistulas [18] may require ureteral resection.

The first trifecta outcome was preserved renal function. Few studies have reported renal function alteration after ureteral reconstruction. In this study, renal function improved in 51.7% of the patients and remained stable in 42.1% of the patients. Only 6.2% of the patients exhibited renal function deterioration after ureteral reconstruction surgery. The renal function recovery rate was higher in the non-iatrogenic group (57.4%) than in the iatrogenic group (42.9%). Because most patients in the iatrogenic group (65.7%) were treated

with immediate repair during surgery, they did not experience obstructive uropathy before ureteral reconstruction. By contrast, the patients in the non-iatrogenic group exhibited inferior renal function at baselinecompared with those in the iatrogenic group. The percentage of preoperative hydronephrosis, which represents chronic obstruction, was higher in the non-iatrogenic group (69.4%) than in the iatrogenic group (35.7%). Nevertheless, both groups exhibited excellent outcomes after 1 year of follow-up. Most of our patients (93.8%) exhibited improved or stable renal function after ureteral reconstruction surgery.

Patients without chronic renal disease are more likely to recover from acute obstructive kidney injuries after relief of obstruction. Hamdi et al reported renal recovery after release of urinary tract obstruction in 79% of the patients-with severe postrenal acute kidney injuries [19]. Khalaf et al reported a preoperative eGFR of 10 mL/min/1.73 m^2 as a cutoff point to determine the optimal prediction of stabilization or improvement of renal function after obstruction relief [20]. In this study, patients with chronic kidney disease stage III–V exhibited a 2.38-fold increase in trifecta outcome failure (95% CI 1.01–5.59, $p = 0.047$).

The second trifecta outcome was no progression of hydronephrosis. Hydronephrosis was measured using the widely employed Society for Fetal Urology system [21]. Although the non-iatrogenic group had a higher rate of preoperative hydronephrosis than did the iatrogenic group (70.4% vs 35.7%, $p < 0.001$), the anatomical outcomes were excellent in both groups but were statistically nonsignificant (88.8% vs 84.3%, $p = 0.128$). Benson et al [22] revealed excellent anatomical outcomes in 83% of the patients who had undergone Boari flap based on the resolution of pre-existing hydronephrosis. Wenske et al reported hydronephrosis resolution in 81% of the patients who had undergone distal ureteral reconstruction [6].

The third trifecta outcome was no long-term stenting. Some studies have defined successful outcomes similar to those where no further intervention after ureteral reconstruction surgery is required [8, 11]. Indications for further intervention include ureteral stenosis, urine leakage, and ureteral necrosis. The common management approach is placing of long-term double-J stents to bypass the stricture site or external drainage caused by placing a percutaneous nephrostomy tube. Mauck et al. [8] reported overall long-term success rates without nephrectomy or recurrent stricture of 83% and 88% in patients who had undergone Boari bladder flap in the proximal third and distal two-thirds of the ureter, respectively. In this study, the patients in the iatrogenic and non-iatrogenic groups attained similar rates of successful outcomes (84.3% vs 75.9%, $p = 0.179$). However, we observed a high rate of surgical failure requiring further intervention in the patients who had undergone UU (29.5%) than in those who had undergone UNC (13.9%). In previous kidney transplantation studies, UU has been associated with higher rates of ureteral obstruction but lower rates of reflux and urine leakage [23, 24].

The present study revealed risk factors for trifecta failure, including malignant diseases, history of pelvic radiation, poor baseline renal function (creatinine clearance, CCr < 60), and reconstruction with UU. Other factors, including patient age, length of defect, and laterality, revealed no significant associations with trifecta failure. Underlying malignant diseases had the strongest influence on the study outcomes. Patients with cancer may have poor nutritional status, which can obstruct the healing process at the anastomosis site. A pelvic radiation therapy history also affects wound healing through tissue damage, devascularization, and necrosis [25, 26]. Patients with poor baseline renal function due to chronic ureteral obstruction have a higher likelihood of renal failure; even hydronephrosis resolution cannot improve renal function in such patients [6]. In other series, prior surgery, inflammation, and extensive tumor have been clearly identified as significant risk factors for repair failure [11, 27]. Among those patients who required a long-term ureteral stent or external drainage, patients who underwent UU had a higher rate of recurrent stricture. The overall success rates of the trifecta outcome for UU and UNC were 61.0% and 75.2%, respectively.

Our study had several advantages over previous studies, including a relatively large number of patients who had undergone ureteral reconstruction surgery, more comprehensive data with various aspects of outcomes, and a multivariate regression model to control for confounding factors. However, our study also had some limitations. First, the retrospective nature of this study generated intrinsic bias, and the patient characteristics were largely heterogeneous. Second, although the reconstruction surgeries described in this paper were performed by urologists, the urologists had varying levels of experience and used different techniques. Third, without diuretic nephrography use, which is heavily limited by the local health reimbursement system, split renal function and obstructive conditions could not be accurately evaluated. Fourth, some patients with low eGFR may have medical renal disease and would progress with a decrease in renal function despite a patent ureter. Finally, the follow-up time and frequency, lab data, and various imaging modalities were limitations that render drawing comparisons more difficult. A prospective study with a more homogenous cohort and standardized protocol is required to further investigate these factors of trifecta outcome in future.

In conclusion, the trifecta outcome could serve as an evaluation tool for all types of ureteral reconstructive surgeries. This study revealed that nearly 70% of the analyzed patients achieved the trifecta outcome in the iatrogenic injury and non-iatrogenic ureteral lesion groups, and the difference between the groups was statistically nonsignificant. Risk

factors for repair failure, including malignant diseases, history of pelvic radiation, poor preoperative renal function (CCr < 60), and a type of UU reconstruction, should be considered before surgical interventions are implemented.

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Authors' contribution CST: Project development, Data management, Data analysis, and Manuscript writing. TET: Project development and Data collecting. CHH: Data management. CHC: Data analysis and Manuscript editing. INC: Data analysis and Manuscript editing. YCL: Data analysis and Manuscript editing. SHH: Data collecting. KHH: Data analysis and Manuscript editing. CYH: Project development. HCC: Project development. YSP: Project development. PMC: Project development, Data analysis, Manuscript editing, and Manuscript writing.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For retrospective studies, formal consent is not required.

Research involving human participants and/or animals In accordance with the Helsinki declaration, approval of the chart review was obtained from the Institutional Review Board of National Taiwan University Hospital.

Informed consent The Institutional Review Board of National Taiwan University Hospital approved this study, including patient recruitment, chart review, informed consent, and all study methods.

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