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Long-term urinary tract effect of ileal conduit after radical cystectomy compared with bladder preservation: a nationwide, population-based cohort study with propensity score-matching analysis

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ABSTRACT

Objective Ileal conduit urinary diversion (ICUD) is the most common procedure after radical cystectomy. Although complications have been reported, few patients with ICUD and bladder preservation controls have been available for long-term follow-up. This study compared the long-term effect of structural changes after cystectomy with ICUD to that in bladder preservation controls.

Design A retrospective nationwide cohort study.

Setting Data retrieved from the Taiwan National Health Insurance Research Database.

Participants The National Health Insurance database was explored for patients diagnosed with bladder cancer between 1997 and 2006. Only cancer-free patients without chemotherapy and other types of urinary diversion who lived for >5 years were included in the analysis.

Outcome measures Patient characteristics, comorbidity and postoperative urinary tract disease were statistically analysed and compared. Cox proportional hazards model was used to evaluate the incidence rates of outcomes after adjustment for covariates. Propensity scores analysis was used to balance the clinical parameters between groups. The primary outcomes were postoperative new-onset urinary tract disease such as urinary tract infection (UTI), UTI with septicaemia and chronic kidney disease (CKD), or calculus of kidney and ureter.

Results There were 11 185 patients included in our cohort, among which 703 (6.3%) and 10 482 (93.7%) patients received ICUD and bladder preservation procedure, respectively. Compared with patients who only underwent a bladder preservation procedure, those who had undergone ICUD after cystectomy were independently associated with postoperative de novo urinary tract disease. Propensity score analysis (1:4) was also performed. ICUD contributed to significantly higher new-onset UTI, UTI with sepsis and CKD (HR=1.30, 3.16, 1.35, respectively) compared with bladder preservation procedure after adjustment for age, gender and comorbidities.

Conclusion ICUD after radical cystectomy was associated with a higher incidence of UTI, UTI with septicaemia and CKD during long-term follow-up than the incidences following a bladder preservation procedure.

Strengths and limitations of this study

- This is the first nationwide population-based cohort study to demonstrate the long-term urinary tract effect of ileal conduit after radical cystectomy compared with bladder preservation.
- Multivariable Cox proportional hazard model and a propensity score-matching study were conducted to identify the differences between ileal conduit urinary diversion and transurethral resection of bladder tumour groups.
- We obtained data from those patients with cured status and could therefore focus on the effect of urinary tract structure change without cancer-related effect.
- The nationwide database covers >99% of the Taiwanese population.
- These data may be less accurate than those from cases diagnosed in a prospective setting using standardised procedures, which is an inevitable weakness in all database research.

INTRODUCTION

Radical cystectomy is the current standard treatment for patients with muscle-invasive bladder cancer, offering substantial benefits in terms of cancer-specific survival.[1 2] Ileal conduit urinary diversion (ICUD) is the least complication-prone and most common procedure after radical cystectomy.[3] Several complications have been analysed in previous studies including urinary tract infection (UTI) as a common complication after cystectomy with urinary diversion.[4] Upper tract stones as well as calculi within the diversion segment[5]

and progressive decrease of renal function are noted in most patients during long-term follow-up after radical cystectomy.[6] One potential risk factor is the postoperative structural change of the urinary tract. The risk came from possible ureteroileal stricture, stomal stenosis, shortening of the upper urinary tract to the conduit and hydronephrosis. Previous studies have reported complication rates after ICUD but lack comparisons with bladder preservation controls.[7 8] In the real world, it is still not fully understood how much the risk of complications increases in patients undergoing cystectomy compared with those with preserved bladder; therefore, we designed a database study with bladder preservation control in patients cured for bladder cancer with sufficient follow-up duration to compare the long-term postoperative de novo diseases between the different structural conditions.

The result provides urological information about UTI/chronic kidney disease (CKD) risk, and this might be helpful when providing clinical consultation about bladder preservation treatment strategy or establishment of a UTI/CKD prevention protocol. The aim of this study was to analyse the long-term effects on the urinary tract through a comparison between radical cystectomy with ICUD and a bladder preservation procedure (transurethral resection of bladder tumour, TURBT) using data from a nationwide cohort in Taiwan.

MATERIALS AND METHODS

Database

The National Health Insurance Research Database (NHIRD) was used in this study; since 1995, this database has included all claims data provided by Taiwan's National Health Insurance (NHI) Scheme, a compulsory universal health insurance programme which covers the healthcare costs of virtually all Taiwanese residents except for prison inmates. The programme requires all medical institutions to use standard computerised claim documents for reimbursement of medical expenses and the database provides a great deal of information, including sex, birth dates, dates of admission and discharge, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure codes. The validity and clinical consistency of this database have been reported in many previous studies.[9] The NHIRD provides de-identified secondary data for research purposes; additionally, all personal identification information on files connected with the present study was scrambled using surrogate identification numbers to ensure patient confidentiality.

Study population

Figure 1 shows the flow chart of patient selection in this series. In the 10 years from 1 January 1997 to 31 December 2006, all in-patient data from the NHIRD and data on patients diagnosed with bladder cancer (188.xx) were collected for analysis. The end date of this cohort study was 31 December 2011.

Identification of the ileal conduit cohort

Those with first-time hospitalisations with an ICD-9 procedure code for radical cystectomy (57.71) during the study period were enrolled. In order to determine possible differences in long-term postoperative outcomes between ICUD and a bladder preservation procedure without cancer and disease recurrence-related effect, subjects with any cancer recurrences (198.1×) including urethral recurrence or cases of ureteral cancer (189.2), renal pelvis cancer (189.1), chemotherapy (99.25) or death within 5 years after surgery were excluded. Furthermore, subjects with end-stage renal disease (ESRD) (585.6), ileal neobladder (57.87), ureterocutaneostomy (56.61) and percutaneous nephrostomy (PCN) (55.03) were excluded from the cohort to avoid the interference of other types of urinary diversion. The remaining subjects after exclusion were enrolled as the ICUD group. The first day of follow-up was defined as the date of surgery.

Identification of the transurethral resection of bladder tumour cohort

All subjects who only underwent last TURBT (57.49) followed by cancer-free status (follow-up >5 years) during the study period were enrolled as the control group. The exclusion criteria were the same in this cohort. The first day of follow-up was defined as the date of surgery.

Patient and public involvement

This study used data from the NHIRD and patients were not involved in setting the research question or developing the outcome measures.

Covariates

Covariates included age, gender, cardiovascular disease, diabetes mellitus, hypertension, stroke, UTI, UTI with septicaemia, CKD, and calculus of kidney and ureter. Comorbidities, including cardiovascular disease (410–4.×, 420–9.×, 430–8.×, 440–9.×, 451–9.×), diabetes (250.×), hypertension (401–5.×), stroke (430–4.×), UTI (599.0, 590.1), CKD (582,585,586,587,588,590.0), and calculus of kidney and ureter (592.×) were determined by the discharge codes in hospitalisation records before surgery.

Outcome assessment

The endpoint of this study was postoperative new-onset urinary tract disease such as UTI, UTI with septicaemia (038), CKD, or calculus of kidney and ureter. Postoperative de novo diseases were defined as new-onset diseases recorded during our follow-up period started after the operation. These diseases were identified in subjects with new-onset discharge codes after surgery. Follow-ups were only censored when subjects expired on the date of outcome incidence or at the end of this study.

Statistical analysis

All data were analysed using SAS software, V.9.3 and R software, V.3.1.0. The χ^2 test and an independent *t*-test were used to assess differences in age, sex and comorbidities, and the Kaplan-Meier method was used to estimate

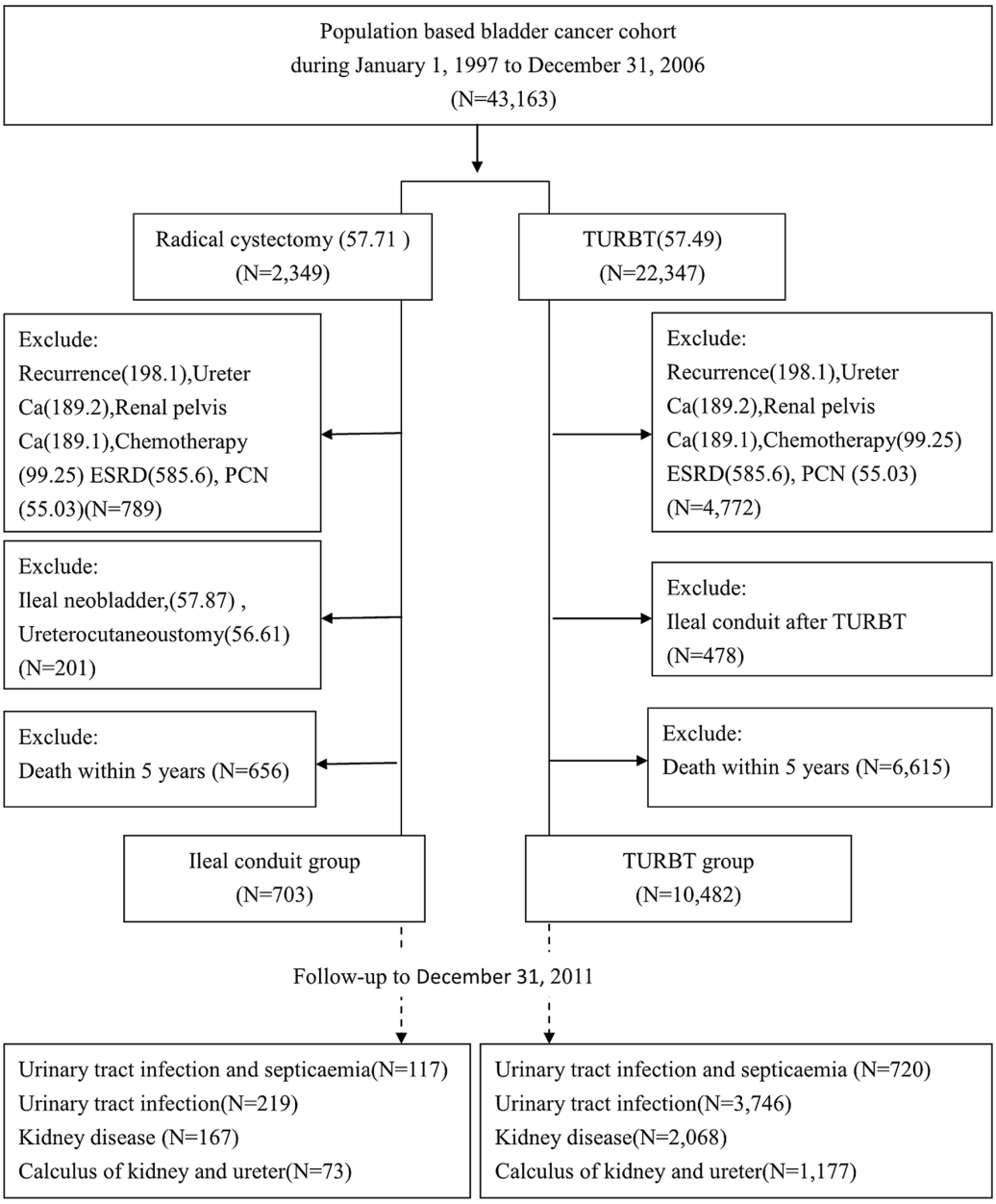

Figure 1 Flow chart of patient selection. ESRD, end-stage renal disease; PCN, percutaneous nephrostomy; TURBT, transurethral resection of bladder tumour; UTI, urinary tract infection.

the incidence rates of outcomes after surgery. A multivariable Cox proportional hazards model was used to calculate incidence rates of outcomes after adjustment for covariates. To avoid interference due to underlying susceptibility to observed disease, patients with preprocedure baseline UTI, CKD or urinary tract calculus were separately excluded from the assessment of new-onset UTI, CKD or urinary tract calculus while performing Kaplan-Meier or propensity score-matching analysis. We used 'patients at risk' to represent this group, defined as those without preoperative or new-onset UTI, CKD or urinary tract calculus. To reduce selection bias, we adopted propensity score matching to select the control group at a ratio of 1:4, and the paired groups were well balanced. The p values were recalculated. The risks of new-onset UTI, UTI with sepsis and CKD were compared, and the adjusted HR was calculated. A two-tailed p value of 0.05 was considered statistically significant.

RESULTS

In our analytical sample of 11 185 patients (2888 women; 26%), the mean age at baseline was 64.4 years (SD 12). Of these, 703 patients (173 women; 25%) were in the ICUD group and 10 482 (2715 women; 26%) were in the TURBT group (table 1). The median follow-up duration was 8.4 years in the ICUD group and 8.46 years in the TURBT group. Patients in the ICUD group were relatively younger and had a lower incidence of preoperative stroke than the TURBT group. In addition, the prevalence of

Table 1 Patient characteristics

	ICUD		TURBT		
Variables	n	%	n	%	P value
Total	703		10482		
Age group (years)					
Mean (SD)	62.61	(11.09)	64.48	(13.13)	<0.0001
<40	14	1.99	511	4.88	
40–49	91	12.94	1029	9.82	
50–59	154	21.91	1872	17.86	
60–69	256	36.42	2965	28.29	
70–79	164	23.33	3158	30.13	
80+	24	3.41	947	9.03	
Gender					
Female	173	24.61	2715	25.90	0.69
Male	529	75.25	7763	74.06	
Missing	1	0.14	4	0.04	
Comorbidities					
Cardiovascular disease	312	44.38	4943	47.16	0.15
Diabetes	147	20.91	2408	22.97	0.21
Hypertension	307	43.67	4772	45.53	0.34
Stroke	37	5.26	821	7.83	0.01
UTI	361	51.35	3973	37.90	<0.0001
UTI with septicaemia	8	1.14	53	0.51	0.03
CKD	173	24.61	1679	16.02	<0.0001
Calculus of kidney and ureter	214	30.44	2900	27.67	0.11

CKD, chronic kidney disease; ICUD, ileal conduit urinary diversion; TURBT, transurethral resection of bladder tumour; UTI, urinary tract infection.

new-onset UTI and CKD was higher in the ICUD group than in the TURBT group. Otherwise, gender and preoperative comorbidities were symmetrically distributed in both groups. Univariate analysis revealed differences in the risk of postoperative UTI, UTI with septicaemia and CKD between the groups (table 2). In a multivariable Cox proportional hazards model, new-onset UTI, UTI with septicaemia and CKD (all p<0.001, HR=1.49, 5.02 and 3.07, respectively) were significantly associated with ICUD (table 3). Kaplan-Meier plots showed that patients who had undergone ICUD had a significantly increased incidence of UTI, UTI with septicaemia and CKD compared with patients who had only undergone TURBT (p=0.01, p<0.001 and p<0.001, respectively; figures 2A–C). In this study, age, gender and preoperative comorbidities were adjusted using propensity score-matching analysis. After propensity score matching for the TURBT and ICUD groups, significantly more patients who had new-onset UTI or UTI with sepsis were present in the ICUD group than in the TURBT group (table 4). In the adjusted data, postoperative CKD occurred more frequently in the ICUD group than in the TURBT group (table 5). We also

Table 2 Univariate analysis revealed differences in the risk of postoperative UTI, UTI with septicaemia and CKD between ICUD and TURBT groups

Procedure	ICUD			TURBT			
Postop. disease	n	Subjects at risk	(%)	n	Subjects at risk	(%)	P value
UTI	219	342	64.04	3746	6509	57.55	0.02
UTI with septicaemia	117	695	16.83	720	10429	6.90	<0.0001
CKD	167	530	31.51	2068	8803	23.49	<0.0001
Calculus of kidney and ureter	73	489	14.93	1177	7582	15.52	0.72

CKD, chronic kidney disease; ICUD, ileal conduit urinary diversion; TURBT, transurethral resection of bladder tumour; UTI, urinary tract infection.

Table 3 Multivariable Cox proportional hazard model showed new-onset UTI, UTI with septicaemia and CKD were significantly associated with ICUD

Postop. disease	UTI		UTI and septicaemia		CKD		Calculus of kidney and ureter	
Variables	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
ICUD/TURBT	1.49 (1.29 to 1.71)	<0.0001	5.02 (4.05 to 6.23)	<0.0001	3.07 (2.60 to 3.62)	<0.0001	1.16 (0.91 to 1.48)	0.24
Age	1.01 (1.01 to 1.01)	<0.0001	1.04 (1.03 to 1.05)	<0.0001	1.01 (1.01 to 1.02)	<0.0001	0.99 (0.99 to 1.00)	0.003
Female	1.39 (1.29 to 1.50)	<0.0001	1.38 (1.19 to 1.60)	<0.0001	1.02 (0.93 to 1.13)	0.66	0.95 (0.84 to 1.09)	0.48
Preop. comorbidities								
UTI	–	–	–	–	0.99 (0.90 to 1.09)	0.83	1.07 (0.95 to 1.21)	0.28
Stroke	1.09 (0.96 to 1.24)	0.19	1.35 (1.07 to 1.69)	0.01	0.93 (0.79 to 1.09)	0.38	0.91 (0.71 to 1.16)	0.44
CKD	0.83 (0.75 to 0.92)	0.0003	0.82 (0.68 to 1.00)	0.05	–	–	0.69 (0.57 to 0.83)	<0.0001
Calculus of kidney and ureter	1.17 (1.08 to 1.26)	<0.0001	1.10 (0.94 to 1.29)	0.24	1.04 (0.94 to 1.15)	0.48	–	–
Cardiovascular disease	1.07 (0.99 to 1.16)	0.07	0.99 (0.84 to 1.17)	0.91	0.92 (0.84 to 1.02)	0.11	1.11 (0.97 to 1.27)	0.13
Diabetes	1.03 (0.95 to 1.16)	0.45	1.17 (0.99 to 1.37)	0.06	0.96 (0.87 to 1.07)	0.49	0.68 (0.58 to 0.80)	<0.0001
Hypertension	1.01 (0.94 to 1.09)	0.73	1.12 (0.95 to 1.31)	0.18	1.20 (1.09 to 1.35)	0.0002	0.94 (0.82 to 1.07)	0.33

CKD, chronic kidney disease; ICUD, ileal conduit urinary diversion; TURBT, transurethral resection of bladder tumour; UTI, urinary tract infection.

compared patients with new-onset diseases during the follow-up period within and after 90 days of operation. Table 6 lists the comparison of new-onset UTI and CKD within 90 days after surgery between TURBT and ICUD groups. Patients with ileal conduit had significantly higher risk of 90-day postoperative CKD (OR 4.63, 95% CI 2.20 to 9.74, p<0.001), whereas there was no significant difference in the risk of 90-day postoperative UTI (p=0.37). As seen in table 7, compared with patients with bladder preservation, patients with ICUD had significantly higher risks of developing postoperative de novo diseases after 90 days of operation including UTI (OR 1.53, 95% CI 1.18 to 1.99, p<0.05) and CKD (OR 1.35, 95% CI 1.09 to 1.67, p<0.05).

DISCUSSION

ICUD is the most common surgical intervention after radical cystectomy for muscle-invasive bladder cancer. This procedure carries acceptable perioperative complications and is commonly performed worldwide according to the literature.[3] However, the long-term urinary tract health effects related to urinary tract structural changes have been reported in few studies, and the results were not compared with those following a bladder preservation procedure.[7 8] Long-term follow-ups with adequate patient numbers and well-designed control groups would provide results useful for the development of follow-up protocols and perioperative counselling.

This study included patients without upper urinary tract or systemic urothelial cancer recurrence, who had lived >5 years following intervention or surgery. Other types of urinary diversion performed during the study period were excluded. Patients who had received chemotherapy and had hydronephrosis requiring PCN were also excluded to avoid potential bias caused by adverse effects on the urinary tract, as were patients with ESRD and no need of urinary diversion. Therefore, only patients cured for bladder cancer with sufficient follow-up duration and without other factors that affected the urinary tract were enrolled in this long-term observational study on the incidence of urinary tract disease associated with ICUD compared with TURBT.

Patients who had undergone ICUD had a higher incidence of UTI and UTI with septicaemia during long-term follow-up. The major concern following ICUD is the potential for bacterial colonisation of the intestinal conduit. However, asymptomatic bacterial tolerance is common in patients who have undergone ICUD.[10 11] Although the incontinent design of the ileal conduit reduces the pressure in the urinary reservoir, urinary reflux is still common and pressure-independent.[12] Such urinary diversion methods may still carry a higher risk of bacterial migration and UTI compared with that in a normal urinary bladder reservoir during long-term observation. The ICUD increases the risk of UTI with septicaemia about fivefold, and the mortality rate of septicaemia increases with age.[13] Perioperative prophylactic antibiotic

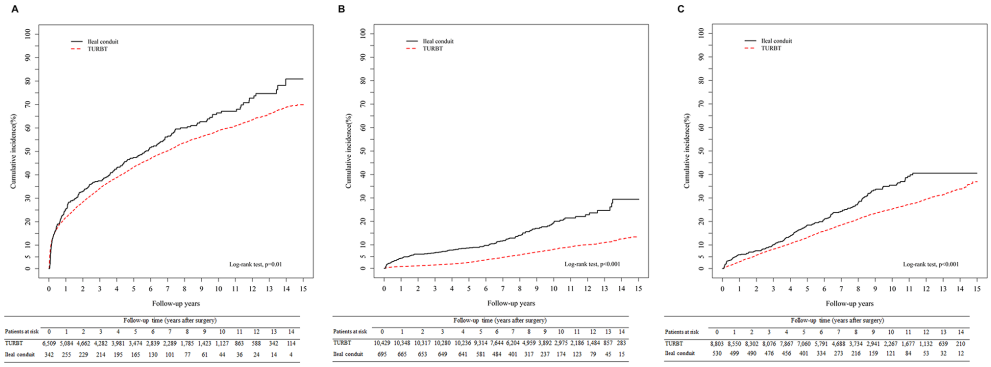

Figure 2 Cumulative incidence of UTI (A), UTI with septicaemia (B) and CKD (C). CKD, chronic kidney disease; UTI, urinary tract infection.

treatment has been proven to be effective.[14] According to our observations, prophylactic antibiotic treatment or regular monitoring of the amount or species of bacteria in the ileal conduit should be considered to prevent fatal complications.

Surgeons have developed many methods of urinary diversion after radical cystectomy. The incontinent urinary conduit is thought to be correlated with less renal scarring compared with continent urinary diversion.[15] However, Samuel *et al* reported deterioration of renal function in patients who had received an ileal conduit.[16] The incidence of impaired renal function increases with age and the number of comorbidities.[17–19] This study further confirmed a threefold increased incidence of CKD in patients who underwent ICUD compared with that in a bladder preservation control group. It is likely that repeated and severe upper UTI will cause renal scarring, even with incontinent urinary diversion, as confirmed in this study. CKD results in a higher incidence of all-cause mortality according to a

Table 4 Patient demography of new-onset UTI after propensity score 1:4 matching

	ICUD	TURBT		
A	**(n=341)**	**(n=1364)**		
Variables	**n (%)**	**n**		**P value**
Age (means, SD), years	61.53 (11.53)	61.48 (11.61)		0.95
Gender				
Female	73 (21.41)	279 (20.45)		0.82
Male	268 (78.59)	1084 (79.47)		
Preop. comorbidities				
Stroke	14 (4.11)	76 (5.57)		0.28
CKD	78 (22.87)	170 (12.46)		<0.0001
Calculus of kidney and ureter	73 (21.41)	328 (24.05)		0.30
Cardiovascular disease	116 (34.02)	506 (37.10)		0.29
Diabetes	68 (19.94)	272 (19.94)		1.00
Hypertension	128 (37.54)	503 (36.88)		0.82
B. Risk of UTI after propensity score matching				
Variables	**Events**	**HR**	**(95% CI)**	**P value**
TURBT	760/1,364	1.00		
ICUD	218/341	1.30*	1.11–1.51	0.001
C. Risk of UTI and sepsis after propensity score matching				
Variables	**Events**	**HR**	**(95% CI)**	**P value**
TURBT	77/1,360	1.00		
ICUD	53/340	3.16*	2.22–4.50	<0.001

*Adjusted for CKD.
CKD, chronic kidney disease; ICUD, ileal conduit urinary diversion; TURBT, transurethral resection of bladder tumour; UTI, urinary tract infection.

Table 5 Patient demography of new-onset CKD after propensity score 1:4 matching

A	ICUD (n=530)	TURBT (n=2120)	
Variables	**n (%)**	**n (%)**	**P value**
Age (means, SD), years	63.52 (10.94)	63.87 (11.52)	0.52
Gender			
Female	96 (18.11)	472 (22.26)	0.81
Male	433 (81.70)	1647 (77.69)	
Preop. comorbidities			
UTI	266 (50.19)	731 (34.48)	<0.0001
Stroke	25 (4.72)	133 (6.27)	0.18
Calculus of kidney and ureter	163 (30.75)	564 (26.60)	0.06
Cardiovascular disease	204 (38.49)	904 (42.64)	0.08
Diabetes	102 (19.25)	375 (17.69)	0.40
Hypertension	205 (38.68)	832 (39.25)	0.81

B. Risk of CKD after propensity score matching

Variables	Events	HR	(95% CI)	P value
TURBT	515/2,120	1.00		
ICUD	167/530	1.35*	1.13–1.61	0.001

*Adjusted for UTI.
CKD, chronic kidney disease; ICUD, ileal conduit urinary diversion; TURBT, transurethral resection of bladder tumour; UTI, urinary tract infection.

large cohort study.[20] Prevention of factors predisposing to CKD in patients with ICUD might help prolong the postoperative life span.

There are several limitations to this study. First, only the ICD-9-CM codes could be obtained from the Taiwan NHIRD, and the lack of detailed lab data prevented confirmation of disease severity. In addition, data on stone composition and bacterial cultures were not available. Detailed perioperative factors such as patients' body mass index and length of the ileal conduit might differ among medical centres. In the TURBT group, the data of malignant involvement of ureteral orifice and administration of intravesical instillation were not available. Thus, data on the increased associations of UTI, UTI with septicaemia and CKD in patients with ICUD could not be used to determine a causal relationship; however, we tried to explore the effect of ICUD and possible subsequent comorbidities by excluding patients with similar disease codes before surgical intervention. This would avoid interference due to disease susceptibility and would only identify postoperative de novo UTI, UTI with septicaemia and CKD. We also created propensity score-matched pairs to obtain a more objective outcome analysis. Second, asymmetric baseline characteristics such as preoperative stroke and UTI in the study group reflect the real-world situation. It is reasonable that patients who had undergone bladder preservation procedures were older and had more preoperative comorbidities. Patients with higher operative risk tend to be managed with more conservative methods. Therefore, this study further examined the effects of ICUD using a multivariable Cox regression model. In addition, propensity score-matching analysis was performed to overcome the weakness of asymmetric baseline characteristics. Third, the severity of bladder cancer could not be precisely extracted from ICD-9-CM codes, and further, the database does not contain information on immunosuppressive or nephrotoxic agent use, tobacco use, dietary habits, carcinogen exposure and BMI, which may also be risk factors for bladder cancer. Finally, most of our study subjects were ethnic Taiwanese, and the generalisability of our results to other ethnicities needs to be confirmed.

The major advantage of this study is its monopolistic feature, with an extremely high coverage rate of >99%

Table 6 Risk of new-onset disease within 90 days after propensity score matching

A. Risk of UTI within 90 days after propensity score matching

Variables	Events	OR	(95% CI)	P value
TURBT	168/1,364	1.00		
ICUD	47/341	1.17*	0.83 to 1.67	0.37

B. Risk of CKD within 90 days after propensity score matching

Variables	Events	OR	(95% CI)	*P* value
TURBT	14/2,120	1.00		
ICUD	15/530	4.63*	2.20–9.74	<0.0001

*Adjusted for UTI.
CKD, chronic kidney disease; ICUD, ileal conduit urinary diversion; TURBT, transurethral resection of bladder tumour; UTI, urinary tract infection.

Table 7 Risk of new-onset disease after 90 days after propensity score matching

A. Risk of UTI after 90 days after propensity score matching

Variables	Events	OR	(95% CI)	P value
TURBT	592/1196	1.00		
ICUD	171/294	1.53*	1.18 to 1.99	0.002

B. Risk of CKD after 90 days after propensity score matching

Variables	Events	OR	(95% CI)	P value
TURBT	501/2,106	1.00		
ICUD	152/515	1.35*	1.09–1.67	0.01

*Adjusted for UTI.
CKD, chronic kidney disease; ICUD, ileal conduit urinary diversion; TURBT, transurethral resection of bladder tumour; UTI, urinary tract infection.

of the population, yielding a unique system that finances healthcare for the entire population and offers unrestricted access to any healthcare provider. Therefore, few patients are lost to follow-up in this nationwide representative cohort.

CONCLUSIONS

This study, using an all-inclusive national cohort, found that ICUD is significantly associated with UTI, UTI with septicaemia and CKD compared with bladder preservation (TURBT only) during long-term observation. Increased effort is required to ensure early bladder cancer detection or develop a bladder preservation treatment protocol. This result provides information for perioperative counselling and monitoring when radical cystectomy is inevitable.

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