Prognostic model using postoperative normalization of C-reactive protein levels in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy

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ABSTRACT

INTRODUCTION: To improve the prediction of outcomes in patients who will undergo radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC), we investigated the preoperative prognostic factors and developed a risk classification model.

METHODS: A total of 144 patients who underwent RNU with history of neither neoadjuvant nor adjuvant chemotherapy between 2008 and 2022 were retrospectively reviewed. Associations between perioperative/clinicopathologic factors and outcomes, including cancer-specific survival (CSS), were assessed. We specifically focused on preoperative serum C-reactive protein (CRP) and its postoperative normalization.

RESULTS: Non-normalization of postoperative serum CRP level and pathologic T3 stage were identified as independent predictive factors of shorter CSS in univariate and multivariate analysis (p=0.0150 and 0.0037, hazard ratio: 3.628 and 4.470, respectively). We classified the patients into three groups using these factors and found that five-year CSS was 88%, 42.5%, and 0% in the low-risk group (zero factors), intermediate-risk group (one factor), and high-risk group (two factors), respectively (p<0.0001).

CONCLUSIONS: Non-normalization of postoperative serum CRP level and pathologic T stage were identified as independent postoperative prognostic factors in patients with UTUC who underwent RNU. These factors can stratify three prognostic groups and may help urologists in clinical decision-making for adjuvant therapy.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) accounts for 5–10% of urothelial carcinoma.[1] Radical nephroureterectomy (RNU) has been a standard surgical option for UTUC free from metastasis. Five-year cancer-specific survival (CSS) is <50% for cases with pathologic T2 and T3 (pT2/3) stages and <10% for those with pT4 stage.[2] Randomized control trials (RCTs) have demonstrated that adjuvant systemic therapy using combination chemotherapy or an immune-checkpoint inhibitor (ICI) improved survival after RNU in high-risk cases.[3,4]

With such effective adjuvant therapies being reported, it is becoming increasingly important to predict the postoperative prognosis of UTUC and identify high-risk UTUCs for which adjuvant therapy is warranted. Inflammatory responses are known to reflect the grade of malignancy in various cancers, and previous reports have shown that inflammation-related markers, such as C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio, can be useful in predicting cancer prognosis and treatment response.[5,6] CRP is a representative inflammation-related marker and has been reported as a biomarker for urologic malignancies.[7]

The goal of this study was to identify factors that can predict the postoperative prognosis of UTUC, focusing on CRP, one of the representative inflammation-related markers, and its postoperative changes, and to develop a risk-classification model.

METHODS

Patients

This retrospective study was approved by the Ethics Committee of Kobe City Medical Center West Hospital (authorization number: 22-019). The medical records of patients who underwent RNU for unilateral UTUC at Kobe City Medical Center West Hospital between January 2009 and December 2019 were retrospectively reviewed. RNU was conducted using a laparoscopic approach with open distal ureteric excision in all patients. Patients who received neoadjuvant (NAC) or adjuvant chemotherapy (AC) were excluded from this study.

Regional lymphadenectomy was conducted at the discretion of the surgeon, and the template of lymphadenectomy was used as described by Kondo et al.[8] Using these criteria, 144 patients were included in this study.

We obtained relevant clinicopathologic data from medical records, including age, sex, tumor location, pathologic TNM stage, tumor grade, concomitant carcinoma in situ, and lymphovascular invasion. We focused on preoperative serum CRP and its postoperative normalization. Preoperative C-reactive protein was measured one month before surgery, along with other preoperative screening tests. Although some patients who developed infections or other problems underwent multiple measurements of CRP, the postoperative CRP value was defined as the value measured one month after surgery. Patients whose preoperative CRP level was ≤0.3 mg/dL were classified in the low-CRP group, and others were in the higher CRP group. The higher CRP group was further classified into two groups: those whose serum CRP level decreased to ≤0.3 mg/dL at one month after RNU as the normalized CRP group, and those whose CRP level was >0.3 mg/dl at one month after RNU as the non-normalized CRP group.

Followup regimen

Our followup protocol consisted of urine analysis and chest-abdomen-pelvis computed tomography (CT) scans, with or without contrast, every 3–6 months for at least five years. Cystoscopy and urinary cytology were conducted at three months as the screening for intravesical recurrence. If negative, cystoscopy and cytology were repeated every three months for two years and every six months thereafter until the five-year mark, then annually. Disease progression was defined as local failure at the operative site, regional lymph node

Table 1. Characteristics of patients

	Lower CRP (n=98)	Higher CRP (n=46)	p	Total (n=144)
Age, n (%)				
≤75 years	47 (48.0)	23 (50.0)	0.8193	70 (48.6)
>75 years	51 (52.0)	23 (50.0)		74 (51.4)
Sex, n (%)				
Male	56 (57.1)	28 (60.9)	0.6723	84 (58.3)
Female	42 (42.9)	18 (39.1)		60 (41.7)
Tumor location, n (%)				
Renal pelvis	49 (50.0)	25 (54.3)	0.6265	74 (51.4)
Ureter	49 (50.0)	21 (45.7)		70 (48.6)
Tumor grade, n (%)				
G1/2	74 (75.5)	36 (78.3)	0.7171	110 (76.4)
G3	24 (24.5)	10 (21.7)		34 (23.6)
Pathologic T stage, n (%)				
pT1/2	75 (76.5)	32 (69.6)	0.3724	107 (74.3)
pT3/4	23 (23.5)	14 (30.4)		37 (25.7)
Lymphovascular invasion, n (%)				
Absent	81 (82.7)	38 (82.6)	0.9548	119 (82.6)
Present	17 (17.3)	8 (17.4)		25 (17.4)
Lymph node stage, n (%)				
pN0	28 (28.6)	13 (28.3)	0.4123*	41 (28.5)
pN1/2	5 (5.1)	1 (2.2)		6 (4.2)
pNx	65 (66.3)	32 (69.6)		97 (67.4)
Margin status, n (%)				
Negative	94 (95.9)	42 (91.3)	0.2597	136 (94.4)
Positive	4 (4.1)	4 (8.7)		8 (5.6)
Hydronephrosis, n (%)				
Absent	57 (58.2)	22 (47.8)	0.2451	79 (54.9)
Present	41 (41.8)	24 (52.2)		65 (45.1)
Surgical approach, n (%)				
Laparoscopic	88 (89.8)	44 (95.7)	0.2358	132 (91.7)
Open	10 (10.2)	2 (4.4)		12 (8.3)
Laterality, n (%)				
Right	44 (44.9)	13 (28.3)	0.0570	57 (39.6)
Left	54 (55.1)	33 (71.7)		87 (60.4)

*pN0 and pNx vs. pN1/2. CRP: C-reactive protein.

Table 2. Characteristics of patients in higher CRP group

	Normalized CRP (n=27)	Non-normalized CRP (n=19)	p	Total (n=46)
Age, n (%)				
≤75 years	11 (40.7)	12 (63.2)	0.1848	23 (50.0)
>75 years	16 (59.3)	7 (36.8)		23 (50.0)
Sex, n (%)				
Male		14 (73.7)	0.1852	28 (60.9)
Female	13 (48.1)	5 (26.3)		18 (39.1)
Tumor location, n (%)				
Renal pelvis	15 (55.6)	10 (52.6)	0.8446	25 (54.3)
Ureter	12 (44.4)	9 (47.4)		21 (45.7)
Tumor grade, n (%)				
G1/2	20 (74.1)	16 (84.2)	0.4118	36 (78.3)
G3	7 (25.9)	3 (15.8)		10 (21.7)
Pathologic T stage, n (%)				
pT1/2	18 (66.7)	14 (73.7)	0.6105	32 (69.6)
pT3/4	9 (33.3)	5 (26.3)		14 (30.4)
Lymphovascular inva-sion, n (%)				
Absent	22 (81.5)	16 (84.2)	0.8100	38 (82.6)
Present	5 (18.5)	3 (15.8)		8 (17.4)
Lymph node stage, n (%)				
pN0	7 (25.9)	6 (31.6)	0.3964*	13 (28.3)
pN1/2	1 (3.7)	0 (0)		1 (2.2)
pNx	19 (70.4)	13 (68.4)		32 (69.6)
Margin status, n (%)				
Negative	26 (96.3)	16 (84.2)	0.1520	42 (91.3)
Positive	1 (3.7)	3 (15.8)		4 (8.7)
Hydronephrosis, n (%)				
Absent	14 (51.9)	8 (42.1)	0.5147	22 (47.8)
Present	13 (48.1)	11 (57.9)		24 (52.2)
Surgical approach, n (%)				
Laparoscopic	26 (96.3)	18 (94.7)	0.7984	44 (95.7)
Open	1 (3.7)	1 (5.3)		2 (4.4)
Laterality, n (%)				
Right	9 (33.3)	4 (21.1)	0.3624	13 (28.3)
Left	18 (66.7)	15 (78.9)		33 (71.7)

*pN0 and pNx vs. pN1/2. CRP: C-reactive protein.

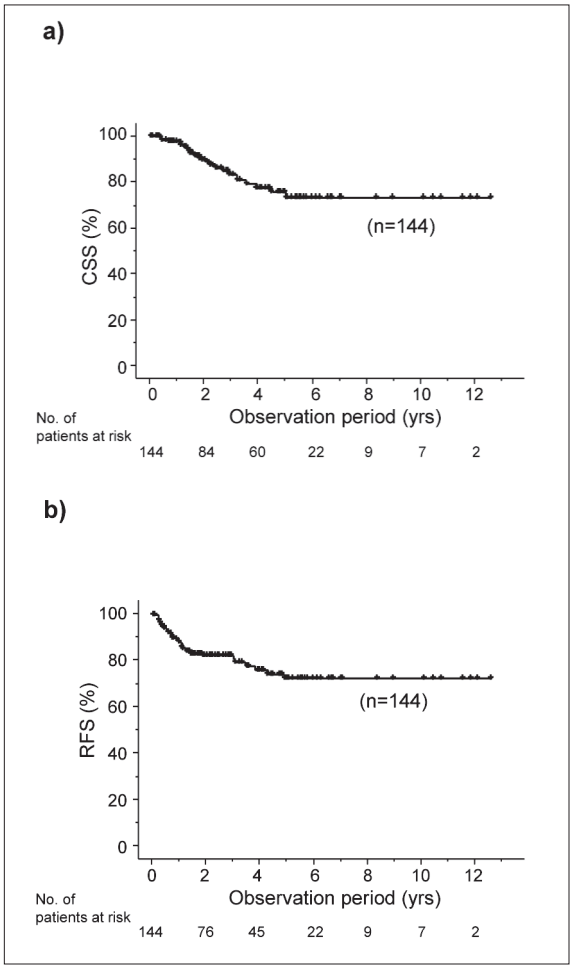

Figure 1. (a) Cancer-specific survival (CSS); and (b) recurrence-free survival (RFS) in entire cohort.

metastasis, or distant metastasis. Intravesical recurrence was not considered disease progression.

Statistical analysis

Differences in the distribution of variables among groups were analyzed by conducting a Chi-squared test for categorical variables and Mann-Whitney test for continuous variables. Recurrence-free survival (RFS) and CSS probabilities were estimated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank testing. The Cox proportional hazards regression model was used for multivariate analyses. All statistical analyses were conducted using the Statview 5.0 software (Abacus Concepts, Inc., Berkeley, CA, U.S.), and $p<0.05$ were determined as statistically significant.

RESULTS

This study cohort consisted of 144 patients undergoing RNU for UTUC. The characteristics of these patients are listed in Table 1. The median age of patients was 76 years (50–93). Ninety-eight (68.1%) and 46 (31.9%) patients were categorized in the lower CRP and higher CRP groups, respectively. There was no significant difference in patient background between these two groups. Of the patients in the higher CRP group, 27 (58.7%) and 19 (41.3%) were classified in the normalized CRP and non-normalized CRP groups, respectively. There were no significant differences in patient background between these two groups (Table 2).

The CSS and RFS curves after RNU for the entire cohort of patients are shown in Figure 1. The median of the observation period was 38.6 months, and 118 of the 144 patients (81.9%) survived. The one-, two- and three-year CSS rates for the entire cohort were 97.7%, 89.3%, and 83.3%, respectively. The one-, two- and three-year RFS rates for the entire cohort were 88.8%, 81.8%, and 81.8%, respectively. There was no significant difference in the CSS for the lower CRP group compared with those for the normalized CRP group (p=0.9406) (Figure 2a), while the CSS rates for the non-normalized postoperative CRP group were significantly worse than those for the others (p=0.0107) (Figure 2b).

Both the CSS and RFS rates for the group with pT3/4 stage were significantly worse than those with pT1/2 stages (p<0.0001) (Figures 2c, 3c), while there was no significant difference in RFS rates between the groups with non-normalized postoperative CRP and those with others (p=0.1210) (Figures 3a, 3b).

Non-normalization of postoperative serum CRP level and pT3 stage were identified as independent predictive factors of shorter CSS in univariate and multivariate analysis (Table 3). We classified into four groups based on these two factors; no applicable factor, CRP non-normalization only, pT3/4 only, and both factors, so that the difference in weight of the two factors can be seen (Figure 4a). As the results showed no significant difference in the CSS for the two groups with only one applicable

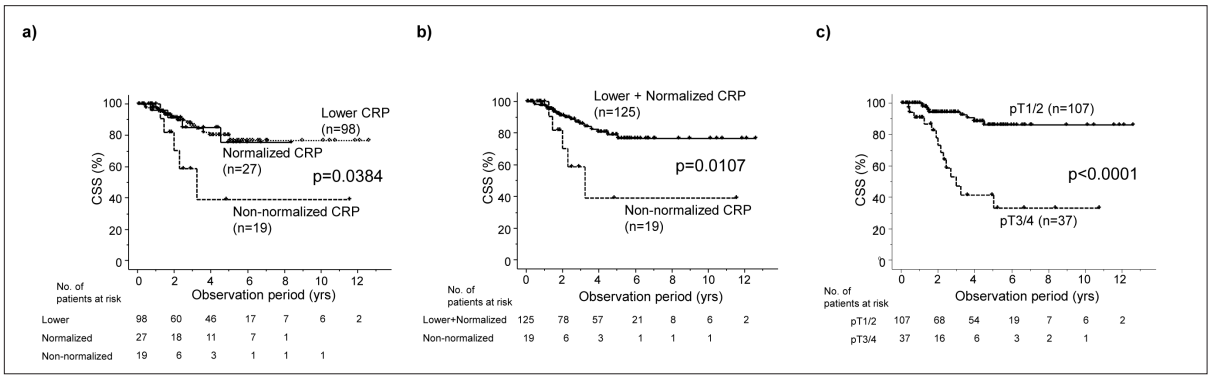

Figure 2. Cancer-specific survival (CSS) stratified by (a) lower, normalized, and non-normalized CRP group; (b) non-normalized C-reactive protein (CRP) group and others; and (c) pathologic (p) T1/2 for (a) and pT3/4 for (b).

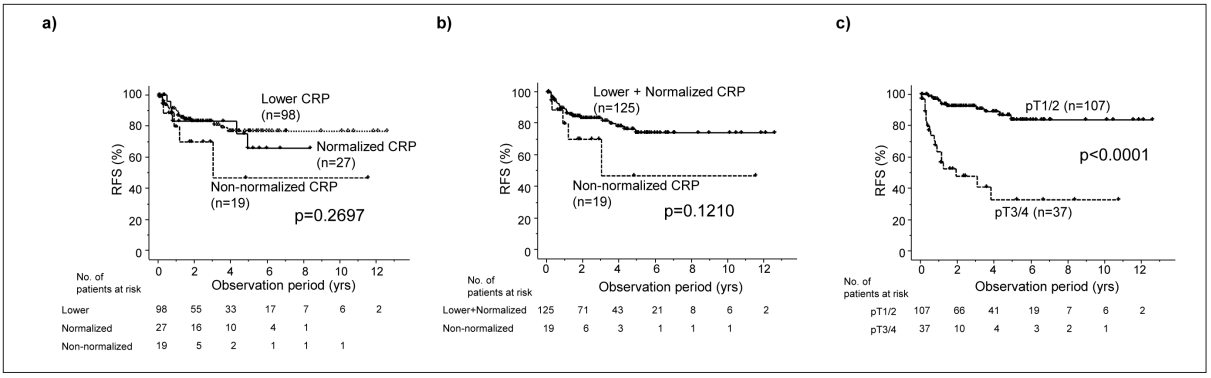

Figure 3. Recurrence-free survival (RFS) stratified by (a) lower, normalized, and non-normalized C-reactive protein (CRP) groups; (b) non-normalized CRP group and others; and (c) pT1/2 and pT3/4.

Table 3. Uni- and multivariate analysis of predictive factor for CSS in patients with UTUC undergoing RNU

	Univariate HR	95% CI	p	Multivariate HR	95% CI	p
Age						
<75	Reference		0.1549			
≥75	1.998	0.770–5.185				
Sex						
Male	Reference		0.9181			
Female	1.044	0.458–2.383				
Tumor location						
Renal pelvis	Reference		0.3786			
Ureter	1.449	0.634–3.310				
Tumor grade						
G1/2	Reference		0.1069			
G3	2.069	0.849–5.040				
Pathologic T stage						
pTa/1/2	Reference		<0.0001	Reference		0.0033
pT3/4	7.120	3.060–16.568		4.470	1.648–12.121	
Lymphovascular invasion						
(-)	Reference		<0.0001	Reference		0.0598
(+)	6.010	2.600–13.894		2.581	0.962–6.930	
Margin status						
Negative	Reference		0.2642			
Positive	1.998	0.593–6.734				
Pathological N stage						
pN0 or pNx	Reference		0.9722			
pN1	0.965	0.130–7.184				
Hydronephrosis						
(-)	Reference		0.0632	Reference		0.3315
(+)	2.221	0.957–5.156		1.526	0.650–3.578	
CRP normalization						
Normalized	Reference		0.0163	Reference		0.0150
Non-normalized	3.430	1.254–9.381		3.628	1.284–10.254	

CI: confidence interval; CRP: C-reactive protein; CSS: cancer-specific survival; HR: hazard ratio; RNU: radical nephroureterectomy; UTUC: upper tract urothelial carcinoma.

factor (p=0.3650), we classified the patients into three groups using the number of applicable factors and found that five-year CSS was 88%, 42.5%, and 0% in the low-risk (zero factors), intermediate-risk (one factor), and high-risk groups (two factors), respectively. (p<0.0001) (Figure 4b).

DISCUSSION

We determined the predictive factors for the prognosis in patients with UTUC undergoing RNU, then developed a prognostic model based on the involvement of risk factors, pT, and normalization of CRP. To the best of our knowledge, this is the first report on a prognostic model of UTUC after RNU based on these factors.

UTUC includes cases with rapid progression and poor prognosis after surgery and require some optional treatments, such as AC or NAC. For muscle-invasive bladder cancer (MIBC), NAC has been shown to improve prognosis,[9] and NAC also may be an option for UTUC, considering the decline in renal function after RNU.[10] While there have been efforts to improve the accuracy of the staging examination for UTUC,[11] it is difficult to accurately assess the risk of UTUC by preoperative imaging. Therefore, to avoid overtreatment for UTUC, in addition to RNU, adjuvant therapy for selective patients based on postoperative information is appropriate to improve prognosis.[12] However, even AC for UTUC was controversial.

Certain studies demonstrated the effect of AC on reducing distant metastases[13] and intravesical recurrence,[14] while other retrospective studies reported no impact on prognosis.[15,16] An RCT reported the results of postoperative adjuvant therapy using an ICI for locally advanced UC.[3] The study demonstrated the benefit mainly for patients with MIBC who often receive NAC. Another RCT, however, showed the benefit of AC with gemcitabine and cisplatin anticancer chemotherapy for patients with UTUC who were not treated with NAC.[4] Advances in postoperative systemic therapy for UTUC is expected to improve oncologic outcomes after RNU.

To decrease the risk of adverse events caused by such modalities, however, the choice of patients who undergo adjuvant therapy is an important issue. Therefore, the goal of this study was to analyze prognostic factors after RNU to identify UTUC patients with high risk of postoperative recurrence and/or progression. The association between the prognosis of UTUC and inflammatory response has been previously demonstrated.[17,18] These inflammation-related factors can reflect the presence or absence of disease progression and may be prognostic factors.[19]

Our results indicate that in addition to pT3 stage or higher, postoperative CRP non-normalization was an

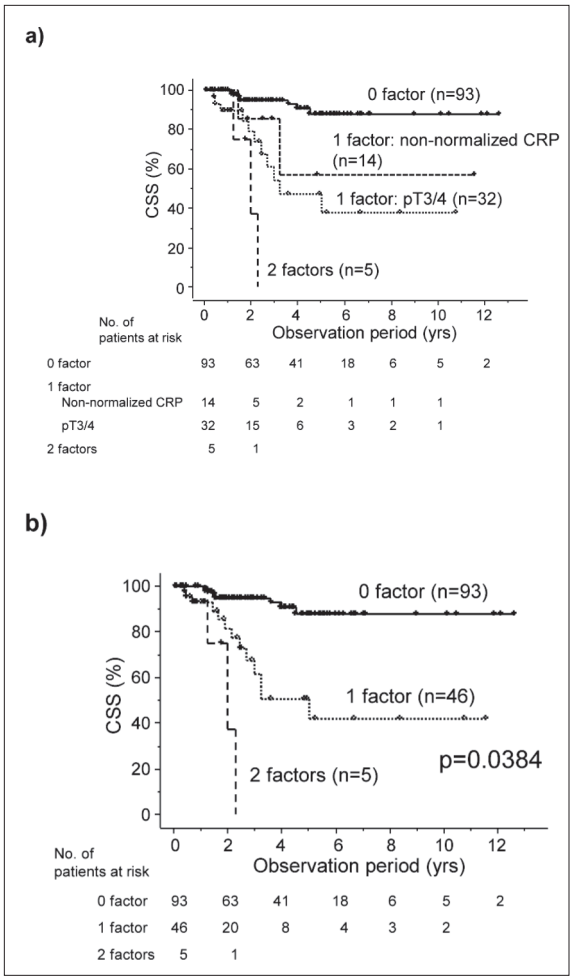

Figure 4. (a) Cancer-specific survival (CSS) stratified by four groups: no applicable factor, C-reactive protein (CRP) non-normalization only, pT3/4 only, and both factors; and (b) those stratified by the number of applicable risk factors.

independent poor prognostic factor. The finding that high CRP levels after RNU surgery are associated with poor prognosis regardless of preoperative CRP levels is consistent with the results of our previous study.[20] The association between inflammatory response and disease activity has already been reported previously in UTUC, and high CRP levels are thought to reflect inflammatory cytokine production from the tumor. The present study focuses on elevated CRP levels after radical surgery, which may reflect the presence of micrometastases.[21]

Other studies demonstrated several prognostic factors, including pathologic lymph node metastasis,[21] histologic high grade,[22] lymphovascular invasion,[23,24] and hydronephrosis;[17] however, these were not determined as independent prognostic factors by multivariate analysis in our study. Therefore, our prognostic model uses these two factors, showing it is possible to stratify prognosis on the basis of the number of factors. Only patients who had not undergone preoperative treatment were included, and the results provide useful information for predicting prognosis and selecting adjuvant therapy.

Limitations

There are several limitations to this study. One is its small study cohort and retrospective nature based on real-world data. Some other, well-known predictors of poor prognosis, such as lymph node metastasis, were not factored into the present model. In this study, lymph node dissection was performed in only 47 cases (32.7% of the total), and it is thought that there were cases with pathologic lymph node metastasis among those who did not undergo lymph node dissection.

While the perioperative change in CRP was a significant predictor of CSS, there was no statistical significance, only a tendency toward RFS. Possible reasons for this result may be the size of the study or the variety of postoperative therapeutic options. For UC with metastasis, chemotherapy and subsequent therapy using ICI or antibody-drug conjugate have been a standard option.[25,26] Inflammatory response has been reported to be associated with the efficacy of such regimens for UC.[27,28] The inclusion of postoperative CRP as a parameter in our model may also reflect its association with the effect of systemic therapy after recurrence and may have been statistically significant in CSS rather than RFS.

Another limitation is that our prognostic model is based on postoperative information and cannot predict prognosis at the preoperative time point. The indication and extent of lymph node dissection were also determined by each surgeon. Although the indications for LND remains unestablished, its impact on prognosis in patients with UTUC undergoing RNU needs to be considered. It is hoped that that the results of this study will be evaluated and confirmed in well-designed, larger prospective studies.

CONCLUSIONS

We presented a prognostic model for UTUC that considers the inflammatory response. With the introduction of more sophisticated and accurate imaging and new preoperative treatments, prognostic prediction will become even more important to enable individualization of treatment.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this works.

This paper has been peer-reviewed.

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