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Original Research

Clinicopathological and prognostic significance of preoperative plasma fibrinogen level in patients with upper urinary tract urothelial carcinoma: A retrospective tumor marker prognostic study

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ABSTRACT

Purpose: To retrospectively evaluate the prognostic value of preoperative plasma fibrinogen to predict oncological outcome and intravesical recurrence in upper urinary tract urothelial carcinoma.

Methods: This retrospective study comprised 130 patients with non-metastatic upper urinary tract urothelial carcinoma who underwent surgery between June 2009 and June 2017 at a single center. Patients were categorized base on an optimal value of preoperative plasma fibrinogen. Progression-free and cancer-specific survival were assessed using Kaplan-Meier method. The associations between plasma fibrinogen and clinical outcomes were assessed with univariate and Multivariate analysis.

Results: Elevated plasma fibrinogen was associated with advance tumor stage, high tumor grade and tumor size. No significant association was found between plasma fibrinogen and intravesical recurrence. Multivariate analysis revealed that plasma fibrinogen ≥3.602 g/L was an independent prognostic indicator for progression-free survival (HR = 2.18; 95% CI: 1.17–4.06; p = 0.01) and cancer-specific survival (HR = 2.2; 95% CI: 1.13–4.28; p = 0.02), as well as pathological T stage and tumor grade.

Conclusions: Elevated preoperative plasma fibrinogen is an independent unfavorable prognostic factor for oncological outcomes in patients with upper urinary tract urothelial carcinoma. However, there is no association between preoperative plasma fibrinogen and intravesical recurrence. As an effective and easily accessible biomarker, this parameter can be applied in pre-intervention risk stratification of upper urinary tract urothelial carcinoma.

1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) is relatively uncommon and account for 5–10% of urothelial carcinoma [1]. Radical nephroureterectomy (RNU) is considered as the standard treatment for high-risk UTUC, combined with adjuvant bladder instillation [2]. Nevertheless, the rate of intravesical recurrence (IVR) following RNU for UTUCs is 22%–47% [3,4]. According to the literature, pathological T stage and tumor grade are prognostic factors for UTUC [5,6]. However, the available preoperative prognostic factors for UTUC is still limited.

Increasing evidence have suggested that there is an interactive relationship between hemostatic factors and tumor biology [7–9]. Plasma fibrinogen is found over expressed in many types of tumors [10]. Several studies had proven the prognostic value of plasma fibrinogen in UTUC [11–13]. However, the potential relationship between preoperative plasma and postoperative intravesical recurrence (IVR) has not been confirmed. Besides, the role of plasma fibrinogen in predicting patients' progression-free survival was not examined.

The objective of this study is to validate the prognostic value of preoperative plasma fibrinogen in a Chinese cohort of patients underwent radical nephroureterectomy for UTUC.

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2. Material and methods

2.1. Study population

The work has been reported in line with the REMARK criteria. This retrospective study included a total of 130 patients, who were diagnosed with UTUC without signs of metastasis, and subsequently underwent radical nephroureterectomy (RNU) from June 2009 to June 2017 in XXX Hospital, XXX. None of the patients received preoperative chemotherapy or radiotherapy. All patients underwent routine hematological examination, computed tomography and/or ureteroscopy with biopsy before RNU. All surgical specimens were processed according to standard pathological procedures. The specimens were confirmed as UTUC based on the International Union against Cancer TNM classification system. Histological grade was assessed according to the 1998 World Health Organization/International Society of Urologic Pathology consensus classification [14]. Medical records of all patients were reviewed for clinical and pathological information. Patients underwent radical cystectomy simultaneously were excluded. Adjuvant intravesical instillation and/or postoperative cisplatin-based chemotherapy was administered by clinician's discretion base on tumor stage and grade. The plasma fibrinogen levels were measured by collecting 2–3 ml of blood samples in coagulation tube from all patients before surgical intervention. Plasma fibrinogen levels were determined via the Clauss method [15] with bovine thrombin (100 NIH U/mL). The inter-assay coefficient of variation was < 3% and < 7.5% for the plasma control in the normal and pathological range, respectively.

2.2. Surgical technique

All surgery were performed by several skilled surgeons in this tertiary care center. RNU was performed either open or laparoscopically based on the surgeon's preference. The kidney, Gerota fascia, perinephric fat, ureter and bladder cuff were removed en bloc. The bladder cuff was resected through extravesical approach. The bladder was sutured in two layers. The hilar and regional lymph nodes were resected, while extended lymphadenectomy was not routinely performed.

2.3. Follow-up regimen

All patients were followed every 3–4 months in the first year after RNU, every 6 months from the second year through the third year, and annually thereafter. Follow-up consisted of a medical history, physical examination, routine urine test, chest radiography, ultrasonic evaluation of urinary system and cystoscopy. Elective measures such as bone scans, computed tomography, or magnetic resonance imaging were performed when clinically indicated. The median follow-up period was 30 months (range 3–103 months).

The cancer-specific survival (CSS) (time from the initial surgical treatment to the UTUC specific death) and progression-free survival (PFS) (period from the initial surgical resection to the first recurrence or metastasis or death) were selected as primary endpoints. Disease recurrence was define as tumor relapsed in operative field, regional lymph nodes or metastasis, while IVR was not included. Cause of death was determined by treating physicians or medical records. All patients who were categorized as dead of cancer had previous disease recurrence.

2.4. Statistical analysis

The optimal cutoff value of plasma fibrinogen was determined using validated web-based software [16]. Each possible cutoff value was examined for survival analysis, and the most significant (log-rank test) cutoff value was selected as the optimal cutoff value. All patients were categorized into two groups base on the optimal cutoff value of plasma fibrinogen. Differences in continuous variables across two groups were assessed using Mann-Whitney test, and categorical variables were assessed with Chi-square test. To evaluate the risk factors for IVR after surgery, univariate logistic regression was performed to evaluated differences between IVR and non-IVR group. Selected variables that showed significant difference were included in multivariate regression analysis to identify risk factors for IVR. The impact of variables on PFS and CSS after RNU was evaluated with univariate and multivariate Cox proportional hazard models. All reported p value were two-sided, and statistical significance was set at 0.05. The optimal cutoff value was determined by software based on R package, and other statistical analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Table 1
Clinical characteristics of all the patients grouped by preoperative plasma fibrinogen level.

	Overall	Plasma fibrinogen ≥3.602 g/L	Plasma fibrinogen < 3.602 g/L	p-value
Patients (n, %)	130	35 (26.9%)	95 (73.1%)	
Sex (n, %)				
Male	90 (69.2%)	26 (74.3%)	64 (67.4%)	0.45
Female	40 (30.8%)	9 (25.7%)	31 (32.6%)	
Age (continuous)				
Median, IQR	68 (59.75–75)	70 (62–75)	66 (59–75)	0.4
Location (n, %)				
Pelvic and PUJ	71 (54.6%)	13 (37.1%)	58 (61.1%)	0.11
Ureter	44 (33.8%)	15 (42.9%)	29 (30.5%)	
Both	11 (8.5%)	4 (11.4%)	7 (7.4%)	
Missing	4 (3.1%)	3 (8.6%)	1 (1.1%)	
Hydronephrosis (n, %)				
Yes	73 (56.2%)	22 (62.9%)	51 ((53.7%)	0.47
No	42 ((32.3)	10 (28.6%)	32 (33.7%)	
Missing	15 (11.5%)	3 (8.6%)	12 (12.6%)	
Surgical approach (n, %)				
Open	41 (31.5%)	14 (40%)	27 (28.4%)	0.21
Laparoscopic	89 (68.5%)	21 (60%)	68 (71.6%)	
Surgical margin (n, %)				
Positive	3 (2.3%)	1 (2.9%)	2 (2.1%)	0.8
Negative	127 (97.7%)	34 (97.1%)	93 (97.9%)	
Tumor size (n, %)				
≤2 cm	35 (26.9%)	16 (45.7%)	19 (20%)	< 0.01
> 2 cm	95 (73.1%)	19 (54.3%)	76 (80%)	
Multifocality (n, %)				
Yes	24 (18.5%)	10 (28.6%)	14 (14.7%)	0.07
No	106 (81.5%)	25 (71.4%)	81 (85.3%)	
Pathological T stage (n, %)				
Ta + T1	48 (36.9%)	8 (22.9%)	40 (42.1%)	0.03
≥T2	75 (57.7%)	26 (74.3%)	49 (51.6%)	
Missing	7 (5.4%)	1 (2.9%)	6 (6.3%)	
Tumor grade (n, %)				
Low grade	55 (42.3%)	7 ((20%)	48 (50.5%)	< 0.01
High grade	75 (57.7%)	28 (80%)	47 (49.5%)	
Lymph node involvement (n, %)				
Yes	7 (5.4%)	2 (5.7%)	5 (5.3%)	0.92
No	123 (94.6%)	33 (94.3%)	90 (94.7%)	
Previous bladder cancer (n, %)				
Yes	10 (7.7%)	3 (8.6%)	7 (7.4%)	0.82
No	120 (92.3%)	32 (91.4%)	88 (92.6%)	

Abbreviations: IQR interquartile range; PUJ pelvi-ureteric junction.

3. Results

A total of 130 patients were enrolled in this study, including 90 males (69.2%) and 40 females (30.8%). Median age was 68 years old (interquartile range: 59.75–75). The descriptive characteristics of the patients are shown in Table 1. Of all the patients, 19 (14.6%) suffered postoperative intravesical recurrence. Base on the software mentioned previously, the optimal cutoff value of plasma fibrinogen was set as 3.602 g/L (Fig. 1, Fig. 2). Of all the patients, 35 (26.9%) had a preoperative plasma fibrinogen level of 3.602 g/L or above, 95 (73.1%) had a level less than 3.602 g/L. Significant difference was observed in

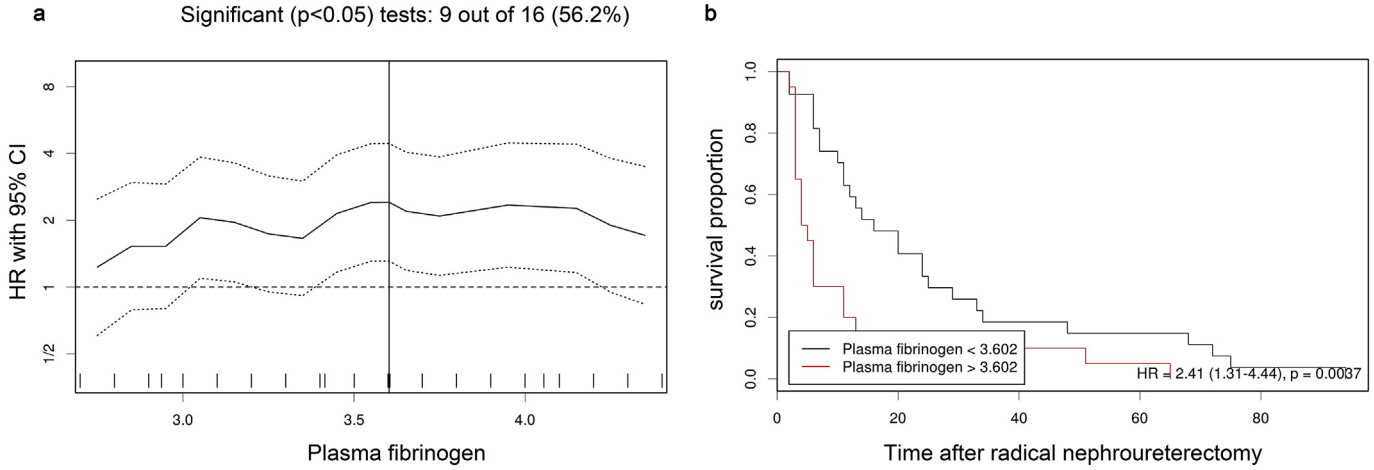

Fig. 1. (a) Hazard Ratio (HR) for PFS based on each cutoff value of plasma fibrinogen level. A vertical line indicate the optimal cutoff value (3.602 g/L). (b) The Kaplan-Meier survival curve of PFS stratified by the optimal cutoff value.
Abbreviation: PFS progression-free survival.

tumor size, pathological T stage and tumor grade between two groups. However, no significant difference was found in age, gender, tumor location, previous hydronephrosis, surgical approach, surgical margin status, multifocality, lymph node status and previous history of bladder cancer between two groups. Patients with elevated plasma fibrinogen had higher UTUC specific mortality than patients with levels below cutoff (15 [42.9%] versus 25 [26.6%]).

Univariate logistic regression was performed to evaluate each variable between IVR and non-IVR groups (Table 2). Tumor multifocality (OR = 3.23, p = 0.03), and tumor size (OR = 7.95, p = 0.04) were significant factors associated with intravesical recurrence.

Multivariate analysis was performed to adjust for potential factors associated with intravesical recurrence. Surgical margin status, tumor grade, pathological T stage, previous history of bladder cancer, plasma fibrinogen levels and factors significant in univariate analysis were further adjusted with multivariate logistic regression model (Table 2). The results suggested that postoperative intravesical recurrence was associated with tumor multifocality (OR = 4.99, p = 0.02).

Cox regression was performed to evaluate the association between each factor and oncological outcomes (Table 3). In univariate Cox regression, age, tumor grade, pathological T stage and plasma fibrinogen were significantly associated with PFS ($p < 0.05$), while age, tumor grade, pathological T stage, postoperative intravesical instillation and plasma fibrinogen were significantly associated with CSS ($p < 0.05$). Multivariate Cox regression suggested that higher T stage, higher tumor grade and elevated plasma fibrinogen were independent factors predicting worse PFS and CSS ($p < 0.05$). Patents with preoperative plasma fibrinogen level ≥ 3.602 g/L had a higher risk for progression (p = 0.01) and cancer-specific mortality (p = 0.02) than those with plasma fibrinogen level < 3.602 g/L.

4. Discussion

The prognosis in UTUC is poor because approximately 60% patients with UTUC are invasive at diagnosis [17]. Despite the progression in identifying molecular markers to predict postoperative survival, the prognostic risk assessment of patients with UTUC still depend on established postoperative factors such as pathological T stage and tumor grade [5,6]. Effective and simple preoperative indicator for predicting survival after RNU remain to explore.

To date there are three studies revealing the prognostic value in UTUC [11–13]. These prior studies revealed that elevated preoperative plasma fibrinogen was associated with poorer survival (CSS and/or OS) after RNU. Nevertheless, the potential relation between plasma fibrinogen and progression of disease was not confirmed in previous studies. Besides, the association between plasma fibrinogen and IVR

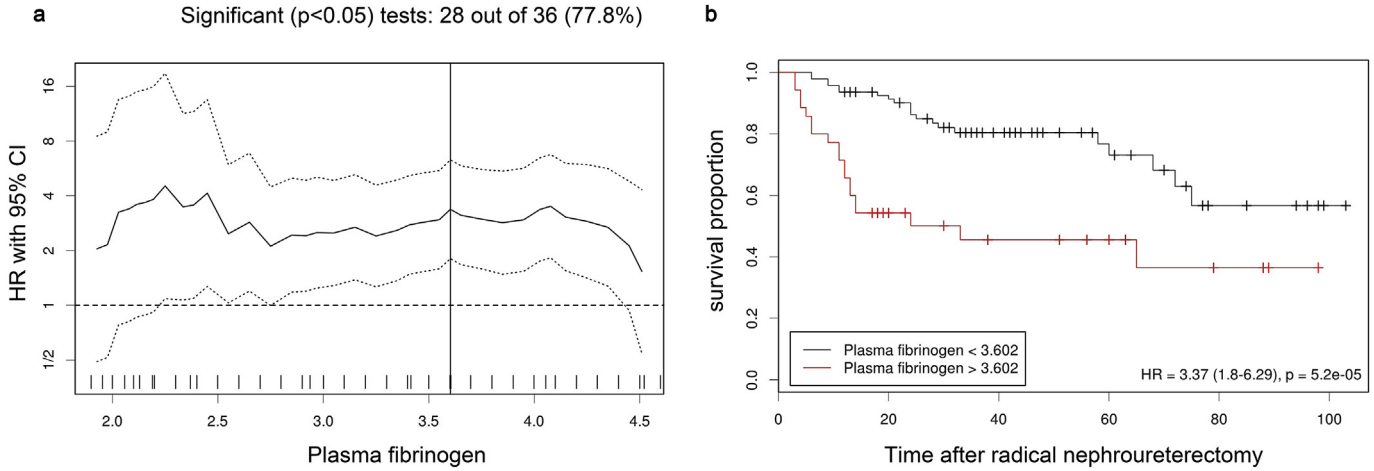

Fig. 2. (a) Hazard Ratio (HR) for CSS based on each cutoff value of plasma fibrinogen level. A vertical line indicate the optimal cutoff value (3.602 g/L). (b) The Kaplan-Meier survival curve of CSS stratified by the optimal cutoff value.
Abbreviation: CSS cancer-specific survival.

Table 2
Univariate and multivariate logistic regression analysis evaluating the risk factors for intravesical recurrence.

Factors	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Sex	1.38	0.5–3.81	0.54			
Age	1.03	0.98–1.08	0.27			
Location						
Pelvic and PUJ	1	Referent	–			
Ureter	0.61	0.18–2.08	0.43			
Both	3.49	0.86–14.12	0.08			
Hydronephrosis	2.25	0.69–7.36	0.18			
Surgical approach	1.34	0.45–4.02	0.6			
Surgical margin	3.03	0.26–35.15	0.38	4.44	0.20–100.59	0.35
Tumor size	7.95	1.02–61.97	0.04*	7.17	0.82–62.56	0.08
Multifocality	3.23	1.11–9.36	0.03*	5.14	1.28–20.58	0.02*
Pathological T stage	0.52	0.19–1.39	0.19	0.50	0.13–1.94	0.31
Tumor grade	0.61	0.23–1.63	0.33	0.61	0.15–2.51	0.49
Lymph node involvement	2.49	0.45–13.9	0.3	4.29	0.55–33.19	0.16
Previous Bladder Cancer	2.79	0.65–11.89	0.16	1.32	0.18–9.79	0.79
Intravesical instillation	2.43	0.9–6.56	0.08	2.67	0.88–8.13	0.08
Adjuvant chemotherapy	1.75	0.34–9.13	0.51	1.43	0.19–10.91	0.73
Plasma fibrinogen	0.56	0.17–1.79	0.32	0.87	0.19–4.02	0.86

Abbreviation: PUJ pelvi-ureteric junction.
*significant ($p < 0.05$).

was not examined before.

In our study, plasma fibrinogen ≥3.602 g/L was associated with pT stage ≥2, high tumor grade and tumor size. Meanwhile, plasma fibrinogen ≥3.602 g/L was independent unfavorable prognostic indicator for PFS (HR = 2.18; 95% CI: 1.17–4.06; p = 0.01) and CSS (HR = 2.2; 95% CI: 1.13–4.28; p = 0.02), as well as pathological T stage and tumor grade. However, no statistically significant relationship was found between plasma fibrinogen and IVR.

Based on our findings, patients with elevated preoperative fibrinogen level have an increasing risk for disease progression and CSM. Comprehensive intervention should be considered in these patients. Platinum-based chemotherapy is expected efficacious in UTUC [18]. Meanwhile, the administration of adjuvant chemotherapy may result in increasing risk for postoperative renal dysfunction owing to nephrotoxicity. Consequently, neoadjuvant chemotherapy may be a preferable intervention. Extrapolating from the study addressing bladder cancer, neoadjuvant chemotherapy may have potential survival benefit for patients with high risk UTUC [19]. The use of neoadjuvant chemotherapy may bring disease-specific survival benefit with favorable pathological response rate [20]. However, the evidence is insufficient without further prospective trial.

According to the literature, the role of plasma fibrinogen in predicting patients' survival has been revealed in various malignant tumors [20–23]. Several possible mechanisms through which fibrinogen promote tumor growth and invasion were raised. One possible explanation could be that increased level of coagulation facilitate tumor growth by the activation of macrophages and secretion of many cytokines and chemokines, including NF-KB, TNF and macrophage inflammatory protein-1 [24,25]. In addition, Redman et al. reported that cells transfected with fibrinogen gene showed enhanced lipogenesis, which is an important metabolic hallmarks of tumor cells [26]. On the other hand, Palumbo et al. reported that the development of lung metastasis was strongly diminished in fibrinogen-deficient mice model [27]. Additionally, fibrinogen was found to increase metastatic potential in part by impeding natural killer cell–mediated elimination of tumor cells [28]. The interaction of fibrinogen and several growth factors (VEGF and FGF-2) may also play a role in promoting adhesion, proliferation and migration of tumor cells [10,29].

The present study has some limitations. First, it was a retrospective and small-sample research, which is a result of rare incidence of UTUC. Second, no information on inflammatory status of patients was analysed in our study, which may influence the level of fibrinogen. Third, the enrolled cohort including patients underwent RNU, in which patients may harbour more advanced or larger tumor. While the outcomes of patients treated with endoscopic surgery or segmental resection were not examined in this study. The effect of comorbidities was not evaluated due to incomplete data of medical record.

Table 3
Univariate and multivariate Cox regression analysis for PFS and CSS.

Factor	Progression-free Survival		Cancer-specific Survival	
	Univariate	Multivariate	Univariate	Multivariate
Sex	1.13 (0.62–2.06) p = 0.7		1.03 (0.53–1.99) p = 0.93	
Age	1.04 (1.01–1.07) p = 0.02*	1.02 (0.99–1.06) P = 0.15	1.04 (1.01–1.07) p = 0.02*	1.02 (0.99–1.05) p = 0.27
Location				
Pelvic and PUJ	1.0(Referent)		1.0(Referent)	
Ureter	1.74 (0.96–3.17) p = 0.07		1.67 (0.87–3.21) p = 0.12	
Both	0.9 (0.27–3.01) p = 0.86		1.08 (0.32–3.68) p = 0.9	
Hydronephrosis	1.34 (0.69–2.59) p = 0.38		1.4 (0.68–2.83) p = 0.35	
Surgical approach	1.1 (0.59–2.05) p = 0.76		1.1 (0.57–2.13) p = 0.78	
Surgical margin	2.14 (0.52–8.86) p = 0.29		2.44 (0.59–10.18) p = 0.22	
Tumor size	0.9 (0.48–1.68) p = 0.74		1.03 (0.51–2.06) p = 0.94	
Multifocality	1.41 (0.72–2.78) p = 0.32		1.67 (0.84–3.34) p = 0.15	
Tumor grade	5.86 (2.7–12.52) p < 0.01*	3.7 (1.46–9.41) p = 0.01*	8.5 (3.44–20.94) p < 0.01*	4.89 (1.70–14.11) p < 0.01*
Pathological T stage	3.71 (1.71–8.04) p < 0.01*	2.85 (1.21–6.67) p = 0.02*	3.81 (1.67–8.68) p < 0.01*	2.66 (1.08–6.60) p = 0.03*
Lymph node involvement	2.43 (0.86–6.9) p = 0.09		2.38 (0.83–6.8) p = 0.1	
Intravesical instillation	0.45 (0.09–2.54) p = 0.09		0.41 (0.18–0.92) p = 0.03*	0.45 (0.19–1.11) p = 0.08
Adjuvant chemotherapy	0.28 (0.04–2.02) p = 0.21		0.35 (0.05–2.51) p = 0.29	
Previous bladder cancer	0.78 (0.28–2.17) p = 0.63		0.6 (0.18–1.95) p = 0.39	
IVR	0.99 (0.45–2.23) p = 0.99		1.14 (0.51–2.58) p = 0.75	
Plasma fibrinogen	2.95 (1.66–5.24) p < 0.01*	2.18 (1.17–4.06) p = 0.01*	3.53 (1.91–6.55) P < 0.01*	2.2 (1.13–4.28) p = 0.02*

Abbreviations: PUJ pelvi-ureteric junction; PFS progression-free survival; CSS cancer-specific survival; IVR intravesical recurrence.
*significant ($p < 0.05$).

5. Conclusions

Elevated preoperative plasma fibrinogen is an independent unfavorable factor of PFS and CSS in patients with UTUC. Additionally, no statistically significant association was found between plasma fibrinogen and IVR. As an effective and easily accessible biomarker, this parameter can be applied in pre-intervention risk stratification of UTUC.

Ethical approval

This was a retrospective study and clinical data were de-identified before analysis; therefore, ethical approval was not required.

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Author contribution

Rongzong Liu: Project development, Data collection, Data analysis, Manuscript writing.

Xuejian Zhou: Project development, Data collection, Data analysis, Manuscript writing.

Lujia Zou: Data collection, Data analysis, Manuscript editing.

Qi Chen: Data collection, Manuscript writing.

Yun Hu: Data collection, Data analysis.

Jiming Hu: Data analysis, Manuscript editing.

Xiaobo Wu: Data collection.

Haowen Jiang: Project development, Data analysis, Manuscript editing.

Conflicts of interest

The authors report no conflicts of interest in this work.

Trial registry number

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Guarantor

Haowen Jiang.

Data statement

All data included in this study are available upon request by contact with the corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Rongzong Liu: Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Xuejian Zhou:** Conceptualization, Investigation, Data curation, Formal analysis, Writing - original draft. **Lujia Zou:** Methodology, Writing - review & editing. **Qi Chen:** Data curation, Writing - original draft. **Yun Hu:** Software, Investigation. **Jimeng Hu:** Methodology, Writing - review & editing. **Haowen Jiang:** Project administration, Funding acquisition, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

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References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, Ca - Cancer J. Clin. 66 (2016) (2016) 7–30, https://doi.org/10.3322/caac.21332.

[2] M. Roupret, M. Babjuk, E. Comperat, R. Zigeuner, R.J. Sylvester, M. Burger, N.C. Cowan, A. Bohle, B.W.G. Van Rhijn, E. Kaasinen, J. Palou, S.F. Shariat, European association of urology guidelines on upper urinary tract urothelial cell carcinoma: 2015 update, Eur. Urol. 68 (2015) 868–879, https://doi.org/10.1016/j.eururo.2015.06.044.

[3] T. Seisen, B. Granger, P. Colin, P. Leon, G. Utard, R. Renard-Penna, E. Comperat, P. Mozer, O. Cussenot, S.F. Shariat, M. Roupret, A systematic review and meta-analysis of clinicopathologic factors linked to intravesical recurrence after radical nephroureterectomy to treat upper tract urothelial carcinoma, Eur. Urol. 67 (2015) 1122–1133, https://doi.org/10.1016/j.eururo.2014.11.035.

[4] V. Fradet, J. Mauermann, W. Kassouf, R. Rendon, N. Jacobsen, A. Fairey, J. Izawa, A. Kapoor, P. Black, S. Tanguay, J. Chin, A. So, J.-B. Lattouf, D. Bell, F. Saad, B. Sheyegan, D. Drachenberg, I. Cagiannos, L. Lacombe, Risk factors for bladder cancer recurrence after nephroureterectomy for upper tract urothelial tumors: results from the Canadian Upper Tract Collaboration, Urol. Oncol. 32 (2014) 839–845, https://doi.org/10.1016/j.urolonc.2014.04.006.

[5] S.J. Drouin, D.R. Yates, V. Hupertan, O. Cussenot, M. Roupret, A systematic review of the tools available for predicting survival and managing patients with urothelial carcinomas of the bladder and of the upper tract in a curative setting, World J. Urol. 31 (2013) 109–116, https://doi.org/10.1007/s00345-012-1008-9.

[6] M. Roupret, V. Hupertan, T. Seisen, P. Colin, E. Xylinas, D.R. Yates, H. Fajkovic, Y. Lotan, J.D. Raman, R. Zigeuner, M. Remzi, C. Bolenz, G. Novara, W. Kassouf, A. Ouzzane, F. Rozet, O. Cussenot, J.I. Martinez-Salamanca, H.-M. Fritsche, T.J. Walton, C.G. Wood, K. Bensalah, P.I. Karakiewicz, F. Montorsi, V. Margulis, S.F. Shariat, Prediction of cancer specific survival after radical nephroureterectomy for upper tract urothelial carcinoma: development of an optimized postoperative nomogram using decision curve analysis, J. Urol. 189 (2013) 1662–1669, https://doi.org/10.1016/j.juro.2012.10.057.

[7] C.S.D. Roxburgh, J.E.M. Crozier, F. Maxwell, A.K. Foulis, J. Brown, R.F. McKee, J.H. Anderson, P.G. Horgan, D.C. McMillan, Comparison of tumour-based (Petersen Index) and inflammation-based (Glasgow Prognostic Score) scoring systems in patients undergoing curative resection for colon cancer, Br. J. Canc. 100 (2009) 701–706, https://doi.org/10.1038/sj.bjc.6604926.

[8] L.M. Coussens, Z. Werb, Inflammation and cancer, Nature 420 (2002) 860–867, https://doi.org/10.1038/nature01322.

[9] M. Pichler, G.C. Hutterer, C. Stoeckigt, T.F. Chromecki, T. Stojakovic, S. Golbeck, K. Eberhard, A. Gerger, S. Mannweiler, K. Pummer, R. Zigeuner, Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients, Br. J. Canc. 108 (2013) 901–907, https://doi.org/10.1038/bjc.2013.28.

[10] A. Sahni, P.J. Simpson-Haidaris, S.K. Sahni, G.G. Vaday, C.W. Francis, Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2 (FGF-2), J. Thromb. Haemost. 6 (2008) 176–183, https://doi.org/10.1111/j.1538-7836.2007.02808.x.

[11] M. Pichler, O. Dalpiaz, G.C. Ehrlich, T. Stojakovic, J.M. Martin Hernandez, S. Mannweiler, K. Pummer, R. Zigeuner, G.C. Hutterer, Validation of the preoperative plasma fibrinogen level as a prognostic factor in a European cohort of patients with localized upper tract urothelial carcinoma, J. Urol. 191 (2014) 920–925, https://doi.org/10.1016/j.juro.2013.10.073.

[12] N. Tanaka, E. Kikuchi, K. Matsumoto, N. Hayakawa, H. Ide, A. Miyajima, S. Nakamura, M. Oya, Prognostic value of plasma fibrinogen levels in patients with localized upper tract urothelial carcinoma, BJU Int. 111 (2013) 857–864, https://doi.org/10.1111/j.1464-410X.2012.11353.x.

[13] B. Zhang, Y. Song, J. Jin, L.-Q. Zhou, Z.-S. He, C. Shen, Q. He, J. Li, L.-B. Liu,

C. Wang, X.-Y. Chen, Y. Fan, S. Hu, L. Zhang, W. Yu, W.-K. Han, Preoperative plasma fibrinogen level represents an independent prognostic factor in a Chinese cohort of patients with upper tract urothelial carcinoma, PLoS One 11 (2016) e0150193, , https://doi.org/10.1371/journal.pone.0150193.

[14] J.I. Epstein, M.B. Amin, V.R. Reuter, F.K. Mostofi, The World Health organization/international society of urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder consensus conference committee, Am. J. Surg. Pathol. 22 (1998) 1435–1448.

[15] A. CLAUSS, [Rapid physiological coagulation method in determination of fibrinogen], Acta Haematol. 17 (1957) 237–246, https://doi.org/10.1159/000205234.

[16] J. Budczies, F. Klauschen, B.V. Sinn, B. Gyorffy, W.D. Schmitt, S. Darb-Esfahani, C. Denkert, Cutoff Finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization, PLoS One 7 (2012) e51862, , https://doi.org/10.1371/journal.pone.0051862.

[17] V. Margulis, S.F. Shariat, S.F. Matin, A.M. Kamat, R. Zigeuner, E. Kikuchi, Y. Lotan, A. Weizer, J.D. Raman, C.G. Wood, Outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration, Cancer 115 (2009) 1224–1233, https://doi.org/10.1002/cncr.24135.

[18] J.J. Leow, W. Martin-Doyle, A.P. Fay, T.K. Choueiri, S.L. Chang, J. Bellmunt, A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma, Eur. Urol. 66 (2014) 529–541, https://doi.org/10.1016/j.eururo.2014.03.003.

[19] H.B. Grossman, R.B. Natale, C.M. Tangen, V.O. Speights, N.J. Vogelzang, D.L. Trump, R.W. deVere White, M.F. Sarosdy, D.P.J. Wood, D. Raghavan, E.D. Crawford, Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer, N. Engl. J. Med. 349 (2003) 859–866, https://doi.org/10.1056/NEJMoa022148.

[20] S. Polterauer, C. Grimm, V. Seebacher, N. Concin, C. Marth, C. Tomovski, H. Husslein, H. Leipold, K. Hefler-Frischmuth, C. Tempfer, A. Reinthaller, L. Hefler, Plasma fibrinogen levels and prognosis in patients with ovarian cancer: a multicenter study, Oncologist 14 (2009) 979–985, https://doi.org/10.1634/theoncologist.2009-0079.

[21] V. Seebacher, S. Polterauer, C. Grimm, H. Husslein, H. Leipold, K. Hefler-Frischmuth, C. Tempfer, A. Reinthaller, L. Hefler, The prognostic value of plasma fibrinogen levels in patients with endometrial cancer: a multi-centre trial, Br. J. Canc. 102 (2010) 952–956, https://doi.org/10.1038/sj.bjc.6605547.

[22] L. Tang, K. Liu, J. Wang, C. Wang, P. Zhao, J. Liu, High preoperative plasma fibrinogen levels are associated with distant metastases and impaired prognosis after curative resection in patients with colorectal cancer, J. Surg. Oncol. 102 (2010) 428–432, https://doi.org/10.1002/jso.21668.

[23] S. Erdem, A.S. Amasyali, O. Aytac, K. Onem, H. Issever, O. Sanli, Increased preoperative levels of plasma fibrinogen and D dimer in patients with renal cell carcinoma is associated with poor survival and adverse tumor characteristics, Urol. Oncol. 32 (2014) 1031–1040, https://doi.org/10.1016/j.urolonc.2014.03.013.

[24] T. Jensen, P. Kierulf, P.M. Sandset, O. Klingenberg, G.B. Joo, H.C. Godal, O.H. Skjonsberg, Fibrinogen and fibrin induce synthesis of proinflammatory cytokines from isolated peripheral blood mononuclear cells, Thromb. Haemostasis 97 (2007) 822–829.

[25] S.T. Smiley, J.A. King, W.W. Hancock, Fibrinogen stimulates macrophage chemokine secretion through toll-like receptor 4, J. Immunol. 167 (2001) 2887–2894.

[26] C.M. Redman, H. Xia, Fibrinogen biosynthesis. Assembly, intracellular degradation, and association with lipid synthesis and secretion, Ann. N. Y. Acad. Sci. 936 (2001) 480–495.

[27] J.S. Palumbo, K.W. Kombrinck, A.F. Drew, T.S. Grimes, J.H. Kiser, J.L. Degen, T.H. Bugge, Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells, Blood 96 (2000) 3302–3309.

[28] J.S. Palumbo, K.E. Talmage, J.V. Massari, C.M. La Jeunesse, M.J. Flick, K.W. Kombrinck, M. Jirouskova, J.L. Degen, Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells, Blood 105 (2005) 178–185, https://doi.org/10.1182/blood-2004-06-2272.

[29] A. Sahni, C.W. Francis, Vascular endothelial growth factor binds to fibrinogen and fibrin and stimulates endothelial cell proliferation, Blood 96 (2000) 3772–3778.