Original Article

A dynamic nomogram integrated with blood inflammation markers for predicting overall survival in patients with upper tract urothelial carcinoma

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Background: Upper tract urothelial carcinoma (UTUC) is a relatively rare disease with a poor prognosis. A growing body of evidence demonstrates that inflammation and the inflammatory microenvironment play a crucial role in tumorigenesis and tumor progression. Our aim was to evaluate the prognostic value of blood inflammation markers and develop a prediction model that incorporates inflammation markers in order to predict overall survival (OS) of UTUC.

Methods: We included 304 localized UTUC patients from two medical institutions who had undergone radical nephroureterectomy (RNU) (167 in the training cohort, 137 in the validation cohort). Univariate and multivariate Cox regression analyses were performed to screen the prognostic factors, and a nomogram and a web-based calculator were generated based on these predictors. The Harrell's concordance index (C-index), the area under the receiver operating characteristic (ROC) curve, the calibration curve, and decision curve analysis (DCA) were used to evaluate the performance of the nomogram.

Results: Independent predictors incorporated in the nomogram were pathological stage, surgical margin, albumin-to-globulin ratio (AGR), and hemoglobin-to-red cell distribution width ratio (HRR). The c-index value was 0.726 in the training cohort and 0.761 in the validation cohort. The area under the ROC of the nomogram at 1-, 3- and 5-year in the training and validation sets were 0.765, 0.755, 0.763, and 0.791, 0.833, 0.802, respectively. Both the internal and external validation calibration plots showed a subtle distinction between the predicted and the actual probabilities. And it appears to provide incremental benefits for clinical decision-making in comparison to the American Joint Committee of Cancer (AJCC) staging system.

Conclusions: In patients with UTUC after RNU, lower preoperative AGR and HRR were independent predictors of inferior survival. In addition, we created a novel blood inflammation marker-based dynamic nomogram that may be useful for surgeons or oncologists in risk stratification and patient selection for more intensive therapy and closer follow-up.

Keywords: Nomogram; upper tract urothelial carcinoma (UTUC); prognosis; web-based calculator; red blood cell distribution width

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Introduction

Although upper tract urothelial carcinoma (UTUC) accounts for only 5–10% of all urothelial malignancies (1), it has shown a gradual increase in incidence (2). Radical nephroureterectomy (RNU) with ipsilateral bladder-cuff excision is the industry-recognized standard surgical procedure for patients with localized disease (3). Due to the highly malignant nature of UTUC, approximately 40% of UTUC are fatal within 5 years (4). At present, some predictors related to oncological outcomes have been identified, such as pathological stage, pathological grade, status of lymph node, and lymphovascular invasion (LVI) (3). These prognostic factors, however, are still insufficient to predict the prognosis in UTUC. Hence, it makes sense to investigate new prognostic factors to determine the patient populations that would benefit from adjuvant chemotherapy or closer monitoring.

The importance of inflammation and the inflammatory microenvironment in tumorigenesis and tumor progression is being supported by a growing body of evidence (5). Inflammatory marker, as one of the objective indicators of reflecting the degree of host inflammation, has been increasingly associated with the prognosis of cancer. Previous studies have suggested that blood inflammation markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), prognostic nutritional index (PNI), albumin-to-globulin ratio (AGR), systemic immune–inflammation index (SII), etc., could be informative in predicting outcomes for urological tumors (6-11). Remarkably, one of them was hemoglobin-to-red cell distribution width ratio (HRR, Hb/RDW), which is a novel biomarker first proposed by Sun *et al.* in 2016 (12,13). However, because of the rarity of UTUC, most predictors were obtained based on pathological characteristics, and readily available preoperative indicators such as blood parameters were often ignored. Our primary goal was to identify powerful predictors from a large pool of potential biomarkers and to develop and externally validate a novel prediction model incorporating inflammation markers to predict overall survival (OS) in UTUC patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-133/rc).

Highlight box

Key findings

- A dynamic nomogram was constructed based on inflammation markers and pathologic data to predict overall survival in patients with upper tract urothelial carcinoma.

What is known and what is new?

- The current prognostic tools and factors can no longer meet the demand of clinic. Blood inflammatory markers have shown promising prognostic value in a variety of cancers. However, until now, few inflammatory markers have been integrated into the nomogram models in UTUC.
- We developed a convenient dynamic nomogram that includes inflammatory markers, which performed well in both the training set and the validation set.

What is the implication, and what should change now?

- The prediction model may be useful for surgeons or oncologists in risk stratification and patient selection for more intensive therapy and closer follow-up.

Methods

Patient selection

We included consecutive patients with non-metastatic UTUC treated with RNU at Huadong Hospital Affiliated to Fudan University from March 2010 to July 2022 in the training cohort. In addition, between January 2010 and April 2017, patients diagnosed with non-metastatic UTUC and underwent RNU at Huashan Hospital Affiliated to Fudan University were available for external validation. The exclusion criteria were shown as below: (I) patients who accepted neoadjuvant therapy; (II) patients who underwent red blood cell transfusions within one month before radical resection; (III) incomplete clinicopathological data and follow-up information. (IV) follow-up time <3 months. (V) incomplete blood tests within one week before RNU; (VI) patients who had concomitant autoimmune diseases, acute and chronic infectious diseases, hematological diseases or chronic liver diseases. In total, 167 and 137 subjects were enrolled in the training cohort and validation cohort respectively, and the patient selection process is illustrated by the flowchart in *Figure 1*.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Approval was granted by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (No. 2022K116) and the Institutional Review Board of Huashan Hospital, Fudan University (No. 2019-010). Informed consent was waived by Ethics Committees due to the retrospective nature of the study.

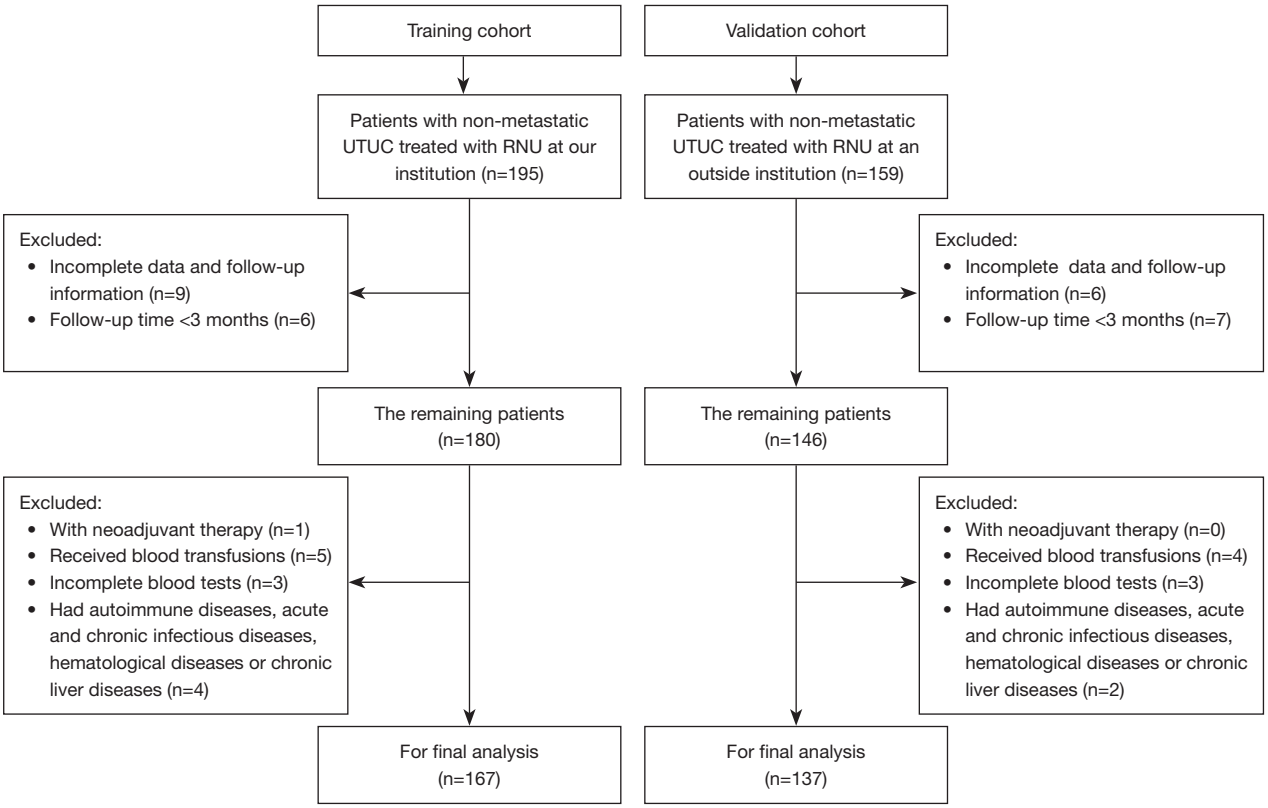

Figure 1 Flowchart of patient selection. UTUC, upper tract urothelial carcinoma; RNU, radical nephroureterectomy.

Definitions and follow-up

The formulas for calculating the NLR, PLR, MLR, PNI, SII, AGR, and HRR were as follows: [NLR = neutrophil count ($\times10^9$/L)/lymphocyte count ($\times10^9$/L) (14)]; [PLR = platelet count ($\times10^9$/L)/lymphocyte count ($\times10^9$/L) (15)]; [MLR = monocyte count ($\times10^9$/L)/lymphocyte count ($\times10^9$/L) (16)];[PNI = serum albumin (g/L) + 5 × lymphocyte count ($\times10^9$/L) (17)]; [SII = neutrophil count ($\times10^9$/L) × platelet count ($\times10^9$/L)/lymphocyte count ($\times10^9$/L) (18)]; [AGR = serum albumin (g/L)/(total protein – serum albumin) (g/L) (19)]; [HRR = hemoglobin (g/dL)/red cell distribution width (%) (12)]; Laboratory analyses were performed using the Sysmex XN-2000 analyzer (Japan) and Hitachi 7170 Automatic Biochemical Analyzer (Japan) in training cohort, while blood tests were analysed using the Sysmex XN-1000 analyzer (Japan) and Hitachi 7600 Automatic Biochemical Analyzer (Japan) in validation cohort.

The pathological grade and stage were assessed in accordance with the 2022 World Health Organization (20) and the 8th Edition American Joint Committee of Cancer (AJCC) Tumor-Node-Metastasis (TNM) classification (21), respectively. Ipsilateral hydronephrosis state was determined from radiographic reports of preoperative computed tomography (CT) or magnetic resonance imaging (MRI). When the tumor grows in the renal pelvis and ureter simultaneously, tumor location was consistent with the location of dominant lesion determined in the following order of priority: stage, grade, and size.

Doctors assessed the patients every 3–4 months during the first year, and every 6 months for the following 2 years, and then annually thereafter. The way of evaluation contained history, physical examination, blood tests, urinary cytology, cystoscopy, chest radiography and abdominopelvic CT scan. OS was calculated as the interval from the date of surgery until the last follow-up visit or death from any cause.

Statistical analysis

Group comparison analyses were using the Student's *t*-test or Mann-Whitney test (without normal distribution) for

continuous variables and using Fisher 's exact test and chi-squared test for noncontinuous variables. The receiver operating characteristic (ROC) curve was applied for selecting the best cut-off values. Variables with P<0.05 in a univariate Cox regression and considered potentially significant based on clinical experience and prior studies were included in the multivariate Cox regression analysis. Covariates multicollinearity was checked before constructing the model. Variance inflation factor (VIF) >4.0 in Collinearity diagnosis indicates the existence of close relations among the selected variables (22,23), which leads to false associations and potentially unreliable effect estimates.

Nomogram was generated based on multivariable regression coefficients of training cohort. The DynNom package was applied to construct a convenient web-based survival rate calculator. Discrimination validity of the prediction model was quantified by Harrell's concordance index (c-index) and the areas under the ROC curves at 1-, 3- and 5-year. Calibration plots at 1-, 3- and 5-year were conducted with 1,000 bootstrap resampling to evaluate the calibration performance by comparing the model-predicted probabilities with the actual observed frequencies. To visualize and evaluate the clinical benefit of the nomogram, additionally we performed decision curve analysis (DCA). Finally, based on the total points from nomogram of each patient, the validation cohort was divided into three risk subgroups. The X-tile plot enables a comprehensive evaluation of every method for dividing a population into high- and low-risk subsets for survival. The "minimum P value" approach is then used to determine the best cut-off value for continuous variables (24). We used the Kaplan-Meier curve to assess OS, and the log-rank test for comparison among subgroups. All the above steps were conducted using R software (version 4.2.1, with survival, rms, ggprism, ggplot2, ggsci, Hmisc, riskRegression, prodlim, ggDCA, DynNom packages), IBM SPSS (version 26.0) and X-tile software (version 3.6.1). A two-tailed value of P<0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 provided a summary of baseline data of the two sets. In the training and validation cohorts, a total of 46 (27.5%) and 43 (31.4%) patients died of UTUC, and 57 (34.1%) and 51 (37.2%) patients died of any cause, respectively. Owing to the patient heterogeneities in different medical institutions, statistical differences in gender (P=0.02) and pathological stage (P=0.036) were discovered between the training set and the validation set.

Development of the dynamic nomogram

The general statistical characteristics of the seven inflammatory markers were presented in *Table 2*. The optimal cut-off points for NLR, PLR, MLR, PNI, SII, AGR, and HRR were identified as 2.334, 110.503, 0.462, 44.969, 681.783, 1.588, and 1.020 by calculating the maximal Youden Index. Hence, based on each threshold, all patients could be separated into two groups (low level and high level). High SII, low AGR, and low HRR were found

Table 1 Clinicopathologic features of the training and validation cohorts

Variable	All patients (n=304)	Training cohort (n=167)	Validation cohort (n=137)	P value
Age, years, mean (±SD)	67.09 (±10.38)	67.95 (±10.35)	66.05 (±10.36)	0.567
Gender, n (%)				0.020
Male	189 (62.2)	94 (56.3)	95 (69.3)	
Female	115 (37.8)	73 (43.7)	42 (30.7)	
Follow-up, months, median (IQR)	–	55.5 (37.8–93.1)	51.0 (25.1–74.8)	–
Smoking history, n (%)				0.432
Yes	52 (17.1)	26 (15.6)	26 (19.0)	
No	252 (82.9)	141 (84.4)	111 (81.0)	

Table 1 *(continued)*

Table 1 *(continued)*

Variable	All patients (n=304)	Training cohort (n=167)	Validation cohort (n=137)	P value
Previous UCB, n (%)				0.476
Yes	23 (7.6)	11 (6.6)	12 (8.8)	
No	281 (92.4)	156 (93.4)	125 (91.2)	
Hydronephrosis, n (%)				0.717
Yes	203 (66.8)	113 (67.7)	90 (65.7)	
No	101 (33.2)	54 (32.3)	47 (34.3)	
Tumor location, n (%)				0.679
Renal pelvis	146 (48.0)	82 (49.1)	64 (46.7)	
Ureter	158 (52.0)	85 (50.9)	73 (53.3)	
Pathological grade, n (%)				0.227
High	259 (85.2)	146 (87.4)	113 (82.5)	
Low	45 (14.8)	21 (12.6)	24 (17.5)	
Pathological stage, n (%)				0.036
Ta	75 (24.7)	44 (26.3)	31 (22.6)	
T1/Tis	53 (17.4)	29 (17.4)	24 (17.5)	
T2	50 (16.4)	18 (10.8)	32 (23.4)	
T3	111 (36.5)	65 (38.9)	46 (33.6)	
T4	15 (4.9)	11 (6.6)	4 (2.9)	
Multifocality, n (%)				0.414
Yes	71 (23.4)	42 (25.1)	29 (21.2)	
No	233 (76.6)	125 (74.9)	108 (78.8)	
LVI, n (%)				0.320
Yes	59 (19.4)	29 (17.4)	30 (21.9)	
No	245 (80.6)	138 (82.6)	107 (78.1)	
Lymph node status, n (%)				0.150
pN0	20 (6.6)	15 (9.0)	5 (3.6)	
pNx	275 (90.5)	148 (88.6)	127 (92.7)	
pN+	9 (3.0)	4 (2.4)	5 (3.6)	
Surgical margin, n (%)				0.879
Positive	28 (9.2)	15 (9.0)	13 (9.5)	
Negative	276 (90.8)	152 (91.0)	124 (90.5)	
Surgical approach, n (%)				0.108
Open	149 (49.0)	91 (54.5)	58 (42.3)	
Laparoscopic	145 (47.7)	71 (42.5)	74 (54.0)	
Robot-assisted	10 (3.3)	5 (3.0)	5 (3.6)	

SD, standard deviation; IQR, interquartile range; UCB, urothelial carcinoma of bladder; LVI, lymphovascular invasion.

Table 2 Representative value of blood inflammation markers

Representative value	NLR	PLR	MLR	PNI	SII	AGR	HRR
Mean	3.371	152.722	0.295	47.979	723.605	1.538	0.963
Median	2.719	135.790	0.255	48.004	602.090	1.519	0.960
Range	19.262	409.178	0.728	26.673	3188.662	1.766	0.849
Standard deviation	2.369	67.375	0.143	4.956	520.953	0.293	0.133
Cut-off points	2.334	110.503	0.462	44.969	681.783	1.588	1.020

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune–inflammation index; AGR, albumin-to-globulin ratio; HRR, hemoglobin-to-red cell distribution width ratio.

to be significantly related to poor OS in the univariate regression analysis (P=0.022, 0.002, 0.011, respectively; *Table 3*). Hydronephrosis (P=0.009), advanced stage (P<0.001), multiple tumors (P=0.04), and positive surgical margin (P=0.012) were also associated with poor outcomes. Given the importance of pathological grade in predicting prognosis, pathological grade was also incorporated into the final Cox regression analysis (P=0.111).

VIF were all <4, which means that no variables entered into the multivariate regression had significant multicollinearity (*Table 3*). By adopting a forward selection method, multivariate regression analysis revealed that pathological stage (P<0.001), surgical margin (P=0.031), AGR level (P=0.009), HRR level (P=0.026) were independently associated with OS (*Table 3*). The prognostic nomogram was generated based on multivariate regression coefficients of these predictors (*Figure 2*). For convenience, we further constructed a web-based survival rate calculator (available from: https://dids.shinyapps.io/DynNomappOS/). With the help of this tool, it is quick and easy to determine the survival probability and its 95% confidence interval (95% CI) for UTUC patients at any time point after RNU (*Figure 3*). For example, for patients with T2 stage, negative margins, AGR <1.588 and HRR ≥1.020, the probability of OS at 18 months was approximately 0.88 (95% CI: 0.770–1.000) (*Figure 3A*,*3B*).

Performance and clinical utility of nomogram

The c-index value was 0.726 (95% CI: 0.666–0.786) in the training cohort while 0.761 (95% CI: 0.692–0.830) in the validation cohort. In the primary sample, the AUC of nomogram at 1-, 3- and 5-year were 0.765, 0.755, 0.763, respectively (*Figure 4A*). Meanwhile, the AUC of nomogram at 1-, 3- and 5-year were 0.791, 0.833, 0.802 in the validation sample (*Figure 4B*), which indicated that this model achieved a favorable discrimination accuracy. Additionally, both the internal and external validation calibration plots showed a subtle distinction between the predicted and the actual probabilities (*Figure 5*).

DCA offers a visual representation of clinical net benefit for model compared with scheme of intervention for all patients (oblique line) and for none (horizontal line). When the risk threshold was 0.2–0.9, the model showed favorable clinical net benefit gains in predicting 5-year OS (*Figure 6A*). Furthermore, using the nomogram to make treatment decision for the validation sample was satisfactory as long as the risk threshold was >0.2 (*Figure 6B*). When comparing our nomogram to the AJCC staging system, we found the nomogram performed better across nearly all risk thresholds in both the training and validation cohorts (*Figure 6*).

Use in risk stratification

The best cut-off values of total points were 94.5 and 130.5 by using X-tile (*Figure 7A*,*7B*), and the validation cohort was then divided into low risk subgroup (points ≤94.5), moderate risk subgroup (94.5< points ≤130.5), and high risk subgroup (points >130.5). The Kaplan-Meier curve and log-rank test showed that survival rates in the three risk subsets were statistically different from one another (5-year OS in low, moderate, high-risk subgroup were 81.3%, 61.0%, 19.6%, respectively, P<0.05; *Figure 7C*).

Discussion

Due to the peculiar nature of anatomic structures in the renal pelvis and ureter, preoperative evaluation of UTUC using modern medical imaging methods is currently difficult and may lead to under- or over-treatment (25). Preoperative blood inflammation markers may be useful in screening the cases that are suitable for kidney-sparing surgery with

Table 3 Univariable and multivariable Cox regression analyses and multicollinearity test

Variables	Univariate Cox regression		VIF	Multivariate Cox regression	
	HR (95% CI)	P value		HR (95% CI)	P value
Age, years (<68 *vs.* ≥68)	1.293 (0.767–2.179)	0.333			
Gender (male *vs.* female)	0.872 (0.518–1.470)	0.607			
Smoking history	1.110 (0.561–2.196)	0.765			
Previous UCB	1.113 (0.403–3.079)	0.836			
Hydronephrosis	2.491 (1.258–4.931)	0.009	1.105	1.796 (0.870–3.710)	0.113
Tumor location (ureter *vs.* renal pelvis)	1.146 (0.681–1.928)	0.607			
Pathologic grade (high *vs.* low)	2.284 (0.826–6.313)	0.111	1.388	0.477 (0.102–2.230)	0.347
Pathological stage	–	<0.001	1.372	–	<0.001
Ta	1.000	Referent		1.000	Referent
T1/Tis	2.254 (0.782–6.499)	0.133		2.527 (0.613–10.420)	0.200
T2	2.810 (0.905–8.721)	0.074		3.545 (0.772–16.290)	0.104
T3	4.282 (1.785–10.271)	0.001		4.196 (1.178–14.940)	0.027
T4	6.693 (2.148–20.849)	0.001		11.344 (2.493–51.610)	0.002
Multifocality	1.782 (1.026–3.096)	0.040	1.050	1.362 (0.767–2.420)	0.292
LVI	1.434 (0.757–2.715)	0.268			
Surgical margin (positive *vs.* negative)	2.642 (1.241–5.626)	0.012	1.032	2.391 (1.082–5.290)	0.031
Surgical approach	–	0.070			
Open	1.000	Referent			
Laparoscopic	0.504 (0.274–0.926)	0.027			
Robot-assisted	0.963 (0.233–3.986)	0.958			
NLR (high level *vs.* low level)	1.470 (0.833–2.593)	0.184			
PLR (high level *vs.* low level)	1.504 (0.778–2.906)	0.225			
MLR (high level *vs.* low level)	1.797 (0.930–3.472)	0.081			
PNI (low level *vs.* high level)	0.891 (0.471–1.686)	0.723			
SII (high level *vs.* low level)	1.840 (1.093–3.097)	0.022	1.052	1.421 (0.828–2.440)	0.202
AGR (low level *vs.* high level)	2.580 (1.411–4.718)	0.002	1.091	2.330 (1.240–4.380)	0.009
HRR (low level *vs.* high level)	2.437 (1.231–4.825)	0.011	1.096	2.250 (1.104–4.590)	0.026

VIF, variance inflation factor; UCB, urothelial carcinoma of the bladder; LVI, lymphovascular invasion; CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune–inflammation index; AGR, albumin-to-globulin ratio; HRR, hemoglobin-to-red cell distribution width ratio.

low-risk features or accepting neoadjuvant chemotherapy with a high likelihood of adverse outcomes (26,27). Unfortunately, none of the six prognostic models (28-33) recommended by the EAU guideline (3) took inflammatory markers into account in both univariate and multivariate analyses. Our study included a relatively comprehensive set of inflammatory indicators, aiming to select the powerful predictors from a large pool of biomarkers. The findings suggested that in addition to advanced T staging and positive surgical margin, low AGR (≤1.588) and low HRR (≤1.020) were independent risk factors of UTUC. As far as we know, this is the first prediction nomogram in UTUC

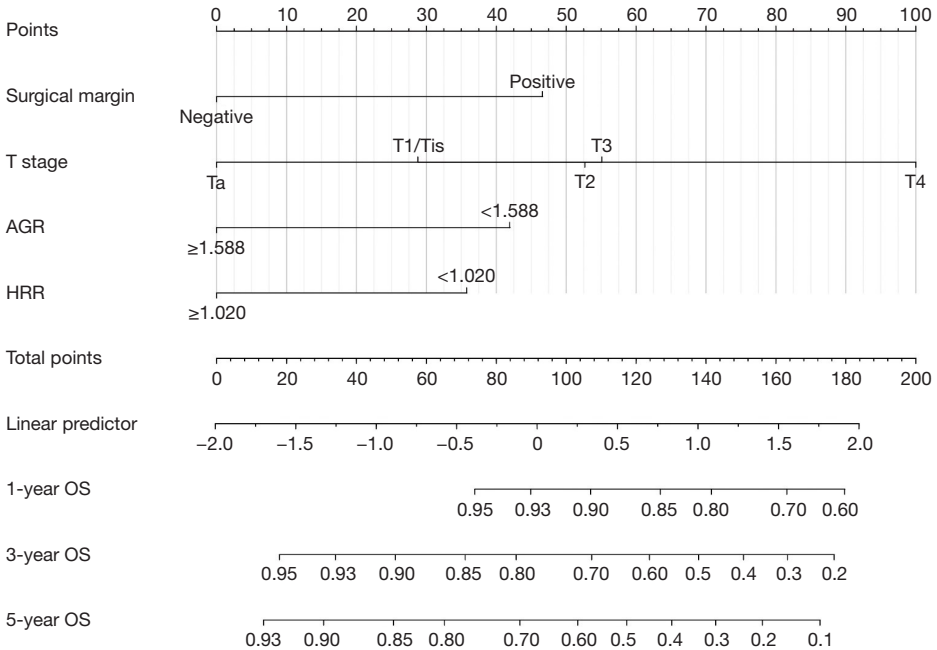

Figure 2 Nomogram to predict 1-, 3- and 5-year OS post RNU for UTUC. Firstly, individual subject's value is located on each axis. Secondly, draw a vertical line upward to the "Points" axis, so the point is generated. Thirdly, sum the points for all variables and locate the sum on the "Total points" line. Finally, this point projected on the 1-, 3-, and 5-year OS lines indicates the 1-, 3-, and 5-year probabilities of OS, respectively. AGR, albumin-to-globulin ratio; HRR, hemoglobin-to-red cell distribution width ratio; OS, overall survival; RNU, radical nephroureterectomy; UTUC, upper tract urothelial carcinoma.

that incorporated either AGR or HRR. In comparison with the AJCC staging system, the nomogram led to superior net benefit across nearly all threshold probabilities in both the training and validation cohorts. Finally, we divided the validation cohort into three risk subgroups according to the total points of patients from nomogram. The results showed that the high-risk subgroup was significantly worse than the other two subgroups in OS, suggesting that the high-risk subgroup may benefit more from a more aggressive treatment strategy.

By integrating multiple prognostic factors, the nomogram can predict the prognosis of patients and thus guide medication, operation and follow-up. The prognostic impact of T2 is very close to that of T3 as seen in our established nomogram, suggesting that the significance of preoperative differentiation between T2 and T3 may be limited, while preoperative identification of T4 is necessary. We also carried out a subgroup analysis in light of the possibility that pT3 renal pelvis carcinoma and pT3 ureteral carcinoma have different prognosis (34,35). Unfortunately, there was no statistically significant difference in OS between pT3 renal pelvis carcinoma, pT3 ureteral carcinoma, and pT2 UTUC (Figure S1). It might be due to the relatively small sample size. Nomograms may be useful, but it is not easy to convince doctors to use them in clinical practice. Therefore, we built a web-based tool that can dynamically predict the OS of UTUC patients based on the nomogram. We found a high risk of death in the first 3.5 years after RNU (*Figure 3C*) and therefore strongly recommend regular follow-up and treatment in the first 3.5 years for all cases.

Sufficient evidence supports that inflammation participates in disease progression of UTUC (36,37). As one of the components of AGR, serum albumin (ALB) is closely related to inflammation and cancer. Firstly, malignant tumors can induce systemic inflammation response and stimulate the production of cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF), which inhibited ALB synthesis and increase capillary permeability, thus leading to more ALB loss (38). Secondly, as an antioxidant, ALB produces an effect on keeping DNA replication stable and inhibiting abnormal cell proliferation (39,40). Lastly, albumins, as vital transporters, in turn affect the distribution and efficacy of anticancer drugs. In addition, hyperglobulinemia also reflects the status of an

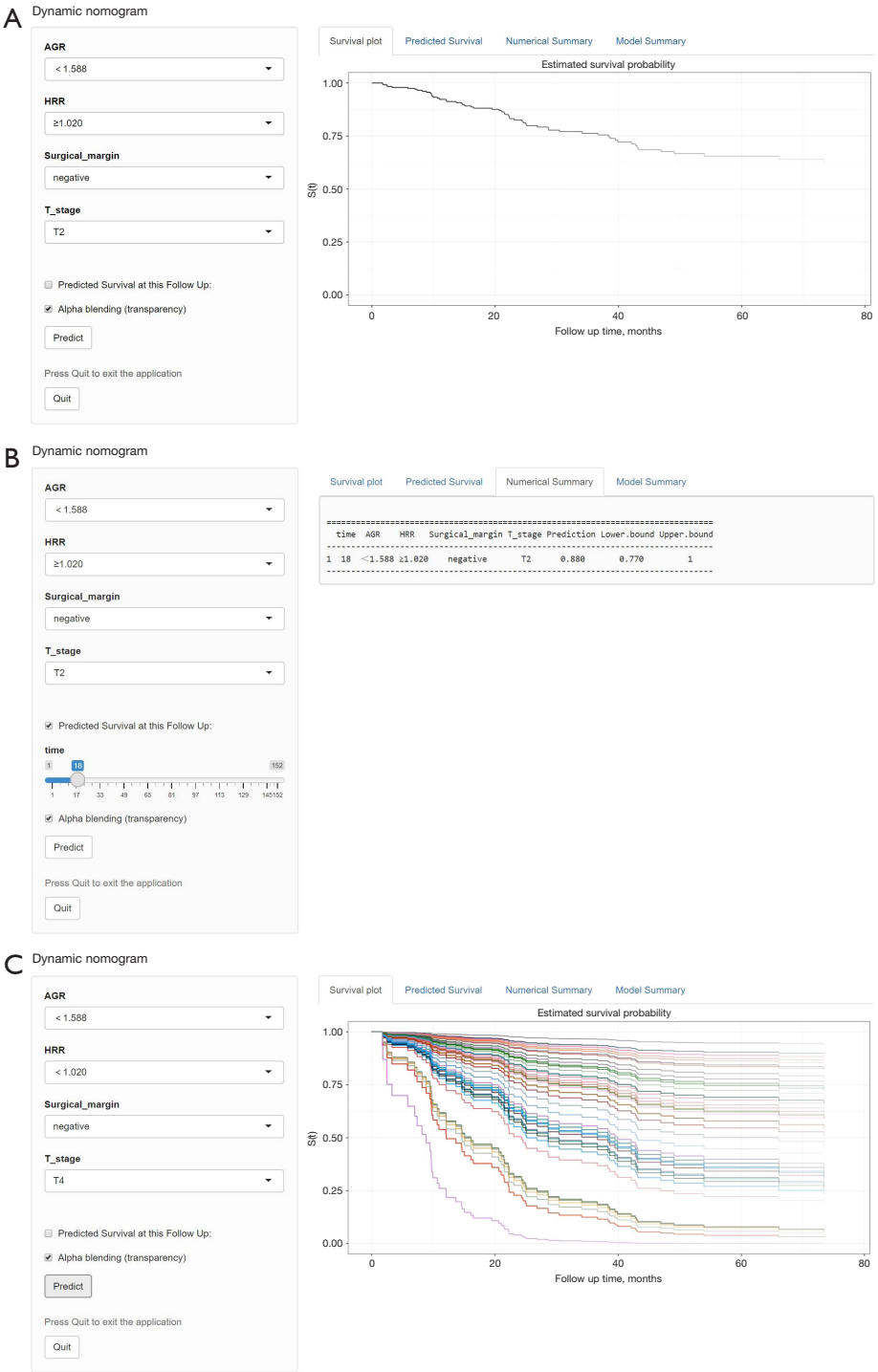

Figure 3 A dynamic web-based survival rate calculator. Survival plot for patients with certain clinicopathologic features during the follow-up period (A). Survival probability and its 95% confidence interval for patients with certain clinicopathologic features at 18 months after RNU (B). Survival plot for all patients during the follow-up period (C). AGR, albumin-to-globulin ratio; HRR, hemoglobin-to-red cell distribution width ratio; RNU, radical nephroureterectomy.

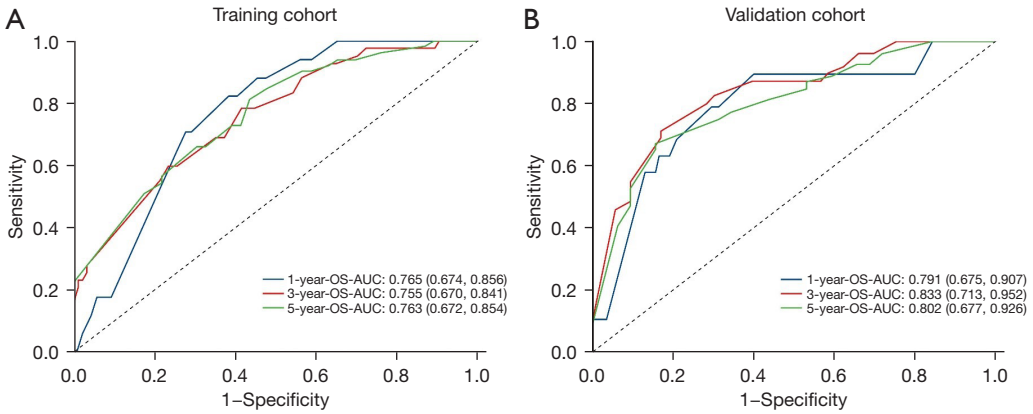

Figure 4 ROC curves of the nomogram for 1-, 3- and 5-year OS in the training cohort (A) and validation cohort (B). OS, overall survival; AUC, area under curve; ROC, receiver operator characteristic.

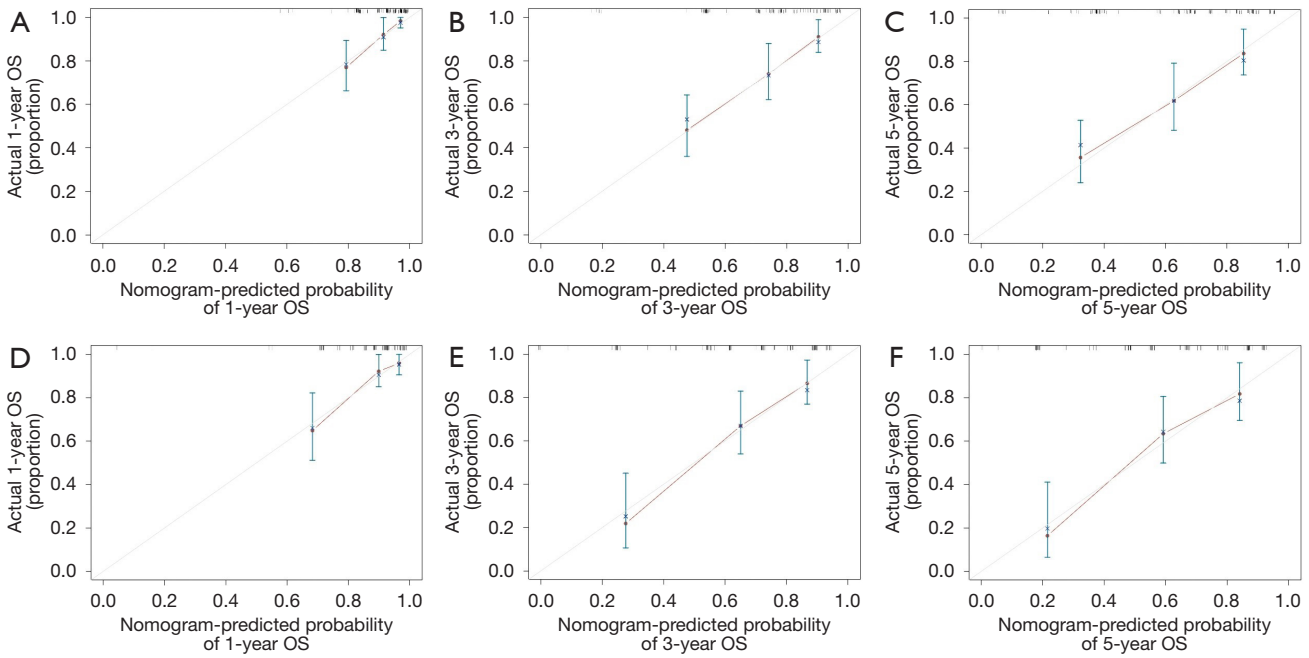

Figure 5 Calibration plots of the nomogram for 1-, 3- and 5-year OS in the training cohort (A-C) and validation cohort (D-F). OS, overall survival.

accumulative effect of exposure to inflammation (41). AGR consists of two identified predictors and is therefore more compelling in reflecting physical condition and reducing the perturbations of blood dilution or hemoconcentration. Interestingly, in addition to finding that low preoperative AGR was an independent risk factor for poor disease-free and OS, Fukushima *et al.* discovered that those patients with postoperative AGR recovery had a better prognosis than those without, but it did not achieve statistical significance (42). Although the recovery of the markers is much more affected by intensive postoperative medications (human albumin infusion, red blood cell transfusion, etc.), it provides for us a new perspective on how to optimize the prediction model in the future.

Since the HRR is a newly emerging biomark, studies involving its prognostic value in urothelial carcinoma continue to be scarce. Consistent with the previous study (43), the present study demonstrated that low HRR

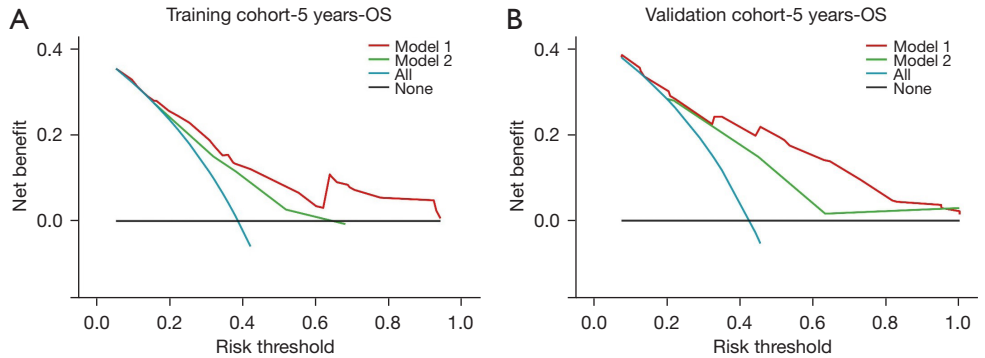

Figure 6 Comparison of the decision curve analysis of the nomogram (Model 1) and the AJCC staging system (Model 2) for 5-year OS in the training cohort (A) and validation cohort (B). OS, overall survival; AJCC, American Joint Committee of Cancer.

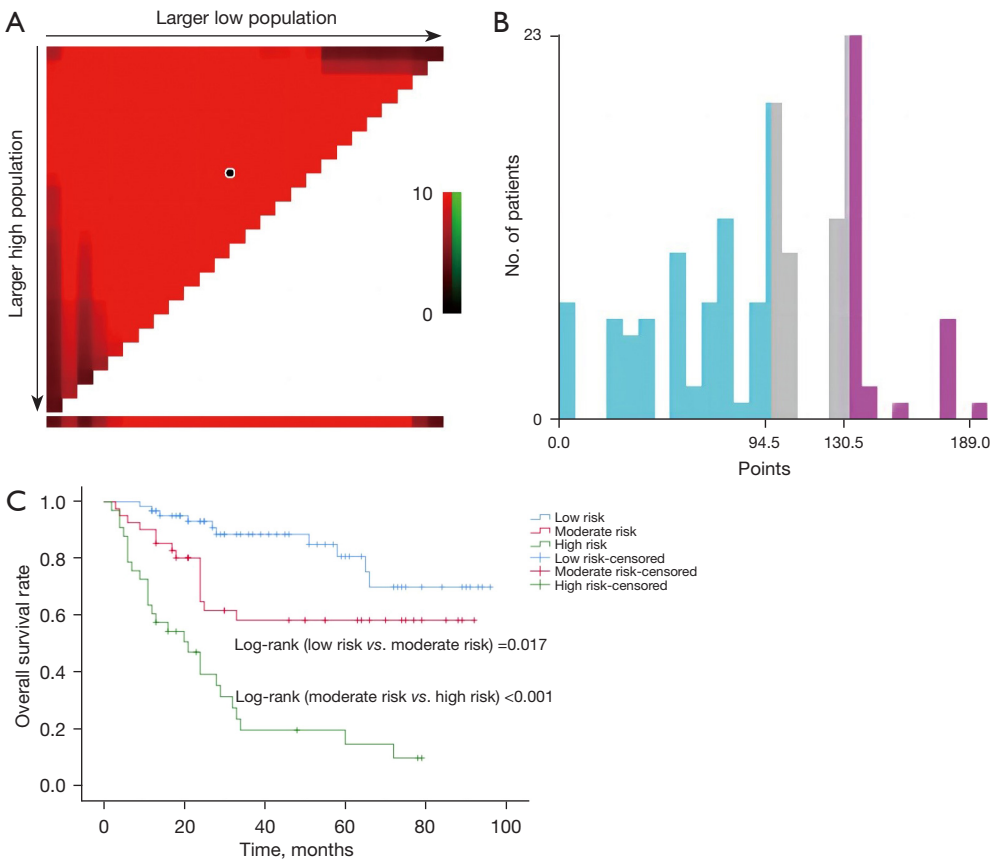

Figure 7 X-tile analysis and Kaplan-Meier method. (A) The X-tile plots show the χ^2 log-rank values with cut points, producing low, moderate, and high-risk subgroups. The X-axis represents all potential cut-points from low to high (left to right) that define a low subset, whereas the Y-axis represents cut-points from high to low (top to bottom), that define a high subset. Red coloration of cut-off values indicates an inverse correlation with OS, and green coloration represents direct associations. The optimal cut-point occurs at the brightest pixel (green or red). The number of cases in three subgroups is displayed in (B) (low risk: blue, moderate risk: gray, high risk: magenta). Kaplan-Meier curves in low, moderate, high-risk subgroups (C) are drawn. OS, overall survival.

was associated with inferior survival and we obtained a cut-off value similar to that found in the previous study (1.02 and 1.05, respectively). Furthermore, the present study showed that low HRR had a comparable hazard ratio to positive margin status and low AGR (HR =2.250, 2.391, and 2.330, respectively) in predicting OS for non-metastatic UTUC treated RNU. According to the evidence presented above, it can be concluded that HRR is a reliable, efficient, and powerful predictor of UTUC.

The mechanism of alterations of HRR on oncogenesis and tumor development has not been fully elucidated at present. Cancer-related inflammation inhibits the production of erythropoietin (EPO) and promotes the release of immature red blood cells, thus leading to an increase in RDW and a drop in Hb (44). These alterations in RDW and Hb, in turn, will contribute to tumor invasion and metastasis further. The hypoxic microenvironment accelerates tumor neovascularization by stimulating the production of vascular endothelial growth factor (VEGF) when the number of red blood cells is reduced or their function is impaired (45). Compared to Hb or RDW alone, HRR could help to minimize the confounding factors caused by non-neoplastic diseases.

The present study is limited by the retrospective nature of design. Moreover, due to the retrospective nature of the study, laboratory analysis and adjuvant chemotherapy dose schedule were difficult to standardize across the two medical institutions. Also, patients with positive nodes were rare as regional or extended node dissection was not done routinely. Eventually the status of lymph nodes was not included in the regression analysis due to the imbalanced sample distribution. And finally, since the data of pathological stage and surgical margin were obtained postoperatively, the nomogram in this study is not capable of guiding neoadjuvant chemotherapy or lymph node dissection. However, at least we have confirmed the important prognostic value of AGR and HRR in UTUC, and we expect that AGR and HRR will be applied to pre-operative prediction models in the future. Therefore, further large-scale, prospective analyses are warranted to provide higher-level evidence.

Conclusions

In patients with UTUC after RNU, lower preoperative AGR and HRR were independent predictors of inferior survival. We developed a blood inflammation markers-based dynamic nomogram that predicted OS with good accuracy and calibration. Hence, these biomarkers and the proposed nomogram will be helpful to assist surgeons or oncologists in risk stratification and selection of patients for more intensive therapy and closer follow-up. Multi-institutional prospective validation work is necessary for future clinical use.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-133/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-133/dss

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-133/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-133/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Approval was granted by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (No. 2022K116) and the Institutional Review Board of Huashan Hospital, Fudan University (No. 2019-010). Informed consent was waived by Ethics Committees due to the retrospective nature of the study.

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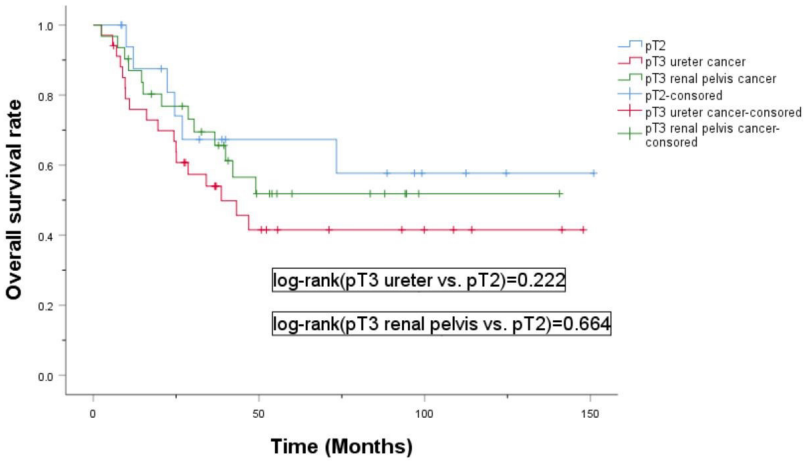

Figure S1 Kaplan-Meier analyses for overall survival stratified by tumor location and stage in pT_{2-3} UTUC. OS, overall survival; UTUC, upper tract urothelial carcinoma.

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