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ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

Acute Kidney Injury After Radical Cystectomy for Bladder Cancer is Associated with Chronic Kidney Disease and Mortality

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ABSTRACT

Purpose. The aim of this study was to investigate the prevalence of acute kidney injury (AKI) after radical cystectomy, and evaluate its impact on chronic kidney disease (CKD) and mortality.

Methods. The medical records of 866 patients who underwent radical cystectomy for bladder cancer were reviewed. AKI was assessed within 7 days after surgery according to the Acute Kidney Injury Network criteria. The prevalence of AKI after surgery was examined, and the significance of AKI for CKD and mortality was analyzed.

Results. Of 866 patients, 269 (31.1 %) developed AKI in the first week after surgery. Of these, 231 (85.9 %) were at stage 1, 32 (11.9 %) at stage 2, and 6 (2.2 %) at stage 3. Of 722 patients with a preoperative Modification of Diet in Renal Disease estimated glomerular filtration rate (eGFR) of >60 ml/min/1.73 m^2, CKD developed in 23.0 % (118/513) of patients in the non-AKI group and 32.5 % (68/209) of patients in the AKI group. Independent factors predicting new-onset CKD were a preoperative eGFR ($p < 0.001$), age ($p = 0.011$), urinary tract complication ($p < 0.001$) and AKI ($p = 0.015$). In all, 297 patients died (191 in the non-AKI group and 106 in the AKI group). AKI also correlated significantly with overall survival ($p = 0.001$).

Conclusions. AKI is not only commonly encountered after radical cystectomy but is also associated with higher CKD rates and mortality. There is a critical need for strategies to increase the identification of patients at risk of postoperative AKI, and to improve the management of patients, with an aim toward preventing AKI and improving the treatment of AKI once it occurs.

Radical cystectomy combined with urinary diversion (UD) has become a standard surgical procedure for patients with muscle invasive bladder cancer and a high risk of non-muscle invasive disease;[1,2] however, this invasive surgical procedure is associated with the risk of developing complications.[3,4] A deterioration in renal function is one of the most important adverse events associated with radical cystectomy and UD. Special attention should be paid to this loss of function by putting patients under long-term observation because a number of recent studies have clearly shown a significantly higher risk of progression to renal failure, cardiovascular disease, and mortality in patients developing chronic kidney disease (CKD).[5,6]

To date, various studies have evaluated renal function in patients who undergo radical cystectomy with subsequent UD, and multiple factors possibly involved in the development of postoperative renal impairment have been suggested, including age-related changes, patient comorbidities, additional treatment with nephrotoxic chemotherapeutic agents, urinary tract obstruction, and other postoperative complications.[7–9]

Acute kidney injury (AKI), defined as an acute rise in serum creatinine levels, commonly occurs in surgical patients and has a detrimental impact on patient outcome. In fact, AKI is associated with high cost, lengthy hospital stays, and high mortality.[10–12] Even minimum increases in postoperative creatinine are correlated with augmented 30-day mortality.[13] A meta-analysis also showed that the occurrence of AKI is correlated with an increased risk of late mortality.[13,14] The clinical characteristics and impact of AKI in cardiac surgery have been extensively studied and most of the published data regarding AKI in the non-

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cardiac surgery population are limited to high-risk aortic procedures.[15,16] Only a few studies have addressed AKI after non-cardiac and non-vascular surgery, which has a pathophysiology that is distinct from that after cardiac and vascular surgery.[17,18] Moreover, while the perioperative and long-term renal functional outcomes after radical cystectomy have been explored,[7,8,19] it remains unclear whether the prevalence of AKI after radical cystectomy for bladder cancer affects the prognosis. Therefore, we investigated the prevalence of AKI after radical cystectomy, and evaluated its impact on CKD and mortality.

MATERIALS AND METHODS

Study Participants

This study protocol was performed with the oversight and approval of the Institutional Review Board of our institute, and the requirement for informed consent was waived due to the retrospective design of the study. The medical records of 905 consecutive patients who underwent radical cystectomy for bladder cancer between 1990 and 2012 were retrospectively reviewed. The 20 patients receiving neoadjuvant chemotherapy or radiotherapy were excluded. In addition, 19 patients who were not receiving UD because of end-stage renal disease were excluded. Finally, a total of 866 patients who underwent radical cystectomy with UD for bladder cancer were involved in our study. Patient demographics and clinical information were collected. A preoperative chest X-ray, computerized tomography of the abdomen and pelvis, and a bone scan for disease staging were performed for all patients. No patient showed evidence of metastatic disease on physical examination or staging.

Surgical Procedures and Pathological Evaluation

Radical cystectomy and UD were performed by three senior surgeons (CSK, BH and HA), as previously described in detail.[20] UDs, including orthotopic bladder substitution and ileal conduit diversion, were performed following radical cystectomy and bilateral pelvic lymphadenectomy.[21] All surgical specimens were processed according to standard pathological procedures. Genitourinary pathologists assigned a tumor grade according to the 2004 WHO grading system,[22] and pathological stage was reassigned according to the 2010 American Joint Committee on Cancer tumor node metastasis (TNM) staging system.[23] Lymphovascular invasion was defined as the unequivocal presence of tumor cells in an endothelium-lined space without underlying muscular walls.[24]

Follow-Up

After radical cystectomy, patients were generally followed up every 3 months during the first year, every 6 months during years 2–6, and annually thereafter. The follow-up consisted of noting patient medical history and performing a physical examination, blood laboratory investigations, urine sedimentation, culture, and cytology. Imaging studies included chest radiography, computed tomography of the abdomen and pelvis, and bone scanning, all of which were carried out 6 and 12 months postoperatively and annually thereafter. All available serum creatinine data were reviewed, and the largest increase in serum creatinine within 7 days postoperatively was used for the diagnosis and staging of AKI based on the Acute Kidney Injury Network (AKIN) criteria (Table 1).[7] We chose to use the AKIN criteria as our outcome for AKI because of its more commonly recognized and increased sensitivity compared with the other criteria.[25,26] The median follow-up duration of renal function and survival was 49.8 months (range 1–231.4) and 62.1 months (range 1–231.4), respectively.

Statistical Analysis

Clinicopathological features in patients with AKI after surgery and those without AKI were compared using Pearson's χ^2 test for categorical variables and Student's *t* test for continuous variables. Quantitative data are expressed as the mean ± standard deviation. Postoperative new-onset CKD (maintained estimated glomerular filtration rate [eGFR] $\leq$60 ml/min/1.73 m^2 after surgery) was assessed using a logistic regression model in patients with preoperative eGFR in the normal range. The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation.[27] To verify the difference in mean serum creatinine during the follow-up period in patients with or without postoperative AKI, data were

TABLE 1 Criteria for the diagnosis of acute kidney injury based on the Acute Kidney Injury Network

Stage	sCr criteria	Urine output criteria
1	Increased sCr $\geq$0.3 mg/dl or increase for $\geq$150–200 %	<0.5 ml/kg/h in >6 h
2	Increased sCr for >200–300 % basal value	<0.5 ml/kg/h in >12 h
3	Increased sCr for >300 % basal value, or sCr $\geq$4.0 mg/dl with an acute increase of at least 0.5 mg/dl	<0.3 ml/kg/h in 24 h, or anuria for 12 h

sCr serum creatinine

assessed annually. Overall survival (OS) was the time of diagnosis to death from any cause. Survivors were censored at the date of last contact. Kaplan–Meier survival curves to estimate OS were generated and compared using the log-rank test, and a Cox proportional hazards model was used to estimate the prognostic significance of each variable. The correlations between outcomes and the assessed variables are expressed as hazard ratios (HRs) and 95 % confidence intervals (CIs). All statistical tests were two-sided and a p-value <0.05 was considered to indicate significant difference. The data were analyzed using the Statistical Package for Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA)

RESULTS

The descriptive characteristics of the 866 patients are shown in Table 2. Of these patients, 269 (31.1 %) developed AKI in the first week after surgery; 231 patients (85.9 %) were at stage 1, 32 patients (11.9 %) at stage 2, and 6 patients (2.2 %) at stage 3. The two groups differed significantly in terms of sex, anesthesia time, and preoperative eGFR. Therefore, while the mean anesthesia time was 439.3 min, the mean anesthesia times of the AKI group and non-AKI group were 467.8 and 425.5 min, respectively ($p = 0.001$). The mean preoperative eGFR of the whole cohort was 78.6 ml/min/1.73 m^2, but the AKI and non-AKI groups differed with respect to this variable (75.9 vs. 79.9 ml/min/1.73 m^2; $p = 0.016$); however, the two groups did not differ significantly with respect to other variables. Severe complications requiring procedures that may have affected renal function and confounded the results occurred in 67 (7.7 %) patients. In 34 of the 67 patients, surgery-related events such as vesicoureteral reflux, acute pyelonephritis, and urinary obstruction were the cause of complications, while urinary tract involvement due to tumor progression was the cause of complications in the remaining patients.

The eGFR decreased from 78.6 to 67.8 ml/min/1.73 m^2 during the 5-year study period. There was a significant decrease in eGFR 1 week postoperatively, with no significant further change thereafter (Fig. 1a). The eGFR decreased from 79.9 to 67.3 ml/min/1.73 m^2 in non-AKI patients and 75.9 to 43.2 ml/min/1.73 m^2 in AKI patients within 1 week postoperatively. The eGFR at 5 years after surgery was 61.9 and 70.5 ml/min/1.73 m^2 in AKI and non-AKI patients, respectively. AKI patients showed a larger decrease in eGFR than non-AKI patients at 1 week and 5 years after surgery ($p < 0.001$) (Fig. 2b). The eGFR at last follow-up was 61.3 and 71.3 ml/min/1.73 m^2 in AKI and non-AKI patients, respectively.

Of 722 patients with a preoperative MDRD eGFR of >60 ml/min/1.73 m^2, CKD developed in 185 (25.6 %) patients after surgery. CKD developed in 23.0 % (118/513) of patients in the non-AKI group and 32.5 % (68/209) of patients in the AKI group. Independent factors predicting new-onset CKD were preoperative eGFR (odds ratio [OR] 0.96, 0.94–0.97; $p < 0.001$), age (OR 1.03, 1.01–1.06; $p = 0.011$), urinary tract complication (OR 59.0, 13.4–259.8; $p < 0.001$) and AKI (OR 1.71, 1.11–2.62; $p = 0.015$) (Table 3).

Overall, 297 patients died (191 in the non-AKI group and 106 in the AKI group). The overall 5- and 10-year OS rates were 66.5 and 58 %, respectively; however, the 5-year OS rate was significantly lower for patients with AKI than for those without AKI (60.2 vs. 69.0 %; $p = 0.001$) (Fig. 2a). In addition, the OS rate differed significantly according to AKI stage ($p = 0.029$) (Fig. 2b). Multivariable analysis showed that factors significantly predictive of OS included age (HR 1.04, 95 % CI 1.03–1.06; $p < 0.001$), pathologic T stage (HR 1.96, 95 % CI 1.44–2.68; $p < 0.001$), lymph node metastasis (HR 2.58, 95 % CI 1.96–3.48; $p < 0.001$), and lymphovascular invasion (HR 1.56, 95 % CI 1.18–2.07; $p = 0.002$). AKI after surgery also correlated significantly with OS (HR 1.54, 95 % CI 1.20–2.01; $p = 0.001$) (Table 4).

DISCUSSION

While the long-term renal functional outcomes after radical cystectomy have so far been reported,[7,8,28] it remains unclear whether the prevalence of AKI after radical cystectomy for bladder cancer affects the prognosis. AKI is a common postoperative complication whose pervasiveness was appreciated recently with the adoption of standardized reporting using consensus definitions such as AKIN, Kidney Disease: Improving Global Outcomes (KDIGO) and Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria.[7,29,30] The incidence of AKI after adult cardiac surgery has been reported to be between 5 and 10 %,[16] while the incidence of AKI after major abdominal surgery is approximately 22.4 %.[10] The relatively high rate of postoperative AKI in our study might be attributed to several features of the surgery procedure, such as UD, bowel handling, bleeding, and the long operative time; however, high-stage AKI was lower than that associated with other surgeries because, unlike cardiac surgery, cystectomy is a hemodynamically stable surgery.[13] Besides, broad definition of AKIN criteria would contribute to the higher rate of AKI than the National Surgical Quality Improvement Program (NSQIP) study.[19]

TABLE 2 Clinical/pathological characteristics of the patient cohort

	Overall	Non-acute kidney injury	Acute kidney injury	*p*-Value
No. of patients (%)	866	597	269	
AKI stage 1			231 (85.9)	
AKI stage 2			32 (11.9)	
AKI stage 3			6 (2.2)	
Mean age ± SD (years)	62.6 ± 9.8	62.4 ± 9.8	63.0 ± 9.3	0.365
Sex, *n* (%)				
Male	758 (87.5)	513 (85.9)	245 (91.1)	0.035
Female	108 (12.5)	84 (14.1)	24 (8.9)	
Diabetes, *n* (%)	115 (13.3)	78 (13.1)	37 (13.7)	0.731
Hypertension, *n* (%)	235 (27.1)	161 (27.0)	74 (27.7)	0.860
ECOG performance status, *n* (%)				0.436
0	742 (85.7)	507 (85.0)	235 (87.2)	
≥1	124 (14.3)	90 (15.0)	34 (12.8)	
Serum albumin level (gm/dl), *n* (%)				0.346
<3.5	108 (12.5)	69 (11.6)	39 (14.4)	
≥3.5	758 (87.5)	528 (88.4)	230 (85.6)	
Mean body mass index ± SD, kg/m^2	23.5 ± 3.3	23.4 ± 3.2	23.6 ± 3.5	0.305
Mean anesthesia time ± SD, min	439.3 ± 105.4	425.5 ± 109.1	467.8 ± 91.3	0.001
Preoperative eGFR ± SD, ml/min/1.73 m^2	78.6 ± 21.4	79.9 ± 20.2	75.9 ± 23.7	0.016
Clinical stage, *n* (%)				0.765
≤T2	519 (59.9)	360 (60.3)	159 (59.1)	
≥T3	347 (40.1)	237 (39.7)	110 (40.9)	
Urinary diversion, *n* (%)				0.818
Orthotopic bladder substitutions	565 (65.2)	391 (65.5)	174 (64.7)	
Ileal conduit	301 (34.8)	206 (34.5)	95 (35.3)	
Pathologic T stage, *n* (%)				0.461
≤T2	477 (55.1)	334 (55.9)	143 (53.2)	
≥T3	389 (44.9)	263 (44.1)	126 (46.8)	
Lymph node metastases, *n* (%)				0.358
Yes	224 (25.9)	160 (26.8)	64 (23.8)	
No	642 (74.1)	437 (73.2)	205 (76.2)	
Grade, *n* (%)				0.553
Low	146 (16.8)	105 (17.6)	41 (15.2)	
High	720 (83.2)	492 (82.4)	228 (84.8)	
Lymphovascular invasion, *n* (%)				0.136
Yes	359 (41.5)	237 (39.7)	122 (45.4)	
No	507 (58.5)	360 (60.3)	147 (54.6)	
Carcinoma in situ, *n* (%)				0.933
Yes	211 (25.5)	153 (25.6)	68 (25.3)	
No	645 (74.5)	444 (74.4)	201 (74.7)	
Adjuvant chemotherapy, *n* (%)				0.608
Yes	212 (25.5)	149 (24.9)	63 (23.4)	
No	654 (75.5)	448 (75.1)	206 (76.6)	
Urinary tract complications, *n* (%)	67 (7.7)	34 (5.7)	20 (7.4)	0.392
Postoperative complications	34	20	14	
Tumor progression	33	24	9	
Transfusion, *n* (%)	680 (78.5)	458 (76.7)	222 (82.5)	0.055

AKI acute kidney injury, *SD* standard deviation, *ECOG* Eastern Cooperative Oncology Group, *eGFR* estimated glomerular filtration rate

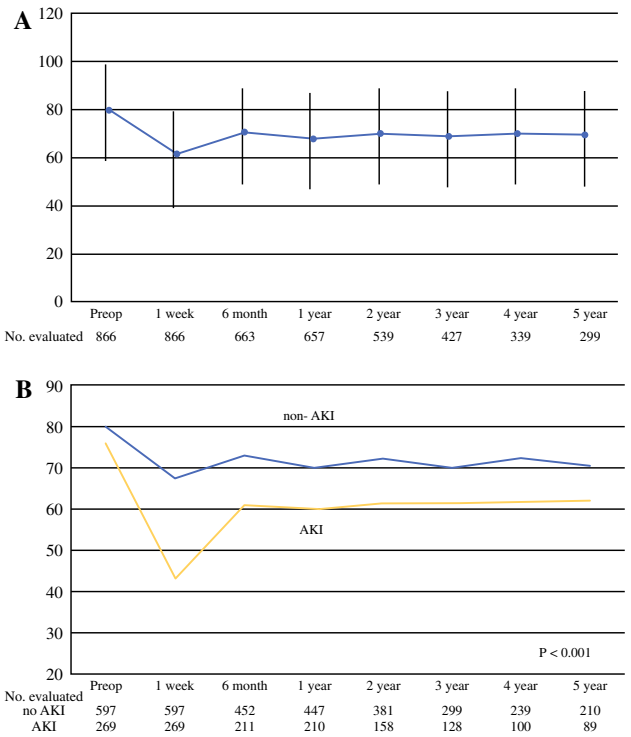

FIG. 1 Glomerular filtration rate change after surgery; **a** in all patients, and **b** according to AKI. *AKI* acute kidney injury, *preop* preoperatively

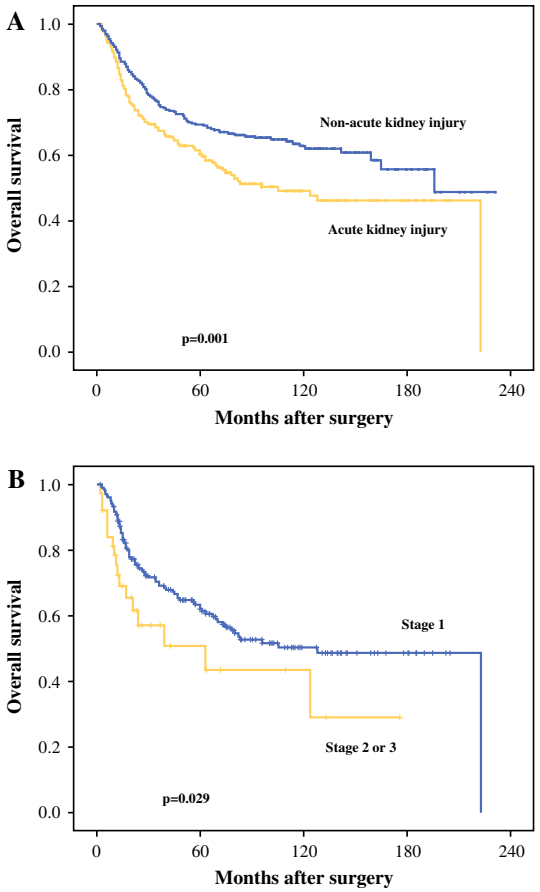

FIG. 2 Kaplan–Meier analysis of overall survival after surgery; **a** according to AKI, and **b** according to AKI stage. *AKI* acute kidney injury

Several recent reports have shown that patients with AKI tend to have higher short- and long-term mortality rates than those without AKI.[14–16] In addition, previous studies reported a relationship between the subsequent development of CKD and progression to dialysis dependence.[5,26] We found that AKI is an independent predictor of CKD, along with age and preoperative GFR. Additionally, AKI was a significant predictor of mortality, along with other pathologic features. AKI is no longer viewed as a sign of severity of disease but rather as a serious complication with significant independent effects on outcomes, such that patients die owing to AKI rather than with AKI.[12,31] AKI is characterized by local and systemic inflammatory reactions in which locally produced cytokines mediate AKI and concomitantly exert distant organ injury through their systemic release from the renal tubular cells.[12,32] Patients with AKI not only have an increased occurrence of infection but exhibit higher morbidity because of inadequate antimicrobial dosing.[31] Additionally, postoperative complications such as urinary tract obstruction and urinary tract inflammation might also be the cause of short- and long-term mortality. In our study, severe complications requiring procedures that may have affected renal function and confounded the results occurred in 67 (7.7 %) patients.

Our study showed that preoperative GFR was an independent prognostic factor of CKD and OS. In 722 patients with a preoperative MDRD eGFR >60 ml/min/1.73 m^2, preoperative GFR was an independent prognostic factor of CKD and OS. Among patient characteristics, preoperative GFR in AKI patients was significantly different from that in non-AKI patients. This has also been observed in several other studies.[10,31] Renal function plays an important role in physiological functions, including water clearance, volume regulation, acid–base disorders, and electrolyte balance. Therefore, patients with decreased renal function are not only unable to adapt after surgery but also experience physiologic derangements that can cause AKI after surgery. Accordingly, it is necessary to be more attentive to patients with decreased renal function.

Previously published work has reported a number of AKI-associated events and procedures after surgery, including comorbidity, increased procedural duration, intraoperative hypotension, the need for blood transfusion, and an increase in postoperative treatment intensity.[14,17,31]

TABLE 3 Factors predictive of new-onset chronic kidney disease (of 722 patients with a preoperative eGFR of >60 ml/min/1.73 m^2, chronic kidney disease developed in 185 after surgery)

	Univariate		Multivariable[a]	
	OR (95 % CI)	*p*-Value	OR (95 % CI)	*p*-Value
Age (continuous)	1.03 (1.01–1.05)	0.003	1.03 (1.01–1.06)	0.011
Sex (female)	1.09 (0.58–2.04)	0.775	1.24 (0.85–2.64)	0.573
Diabetes (yes)	0.89 (0.52–1.52)	0.673	0.62 (0.32–1.20)	0.159
Hypertension (yes)	1.14 (0.75–1.71)	0.535	1.15 (0.72–1.83)	0.554
Body mass index (continuous)	0.96 (0.91–1.02)	0.171	1.01 (0.94–1.07)	0.848
Preoperative eGFR (continuous)	0.96 (0.94–0.97)	<0.001	0.96 (0.94–0.97)	<0.001
Urinary diversion (Ileal conduit)	1.14 (0.77–1.68)	0.517	0.80 (0.48–1.32)	0.387
Pathologic T stage (≥T3)	1.41 (0.98–2.03)	0.061	1.40 (0.83–2.36)	0.198
Lymph node metastasis (yes)	1.25 (0.84–1.88)	0.271	0.89 (0.48–1.66)	0.729
Lymphovascular invasion (yes)	1.35 (0.94–1.95)	0.101	0.97 (0.60–1.58)	0.923
Adjuvant chemotherapy (yes)	1.58 (1.05–2.35)	0.025	1.59 (0.83–3.05)	0.157
Urinary tract complication (yes)	51.9 (12.24–220.16)	<0.001	59.0 (13.4–259.8)	<0.001
Acute kidney injury (yes)	1.55 (1.06–2.27)	0.023	1.71 (1.11–2.62)	0.015

OR odds ratio, *CI* confidence interval, *eGFR* estimated glomerular filtration rate

[a] Logistic regression model

TABLE 4 Univariate and multivariate analysis of factors influencing overall survival (of all 866 patients, 297 died)

	Univariate		Multivariable[a]	
	HR (95 % CI)	*p*-Value	HR (95 % CI)	*p*-Value
Age (continuous)	1.04 (1.02–1.05)	<0.001	1.04 (1.03–1.06)	<0.001
Sex (female)	1.16 (0.78–1.71)	0.452	1.27 (0.85–1.89)	0.340
Diabetes (yes)	0.83 (0.54–1.28)	0.334	0.78 (0.52–1.15)	0.231
Hypertension (yes)	0.82 (0.61–1.11)	0.200	0.89 (0.67–1.23)	0.473
Preoperative eGFR (continuous)	0.98 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	0.043
Urinary diversion (Ileal conduit)	2.02 (1.57–2.60)	0.001	0.97 (0.72–1.30)	0.856
Pathologic T stage (≥T3)	3.49 (2.69–4.54)	<0.001	1.96 (1.44–2.68)	<0.001
Lymph node metastasis (yes)	3.77 (2.92–4.86)	<0.001	2.58 (1.96–3.48)	<0.001
Lymphovascular invasion (yes)	2.89 (2.24–3.73)	<0.001	1.56 (1.18–2.07)	0.002
Acute kidney injury (yes)	1.48 (1.15–1.91)	0.002	1.54 (1.20–2.01)	0.001

[a] Logistic regression model

HR hazard ratio, *CI* confidence interval, *eGFR* estimated glomerular filtration rate

In our study, AKI patients had longer anesthesia times than non-AKI patients. Therefore, it is important to raise the awareness of the individual provider to the importance of screening to identify post-surgical patients who are at risk of postoperative AKI and in need of appropriate perioperative and postoperative management procedures to minimize the risk of AKI.[12] According to the KDIGO guidelines, stage-based management of AKI should be considered as follows: for low-stage AKI, (i) discontinue nephrotoxic agents, (ii) maintain volume status and pressure, (iii) monitor serum creatinine and urine output, (iv) avoid hyperglycemia, and (v) consider alternatives to radiologic procedures; and for high-stage AKI, (i) consider renal replacement therapy, and (ii) consider intensive care unit (ICU) admission.[29] However, larger studies will be required to confirm the effects of prevention and treatment of AKI on outcomes.

The findings of the present study are limited by the retrospective nature of the study and the significant differences between patients with respect to several clinical variables. Second, follow-up loss and excluding patients who did not have long-term creatinine data may have introduced selection bias. Moreover, we did not evaluate the gold standard measures of creatinine clearance, and creatinine reabsorption may have potentially limited the accuracy of serum creatinine measurements in patients

after UD.[8] Nonetheless, the present study is the first study to analyze the prevalence and significance of AKI after radical cystectomy in a relatively large cohort over an extended period. We hope that the results will lay the foundation for future studies and treatments.

CONCLUSIONS

AKI is not only commonly encountered after radical cystectomy but is also associated with higher CKD rates and mortality. We also found an association between weak preoperative renal function and a higher risk of AKI, and thus patients with weak renal function should be followed closely before and after surgery. There is a critical need for strategies to optimize the identification of patients at risk of postoperative AKI, and to improve the management of patients, with an aim toward preventing AKI and to develop better treatments once AKI occurs.

DISCLOSURE Taekmin Kwon, In Gab Jeong, Chunwoo Lee, Dalsan You, Bumsik Hong, Jun Hyuk Hong, Hanjong Ahn, and Choung-Soo Kim have no conflicts of interest or financial disclosures.

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