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ORIGINAL ARTICLE

Preoperative predictive factors focused on inflammation-, nutrition-, and muscle-status in patients with upper urinary tract urothelial carcinoma undergoing nephroureterectomy

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Abstract

Objective The present study evaluated the clinical relevance of an integrative preoperative assessment of inflammation-, nutrition-, and muscle-based markers for patients with upper urinary tract urothelial carcinoma (UTUC) undergoing curative nephroureterectomy (NUx).

Methods The study enrolled 125 patients and the preoperative variables assessed included age, body mass index, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), serum fibrinogen level (Fib), C-reactive protein (CRP), modified Glasgow prognostic score, serum albumin level (Alb), prognostic nutritional index (PNI), skeletal muscle index (SMI), psoas muscle index (PMI), and peak expiratory flow (PEF). The correlations among the variables and their prognostic values after NUx were evaluated.

Results Five inflammation markers (NLR, MLR, PLR, Fib and CRP) were positively correlated. Fib was positively correlated with NLR, PLR and CRP, but inversely correlated with SMI. PNI was inversely correlated with age and the four inflammation markers ($p < 0.001$). Age was not significantly correlated with the inflammation markers, but older age was associated with lower Alb, PNI, SMI, PMI, and PEF. Disease-specific survival was independently predicted by preoperative ipsilateral hydronephrosis and low PNI. Overall survival was independently associated with high Fib and low PNI.

Conclusion The preoperative inflammation-, nutrition-, and muscle-based markers would be useful risk assessment tools for UTUC.

Keywords Upper urinary tract urothelial carcinoma · Preoperative prognostic factor · Nephroureterectomy · Inflammation · Nutrition · Sarcopenia

Abbreviations

UTUC	Upper urinary tract urothelial carcinoma
NUx	Nephroureterectomy
BMI	Body mass index
CRP	C-reactive protein
NLR	Neutrophil-to-lymphocyte ratio
MLR	Monocyte-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
Fib	Serum fibrinogen level
GPS	Glasgow prognostic score
mGPS	Modified Glasgow prognostic score
Alb	Serum albumin level
PNI	Prognostic nutritional index
SMI	Skeletal muscle index
PMI	Psoas muscle index
PEF	Peak expiratory flow
DSS	Disease-specific survival
OS	Overall survival
HR	Hazard ratio
CI	Confidence interval

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Introduction

Upper urinary tract urothelial carcinoma (UTUC) is relatively rare, representing only approximately 5–10% of UCs, but is an aggressive and malignant disease [1, 2].

Patients with UTUCs that invade the muscle layer usually have a poor prognosis. The 5-year disease-specific survival (DSS) is < 50% for pT2 or pT3 disease and < 10% for pT4 [1, 3]. According to the latest published reports [1, 3] on UTUC, pathological T stage and tumor grade are regarded as prognostic indicators of great importance, and several other prognostic parameters, such as tumor size and lymph node involvement, were suggested to predict prognosis in UTUC. It might be relevant to clarify individual risk factors in the future, which would benefit outcome prediction and the treatment choices for individual patients. However, the potential prognostic preoperative factors are still limited in UTUC.

Some research groups revealed certain prognostic indexes or models to predict the clinical outcome of UTUC [4–7]. Increasing evidence shows that systemic inflammatory response and nutritional deficiencies might play crucial roles in the development and progression of human cancer [5]. The host's immune response to malignancy is characterized by systemic inflammation, which leads to changes in the levels of neutrophils, lymphocytes, monocytes, and thrombocytes. In addition, there is a strong relationship between the systemic inflammatory response and disease development and progression. Systemic inflammation in malignant cases is characterized by an imbalance between pro- and anti-inflammatory cytokines, and inflammatory markers can be used to predict prognosis in various malignancies. For example, the prognostic markers for urogenital cancer, multiple myeloma, and colorectal cancer include elevated values for C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and the Glasgow prognostic score (GPS) [5, 8–10].

Furthermore, several studies have shown that preoperative serum fibrinogen level (Fib), which plays a vital part in clot formation, independently predicts prognosis in various human cancers [4, 7, 11, 12]. Meanwhile, serum albumin level (Alb) has been regarded as a crucial parameter of malnutrition. Cui et al. recently reported that Fib and Alb, also known as FA score, could predict the prognosis of patients with UTUC regarding overall survival (OS) and DSS [12].

Moreover, several reports have indicated that systemic inflammation plays a critical role in the pathogenesis of malnutrition, weight loss, and muscle loss in cachexia cases [6, 7, 13, 14]. Abdominal computed tomography (CT) and spirometry are routinely performed during preoperative preparations, which allows researchers to calculate skeletal muscle index (SMI), psoas muscle index (PMI), and respiratory muscle strength [i.e., peak expiratory flow (PEF)]. In addition, survival and postoperative complications after treatment for colorectal cancer are associated with preoperative prognostic nutritional index (PNI) [15]. These nutrition-based markers may be associated with clinical outcomes after nephroureterectomy (NUx). Moreover, previous prognostic studies have only considered a single marker or a combination of a few markers. The present study aimed to perform an integrative and comparative study of pretreatment inflammation-, nutrition-, and muscle-based markers in a single cohort of patients with UTUC who had undergone NUx.

Patients and methods

Patient data collection and follow-up

The methods and procedures for this study were approved by the Ethics Committee of Nara Medical University (NMU-1100), and all participants provided informed consent for the study. The retrospective analyses evaluated data from 183 patients without evidence of distant metastases who underwent NUx between October 1995 and December 2016. However, 58 patients were excluded because of a short follow-up time of less than 6 months, deficits in blood examination and imaging data, and the receipt of neoadjuvant chemotherapy. Finally, 125 patients with UTUC were eligible for this study. The histopathological review was performed by an experienced uropathologist (K.S.), who confirmed the T category (based on the 2002 TNM staging system), tumor grade (based on 1973 WHO classification), lymphovascular invasion, and presence of variant histology. Clinical, pathological, and radiographic data were extracted from the patients' medical records, and laboratory data were obtained from measurements. Postoperative follow-up was performed after the first month, every 3 months for the first 2 years, every 6 months for the following 3 years, and annually thereafter for patients without evidence of recurrent disease, in accordance with our institutional protocol.

Patient allocation for adjuvant chemotherapy was not randomized but depended on the clinician's decision. Two or more courses of adjuvant chemotherapy (AC) were administered to 37 of the 125 patients. The regimens were usually started within 3 months following NUx. M-VAC regimen (30 mg/m^2 methotrexate on Days 1, 15 and 22; 3 mg/m^2 vinblastine on Days 2, 15 and 22; 30 mg/m^2 adriamycin on Day 2 and 70 mg/m^2 cisplatin on Day 2) and the GC regimen (1000 mg/m^2 gemcitabine on Days 1, 8 and 15; and 70 mg/m^2 cisplatin on Day 2) were given every 4 weeks. Most other regimens were based on gemcitabine and CBDCA (1000 mg/m^2 gemcitabine on Days 1 and 8 and area under the curve 4–5 CBDCA on Day 1) and repeated every 3–4 weeks. Other regimens were used for patients with mild-to-moderate postoperative renal dysfunction [16].

Measurements of inflammation- and nutrition-based markers

Eight markers (NLR, PLR, MLR, Fib, CRP, modified GPS [mGPS], Alb, and PNI) were evaluated using laboratory data collected < 30 days before patients underwent NUx. The mGPS scores were assigned as follows: a score of 2 to patients with elevated serum CRP levels (> 0.5 mg/dL) and decreased Alb (< 3.5 g/dL), a score of 1 to patients with 1 abnormal value, and a score of 0 to patients with no abnormal values [9]. PNI was calculated as 10 × Alb (g/dL) + 0.005 × total lymphocyte count (per mm^3) [15].

Skeletal Muscle Index (SMI), Psoas Muscle Index (PMI), and sarcopenia

Unenhanced CT was performed for diagnostic purposes before patients underwent NUx, and the data were entered into the Volume Analyzer SYNAPSE VINCENT image analysis system (Fujifilm Medical, Tokyo, Japan). The cross-sectional area of the skeletal muscle and psoas major muscle at the level of the third lumbar vertebra (L3) was calculated using the analysis system. The measured variables were normalized to height (m^2) obtain SMI (cm^2/m^2) and PMI (cm^2/m^2) for intersubject comparisons. SMI was measured as a continuous variable, and used as an indicator of whole-body muscle mass, as a previous study had established that the total lumbar-skeletal muscle cross-sectional area is linearly associated with whole-body muscle mass [17]. Based on the international sex-specific consensus definitions of sarcopenia, we stratified the patients into sarcopenia and non-sarcopenia groups according to their body mass index (BMI), using a threshold lumbar SMI of < 43 cm^2/m^2 among men with a BMI of < 25 kg/m^2, < 53 cm^2/m^2 for men with a BMI of > 25 kg/m^2, and < 41 cm^2/m^2 for women [18]. Concerning PMI, the definition set by Hamaguchi et al. was adopted for our analyses, as it is founded on a large cohort of Asian adults: PMI < 6.36 cm^2/m^2 for men and < 3.92 cm^2/m^2 for women [19].

Baseline respiratory muscle strength

All patients were tested using spirometry as a part of their preoperative assessment. In people who do not have bronchial asthma, PEF is an indicator of respiratory muscle strength [20]. PEF was expressed in L/min and analyzed as either normal or reduced, based on the cutoff value defined by Berglund et al. [21].

Statistical analysis

Data were shown as bar charts or dot plots and were evaluated using the Student *t* test, the Mann–Whitney *U* test, or the χ^2 test, as appropriate. The relationships among the studied parameters were examined using the Spearman correlation coefficient and linear regression analysis. DSS and OS were assessed using the Kaplan–Meier method and compared using the log-rank test. Multivariate analyses were used to identify independent prognostic variables based on a stepwise Cox proportional hazards regression model and variables that potentially affected survival ($p < 0.05$ in the univariate analyses). Data were analyzed using the PRISM software (version 7.00; San Diego, CA, USA). A p value < 0.05 was considered statistically significant.

Table 1 Clinicopathological characteristics of 125 patients with UTUC undergoing NUx

	Number	%
Total	125	
Age at NUx, median (range)	72 (38–90)	
Gender		
Male/female	96/29	76.8/23.2
ECOG performance status		
0/≥ 1	117/8	93.6/6.4
Tumor location (main tumor)		
pelvis/ureter	68/57	54.4/45.6
Hydronephrosis		
No/yes	61/64	48.8/51.2
Lymph node dissection		
No/yes	72/53	57.6/42.4
Clinical T stage		
Ta/1/is	70	56
T2	36	28.8
T3	15	12
T4	4	3.2
Pathological T stage		
Ta/1/is	54	43.2
T2	17	13.6
T3	48	38.4
T4	6	4
Pathological N stage		
N0/≥ pN1	117/8	93.6/6.4
Tumor grade		
Low/high	26/99	20.8/79.2
Lymphovascular invasion		
Negative/positive	63/62	50.4/49.6
Histological variants		
No/yes	112/13	89.6/10.4
Adjuvant chemotherapy		
No/yes	88/37	70.7/29.3

UTUC upper urinary tract urothelial cancer, *NUx* nephroureterectomy

Results

Patient characteristics

The clinicopathological characteristics of the 125 patients are listed in Table 1. The median follow-up period after NUx was 51 months (interquartile range, 6–227 months). A total of 40 patients died during the follow-up period (32%); 22 died due to UTUC (18%), including 28 cases with progressive disease (22%) and 54 cases with recurrent disease (43%). Among the 125 cases, 22 (17%) received 2–4 cycles of platinum-based adjuvant chemotherapy.

Baseline inflammation-, nutrition-, and muscle-based markers

The baseline mean ± standard deviation values for the nine markers are shown in Table 2. Men had a significantly higher mean SMI (47.3 ± 7.30 vs. 39.3 ± 7.38 cm^2/m^2, $p < 0.001$), PMI (7.20 ± 1.44 vs. 5.58 ± 1.37 cm^2/m^2, $p < 0.001$), and PEF (438 ± 125 vs. 290 ± 76 L/min, $p < 0.001$) compared to women.

Fig. 1 Correlation analysis for baseline inflammation-, nutrition-, and muscle-based markers in 125 patients with UTUC undergoing NUx. **a** The summary results from the correlation analysis of age at NUx and the 10 studied markers (*p* values and Spearman *r* from correlation coefficient analysis and the *Y*-slope from linear regression analysis are indicated) at baseline. Red font indicates significant positive correlation between the tested markers, and blue font indicates significant inverse correlation between the tested markers. Alb, serum albumin level; BMI, body mass index; CRP, C-reactive protein; Fib, serum fibrinogen level; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NUx, nephroureterectomy; PEF, peak expiratory flow; PLR, platelet-to-lymphocyte ratio; PMI, psoas muscle index; PNI, prognostic nutritional index; SMI, skeletal muscle index; UTUC, upper urinary tract urothelial cancer. **b** The relationship between baseline NLR and Fib or PNI were examined using the Spearman correlation coefficient and linear regression analysis

Correlation analyses to investigate the correlations between the inflammation, nutrition, and muscle indexes

We selected continuous variables for analysis using the Spearman correlation coefficient (i.e., age, BMI, NLR,

Table 2 Baseline inflammation-, nutrition-, and muscle-based markers in 125 patients with UTUC undergoing NUx

Variables	Median (IQR) or *n* (%)	Mean ± SD	*p* value
Inflammation markers			
NLR	2.35 (0.79–21.5)	2.94 ± 2.42	
MLR	0.28 (0.11–0.65)	0.32 ± 0.19	
PLR	139 (38–723)	151 ± 90.8	
Fib, mg/dL	330 (159–680)	341 ± 96.4	
CRP, mg/dL	0.10 (0.1–11.7)	0.46 ± 1.25	
mGPS			
0	98 (78.4)		
1	24 (19.2)		
2	3 (2.4)		
Nutrition markers			
Alb, g/dL	4.20 (2.7–5.1)	4.17 ± 0.44	
PNI	50.5 (31.4–63.8)	49.7 ± 5.75	
Muscle index			
Skeletal muscle area at L3, cm^2/m^2			< 0.001†
Male	46.4 (33.0–64.7)	47.3 ± 7.30	
Female	39.3 (23.4–53.9)	39.3 ± 7.38	
Psoas major muscle area at L3, cm^2/m^2			< 0.001†
Male	7.09 (4.04–11.1)	7.20 ± 1.44	
Female	5.41 (2.47–8.98)	5.58 ± 1.37	
PEF in spirometry, L/min			< 0.001†
Male	445 (109–688)	438 ± 125	
Female	295 (71–425)	290 ± 76.2	

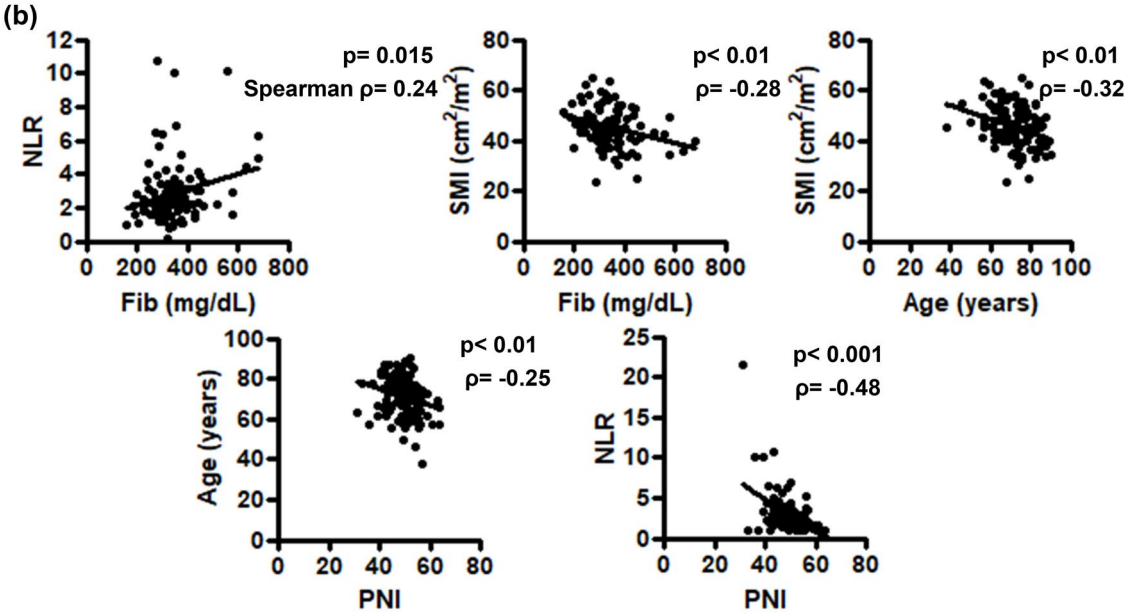
UTUC upper urinary tract urothelial cancer, *NUx* nephroureterectomy, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, Fib serum fibrinogen, *CRP* C-reactive protein, *Alb* Albumin, *mGPS* modified Glasgow prognostic score, *PNI* prognostic nutritional index, *L3* the third lumbar vertebra, *PEF* peak expiratory flow, *SD* standard deviation, *IQR* interquartile range

†Comparing men and women using the Mann–Whitney *U* test

(a)

		Age	BMI	NLR	MLR	PLR	Fib	CRP	Alb	PNI	SMI	PMI	PEF
Age	p value ρ slope												
BMI	p value ρ slope	0.77 0.026 0.011											
NLR	p value ρ slope	0.83 -0.020 -0.005	0.017 -0.21 -0.11										
MLR	p value ρ slope	0.58 0.051 0.001	0.60 -0.049 -0.002	<0.001 0.80 0.063									
PLR	p value ρ slope	0.36 0.084 0.81	0.048 -0.18 -3.71	<0.001 0.78 28.8	<0.001 0.56 0.001								
Fib	p value ρ slope	0.33 0.099 1.02	0.17 -0.14 -2.70	0.015 0.24 12.9	0.22 0.12 <0.001	0.042 0.20 0.17							
CRP	p value ρ slope	0.48 -0.063 -0.008	0.78 0.025 0.007	<0.001 0.64 0.33	<0.001 0.67 4.38	<0.001 0.47 0.006	<0.001 0.53 0.004						
Alb	p value ρ slope	0.019 -0.22 -4.54	0.37 0.007 -0.73	<0.001 -0.60 -1.65	0.19 0.014 -0.10	0.91 <0.001 -2.13	0.51 0.004 15.0	<0.001 -0.35 -0.99					
PNI	p value ρ slope	<0.01 -0.25 -0.42	0.35 0.084 0.072	<0.001 -0.48 -0.20	<0.001 -0.44 -0.015	<0.001 -0.47 -7.34	0.38 -0.088 -1.49	<0.001 -0.36 -0.08	<0.001 0.75 11.4				
SMI	p value ρ slope	<0.001 -0.32 -0.38	<0.001 0.35 0.17	0.091 -0.16 -0.032	0.96 -0.005 0.36	0.32 -0.093 -0.84	0.005 -0.28 -3.20	0.57 -0.053 <0.001	0.033 -0.04 -3.60	0.70 0.037 0.025			
PMI	p value ρ slope	0.005 -0.26 -1.56	<0.001 0.31 0.79	0.71 0.034 0.039	0.92 0.009 0.12	0.18 -0.13 -5.75	0.25 -0.12 -6.70	0.83 -0.02 -0.007	0.40 0.006 -0.67	0.47 0.068 0.24	<0.001 0.65 3.32		
PEF	p value ρ slope	<0.001 -0.32 -5.79	0.76 0.030 1.24	0.29 0.10 10.3	0.56 0.059 <0.001	0.30 -0.10 -0.060	0.14 0.15 0.007	0.93 -0.008 <0.001	0.58 0.003 16.6	0.53 0.061 1.80	0.010 0.25 4.15	0.017 0.24 18.9	

(b)



MLR, PLR, Fib, CRP, Alb, PNI, SMI, PMI, and PEF). Age was not significantly correlated with the inflammation markers, but older age was associated with low Alb, PNI, SMI, PMI, and PEF values. There was a significant inverse correlation between PNI and age, NLR, MLR, PLR and CRP (Fig. 1a). Fib was positively correlated with three inflammation markers, NLR, PLR and CRP, but was negatively correlated with SMI. Figure 1b summarizes the Spearman *p* values from the correlation coefficient analyses and the Y-slopes from the linear regression analyses.

Preoperative hydronephrosis was correlated with high Fib and low SMI in the males. High clinical T stage (≥ T3) was correlated with low PNI and low PEF in the males. Tumor location (pelvis or ureter) was not correlated with any of preoperative continuous variables (Table 3).

Prognostic values of the inflammation-, nutrition-, and muscle-based markers

Uni- and multivariate analyses were used to explore the prognostic value of the studied markers. The cutoff values were defined as 0.3 for MLR, 150 for PLR, 340 mg/dL for Fib, 0.3 for CRP and 50 for PNI using a minimum *p* value approach to identify the cutoff point (Table 2). The NLR cutoff value was defined as 2.6 based on our previous report [22]. Univariate analyses revealed that DSS could be predicted by the presence of hydronephrosis, clinical T category (≥ cT2), and low PNI. OS was predicted by Eastern Cooperative Oncology Group performance status (≥ 1), high Fib, mGPS (≥ 1), and low PNI. In univariate analysis, sarcopenia status defined by SMI and PMI was not associated with a poor prognosis after NUx (Table 4). The multivariate analyses revealed that DSS was independently predicted by the presence of hydronephrosis and low PNI. The independent predictors of OS were high Fib and low PNI. In this study, prognosis after NUx was not associated with high NLR, PLR, or MLR, sarcopenia status, or a reduced PEF, or administration of adjuvant chemotherapy.

When we stratified four groups according to the presence of hydronephrosis separated by tumor location, renal pelvis or ureter, DSS was significantly worse in the ureter tumor with hydronephrosis (Fig. 2). Preoperative hydronephrosis was associated with tumor location (ureter), pathological T stage, and lymphovascular invasion (Table 5).

Furthermore, when we stratified three preoperative risk factors, including the presence of hydronephrosis, high Fib and low PNI, both DSS and OS were significantly worse as risk factors increased (Fig. 3).

PNI was the only common independent risk factor for OS and DSS. In a comparison of the background characteristics using a cut off of PNI, high PNI was significantly correlated with young age and favorable performance status. However, other clinicopathological characteristics including pathological T stage, N stage, tumor grade, lymphovascular invasion and histological variants were not related to PNI status (Table 5).

Discussion

The present study evaluated an integrative evaluation of multiple inflammation-, nutrition-, and muscle-based markers from patients who underwent potentially curative NUx for UTUC. Although many studies have assessed single biomarkers or combinations of several biomarkers [3–7, 12, 13], no studies have evaluated numerous integrated markers in a single cohort. In addition, the present study evaluated a nutritional index, PNI, to address the lack of data regarding the clinical relevance of pretreatment nutritional condition. Our findings show that, the presence of hydronephrosis, high Fib and low PNI were independent prognostic variables (Table 4). These results suggest that local tumor progression, systemic inflammation, and nutrition status affect the clinical outcomes after NUx for UTUC.

Ipsilateral hydronephrosis is common in UTUC patients, and may be attributed to one of several factors, including luminal obstruction, intramural invasion, or extrinsic compression. The presence of ipsilateral hydronephrosis in patients with UTUC has been reported to be associated with advanced disease [23]; however, only two studies revealed a correlation between hydronephrosis and poor prognosis based on small cohort [24, 25]. In this study, preoperative hydronephrosis was associated with ureteral location, pathological T stage, lymphovascular invasion (Table 5). Furthermore, univariate and multivariate analyses revealed that poor DSS was correlated with preoperative hydronephrosis (Table 4).

Fibrinogen is a type of plasma glycoprotein, that plays an essential role in wound healing, clot formation, and sustaining platelet aggregation. It is mainly formed by liver epithelium, and inflammatory stimulation can also promote fibrinogen synthesis in the lung and intestinal epithelium. Increased plasma fibrinogen was reported to predict tumor progression, distant metastasis, and poor oncological outcome in various malignancies [4, 7, 11]. Acting as a molecular bridge, fibrinogen can promote stable adhesion between tumor cells, platelets, and endothelial cells [26]. Palumbo et al. [27] reported that fibrinogen was a critical element of the metastatic ability of circulating tumor cells and stimulated tumor formation and dissemination. Moreover, previous studies have shown that Fib was related to certain pathological characteristics such as T stage, lymph node involvement, tumor size, tumor grade, and lymphovascular invasion in several cancers [4, 7, 11]. Two prior studies have also proven the prognostic value of Fib in UTUC in the Japanese and European populations [4, 7].

Table 3 Correlation analysis for baseline nutrition-, inflammation-, and muscle-based markers of 125 patients with UTUC undergoing NUx

Variables	Median (IQR) or *n* (%)	HN−	HN+	*p* value	Clinical T stage		*p* value	Tumor location		*p* value
					≤ T2	≥ T3		Pelvis	Ureter	
Age	Median (IQR)	72 (46–90)	71 (38–87)	0.55	72.5 (38–90)	68.0 (56–89)	0.68	72 (38–90)	73 (50–87)	0.31
Body mass index	Median (IQR)	22.8 (12.4–35.4)	23.3 (15.2–37.0)	0.57	22.9 (15.2–37.0)	23.7 (19.7–32.7)	0.23	23.2 (15.2–37.0)	23.0 (16.0–32.5)	0.49
Inflammation markers										
NLR	Median (IQR)	2.34 (0.79–21.5)	2.35 (0.92–10.0)	0.78	2.34 (0.79–21.5)	2.43 (0.92–4.92)	0.14	2.20 (0.79–21.5)	2.50 (1.06–10.0)	0.72
MLR	Median (IQR)	0.28 (0.11–0.65)	0.29 (0.11–0.65)	0.39	0.29 (0.13–0.65)	0.26 (0.11–0.45)	0.11	0.24 (0.11–0.65)	0.32 (0.12–0.65)	0.49
PLR	Median (IQR)	139 (38–723)	135 (38–266)	0.17	133 (52–723)	155 (38–225)	0.89	135 (53–723)	142 (38–244)	0.21
Fib, mg/dL	Median (IQR)	314 (159–680)	350 (183–676)	0.013	321 (159–676)	345 (227–680)	0.34	321 (159–680)	343 (197–676)	0.63
CRP, mg/dL	Median (IQR)	0.10 (0–11.7)	0.15 (0–6.2)	0.93	0.10 (0–11.7)	0.20 (0–2.5)	0.81	0.10 (0–11.7)	0.20 (0–6.2)	0.66
Nutrition markers										
Alb, mg/dL	Median (IQR)	4.2 (2.7–5.1)	4.15 (2.8–5.0)	0.7	4.2 (2.7–5.1)	4.0 (3.2–4.7)	0.12	4.3 (2.7–5.1)	4.2 (2.8–5.0)	0.34
mGPS										
0	*n* (%)	47 (77.0)	51 (79.7)	0.82	83 (78.3)	15 (78.9)	0.75	54 (80.6)	44 (77.2)	0.14
1	*n* (%)	12 (19.7)	12 (18.8)		20 (18.9)	4 (21.1)		11 (16.2)	13 (22.8)	
2	*n* (%)	2 (3.3)	1 (1.6)		3 (2.8)	0 (0)		3 (4.4)	0 (0)	
PNI	Median (IQR)	50.4 (31.4–63.8)	50.5 (36.0–63.6)	0.59	50.5 (31.4–63.8)	44.9 (42.0–58.9)	0.046	51.2 (31.4–63.8)	50.0 (36.0–57.0)	0.29
Muscle index										
Skeletal muscle area at L3, cm2/m2										
Male	Median (IQR)	47.9 (35.1–65.7)	45.2 (33.0–63.2)	0.03	46.1 (33.0–64.7)	49.0 (34.8–63.2)	0.42	47.5 (33.0–65.7)	46.2 (34.8–64.7)	0.77
Female	Median (IQR)	39.8 (32.4–44.3)	39.3 (23.4–53.9)	0.8	38.2 (33.4–53.8)	43.4 (39.7–53.9)	0.12	41.0 (24.6–44.3)	38.1 (23.4–48.5)	0.4
Psoas major muscle area at L3, cm2/m2										
Male	Median (IQR)	7.22 (4.78–11.1)	6.76 (4.04–10.3)	0.08	7.05 (4.04–11.1)	7.26 (6.17–10.7)	0.1	7.07 (5.00–10.9)	7.11 (4.04–11.1)	0.77
Female	Median (IQR)	4.91 (3.91–6.07)	6.19 (2.47–8.99)	0.084	5.11 (2.47–8.99)	7.15 (6.56–7.88)	0.03	5.26 (3.91–8.99)	6.55 (2.47–7.15)	0.88
PEF in spirometry, L/min										
Male	Median (IQR)	440 (109–671)	456 (140–688)	0.62	456 (109–688)	361 (140–537)	0.012	438 (109–671)	448 (266–688)	0.62
Female	Median (IQR)	299 (71–425)	274 (169–384)	0.87	297 (71–425)	229 (169–250)	0.1	299 (71–425)	274 (218–377)	0.93

UTUC upper urinary tract urothelial cancer, *NUx* nephroureterectomy, *HN* hydronephrosis, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *Fib* serum fibrinogen, *CRP* C-reactive protein, *Alb* Albumin, *mGPS* modified Glasgow prognostic score, *PNI* prognostic nutritional index, *L3* the third lumbar vertebra, *PEF* peak expiratory flow, *SD* standard deviation, *IQR* interquartile range

Table 4 Baseline prognostic variables for disease-specific and overall survival in 125 patients undergoing nephroureterectomy

Variables	Disease-specific survival						Overall survival					
	Univariate			Multivariate†			Univariate			Multivariate†		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age at NUx												
< 70	1						1					
≥ 70	1.2	0.51–2.80	0.68				1.45	0.73–2.87	0.28			
Gender (%)												
Male	1						1					
Female	1.26	0.49–3.22	0.53				1.52	0.75–3.09	0.25			
ECOG PS												
0	1						1			1		
≥ 1	1.95	0.45–8.40	0.37				3.1	1.07–8.95	0.037	1.12	0.36–3.48	0.85
Tumor location												
Pelvis	1						1					
Ureter	2.2	0.92–5.24	0.37				1.19	0.64–2.25	0.58			
Hydronephrosis												
No	1			1			1					
Yes	2.86	1.11–7.35	0.029	2.67	1.04–6.91	0.042	1.89	0.98–3.62	0.056			
LND												
No	1						1					
Yes	1.51	0.65–3.49	0.34				1.14	0.60–2.13	0.69			
Clinical T stage												
< T2	1			1			1					
≥ T2	2.39	1.00–5.69	0.049	2.21	0.92–5.31	0.075	1.89	1.00–3.56	0.05			
NLR												
< 2.6	1						1					
≥ 2.6	1.91	0.83–4.43	0.13				1.42	0.75–2.67	0.28			
MLR												
< 0.3	1											
≥ 0.3	1.35	0.56–3.25	0.5				1.18	0.62–2.25	0.62			
PLR												
< 150	1						1					
≥ 150	0.55	0.21–1.44	0.22				0.66	0.32–1.33	0.24			
Fib												
< 340	1						1			1		
≥ 340	2.29	0.91–5.79	0.079				2.98	1.43–6.22	0.0036	2.3	1.09–4.87	0.029
CRP												
< 0.3	1						1					
≥ 0.3	1.55	0.67–3.60	0.30				1.21	0.63–2.32	0.57			
mGPS												
0	1						1			1		
1/2	2.2	0.92–5.26	0.075				2.05	1.05–4.01	0.037	2	0.91–4.42	0.086
PNI												
> 50	1			1			1			1		
≤ 50	2.75	1.12–6.78	0.027	2.85	1.16–7.03	0.022	2.16	1.13–4.13	0.02	2.21	1.08–4.53	0.030
SMI												
Normal	1						1					
Sarcopenia	1.73	0.68–4.37	0.25				1.54	0.77–3.09	0.22			
PMI												
Normal	1						1					

Table 4 (continued)

Variables	Disease-specific survival						Overall survival					
	Univariate			Multivariate†			Univariate			Multivariate†		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Sarcopenia	0.62	0.14–2.70	0.52				0.77	0.27–2.20	0.62			
PEF												
Normal	1						1					
Decreased	0.87	0.32–2.34	0.78				1.32	0.65–2.69	0.45			
Adjuvant chemotherapy												
No	1						1					
Yes	2.46	1.06–5.70	0.037				1.84	0.97–3.48	0.063			

HR hazard ratio, *CI* confidence interval, *NUx* nephroureterectomy, *LND* lymph node dissection, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *Fib* serum fibrinogen, *mGPS* modified Glasgow prognostic score, *PNI* prognostic nutritional index, *SMI* skeletal muscle index, *PMI* psoas muscle index, *PEF* peak expiratory flow

†Treatment- and age-adjusted multivariate Cox regression analysis

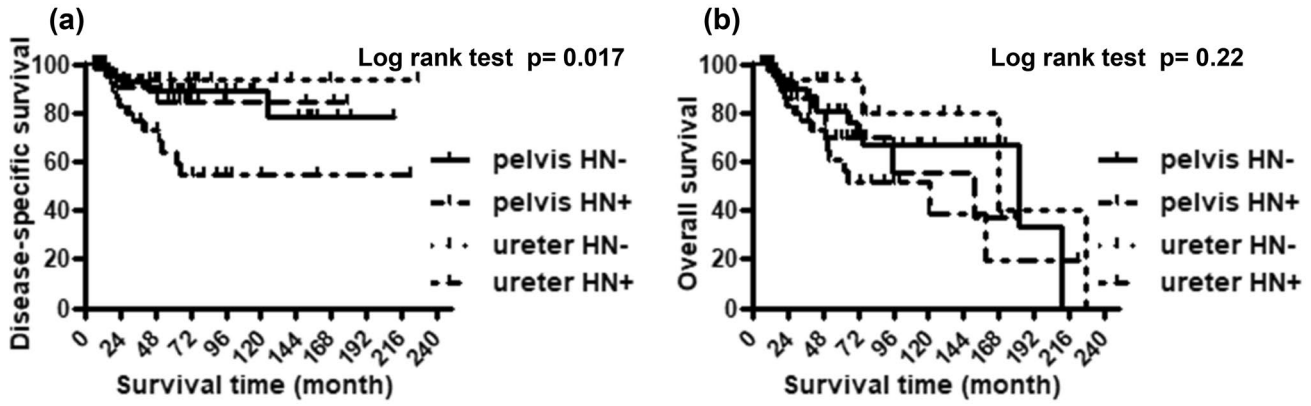


Fig. 2 Kaplan–Meier survival curves of 125 patients with UTUC undergoing NUx stratified by the four groups according to the presence of hydronephrosis (HN) separated by tumor location, renal pelvis or ureter location. a Disease-specific survival (DSS). b overall survival (OS)

PNI, which was described by Onodera et al., is based on Alb and peripheral lymphocyte count [28]. Several studies have confirmed its prognostic value in various cancers such as colorectal carcinoma, hepatocellular carcinoma, lung cancer, and renal cancer [15, 28–31]. PNI was originally developed as a marker to predict the nutritional and immunological statuses of cancer patients before gastrointestinal surgery. It is well recognized that Alb is one of the most generally used markers for assessing nutritional status, and malnutrition is closely connected with poor prognosis and low quality of life, and declining the human defense mechanisms including cellular immunity, anatomic barriers, and phagocyte function [32, 33]. Ku et al. demonstrated that preoperative hypoalbuminemia (Alb < 35 g/L) is an independent prognostic factor of cancer-specific survival and OS in UTUC patients [6]. Another element taken into consideration in PNI is the total lymphocyte count, which plays a primal role in the cell-mediated immune response in tumor formation and progression [34]. The importance of the role of lymphocytes has been demonstrated in several studies that have shown that lymphocytopenia was associated with poor survival outcome, independent of clinicopathological characteristics in patients with UTUC [5]. Taken together, PNI may act as an indicator of nutritional status, systemic inflammatory response, and immunity, and low PNI may associated with poorer outcomes. In this study, the optimal cutoff value of PNI for DSS and OS stratification was determined to be 50. Multivariate analysis identified low PNI as an independent prognostic factor for DSS and OS. However, the optimal cutoff value of PNI to predict OS and DSS remains unclear.

Sarcopenia is reported to be an independent factor for poor prognosis in UTUC patients undergoing NUx, particularly for those with locally advanced disease [35]. This study could not reveal that the baseline sarcopenia status was an independent factor for DSS and OS in UTUC patients.

Table 5 Clinicopathological characteristics of 125 patients with UTUC stratified according to PNI level and the presence of hydronephrosis

	Number (%)	PNI > 50 (%)	PNI ≤ 50 (%)	*p* value	HN −	HN +	*p* value
Total	125	65	60		61	64	
Age at NUx, median (range)	72 (38–90)	70 (38–90)	76 (50–89)	0.002 †	72 (46–90)	73 (38–87)	0.56
Gender							
Male	96 (76.8)	51 (78.5)	45 (75.0)	0.65	51 (83.6)	45 (70.3)	0.078
Female	29 (23.2)	14 (21.5)	15 (25.0)		10 (16.4)	19 (29.7)	
ECOG performance status							
0	117 (93.6)	65 (100)	52 (86.7)	0.007	59 (96.7)	58 (90.6)	0.3
≥ 1	8 (6.4)	0 (0)	8 (13.3)		2 (3.3)	6 (9.4)	
Tumor location							
Pelvis	68 (54.4)	39 (60.0)	29 (48.3)	0.19	44 (72.1)	24 (37.5)	< 0.001
Ureter	57 (45.6)	26 (40.0)	31 (51.7)		17 (27.9)	40 (62.5)	
Hydronephrosis							
No	61 (48.8)	31 (47.7)	30 (50.0)	0.8			
Yes	64 (51.2)	34 (52.3)	30 (50.0)				
Lymph node dissection							
No	72 (57.6)	39 (60.0)	33 (55.0)	0.57	36 (59.0)	36 (56.3)	0.75
Yes	53 (42.4)	26 (40.0)	27 (45.0)		25 (41.0)	28 (43.7)	
Clinical T stage							
Ta/1/is	70 (56.0)	36 (55.4)	34 (56.7)	0.37	38 (62.3)	32 (50.0)	0.59
T2	36 (28.8)	22 (33.8)	14 (23.3)		15 (24.6)	21 (32.8)	
T3	15 (12.0)	6 (9.2)	9 (15.0)		6 (9.8)	9 (14.1)	
T4	4 (3.2)	1 (1.5)	3 (5.0)		2 (3.3)	2 (3.1)	
Pathological T stage							
Ta/1/is	54 (43.2)	28 (43.1)	26 (43.3)	0.73	35 (57.4)	19 (29.7)	< 0.001
T2	17 (13.6)	8 (12.3)	9 (15.0)		8 (13.1)	9 (14.1)	
T3	48 (38.4)	27 (41.5)	21 (35.0)		15 (24.6)	43 (67.2)	
T4	6 (4.8)	2 (3.1)	4 (6.6)		3 (4.9)	3 (4.7)	
Pathological N stage							
N0	117 (93.6)	63 (96.9)	54 (90.0)	0.22	59 (96.7)	58 (90.6)	0.3
≥ pN1	8 (6.4)	2 (3.1)	6 (10.0)		2 (3.3)	6 (9.4)	
Tumor grade							
Low	26 (20.8)	13 (20.0)	13 (21.7)	0.82	17 (27.9)	9 (14.1)	0.057
High	99 (79.2)	52 (80.0)	47 (78.3)		44 (72.1)	55 (85.9)	
Lymphovascular invasion							
Negative	63 (50.4)	35 (53.8)	28 (46.7)	0.42	39 (63.9)	24 (37.5)	0.003
Positive	62 (49.4)	30 (46.2)	32 (53.3)		22 (36.1)	40 (62.5)	
Histological variants							
Yes	13 (10.4)	3 (4.6)	10 (16.7)	0.056	6 (9.8)	7 (10.9)	0.84
No	112 (89.6)	62 (95.4)	50 (82.3)		55 (90.2)	57 (89.1)	

UTUC upper urinary tract urothelial cancer, *PNI* prognostic nutritional index, *HN* hydronephrosis, *NUx* nephroureterectomy

†Comparing two groups using the Mann–Whitney *U* test

However, sarcopenia status defined by SMI was negatively correlated with Fib (Fig. 1a). Our study had fewer patients with pT3 or pT4 stage disease compared to previous studies, so if more progressive cases were included in this study, sarcopenia status may influence prognosis.

In the present study, we confirmed that low PNI was correlated with age and elevated inflammation markers such as NLR, MLR, and PLR. High Fib was correlated with elevated NLR, PLR and decreased SMI (Fig. 1b). Interestingly, NLR, MLR, and PLR were not independent prognostic factors for DSS and OS, but elevated Fib was significantly associated with poor OS (Table 4). Our results implied that increased systemic inflammation may lead to a decrease in PNI and SMI, and subsequently to cachexia and poor outcomes. We

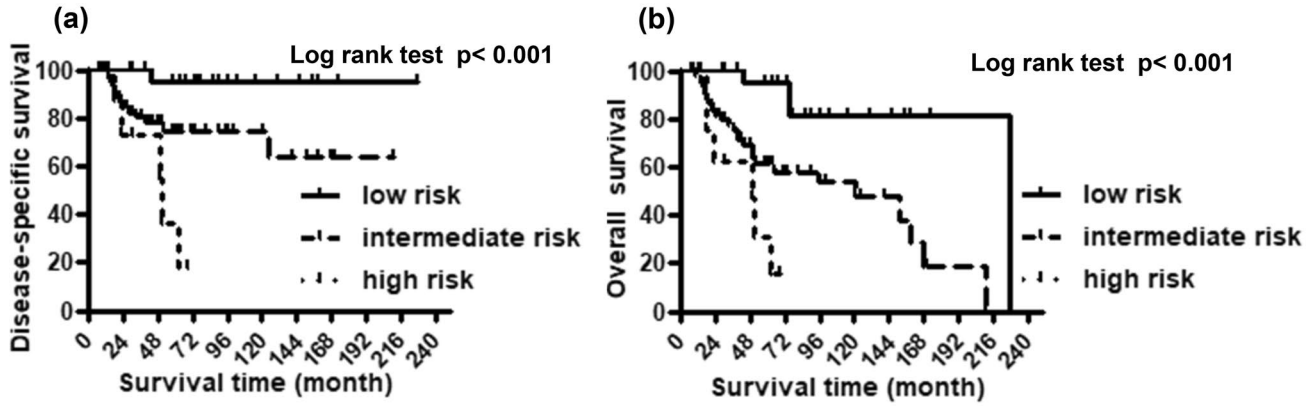


Fig. 3 Kaplan–Meier survival curves of 125 patients with UTUC undergoing NUx stratified by preoperative risk factors, the presence of hydronephrosis, high Fib level, and low PNI. The number of risk factors were defined as the point. It is classified into the three groups according to the number of points as follows: 0 point; low risk, 1–2 point; intermediate risk, 3 point; high risk. **a** Disease-specific survival (DSS). **b** Overall survival (OS)

believe that an integrative assessment of inflammation-, nutrition-, and muscle-based markers is vital for developing appropriate perioperative and therapeutic strategies for patients with cancer. Anorexia, cachexia, and sarcopenia are associated with proinflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and IL-6 [13]. Although we did not evaluate the blood levels of inflammatory cytokines in our study, the results from previous studies suggest that these tumor-induced cytokines may be associated with the increases in NLR, PLR, and MLR that we observed in our patients with UTUC.

In the future, preoperative medication such as molecular targeting therapy (monoclonal antibody against IL6: tocilizumab, and against TNFα: adalimumab, etc.) may be improved the nutrition status and as a result, prognosis of UTUC patients [36].

The limitations of this study must be considered when clarifying our results. Firstly, our retrospective analysis of data from a single institution and a small sample size are associated with a high risk of selection bias. Secondly, the definitions of muscle loss and reduced nutritional status remain controversial, despite their use in previous large-scale studies.

Conclusions

The present study evaluated the clinical significance of an integrative assessment of pretreatment inflammation-, nutrition-, and muscle-based factors in patients with UTUC who underwent NUx. Low baseline PNI, the presence of hydronephrosis, and high Fib were representative prognostic factors among several studied markers. Nevertheless, as our findings may be limited to our cohort, optimal cutoffs should be proven in a large prospective multi-center study.

Compliance with ethical standards

Conflict of interest We declare that we have no conflicts of interest.

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