Pre-existing renal insufficiency synchronous with high preoperative neutrophil-to-lymphocyte ratio as a risk factor of intravesical recurrence in patients with pure upper tract urothelial carcinoma after radical nephroureterectomy

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Abstract. The present study aimed to evaluate the influence of pre-treatment neutrophil-to-lymphocyte ratio (NLR) on bladder recurrence in patients with impaired renal function following radical nephrouretectomy (RNU) to treat pure upper tract urothelial carcinoma (UTUC). Retrospective data of 362 patients with pure UTUC who underwent RNU between 2008 and 2019 were analyzed. Kaplan-Meier analyses were performed to evaluate the association of preoperative NLR and estimation of the glomerular filtration rate (eGFR) with intravesical recurrence-free survival (IVRF). Furthermore, multivariate analyses were conducted to determine independent factors for predicting IVRF. In the retrospective cohort study of 362 patients, 103 patients (28%) had intravesical recurrence in a median follow-up of 50.1 months; among those, 85 (83%) developed bladder recurrence within two years after RNU. The Kaplan-Meier analysis indicated that patients exhibiting lower eGFR and higher NLR showed significantly poor IVRF rates (P=0.044). The simultaneous presence of eGFR <45 and NLR >3.8 was an independent factor for the shorter IVRF time in multivariate analysis with Cox's proportional hazards model. Most intravesical recurrences occurred within two years after RNU, particularly in pre-existing poor eGFR patients with preoperative high NLR. Moreover, pre-existing moderate to severe CKD synchronous with pre-operative NLR >3.8 was demonstrated as an independent factor for subsequent bladder recurrence in patients with pure UTUC following RNU. Therefore, such high-risk patients ought to be provided with close bladder monitoring during the follow-up.

Introduction

Upper tract urothelial carcinoma (UTUC) is a fairly uncommon cancer worldwide (1) and it accounts for only 5% of all urothelial carcinoma (2). However, it represents a relatively higher prevalence in Taiwan than in other countries, especially in the Southwest coast area (3). Based on high risk of tumor recurrence and progression, radical nephroureter-ectomy (RNU) and bladder cuff excision (BCE) remains the gold standard of treatment for localized UTUC. Following surgery, intravesical recurrence is not rare, accounting for 20-50% of all cases (4,5). So, it is necessary to perform routine cystoscopy plus urine cytology for early detection of bladder tumor recurrence. Previous studies have attempted to analyze risk factors for identifying patients who were at risk of high bladder tumor recurrence (6). A systemic review by Seisen *et al* (7) reported that male, previous bladder cancer, preoperative renal impairment, positive preoperative urinary cytology, lower ureteral tumor, multifocality, invasive pT stage and necrosis significantly correlated with the poor intravesical recurrence-free rate. However, the precisely predictive factors for postoperative bladder recurrence remain to be elucidated.

A large-scale retrospective cohort study revealed that moderate to severe chronic kidney disorder [CKD; glomerular filtration rate (eGFR) <45] had a higher risk for urothelial carcinoma incidence (8). CKD is also reported to significantly correlate with bladder recurrence in urothelial carcinoma following surgery (9,10). It is hypothesized that CKD is closely associated with increased inflammation (11). Thus, it results in tumor recurrence and progression based on the important role of inflammation in cancer development and growth (12). In addition, a number of studies have shown

that neutrophil-to-lymphocyte ratio (NLR) is indicated as a systemic inflammation marker that is significantly associated with oncologic outcomes (13,14). Kishimoto *et al* (15) demonstrate that NLR is a prognostic factor affecting intravesical recurrence following RNU and BCE.

Yoshitomi *et al* (16) found that the value of NLR is associated with renal outcomes in patients with CKD. It is reasonable that NLR and CKD are considered for postoperative bladder recurrence in patients with UTUC following RNU. No studies, to the best of the authors' knowledge, suggest any prognostic association of combining preoperative eGFR and NLR with bladder recurrence in patients with UTUC. Therefore, the present study aimed to evaluate the significance of preoperative eGFR and NLR in predicting bladder recurrence in patients following RNU to treat pure UTUC that excluded previous/concomitant bladder cancer and other malignancies.

Patients and methods

Patient population. The present retrospective study was conducted at National Cheng Kung University medical center, Tainan, Taiwan. It collected patients with pure UTUC receiving RNU and BCE at the institute between January 2008 and December 2019 and had approval from the ethical committee of the National Cheng Kung University Hospital (IRB number: A-ER-103-036). Pure UTUC referred to no previous/concomitant bladder cancer or other malignancy. RNU was laparoscopically performed with the extravesical approach to BCE. Demographic data included age, sex, renal function status based on eGFR, hemodialysis, hydronephrosis, hematuria, diabetes mellitus (DM), hypertension (HTN), tumor location (renal pelvis vs. ureter vs. both), pathologic tumor stage, lymph node (LN) metastasis, tumor grade, tumor necrosis and lymphovascular invasion (Table I). Patients diagnosed with distant metastasis and those with history of kidney transplantation, on immunosuppressive agent or neoadjuvant/adjuvant chemotherapy, with a fever episode (>38.3˚C) within 30 days before surgery, or hematological disorder were excluded from the present study.

Pathologic tumor grade was determined using the 2004 World Health Organization (WHO) grading system (17) and tumor staging was determined according to the 7th edition of the American Joint Committee on Cancer TNM classification (18) by various urological pathologists. The eGFR was calculated by the Modification of Diet in Renal Disease (MDRD) Study equation: $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$ (19).

The cut-off value of NLR was determined as 3.8 for predicting intravesical recurrence following RNU, according to Kishimoto *et al* (15).

Basic hemogram data were obtained within 30 days before the surgery. All patients routinely underwent cystoscopy during postoperative follow-up to see whether recurrent bladder tumors. Moreover, the confirmation of bladder cancer recurrence was diagnosed via pathological report. Other postoperative follow-up evaluations involved history-taking, physical examination, urinalysis, urine cytology, cystoscopy, bladder/renal ultrasound and radiologic imaging every three months during the first two years, every six months from the third through the fourth year and annually thereafter.

Statistical analysis. The Chi-square test was used to compare differences according to eGFR (> and <45 ml/min/1.73 m^2) and NLR (> and <3.8). Intravesical recurrence-free survival (IVRF) was defined as the interval from RNU until a pathologically confirmative diagnosis of bladder urothelial malignancy. The effects of preoperative eGFR and NLR on IVRF were estimated using Kaplan-Meier survival plots with the log-rank test. Parameters associated with IVRF were analyzed by univariate and multivariate Cox proportional hazard regression models, which estimated hazard ratio (HR) and evaluated the significance of IVRF. All statistical analyses were performed using SPSS version 21.0 (IBM Corp.). Additionally, R software version 3.5.3 (http://www.r-project.org) was used to construct a nomogram predicting the 2- and 5-year IVRF according to variables resulting from multivariable Cox models. P<0.05 was considered to indicate a statistically significant difference.

Results

Characteristics of the patients with different CKD status and NLR level. A total of 362 eligible patients with pure UTUC who underwent RNU between January 2008 and December 2019 were collected. All enrolled patients were stratified into four groups based on eGFR and NLR and analyzed differences in clinicopathological characteristics between groups, shown in Table I. Except for tumor size, there was no difference in age, sex, hematuria, hydronephrosis, DM or HTN, tumor location, pathological T stage, LN involvement, tumor grade, CIS, tumor necrosis and LVI.

Association of preoperative renal function and NLR with bladder recurrence. The present study showed that preoperative poor renal function and high NLR had a trend of poor IVFR in Kaplan-Meier analyses (Table SI; Figs. S1 and S2). In 362 patients with UTUC, 103 (28%) had bladder recurrence following surgery with a mean and median follow-up time of 51.1 and 50.1 months, respectively (Table II). Among 103 patients with postoperative bladder recurrence, 85 (83%) suffered from bladder recurrence rate within the first two years after RNU. Notably, patients with eGFR <45 and NLR >3.8 had a relatively higher bladder recurrence rate compared with other groups. When preoperative eGFR and NLR were analyzed together for bladder recurrence, Kaplan-Meier analyses showed that eGFR <45 synchronous with NLR >3.8 was significantly associated with a poorer IVRF as compared with eGFR >45 with NLR >3.8, eGFR >45 with <3.8, or eGFR <45 with NLR <3.8 (Fig. 1).

Bladder recurrence according to preoperative renal function and NLR. As the Kaplan-Meier plot revealed that preoperative eGFR <45 and NLR >3.8 was significantly associated with a poor IVRF in patients with UTUC, univariate and multivariate Cox regression analyses were conducted to evaluate the significance of each parameter for IVRF (Table III). In univariate analysis, tumor location involving both pelvis and ureter (HR: 2.018, 95%CI: 1.231-3.309, P=0.005) and preoperative eGFR <45 and NLR >3.8 (HR: 1.819, 95%CI: 1.070-3.092, P=0.027) were apparently associated with an inferior IVRF. In multivariate analysis, tumor location (HR: 1.918, 95%CI: 1.157-3.181, P=0.012) and preoperative eGFR <45 and NLR >3.8 (HR: 1.753, 95%CI: 1.030-2.983, P=0.038) remained significant.

Table I. Clinicopathologic characteristics in patients with upper tract urothelial carcinoma after radical nephroureterectomy stratified by preoperative eGFR and NLR.

Clinicopathologic characteristic	Renal function status NLR Total patients, n=362	eGFR ≥45		eGFR <45		P-value
		<3.8 n=176	>3.8 n=46	<3.8 n=90	>3.8 n=50	
Mean age (year)	70.7±10.5	69.8±10.4	71.1±11.4	72.6±8.9	70.1±12.3	
Age (year)						0.216
≤65	99 (27%)	54 (31%)	14 (30%)	17 (19%)	14 (28%)	
>65	218 (73%)	122 (69%)	32 (70%)	73 (81%)	36 (72%)	
Sex						0.686
Male	151 (42%)	69 (39%)	20 (43%)	42 (47%)	20 (41%)	
Female	211 (58%)	107 (61%)	26 (57%)	48 (53%)	30 (59%)	
Hemodialysis						<0.001
No	329 (90%)	177 (100%)	46 (100%)	72 (80%)	34 (67%)	
Yes	35 (10%)	0 (0%)	0 (0%)	18 (20%)	17 (33%)	
DM or HTN						0.223
Absent	146 (40%)	76 (43%)	22 (48%)	33 (37%)	15 (30%)	
Present	216 (60%)	100 (57%)	24 (52%)	57 (63%)	35 (70%)	
Hematuria						0.376
No	47 (13%)	21 (12%)	6 (13%)	16 (18%)	4 (10%)	
Yes	315 (87%)	155 (88%)	40 (87%)	74 (82%)	46 (90%)	
Hydronephrosis						0.523
No	68 (19%)	33 (19%)	12 (26%)	14 (16%)	9 (18%)	
Yes	294 (81%)	143 (81%)	34 (74%)	76 (84%)	41 (82%)	
Tumor location						0.088
Pelvis	180 (50%)	89 (51%)	30 (65%)	38 (42%)	23 (46%)	
Ureter	121 (33%)	64 (36%)	10 (22%)	30 (34%)	17 (34%)	
Both	61 (17%)	23 (13%)	6 (13%)	22 (24%)	10 (20%)	
Pathological T stage						0.332
pTa/1	147 (40%)	74 (42%)	16 (35%)	38 (42%)	19 (38%)	
pT2	75 (21%)	40 (23%)	5 (11%)	18 (20%)	12 (24%)	
pT3/4	140 (39%)	62 (35%)	25 (54%)	34 (38%)	19 (38%)	
Lymph node status						0.466
Nx/0	343 (95%)	169 (96%)	42 (91%)	86 (96%)	46 (92%)	
N+	19 (5%)	7 (4%)	4 (9%)	4 (4%)	4 (8%)	
Tumor grade						0.107
Low	19 (5%)	14 (8%)	4 (4%)	3 (3%)	0 (0%)	
High	343 (95%)	162 (92%)	44 (96%)	87 (97%)	50 (100%)	
Tumor size (cm)						0.012
≤3	207 (57%)	115 (65%)	19 (41%)	47 (52%)	26 (52%)	
>3	155 (43%)	61 (35%)	27 (59%)	43 (48%)	24 (48%)	
Carcinoma *in situ*						0.346
Absent	287 (79%)	143 (81%)	34 (74%)	74 (82%)	36 (72%)	
Present	75 (21%)	33 (19%)	12 (26%)	16 (18%)	14 (28%)	
Lymphovascular invasion						0.225
Absent	272 (75%)	139 (79%)	31 (67%)	63 (70%)	39 (78%)	
Present	90 (25%)	37 (21%)	15 (33%)	27 (30%)	11 (22%)	
Tumor necrosis						0.123
No	291 (80%)	150 (85%)	36 (78%)	69 (77%)	36 (72%)	
Yes	71 (20%)	26 (15%)	10 (22%)	21 (23%)	14 (28%)	

eGFR, estimated glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; RNU, radical nephroureterectomy; DM, diabetes mellitus; HTN, hypertension.

Table II Comparison of bladder recurrence rate in 362 patients with upper tract urothelial carcinoma after radical nephroureterectomy according to preoperative renal function status and NLR.

		eGFR ≥45		eGFR <45	
Variable	All patients	NLR <3.8 (n=176)	NLR >3.8 (n=46)	NLR <3.8 (n=90)	NLR >3.8 (n=50)
Postoperative time					
Mean time (month)	51.1±31.4	53.8±30.1	43.6±31.8	54.9±32.3	41.2±31.6
Median time (month)	50.1	51.5	46.2	57.5	34.7
BR rate					
2 years BR, n (%)	85 (23%)	43 (24%)	7 (15%)	16 (18%)	19 (38%)
BR, n (%)	103 (28%)	50 (28%)	8 (17%)	26 (29%)	19 (38%)

NLR, neutrophil-to-lymphocyte ratio; eGFR, estimated glomerular filtration rate; BR, bladder recurrence.
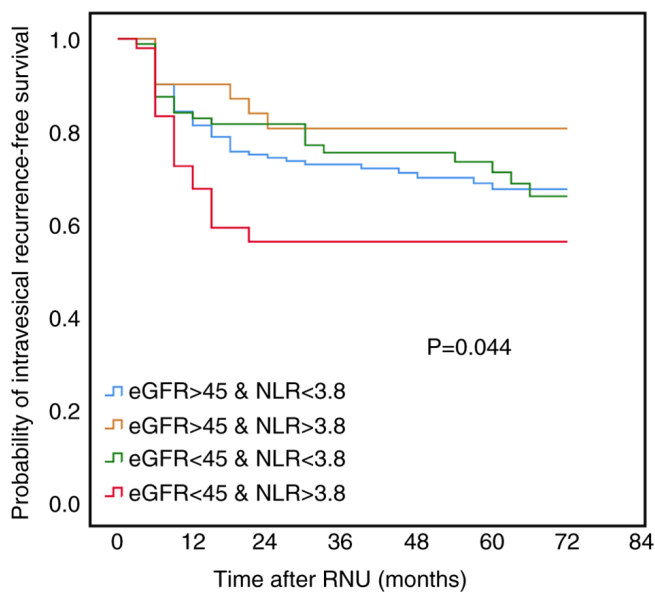

Figure 1. Kaplan-Meier analyses for intravesical recurrence-free survival in patients with UTUC who were divided into four groups according to preoperative eGFR and NLR. UTUC, upper tract urothelial carcinoma; eGFR, estimated glomerular filtration rate; NLR, neutrophile-to lymphocyte ratio; RNU, radical nephrouretectomy.

Discussion

Previously, 22-47% of patients were found to have an intravesical recurrence (IVRF) within the first two years after the use of RNU to treat UTUC (20,21). Similarly, the cohort of the present study showed 24% of patients with bladder recurrence within the first two years after surgery. Notably, when preoperative renal function and NLR were analyzed together, it was found that patients with eGFR <45 and preoperative NLR >3.8 were significantly associated with a higher risk of post-RNU bladder recurrence compared with eGFR <45 or NLR >3.8 alone. Multivariate analysis demonstrated that moderate to severe CKD combined with NLR >3.8 served as an independent factor of IVRF in UTUC patients following RNU.

NLR has been reported to be associated with systemic inflammation (22,23). Studies also suggest that the development/progression and prognosis of cancers were associated with systemic inflammation (24,25). Thus, NLR is hypothesized to serve as a predictive marker for tumor recurrence and progression and a high NLR is associated with poor prognoses in several types of malignancy (14). As for UTUC, a number of studies have noted that preoperative NLR significantly influences postoperative oncological outcomes (13,26). However, there has yet to be consensus regarding the optimal value of NLR. Preoperative NLR has been applied as an indicator for prediction of bladder recurrence following surgery for UTUC. In 2017, Kishimoto *et al* (15) reviewed 192 patients and determined the cut-off value of preoperative NLR as 3.8, which could identify potential patients at risk of intravesical recurrence; NLR was demonstrated to be an independent factor in predicting postoperative bladder recurrence. In the present study, 28% of patients experienced bladder recurrence following surgery within a median follow-up duration of 50.1 months; among those with bladder recurrence, 83% occurred within the first two years after RNU. However, the present study found that NLR >3.8 alone statistically did not reach significance concerning high bladder recurrence.

A previous study reported that moderate to severe CKD patients have a higher bladder incidence (8). Furthermore, a high bladder recurrence was significantly associated with poor kidney function in UTUC (9). Similarly, Momota *et al* (27) reviewed 456 patients with UTUC and found that preoperative moderate to severe renal insufficiency carry a higher risk of disease recurrence, including bladder recurrence. Some studies suggest that advancing renal insufficiency contributes to the accumulation of toxic metabolic products, which result in increased oxidative stress and inflammation, thus potentially enhancing tumor growth/development (11,28). The high incidence of malignant tumor formation in uremia patients is explained by immune system impairment, incorrect DNA repair mechanisms, reduced antioxidant defense, accumulation of carcinogenic toxins, decreased renal elimination and chronic infections and inflammations (29). A more frequent intravesical recurrence rate in CKD patients with UTUC is suggested to link to immunosuppressive conditions, exposure to carcinogenic compounds, lower antioxidant ability and chronic inflammation (9,30,31).

Nevertheless, the present study showed that eGFR <45 apparently had a trend of poor IVFR compared with eGFR

Table III. Univariate and multivariate Cox regression analyses for predicting intravesical recurrence-free survival in patients with upper tract urothelial carcinoma after radical nephroureterectomy.

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at RNU				
>65 yr vs. ≤65 yr	0.730 (0.485-1.098)	0.130		
Sex				
Female vs. male	0.747 (0.507-1.101)	0.140		
Smoking				
Yes vs. no	1.256 (0.672-2.348)	0.475		
DM or HTN				
Present vs. absent	1.015 (0.684-1.506)	0.942		
Hematuria				
Yes vs. no	1.784 (0.900-3.537)	0.097	1.893 (0.946-3.790)	0.071
Hydronephrosis				
Yes vs. no	1.615 (0.919-2.839)	0.096	1.684 (0.939-3.017)	0.080
Tumor location				
Ureter vs. renal pelvis	1.082 (0.692-1.692)	0.730	0.994 (0.624-1.586)	0.981
Both vs. renal pelvis	2.018 (1.231-3.309)	0.005	1.918 (1.157-3.181)	0.012
Pathological T stage				
pT2 vs. <pTa/1	1.246 (0.759-2.044)	0.385		
pT3/4 vs. pTa/1	1.096 (0.702-1.712)	0.687		
Lymph node involvement				
N+ vs. Nx/0	0.765 (0.242-2.413)	0.633		
Tumor grade				
High vs. low	1.638 (0.603-4.452)	0.333		
Carcinoma *in situ*				
Present vs. absent	0.979 (0.606-1.581)	0.930		
Lymphovascular invasion				
Yes vs. no	1.277 (0.822-1.984)	0.276		
Tumor size				
>3 cm vs. ≤3 cm	1.015 (0.677-1.523)	0.942		
Tumor necrosis				
Present vs. absent	0.774 (0.448-1.340)	0.361		
Preoperative eGFR and NLR				
eGFR ≥45 and high NLR vs. eGFR ≥45 and low NLR	0.690 (0.327-1.456)	0.330	0.731 (0.344-1.551)	0.414
eGFR <45 and low NLR vs. eGFR ≥45 and low NLR	1.007 (0.627-1.617)	0.977	0.963 (0.597-1.553)	0.878
eGFR <45 and high NLR vs. eGFR ≥45 and low NLR	1.819 (1.070-3.092)	0.027	1.744 (1.024-2.967)	0.038

HR, hazard ratio; CI, confidence interval; RNU, radical nephroureterectomy; DM, diabetes mellitus; HTN, hypertension; eGFR, estimated glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio.

>45. Yoshitomi et al (16) report that poorer renal function markedly correlates with the higher NLR value, which reflects the effect of renal function on the immune inflammation response. Thus, preoperative renal function status could be considered together with an inflammation marker, NLR, to predict IVRF. After stratifying all patients into four risk groups, including eGFR >45 and NLR <3.8, eGFR >45 and NLR >3.8, eGFR <45 and NLR <3.8 and eGFR <45 and NLR >3.8, Kaplan-Meier plot showed moderate to severe CKD with high NLR had a significant association with a

high bladder recurrence in UTUC patients following RNU. In brief, combining preoperative eGFR and NLR could identify potential patients at high risk of subsequent bladder recurrence following surgery. Furthermore, a combination of preoperative eGFR and NLR was shown to be an independent factor for a poor IVRF in UTUC following RNU. In addition, the present study attempted to create a nomogram to predict the two- and five-year IVRF based on variables included in the multivariable Cox regression models (Fig. S3). This nomogram may help doctors to distinguish patients at risk of subsequent bladder recurrence who needed careful follow-up. In the future, this prediction model should perform the external validation.

Previously, two clonal hypotheses, including intraluminal seeding and field cancerization effect, were proposed to explain bladder tumor multifocality and recurrence (32). The present study cannot confirm that metachronous bladder tumor recurrence came from UTUC tumor seeding or cancer field effect through the understanding of the clinical progress evolution and pathologic characters of tumors. The present study first minimized the influence of clinical confounding factors, such systemic chemotherapy, prior bladder cancer history, concomitant bladder cancer and more, on the development of metachronous bladder tumors. It focused on exploring the effect of NLR and preoperative renal function on bladder tumor recurrence following RNU to treat pure UTUC. Although in the cohort there were only 14% of UTUC patients with pre-existing renal insufficiency (eGFR <45) with elevated NLR (>3.8), as high as 38% of these patients developed new bladder urothelial carcinoma. As aforementioned, it is hypothesized that this phenomenon was due to systemic inflammation and toxic stress attacks involving accumulation of biochemical carcinogens and uremic immunosuppression.

Since decreased eGFR contributed to more oxidative stress, the resultant NLR elevation reflected the intensity of stress and systemic inflammation. An elevated NLR indicated increased serum neutrophil and decreased lymphocyte counts. Increasing circulating neutrophils had more chances to participate in tumor-related inflammatory activities in a tumor microenvironment and then changed to tumor-associated neutrophils to assist tumor progression through multiple mechanisms (25,33). Meanwhile, lowering circulating lymphocyte counts leads to weak anti-tumor immunity (34). Thus, an active inflammatory and stress-rich status potentially drives the processing of malignant transformation and also benefits the viability of seeding tumor cells from the upper urinary tract. This may explain why incorporating a high NLR and poor renal function could act as an indicator for predicting bladder recurrence. However, associations between NLR, CKD and bladder recurrence in patients with UTUC may be multifactorial. Still more substantial, biological evidence is required to further elucidate the pathophysiological mechanism of bladder tumor recurrence.

To the best of the authors' knowledge, the present study was the first clinical study to evaluate the effect of combining preoperative renal function status and NLR on IVFR in patients following RNU to treat UTUC. Physicians should take preoperative renal function and NLR into account when identifying patients with high risk of subsequent bladder recurrence following RNU in clinical practice. Afterwards, intravesical chemotherapy may be considered for these patients at risk of bladder recurrence following RNU.

There were some limitations to the present study. First, this was a retrospective study, which may have led to a selection bias. Second, all patients were Taiwanese. The high incidence of both UTUC and CKD was noted in Taiwan. Third, the present study failed to assess the duration of renal insufficiency and lacked other reliable serum immune-inflammation markers, which may have affected the results. Thus, further multicenter and prospective studies are necessary. Moreover, external validation which involves other ethnic groups is needed.

The present study showed that moderate to severe CKD synchronous with high NLR was significantly associated with a poor IVRF in UTUC following RNU. Furthermore, combining preoperative eGFR and NLR could be considered as an independent factor for predicting high risk of bladder recurrence in patients with UTUC. Thus, one should be more cautious of UTUC patients with preoperative renal insufficiency and high NLR during post-surgery follow-up.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

THC and HCJ were responsible for the conception and design of the current study. CYH, KYW, TYT, HYW, WHY and CHO were involved in the collection of medical records, and acquisition and curation of data. THC and HCJ performed formal analysis and data interpretation. CYH and HCJ developed the methodology. THC and HCJ drafted the manuscript. CYH, KYW, TYT, HYW, WHY and CHO provided resources and revised the manuscript critically for important intellectual content. THC and HCJ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the institutional review board of National Cheng-Kung University Hospital (IRB number: A-ER-103-036; Tainan, Taiwan), which waived the requirement for informed consent from participants and allowed access to the follow-up clinical records. It was conducted based on the guidelines of the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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