Pretreatment elevated fibrinogen level predicts worse oncologic outcomes in upper tract urothelial carcinoma

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This study aimed to further validate the prognostic role of fibrinogen in upper tract urothelial carcinoma (UTUC) in a large Chinese cohort. A total of 703 patients who underwent radical nephroureterectomy were retrospectively identified. Fibrinogen levels of ≥4.025 g l⁻¹ were defined as elevated. Logistic regression analysis was performed to determine the association between fibrinogen and adverse pathological features. Kaplan–Meier analysis and Cox regression models were used to assess the associations of fibrinogen with cancer-specific survival (CSS), disease recurrence-free survival (RFS), and overall survival (OS). Harrell c-index and decision curve analysis were used to assess the clinical utility of multivariate models. The median follow-up duration was 42 (range: 1–168) months. Logistic regression analysis revealed that elevated fibrinogen was associated with higher tumor stage and grade, lymph node involvement, lymphovascular invasion, sessile carcinoma, concomitant variant histology, and positive surgical margins (all P < 0.05). Multivariate Cox regression analysis demonstrated that elevated fibrinogen was independently associated with decreased CSS (hazard ratio [HR]: 2.33; P < 0.001), RFS (HR: 2.09; P < 0.001), and OS (HR: 2.09; P < 0.001). The predictive accuracies of the multivariate models were improved by 3.2%, 2.0%, and 2.8% for CSS, RFS, and OS, respectively, when fibrinogen was added. Decision curve analysis showed an added benefit for CSS prediction when fibrinogen was added to the model. Preoperative fibrinogen may be a strong independent predictor of worse oncologic outcomes in UTUC; therefore, it may be valuable to apply this marker to the current risk stratification in UTUC.

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INTRODUCTION
Radical nephroureterectomy (RNU) with bladder cuff excision is the current standard of care for upper tract urothelial carcinoma (UTUC). However, postoperative survival outcomes are still unsatisfactory, and a large portion of patients inevitably experience disease recurrence and possible death after surgery. Therefore, it is essential to identify patients who might experience the greatest benefit from RNU and neoadjuvant therapy.1,2

Thus far, some preoperative and postoperative factors have been used in the risk stratification of UTUC, based on the European Association of Urology (EAU) guidelines.3 Although tumor stage and grade have been commonly adopted by most urologists to assess the prognosis of patients with cancer, many researchers have begun to explore the potential roles of certain blood-based biomarkers in the risk stratification of UTUC.

Increasing evidence suggests that specific homeostatic factors might play a pivotal role in tumor invasion and metastasis.4–6 Plasma fibrinogen, one of the major components in the coagulation pathway, is often synthesized in large quantities by cancer cells.7 A growing body of literature has indicated the association of elevated fibrinogen levels with worse survival outcomes in prostate,8 ovarian,9 lung,10 bladder,11 and renal cell cancers.12 Similarly, several studies have investigated the predictive value of fibrinogen in patients with UTUC.13–15 Nevertheless, most of these were small sample studies with varying cutoff values for fibrinogen, likely limiting, to some extent, its clinical value for prognostic evaluation.

Therefore, the present study aimed to further validate whether fibrinogen can provide an independent parameter for the assessment of pathological and survival outcomes after RNU in a large cohort with UTUC. In addition, because neutrophil-to-lymphocyte ratio (NLR) is the only serum biomarker recommended in UTUC based on EAU guidelines,3 we also sought to assess the clinical utility of fibrinogen versus NLR in multivariate models.

PATIENTS AND METHODS
Study population
This study was approved by the Committee for Ethics of West China Hospital, Chengdu, China. Between January 2003 and December 2016, 820 consecutive patients were pathologically diagnosed as having UTUC after RNU at the Department of Urology & Institute of Urology, West China Hospital, Chengdu, China. In this study, patients’ data were collected from their clinical medical records, and the formal consent

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is not required due to its respective nature. We excluded patients with coagulation-related diseases or prior anticoagulant therapy \((n = 7)\); inflammatory or autoimmune diseases \((n = 17)\); nonurothelial carcinomas \((n = 13)\); lack of preoperative fibrinogen data \((n = 16)\); and those who were lost to first follow-up \((n = 64)\). Finally, a total of 703 patients with available fibrinogen data within 2 weeks before surgery were qualified and included in our study for further analysis.

All patients had received RNU, which was performed according to the standard procedures (dissection of the kidney with the whole length of the ureter and open bladder cuff excision). Open or laparoscopic RNU was performed in accordance with the urologists’ judgment. Lymph node dissection was performed only in patients with suspected enlarged lymph nodes, which were confirmed via preoperative radiology assessment (computed tomography or magnetic resonance imaging) or intraoperative discovery. When lymph node dissection was performed, the following templates were used: for tumors located in the right pelvis and the upper and middle ureter, dissection included the right renal hilar, paracaval, retrocaval, and inter-aortocaval nodes; for tumors located in the left pelvis and the upper and middle ureter, dissection included the left renal hilar and para-aortic nodes; and for tumors located in the lower ureter, dissection included the ipsilateral common iliac, external iliac, obturator, internal iliac, and presacral nodes.

**Clinicopathological evaluation**

All RNU specimens were independently re-evaluated by two experienced pathologists. Tumor grade and stage were determined based on the World Health Organization/International Society of Urologic Pathology classification of 2004 and the 2002 Union for International Cancer Control tumor node metastasis (TNM) classification system, respectively. Information on tumor architecture (sessile or papillary), lymphovascular invasion (LVI), positive surgical margins (PSM), and concomitant variant histology (CVH, urothelial carcinomas with abnormal histological differentiation) was retrieved from related pathological reports. Preoperative laboratory data, including fibrinogen level, platelet count, white blood cell (WBC) count, alkaline phosphatase (ALP) level, lactate dehydrogenase (LDH) level, NLR, and albumin-to-globulin ratio \((AGR)\), were collected within 2 weeks before surgery (if more than one report was available, the most recent one was recorded). NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count; AGR was defined as the value of albumin divided by the value of globulin. The optimal cutoff value for fibrinogen was defined as 4.025 g l\(^{-1}\), based on the receiver-operating characteristic (ROC) curves. The cutoff values for WBC,\(^{16}\) platelet count,\(^{16}\) ALP,\(^{16}\) LDH,\(^{16}\) NLR,\(^{16}\) and AGR\(^{16}\) were determined as previously reported. In addition, other information, including age, sex, body mass index (BMI), smoking status, tumor side and location, bladder cancer status, hydronephrosis, and multifocality, was documented from the medical record of each patient.

**Follow-up**

Patients were followed up every 3 months in the first year after RNU, every 6 months for the next 2 years, and annually thereafter. Physical examinations, blood laboratory tests, and chest radiography assessments were routinely performed. Computed tomography or magnetic resonance imaging analyses were performed every year or upon suspected recurrence of the disease.

Disease recurrence was defined as recurrence from the operating site, regional or distant lymph nodes, and/or visceral metastasis. Cancer-specific survival (CSS) was defined as the time from RNU to cancer-related death. Disease recurrence-free survival (RFS) was defined as the time from RNU to disease recurrence. Overall survival (OS) was defined as the time from RNU to death from all causes.

**Statistical analyses**

Student’s \( t \)-test and the Chi-squared test were used to evaluate continuous variables and dichotomous variables. Associations between fibrinogen and adverse pathological outcomes were assessed using logistic regression analysis, in which odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated. Probabilities of CSS, RFS, and OS were determined using Kaplan–Meier curves. The log-rank test was used to assess the differences between groups. Multivariable Cox proportional hazard models with forward stepwise methods were used to assess the risk factors for CSS, RFS, and OS. C-index was calculated to assess the improvement in discrimination when adding preoperative laboratory factors to the base model, using the R package “survival.” Decision curve analyses were performed to show the benefit of multivariate models that contained preoperative biomarkers. A two-sided probability \((P) \) value of \(<0.05\) was considered statistically significant. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics version 22.0 (IBM Corp., Armonk, NY, USA).

**RESULTS**

**Baseline characteristics**

Of the 703 patients who exhibited UTUC, the median age at RNU surgery was 67 (interquartile range: 59–74) years and the mean fibrinogen level was 3.8 (standard deviation [s.d.]: 1.3) g l\(^{-1}\). Low- and high-grade UTUC were observed in 186 (26.5%) and 517 (73.5%) patients, respectively. Positive lymph nodes were found in 67 (9.5%) patients. Two hundred and eighty-seven (40.8%) patients had received postoperative adjuvant chemotherapy, and none of the patients had received neoadjuvant therapy. Patients were dichotomized into a high fibrinogen group (fibrinogen \(\geq 4.025 \text{ g l}^{-1}\)) and a low fibrinogen group (fibrinogen \(< 4.025 \text{ g l}^{-1}\)) by ROC curves (Supplementary Figure 1). The area under the ROC curve was 0.689, and the Youden index was 0.316, with a sensitivity of 57.8% and a specificity of 74.7%. There were no significant differences between groups regarding age, BMI, smoking status, tumor side and location, bladder cancer status, hydronephrosis, and adjuvant therapy \((P > 0.05)\). However, differences were observed in terms of gender, multifocality, surgical approach, tumor grade and stage, lymph node status, tumor size, PSM, tumor architecture, CVH, and laboratory biomarkers \((i.e., \text{WBC, platelet count, ALP, LDH, NLR, and AGR})\) \((P < 0.05;\) Table 1).

**Fibrinogen and adverse pathological outcomes**

We investigated the associations between fibrinogen and adverse pathological features. After adjusting for pretreatment factors, including age, BMI, smoking status, gender, hydronephrosis, tumor side, tumor location, history of bladder cancer, multifocality, platelet count, WBC count, ALP, LDH, NLR, and AGR, multivariate logistic analysis revealed that elevated fibrinogen (treated as a continuous variable) was independently associated with increased risks of high-grade carcinoma \((OR: 1.71, P < 0.001)\), high pathological tumor stage \((OR: 1.69, P < 0.001)\), lymph node involvement \((OR: 1.47, P = 0.001)\), LVI \((OR: 1.30, P = 0.007)\), sessile carcinoma \((OR: 1.45, P < 0.001)\), CVH \((OR: 1.35, P = 0.001)\), and PSM \((OR: 1.38, P = 0.021;\) Table 2).

**Fibrinogen and survival outcomes**

With a median follow-up of 42 (range: 1–168) months, 204 (29.0%) patients died of UTUC, 291 (41.4%) experienced disease recurrence,
Table 1: Patients' characteristics in the present study

| Variables                              | Total (n=703) | Fibrinogen <4.025 g l⁻¹ (n=454, 64.6%) | Fibrinogen ≥4.025 g l⁻¹ (n=249, 35.4%) | P    |
|----------------------------------------|---------------|----------------------------------------|----------------------------------------|------|
| Age (year), mean±s.d.                  | 65.8±11.4     | 66.1±11.3                               | 65.4±11.4                               | 0.680|
| Gender, n (%)                          |               |                                        |                                        |      |
| Male                                   | 399 (56.8)    | 276 (60.8)                              | 123 (49.4)                              | 0.004|
| Female                                 | 304 (43.2)    | 178 (39.2)                              | 126 (50.6)                              |      |
| BMI (kg m⁻²), mean±s.d.                | 22.6±4.6      | 22.6±4.7                                | 22.5±4.4                                | 0.470|
| Smoking status, n (%)                  |               |                                        |                                        |      |
| No                                     | 502 (71.4)    | 313 (68.9)                              | 189 (75.9)                              | 0.051|
| Former/current                         | 201 (28.6)    | 141 (31.1)                              | 60 (24.1)                               |      |
| Tumor side, n (%)                      |               |                                        |                                        | 0.216|
| Left                                   | 359 (51.1)    | 224 (49.3)                              | 135 (54.2)                              |      |
| Right                                  | 344 (48.9)    | 230 (50.7)                              | 114 (45.8)                              |      |
| Bladder cancer status, n (%)           |               |                                        |                                        | 0.688|
| No                                     | 602 (85.6)    | 386 (85.0)                              | 216 (86.7)                              |      |
| Previous                               | 22 (3.1)      | 16 (3.5)                                | 6 (2.4)                                 |      |
| Concomitant                            | 79 (11.2)     | 52 (11.5)                               | 27 (10.8)                               |      |
| Hydronephrosis, n (%)                  |               |                                        |                                        | 0.166|
| No                                     | 264 (37.6)    | 179 (39.4)                              | 85 (34.1)                               |      |
| Yes                                    | 439 (62.4)    | 275 (60.6)                              | 164 (65.9)                              |      |
| Tumor location, n (%)                  |               |                                        |                                        | 0.115|
| Pelvicalyceal                          | 376 (53.5)    | 233 (51.3)                              | 143 (57.4)                              |      |
| Ureteric                               | 203 (28.9)    | 143 (31.5)                              | 60 (24.1)                               |      |
| Both                                   | 124 (17.6)    | 78 (17.2)                               | 46 (18.5)                               |      |
| Multifocality, n (%)                   |               |                                        |                                        | 0.032|
| No                                     | 587 (83.5)    | 369 (81.3)                              | 218 (87.6)                              |      |
| Yes                                    | 116 (16.5)    | 85 (18.7)                               | 31 (12.4)                               |      |
| Surgical approach, n (%)               |               |                                        |                                        | <0.001|
| Open RNU                               | 473 (67.3)    | 284 (62.6)                              | 189 (75.9)                              |      |
| Laparoscopic RNU                       | 230 (32.7)    | 170 (37.4)                              | 60 (24.1)                               |      |
| Tumor grade, n (%)                     |               |                                        |                                        | <0.001|
| Low                                    | 186 (26.5)    | 156 (34.4)                              | 30 (12.0)                               |      |
| High                                   | 517 (73.5)    | 298 (65.6)                              | 219 (88.0)                              |      |
| pT stage, n (%)                        |               |                                        |                                        | <0.001|
| pTis, pTa, pT1                          | 217 (30.9)    | 171 (37.7)                              | 46 (18.5)                               |      |
| pT2                                    | 145 (20.6)    | 109 (24.0)                              | 36 (14.5)                               |      |
| pT3                                    | 241 (34.3)    | 141 (31.1)                              | 100 (40.2)                              |      |
| pT4                                    | 100 (14.2)    | 33 (7.3)                                | 67 (26.9)                               |      |
| Lymph node status, n (%)               |               |                                        |                                        | <0.001|
| pN0                                    | 89 (12.7)     | 56 (12.3)                               | 33 (13.3)                               |      |
| pNx                                    | 547 (77.8)    | 373 (82.2)                              | 174 (69.9)                              |      |
| pN+                                    | 67 (9.5)      | 25 (5.5)                                | 42 (16.9)                               |      |
| LVI, n (%)                             |               |                                        |                                        | <0.001|
| No                                     | 596 (84.8)    | 403 (88.8)                              | 193 (77.5)                              |      |
| Yes                                    | 107 (15.2)    | 51 (11.2)                               | 56 (22.5)                               |      |
| Tumor size (cm), n (%)                 |               |                                        |                                        | <0.001|
| ≤3                                     | 225 (32.0)    | 166 (36.6)                              | 59 (23.7)                               |      |
| >3                                     | 478 (68.0)    | 288 (63.4)                              | 190 (76.3)                              |      |
| PSM, n (%)                             |               |                                        |                                        | 0.001|
| No                                     | 646 (91.9)    | 429 (94.5)                              | 217 (87.1)                              |      |
| Yes                                    | 57 (8.1)      | 25 (5.5)                                | 32 (12.9)                               |      |
| Tumor architecture, n (%)              |               |                                        |                                        | <0.001|
| Papillary                              | 221 (31.4)    | 179 (39.4)                              | 42 (16.9)                               |      |
| Sessile                                | 482 (68.6)    | 275 (60.6)                              | 207 (83.1)                              |      |
| CVH                                    |               |                                        |                                        | <0.001|
| No                                     | 543 (77.2)    | 375 (82.6)                              | 168 (67.5)                              |      |
| Yes                                    | 160 (22.8)    | 79 (17.4)                               | 81 (32.5)                               |      |
| Adjuvant chemotherapy, n (%)           |               |                                        |                                        | 0.455|

Contd...
Table 1: Contd...

| Variables | Total (n=703) | Fibrinogen <4.025 g l⁻¹ (n=454, 64.6%) | Fibrinogen ≥4.025 g l⁻¹ (n=249, 35.4%) | P  |
|-----------|---------------|---------------------------------------|---------------------------------------|----|
| No        | 416 (59.2)    | 264 (58.1)                            | 152 (61.0)                            |    |
| Yes       | 287 (40.8)    | 190 (41.9)                            | 97 (39.0)                             |    |

Laboratory tests

| Fibrinogen (g l⁻¹), mean±s.d. | 3.8±1.3 | 3.1±0.6 | 5.1±1.1 | <0.001 |
| Platelet count (×10⁹ l⁻¹), mean±s.d. | 198.4±85.7 | 177.3±64.0 | 237.0±104.8 | <0.001 |
| WBC count (×10⁹ l⁻¹), mean±s.d. | 6.9±2.6 | 6.4±2.2 | 7.8±3.0 | <0.001 |
| ALP (U l⁻¹), mean±s.d. | 81.5±35.9 | 75.6±22.5 | 92.6±50.8 | <0.001 |
| LDH (U l⁻¹), mean±s.d. | 189.1±69.7 | 179.4±39.4 | 207.4±102.9 | <0.001 |
| NLR, mean±s.d. | 3.4±2.0 | 3.0±1.9 | 4.2±2.0 | <0.001 |
| AGR, mean±s.d. | 1.4±0.3 | 1.5±0.3 | 1.3±0.3 | <0.001 |

End points

| Disease recurrence, n (%) | 291 (41.4) | 149 (32.8) | 142 (57.0) | <0.001 |
| Cancer-related death, n (%) | 204 (29.0) | 86 (18.9) | 118 (47.4) | <0.001 |
| Overall death, n (%) | 253 (36.0) | 118 (26.0) | 135 (54.2) | <0.001 |

Table 2: Binary and multivariate logistic regression analysis for fibrinogen level (continuous variable) for pathological outcomes when adjusting for preoperative confounders

| Adverse pathological outcomes | Adjusted OR<sup>a</sup> | 95% CI<sup>a</sup> | P  |
|------------------------------|--------------------------|-------------------|----|
| High-grade disease           | 1.71                     | 1.36–2.13         | <0.001 |
| High pT stage (≥ pT3)        | 1.69                     | 1.40–2.04         | <0.001 |
| Lymph node involvement       | 1.47                     | 1.18–1.84         | 0.001 |
| LVI                          | 1.30                     | 1.08–1.57         | 0.007 |
| Sessile carcinoma            | 1.45                     | 1.19–1.78         | <0.001 |
| CVH                          | 1.35                     | 1.13–1.61         | 0.001 |
| PSM                          | 1.38                     | 1.05–1.80         | 0.021 |

<sup>a</sup>Adjusting for age (continuous), gender, BMI (continuous), smoking status, hydronephrosis, tumor side, tumor location, history of bladder cancer, multifocality, fibrogenin (continuous), platelet count (continuous), WBC count (continuous), ALP (continuous), LDH (continuous), NLR (continuous), and AGR (continuous). LVI: lymphovascular invasion; CVH: concomitant variant histology; PSM: positive surgical margins; pT: pathological tumor; OR: odds ratio; CI: confidence interval; BMI: body mass index; WBC: white blood cell; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; AGR: albumin-to-globulin ratio; HR: hazard ratio; s.d.: standard deviation; RNU: radical nephroureterectomy; LVI: lymphovascular invasion; CVH: concomitant variant histology; PSM: positive surgical margins; pT: pathological tumor; WBC: white blood cell; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; AGR: albumin-to-globulin ratio; HR: hazard ratio; s.d.: standard deviation.

and 253 (36.0%) died of all causes at the time of the last follow-up. The 5-year CSS, RFS, and OS were 72.9%, 59.3%, and 66.7%, respectively, in the low fibrinogen group, compared with 35.5%, 28.1%, and 30.8%, respectively, in the high fibrinogen group.

Kaplan–Meier curves showed that patients with high fibrinogen levels had lower CSS, RFS, and OS than patients with low fibrinogen levels (log-rank tests, all P < 0.001; Figure 1). Table 3 and Supplementary Table 1 show the results from univariate and multivariate Cox regression analyses. Fibrinogen levels >4.025 g l⁻¹ were significantly associated with worse CSS (hazard ratio [HR]: 3.97; 95% CI: 3.00–5.24), RFS (HR: 2.86; 95% CI: 2.27–3.60), and OS (HR: 3.28; 95% CI: 2.56–4.21) in the univariate Cox regression model. Multivariate analysis showed that pathological tumor stage, lymph node involvement, tumor size, NLR, and fibrinogen were independent predictors of CSS, RFS, and OS; tumor grade and CVH were independent predictors of CSS and OS; and ALP was an independent predictor of CSS. The HR values of fibrinogen were 2.33, 2.09, and 2.09 for CSS, RFS, and OS, respectively (Table 3).

**Clinical utility of the prediction models**

We calculated the c-index to determine the predictive accuracy of the multivariate models for survival outcomes (Table 4). The base model was built based on tumor grade, stage, lymph node invasion, tumor size, and CVH; the predictive accuracies for CSS, RFS, and OS were 76.2%, 72.4%, and 75.0%, respectively (derived from the multivariate analyses). The predictive accuracy improved upon adding each laboratory biomarker, including ALP, NLR, and fibrinogen (these were significant in the multivariate models), into the base model. The largest improvement was observed when fibrinogen was added to the base model (c-index improvements for CSS, RFS, and OS were 0.032, 0.020, and 0.028, respectively).

Finally, decision curve analyses were performed to assess the clinical utility of the above findings (Figure 2a). Because these models assist in identifying patients who require more aggressive pre- and postoperative treatments (such as adjuvant therapy, although it remains controversial in the treatment of patients with UTUC), we assumed that a patient would exhibit a relatively high rate of disease recurrence or death before receiving treatment intervention. Therefore, the threshold probability for the decision curve was up to 50%. Our results showed a significant net benefit for CSS gained by adding fibrinogen to the base model when the threshold ability was 0.3–0.5; in contrast, the net benefit gained by adding ALP or NLR to the base model was not obvious (Figure 2).

**DISCUSSION**

Our results suggest that elevated fibrinogen is an independent predictor for adverse pathological outcomes and worse survival outcomes in patients with UTUC. In addition, we demonstrate that the addition of fibrinogen may improve the predictive accuracy of the prediction models; most importantly, we reveal an added benefit for CSS prediction when fibrinogen was added to the base model. To the best of our knowledge, this is the largest single-center retrospective study to investigate the prognostic role of fibrinogen among Chinese patients who had received RNU to treat UTUC.

Using blood-based markers (including NLR, fibrinogen, C-reactive protein [CRP], and albumin-to-globulin ratio) from laboratory examination to predict oncologic outcomes in UTUC is not a novel concept. According to the most recent EAU guidelines, only NLR has been recommended as a preoperative risk factor in UTUC. Therefore, we sought to explore the predictive value of fibrinogen based on several published reports, which showed that an elevated fibrinogen level was an independent risk factor for poor survival in...
UTUC. Of note, our study showed that both NLR and fibrinogen were independent prognostic factors for UTUC, but that fibrinogen might perform better than NLR. In the multivariate Cox regression model, the HRs of fibrinogen versus NLR were 2.33 versus 1.83 for CSS, 2.09 versus 1.56 for RFS, and 2.09 versus 1.67 for OS. More importantly, the addition of fibrinogen, but not NLR, to the base model achieved a
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Table 4: Improvement in discrimination when adding preoperative laboratory factors to the base model

| Model               | C-index for CSS Improvement | C-index for RFS Improvement | C-index for OS Improvement |
|---------------------|----------------------------|----------------------------|----------------------------|
| Base models*        | 0.762                      | 0.724                      | 0.750                      |
| + ALP               | 0.774                      | 0.012                      | 0.732                      |
| + NLR               | 0.778                      | 0.016                      | 0.737                      |
| + Fibrinogen        | 0.794                      | 0.032                      | 0.744                      |

*The base models included tumor grade, stage, lymph node invasion, tumor size, and concomitant variant histology. ALP: alkaline phosphatase; NLR: neutrophil-to-lymphocyte ratio; CSS: cancer-specific survival; RFS: disease recurrence-free survival; OS: overall survival

net benefit in the decision curve analysis. Thus, fibrinogen might be a better prognostic predictor than NLR for UTUC.

Plasma fibrinogen, an important factor reflecting an individual's coagulation function, is routinely measured before surgery. Tanaka et al.12 first described the prognostic role of pretreatment fibrinogen level in patients with localized UTUC in a Japanese population. The study enrolled 218 patients, and the results showed that fibrinogen >450 mg dl⁻¹ independently predicted worse pathological features and survival outcomes (CSS and RFS). Subsequently, data from Europe13 and China (East14 and North15) also supported the independent predictive value of fibrinogen in UTUC. Nevertheless, most of these studies incorporated relatively small numbers of cases with short follow-up durations, which made their results relatively inconclusive. In addition, different cutoff values of fibrinogen were reported in these studies, limiting its use for clinical reference. Our study showed that fibrinogen could not only independently predict outcomes in UTUC, but that it increased the discriminative accuracy of predicting survival outcomes in UTUC and achieved an added net benefit for CSS in the decision curve analysis, based on providing additional information for risk stratification in UTUC.

According to our ROC analysis, the optimal cutoff value was determined to be 4.025 g l⁻¹. The area under the curve (AUC) was 0.689, and the Youden index was 0.316, with a sensitivity of 57.8% and a specificity of 74.7%. In the study conducted by Wang et al.8 in prostate cancer, their cutoff value of fibrinogen was 3.225 g l⁻¹, and the AUC was 0.692, with a sensitivity of 68.3% and a specificity of 65.7%. Both studies had comparable AUC values (0.689 vs 0.692), and sensitivity and specificity all exceeded 50%. It should be noted that using fibrinogen alone to predict survival outcomes might be inappropriate in current clinical practice (57.8% sensitivity); we, thus, incorporate this parameter in our multivariate models; and the predictive accuracy could reach approximately 80% when fibrinogen was added.

To date, progress has been made with regard to determining the potential mechanism by which high fibrinogen level contributes to worse oncologic outcomes among cancer patients. Tumor cells and tumor-associated macrophages might induce elevated fibrinogen levels, and fibrinogen is a determinant of metastatic potential.20 In vitro assays have demonstrated that fibrinogen can promote tumor cell proliferation and migration through various signal pathways. An in vivo study conducted by Steinbrecher et al.21 further demonstrated that fibrinogen contributed to tumor progression through interaction with alpha(M)beta(2). Taken together, these data indicate that the elevated fibrinogen level caused by tumor cells promotes tumor cell invasion and metastasis, which might explain its predictive significance in UTUC.

In addition to fibrinogen, our study revealed that postoperative factors such as tumor stage and grade, CVH, and lymph node involvement independently predicted CSS, RFS, and OS; these findings were consistent with published literature.2 Compared with these pathological predictors, fibrinogen is advantageous in that it provides easy preoperative accessibility and a cost-effective approach for determining the necessity of early intervention before surgery (e.g., neoadjuvant therapy), as well as for assisting in identifying the best candidates for such interventions. Nonetheless, we did not find an independent prognostic value for LVI and PSM in this cohort, although previous studies revealed that these parameters were useful in this regard.22,23 Research on UTUC remains limited because of its low morbidity. Our study had the largest sample size for exploration of the prognostic significance of fibrinogen in UTUC and provided useful information regarding UTUC in the West Chinese population.

As with all retrospective studies, this study was limited by its study design, which might lead to selection bias. Although we strictly limited our study population, we were unable to completely exclude those whose condition might affect the plasma fibrinogen level. In addition, we were unable to assess the potential influence of some factors, such as CRP (reportedly valuable in the prognosis of UTUC20) because they were not routinely assessed preoperatively in our center. Moreover, data on postoperative chemotherapeutic regimens were incomplete, hindering analyzing the effects of the types, dosages, and duration of these drugs on prognosis. Furthermore, the potential role of neoadjuvant therapy remains unclear because our study cohort did not receive this treatment. Further prospective multicenter studies are warranted to support our findings.

CONCLUSIONS

Preoperative fibrinogen is a strong independent factor associated with both adverse pathological features and survival outcomes in UTUC. It might be a better indicator than NLR in predicting oncologic outcomes in UTUC. Adding it into the prediction models might be valuable which might aid in clinical decision-making.

AUTHOR CONTRIBUTIONS

HX, JZA and PT participated in project design and performed data collection and statistical analysis. HX drafted the manuscript. HX, PT, THL, and JZA helped with patients' follow-up. XJ, LNG, and HRL carried out data collection and helped analyze data. LY and QW participated in project design and participated in data explanation and manuscript revision. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary Figure 1: The optimal fibrinogen cutoff level (4.025 g l$^{-1}$) was determined from ROC analysis. The AUC was 0.689, and the Youden index was 0.316, with a sensitivity of 57.8% and a specificity of 74.7%.

ROC: receiver-operating characteristic; AUC: area under the curve; CI: confidence interval.
| Variables | Cancer-specific survival | Recurrence-free survival | OS |
|-----------|-------------------------|-------------------------|-----|
| Age (≥65 vs <65 years) | 0.848 (0.641–1.122) | 0.881 (0.696–1.115) | 0.966 (0.748–1.246) |
| BMI (>25 vs ≤25, kg/m²) | 0.848 (0.616–1.169) | 0.947 (0.729–1.230) | 0.917 (0.691–1.218) |
| Smoking status (former/current vs no) | 0.848 (0.615–1.159) | 0.864 (0.664–1.124) | 0.878 (0.662–1.164) |
| Gender (male vs female) | 0.824 (0.628–1.081) | 0.857 (0.682–1.076) | 0.876 (0.686–1.019) |
| Tumor side (right vs left) | 1.089 (0.830–1.428) | 1.063 (0.847–1.333) | 1.051 (0.824–1.341) |
| Bladder cancer status | 0.203 | 0.376 | 0.136 |
| No | Reference | Reference | Reference |
| Previous | 0.345 (0.085–1.391) | 0.903 (0.425–1.920) | 0.297 (0.074–1.198) |
| Concomitant | 1.205 (0.809–1.795) | 1.263 (0.901–1.770) | 1.198 (0.835–1.719) |
| Hydronephrosis (yes vs no) | 1.249 (0.938–1.664) | 1.401 (1.097–1.788) | 1.342 (1.035–1.740) |
| Tumor location | 0.556 | 0.508 | 0.675 |
| Pelvicalyceal | Reference | Reference | Reference |
| Ureteric | 1.005 (0.729–1.384) | 0.937 (0.715–1.229) | 0.941 (0.704–1.260) |
| Both | 1.217 (0.841–1.762) | 1.152 (0.842–1.577) | 1.118 (0.796–1.569) |
| Multifocality (yes vs no) | 1.059 (0.736–1.524) | 0.993 (0.727–1.358) | 0.971 (0.692–1.361) |
| Surgical approach (Laparoscopic vs Open) | 0.672 (0.485–0.932) | 0.858 (0.662–1.114) | 0.711 (0.529–0.956) |
| Tumor grade (high vs low) | 3.558 (2.305–5.492) | 2.278 (1.675–3.098) | 2.847 (1.992–4.070) |
| pT stage | <0.001 | <0.001 | <0.001 |
| pT2 | 1.632 (0.966–2.757) | 1.502 (1.011–2.233) | 1.635 (1.045–2.558) |
| pT3 | 3.654 (2.372–5.629) | 2.797 (2.005–3.901) | 3.323 (2.222–4.702) |
| pT4 | 9.339 (5.921–14.729) | 6.936 (4.811–9.998) | 7.955 (5.327–11.881) |
| Lymph node status | <0.001 | <0.001 | <0.001 |
| pN0 | 1.496 (0.915–2.446) | 1.505 (1.013–2.235) | 1.507 (0.983–2.311) |
| pNx | 6.124 (3.525–10.638) | 5.546 (3.484–8.831) | 5.361 (3.260–8.814) |
| LVI (yes vs no) | 2.726 (1.991–3.732) | 2.211 (1.676–2.917) | 2.511 (1.884–3.349) |
| Tumor size (>3 vs ≤3), cm | 1.985 (1.439–2.739) | 1.856 (1.425–2.418) | 1.983 (1.486–2.645) |
| PSM (yes vs no) | 2.319 (1.546–3.480) | 1.865 (1.290–2.694) | 2.118 (1.453–3.087) |
| Tumor architecture (Sessile vs Papillary) | 3.675 (2.480–5.447) | 2.500 (1.874–3.335) | 2.928 (2.114–4.055) |
| CVH (yes vs no) | 2.435 (1.825–3.248) | 2.045 (1.595–2.622) | 2.237 (1.722–2.906) |
| Adjuvant chemotherapy (yes vs no) | 0.963 (0.731–1.268) | 1.128 (0.896–1.420) | 0.889 (0.693–1.139) |
| WBC (≥8.3 vs <8.3, ×10³ l⁻¹) | 1.772 (1.305–2.407) | 1.455 (1.111–1.904) | 1.577 (1.189–2.092) |
| Platelet Count (≥230 vs <230, ×10³ l⁻¹) | 2.111 (1.592–2.799) | 1.634 (1.276–2.091) | 1.711 (1.317–2.222) |
| ALP (≥90 vs <90, U l⁻¹) | 1.782 (1.338–2.372) | 1.396 (1.092–1.785) | 1.497 (1.153–1.945) |
| LDH (≥220 vs ≤220, U l⁻¹) | 1.613 (1.145–2.272) | 1.485 (1.109–1.989) | 1.553 (1.141–2.113) |
| NLR (≥2.5 vs <2.5) | 2.362 (1.749–3.190) | 1.854 (1.458–2.358) | 2.104 (1.617–2.737) |
| AGR (<1.45 vs ≥1.45) | 2.381 (1.781–3.183) | 1.818 (1.438–2.298) | 2.141 (1.656–2.767) |
| Fibrinogen (≥4.025 vs <4.025, g l⁻¹) | 3.965 (2.998–5.243) | 2.855 (2.265–3.598) | 3.281 (2.559–4.206) |