Cancer Management and Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Preoperative Risk Classification Using Neutrophil-to-Lymphocyte Ratio and Albumin for Upper Tract Urothelial Carcinoma Treated with Radical Nephroureterectomy

This article was published in the following Dove Press journal:
Cancer Management and Research

Zihan Zhao*
Shangxun Xie*
Baofu Feng
Shiwei Zhang
Yifan Sun
Hongqian Guo
Rong Yang

Department of Urology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Institute of Urology, Nanjing University, Nanjing, People's Republic of China

*These authors contributed equally to this work

Cancer Management and Research downloaded from https://www.dovepress.com/
For personal use only.

Purpose: To improve the preoperative prediction of the outcomes of patients diagnosed with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy (RNU), we explored various preoperative laboratory factors and established a prognostic risk stratification method.

Patients and Methods: We retrospectively reviewed 232 UTUC patients who underwent RNU from September 2010 to October 2019 and analyzed their comprehensive clinicopathologic data and preoperative blood-based biomarkers. Kaplan–Meier analysis, receiver-operating characteristic (ROC) curves analysis and Cox regression analysis were performed to assess the relationship between these factors and the prognosis.

Results: The median follow-up and age were 24 months and 68.5 years, respectively. Preoperative elevated neutrophil-to-lymphocyte ratio (NLR > 3.44) and decreased albumin (ALB < 39.8 g/L) were negatively correlated with progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS) in both univariate and multivariate analyses. Patients were sorted into three groups based on their NLR and ALB: the low-risk group (neither elevated NLR nor decreased ALB), intermediate-risk group (either elevated NLR or decreased ALB) and high-risk group (elevated NLR and decreased ALB). Their 5-year PFS rates were 77.8%, 52.6% and 32.3%; their 5-year CSS rates were 97.7%, 71.4% and 32.9%; and their 5-year OS rates were 92.7%, 70.4% and 29.2%, respectively (all $P < 0.0001$). ROC curves analysis showed that NLR plus ALB had a more accurate prognostic value ($P < 0.05$).

Conclusion: Preoperative risk classification using NLR and ALB was identified as an independent prognostic factor for patients with UTUC. The combination of NLR and ALB may help to determine the most appropriate treatment options before RNU.

Keywords: neutrophil-to-lymphocyte ratio, albumin, upper tract urothelial carcinoma, radical nephroureterectomy, risk classification

Correspondence: Hongqian Guo; Rong Yang
Department of Urology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Institute of Urology, Nanjing University, 321 Zhongshan Road, Nanjing, Jiangsu 210008, People's Republic of China
Tel +86-25-83106666
Email doctorghq@gmail.com; doctoryr@gmail.com

Introduction

Upper tract urothelial carcinoma (UTUC), including ureter carcinoma and renal pelvicalyceal, is infrequent and only accounts for 5–10% of urothelial carcinomas.[1] Regardless of the actual site of the tumor, radical nephroureterectomy (RNU) is the first choice for the treatment of UTUC.[2] Despite the accuracy of diagnosis and the surgical resection of UTUC having been improved in the past few years, the survival outcomes of UTUC patients have not significantly improved.[3]

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/CMAR.S274332

© 2020 Zhao et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

Thus, recognizing the prognostic factors of UTUC after RNU to guide timely treatment is important. The current prognostic factors are mostly postoperative data, and preoperative prognostic factors have hardly been assessed.[4] Although pathological parameters have a strong predictive accuracy for the clinical outcome, this information cannot be obtained before surgery. Recently, a negative correlation between systemic inflammation and tumor prognosis has been reported, which can help guide the use of neoadjuvant therapy.[5] Patients routinely undergo the measurement of blood-based markers before surgery, and there is ample evidence that serum biomarkers reflect systemic inflammation, such as albumin (ALB), globulin (GLB), albumin-globulin ratio (AGR), neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), etc., which can all be used as prognostic indicators for a variety of cancers.[6–10] However, the preoperative blood-based markers that have prognostic value for UTUC have not yet been fully studied.

Herein, we aimed to assess the value of these blood-based biomarkers in forecasting adverse pathological conditions and patient outcomes. Our goal was to establish a prognostic classification model that could be used before surgery.

Patients and Methods

Patients

We retrospectively analyzed the data of 332 UTUC patients undergoing RNU from September 2010 to October 2019. Patients with missing data, the presence of other carcinomas, or those who had received neoadjuvant chemotherapy (NAC) or radiotherapy before surgery were excluded (n = 100). Therefore, a total of 232 patients were analyzed retrospectively. Lymphadenectomy was implemented if a suspicious lymph node status was revealed by preoperative imaging reports or positive lymph nodes were found during the operation.

Clinical and Pathologic Data

Experienced pathologists examined all surgical specimens in accordance with standard procedures. All serum biomarker levels were measured 1 day after the patients were hospitalized. Preoperative elevated NLR was defined as > 3.44, reduced ALB was defined as < 39.8 g/L, elevated GLB was defined as > 28.7 g/L, reduced AGR was defined as < 1.39 and an increased PLT was defined as > 254 $\times 10^9$/L. We determined the cutoff values of these serum biomarkers by using ROC curves analysis and evaluated the following clinical and pathological data to identify the relevant factors for prognostication: age at diagnosis of UTUC, sex, pathologic tumor stage (assessed by the TNM classification),[11] tumor grade (evaluated by the WHO International Society of Urological Pathology consensus classification), pathologic lymph node status (pN0, pNx or pN+), tumor size (we determined a threshold of 3.5 cm using ROC curves), tumor location (renal pelvicalyceal or ureter or both), tumor multifocality (two or more tumors were found), lymphovascular invasion (LVI) (the presence of malignant cells in the endothelial cell line), surgical margin status (the presence of malignant cells at the edge of the surgical specimen) and tumor histology (papillary tumor).

Follow-Up

Patients were usually examined at least once every 3–4 months in the first year, every 6 months in the second year, and at least once a year thereafter. The follow-up examinations included a cystoscopic examination, urine cytology, physical examination, blood tests, computed tomography (CT) or ultrasound and chest radiography. If there were clinical indications, a selective bone scan was performed. Disease progression was defined as a local recurrence, lymph node metastasis and/or distant metastasis that was not detected before the operation. The progression-free survival (PFS) was defined as the date of nephroureterectomy to the date of first progression on imaging examination, the cancer-specific survival (CSS) was defined as the date of nephroureterectomy to the date of cancer-specific mortality, and the overall survival (OS) was the date of followed-up death caused by any reason.

Statistics

All continuous variables are shown as median values and ranges. Pearson's chi-square test and Fisher's exact test were used to compare the distribution of categorical variables. Differences in variables with a continuous distribution among the three groups were tested using one-way ANOVA. Univariate and multivariate Cox regression analyses were implemented to assess the relationships among the parameters and PFS, CSS, and OS. Blood-based biomarkers and clinical/pathological features that reached significance $P < 0.05$ in univariate Cox regression analysis were included in the multivariate Cox regression analysis. Kaplan–Meier analysis was used to determine the survival probability, and the Log rank test was used to compare the differences among the groups. ROC curve analysis was used to compare the prognostic

values of NLR alone, ALB alone and NLR plus ALB for predicting survival outcomes. IBM SPSS Statistics version 26.0 (IBM, Armonk, New York, USA) was used to perform all statistical analyses, except for the Kaplan–Meier analysis and the comparisons of the ROC curves, which were performed using MedCalc version 19.1 (https://www.medcalc.org).

Results

Table 1 lists the clinical/pathological features of 232 patients. The median age of the patients in this cohort was 68.5 years (range: 36–87) and the median follow-up was 24 months (range: 3–104). The median preoperative NLR was 2.56 (range: 0.85–22.44), and 61 (26.3%) patients had an elevated preoperative NLR. The median preoperative ALB was 39.75 g/L (range: 27.6–70.8), and 116 (50.0%) patients had a decreased preoperative ALB. Among them, most of the patients were male (67.2%), and 200 patients (86.2%) had a high-grade tumor. There were 111 cases (47.8%) of renal pelvic tumors, 98 cases (42.2%) of ureteral tumors, and 23 cases (10.0%) of tumors in both sites. Pathologic stage > T2 was diagnosed in 105 (45.3%) patients, a positive surgical margin was found in 15 (6.5%) patients, a positive lymph node was found in 15 (6.5%) patients and LVI was found in 40 (17.2%) patients. In all, 34.9% (81) of the patients underwent local or extended lymphadenectomy. Local recurrence occurred in 26 (11.2%) patients and lymphatic spread and/or distant metastasis occurred in 32 (13.8%) patients during the follow-up period. There were 38 (16.4%) patients who died because of UTUC and 44 (19.0%) patients died from all causes. The 3-year PFS, CSS and OS were 70.9%, 81.5% and 78.9%; and the 5-year PFS, CSS and OS were 60.9%, 75.6% and 71.5%, respectively.

Table 1 Clinicopathologic Features for the Overall Cohort of 232 Patients with UTUC After RNU

Parameters	All Patients
Gender, Male, n (%)	156 (67.2%)
Age at UTUC (yrs.), median (range)	68.5 (36–87)
Follow-up (months), median (range)	24 (3–104)
pT-stage, > T2, n (%)	105 (45.3%)
pN-stage, N+, n (%)	15 (6.5%)
Tumor grade, High, n (%)	200 (86.2%)
Tumor size, > 3.5 cm, n (%)	97 (41.8%)
Location, n (%)	
Pelvis	111 (47.8%)
Ureter	98 (42.2%)
Both	23 (10.0%)
Multifocality, n (%)	35 (15.1%)
LVI present, n (%)	40 (17.2%)
Surgical margin: positive, n (%)	15 (6.5%)
Papillary: present, n (%)	194 (83.6%)
Lymph nodes removed, n (%)	81 (34.9%)
Progression, n (%)	58 (25.0%)
Recurrence, n (%)	26 (11.2%)
Metastasis, n (%)	32 (13.8%)
Cancer-specific mortality, n (%)	38 (16.4%)
Overall mortality, n (%)	44 (19.0%)
NLR, median (range)	2.56 (0.85–22.44)
ALB, g/L, median (range)	39.75 (27.6–70.8)
GLB, g/L, median (range)	25.65 (14.7–50.7)
AGR, median (range)	1.58 (0.71–2.67)
PLT ($\times 10^9$/L), median (range)	204 (44–698)

Abbreviations: LVI, lymphovascular invasion; NLR, neutrophil-to-lymphocyte ratio; ALB, albumin; GLB, globulin; AGR, albumin-globulin ratio; PLT, platelet count.

First, we analyzed the prognostic value of the reported predictive clinicopathological parameters for PFS, CSS and OS (Table 2). Univariate Cox regression analysis showed that NLR, ALB, LVI, pN-stage (N+) and positive surgical margin were associated with a shorter PFS, CSS, and OS (all $P < 0.05$). Although globulin (GLB), albumin-globulin ratio (AGR), platelet count (PLT), pT-stage (> T2), present papillary and tumor grade were related to a shorter CSS and OS, they were not associated with a shorter PFS. Blood-based biomarkers and clinical/pathological features that reached significance $P < 0.05$ for PFS, CSS, and OS by univariate Cox regression analysis were included in the multivariate Cox regression analysis. Multivariate Cox analysis revealed that elevated preoperative NLR, decreased ALB, and positive surgical margins were independent clinical risk predictors for shorter PFS, CSS and OS (all $P < 0.05$) (Table 3).

Second, we performed Kaplan–Meier analysis to assess the risk classification of preoperative NLR and ALB. Patients with an elevated preoperative NLR had significantly worse PFS, CSS and OS (all $P < 0.0001$) (Figure 1). The patients with an ALB ≥ 39.8 g/L had significantly better PFS, CSS and OS (all $P < 0.001$) than those with an ALB < 39.8 g/L (Figure 2). ROC curve analysis showed that both NLR and ALB had diagnostic value for PFS, CSS, and OS (all $P < 0.05$) (Figures 3 and 4). These results indicated that NLR and ALB are useful predictors of PFS, CSS, and OS in UTUC patients after RNU.

Finally, we developed a preoperative risk classification model for patients with UTUC using preoperative NLR

Table 2 Univariate Analyses of the Risk of Disease Progression, Cancer-Specific Mortality and Overall Mortality

Variables	Disease Progression		Cancer-Special Mortality		Overall Mortality	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
NLR > 3.44	2.948 (1.748–4.973)	0.000†	7.069 (3.609–13.845)	0.000†	6.482 (3.499–12.007)	0.000†
ALB < 39.8 g/L	2.669 (1.530–4.658)	0.001†	7.590 (3.091–18.638)	0.000†	6.297 (2.860–13.865)	0.000†
GLB > 28.7 g/L	1.209 (0.669–2.185)	0.529	2.812 (1.478–5.352)	0.002†	2.651 (1.455–4.830)	0.001†
AGR < 1.39	1.438 (0.815–2.537)	0.210	4.088 (2.153–7.762)	0.000†	4.034 (2.224–7.315)	0.000†
PLT > 254 $\times 10^9$/L	1.224 (0.648–2.313)	0.533	2.972 (1.529–5.777)	0.001†	2.611 (1.394–4.891)	0.003†
Gender, Male	0.779 (0.449–1.353)	0.375	0.922 (0.475–1.789)	0.810	0.994 (0.540–1.830)	0.985
Age	1.027 (1.000–1.054)	0.051	1.009 (0.978–1.041)	0.557	1.007 (0.978–1.036)	0.657
pT-stage, > T2	1.659 (0.989–2.783)	0.055	4.273 (2.072–8.816)	0.000†	3.690 (1.927–7.069)	0.000†
pN-stage, N+	2.960 (1.262–6.946)	0.013†	2.961 (1.040–8.432)	0.042†	3.365 (1.273–8.375)	0.014†
Tumor size, > 3.5 cm	1.418 (0.844–2.382)	0.187	2.893 (1.494–5.600)	0.002†	2.679 (1.458–4.923)	0.001†
Location (vs Pelvis)		0.618		0.783		0.843
Ureter	1.224 (0.706–2.123)	0.471	1.270 (0.647–2.495)	0.423	1.183 (0.631–2.219)	0.600
Both	1.456 (0.627–3.381)	0.382	1.183 (0.395–3.541)	0.764	1.233 (0.460–3.304)	0.677
Multifocality	2.045 (1.120–3.735)	0.020†	1.911 (0.902–4.049)	0.091	2.057 (1.037–4.080)	0.039†
LVI present	2.476 (1.367–4.485)	0.003†	6.077 (3.115–11.854)	0.000†	5.204 (2.782–9.733)	0.000†
Surgical margin: positive	2.964 (1.404–6.256)	0.004†	3.781 (1.664–8.592)	0.001†	3.749 (1.742–8.069)	0.001†
Papillary: present	0.555 (0.299–1.032)	0.063	0.373 (0.188–0.740)	0.005†	0.456 (0.234–0.885)	0.020†
Tumor grade, high	1.686 (0.722–3.937)	0.228	7.730 (1.058–56.500)	0.044†	8.984 (1.234–65.389)	0.030†

Note: †Statistically significant.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; ALB, albumin; GLB, globulin; AGR, albumin-globulin ratio; PLT, platelet count; LVI, lymphovascular invasion.

and ALB (NLR plus ALB). We defined patients with both elevated preoperative NLR and decreased ALB as the high-risk group (n = 44, 19%), those with either elevated preoperative NLR or decreased ALB as the intermediate-risk group (n = 89, 38%), and those with neither elevated preoperative NLR nor decreased ALB as the low-risk group (n = 99, 43%). The clinicopathological characteristics of the different risk groups (Table 4) showed that NLR plus ALB was associated with pT-stage (P = 0.000), pN-stage (P = 0.026), tumor size (P = 0.000), LVI present (P = 0.039) and the prognosis (P = 0.000). Kaplan–Meier analysis revealed that there were significant differences in the survival outcomes among the three groups (all P < 0.001). The 5-year PFS was 77.8 ± 6.0%, 52.6 ± 9.9%, and 32.3 ± 11.8%; the 5-year CSS was 97.7 ± 1.6%, 71.4 ± 8.3% and 32.9 ± 10.5%; and the 5-year OS was 92.7 ± 3.9%, 70.4 ± 8.2% and 29.2 ± 9.6% for low-risk group, intermediate-risk group and high-risk group, respectively (Figure 5). ROC curve analysis showed that NLR plus ALB had a greater diagnostic value than NLR alone or ALB alone regarding CSS and OS (all P< 0.05) (Figure 6).

Discussion

In the present study, we have demonstrated that elevated preoperative NLR and decreased ALB are independent prognostic factors for patients with UTUC and can be used as predictors of patient outcomes before surgery. We also proved that the risk stratification

Table 3 Multivariate Analyses for Risk of Disease Progression, Cancer-Specific Mortality and Overall Mortality

Variables	Disease Progression		Cancer-Special Mortality		Overall Mortality	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
NLR > 3.44	2.501 (1.441–4.339)	0.001†	5.226 (2.522–10.829)	0.000†	4.949 (2.550–9.606)	0.000†
ALB < 39.8 g/L	1.945 (1.079–3.507)	0.027†	4.127 (1.629–10.457)	0.003†	3.495 (1.534–7.961)	0.003†
LVI present	1.718 (0.876–3.366)	0.115	4.553 (2.261–9.171)	0.000†	3.812 (1.972–7.372)	0.000†
pN-stage, N+	1.725 (0.647–4.603)	0.276	0.985 (0.321–3.024)	0.978	1.200 (0.434–3.317)	0.726
Surgical margin: positive	2.664 (1.244–5.702)	0.012†	3.969 (1.667–9.450)	0.002†	3.825 (1.715–8.530)	0.001†

Note: †Statistically significant.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; ALB, albumin; LVI, lymphovascular invasion.

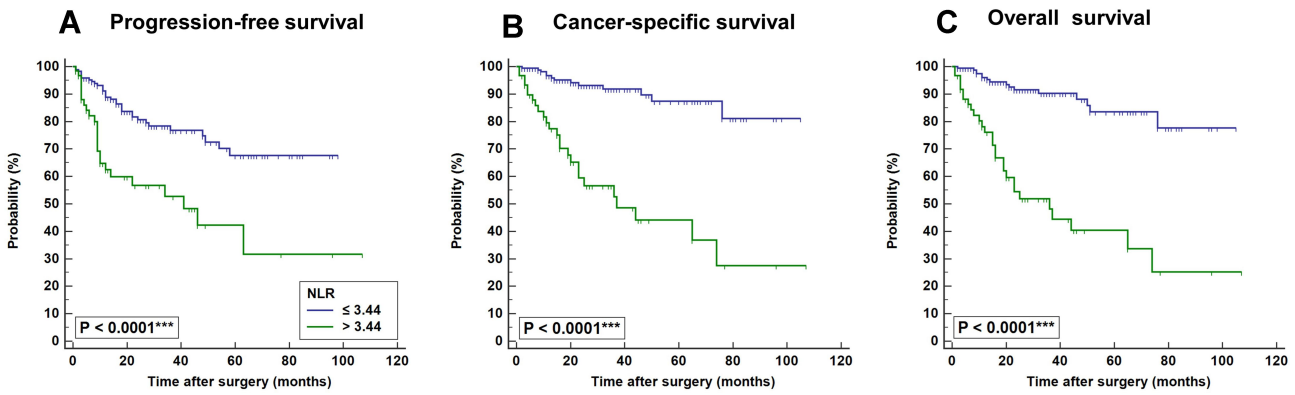

Figure 1 Kaplan–Meier estimates of progression-free survival, cancer-specific survival, and overall survival rates according to preoperative NLR: (**A**) Progression-free survival; (**B**) Cancer-specific survival; (**C**) Overall survival. ***P < 0.001.

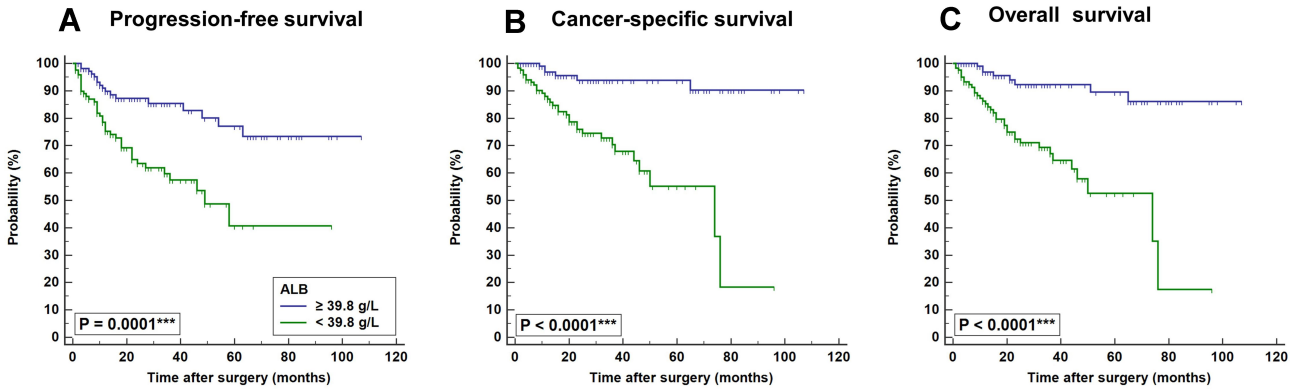

Figure 2 Kaplan–Meier estimates of progression-free survival, cancer-specific survival, and overall survival rates according to preoperative ALB: (**A**) Progression-free survival; (**B**) Cancer-specific survival; (**C**) Overall survival. ***P < 0.001.

based on preoperative NLR and ALB can accurately predict patient outcomes. As far as we know, this is the first proposal to use the combined preoperative NLR and ALB to classify risk groups among UTUC patients.

Currently, the main restriction of treatment plans for UTUC patients is the difficulty in achieving accurate staging before surgery. The tissue obtained by preoperative endoscopic biopsies can be used to diagnose and assess the tumor

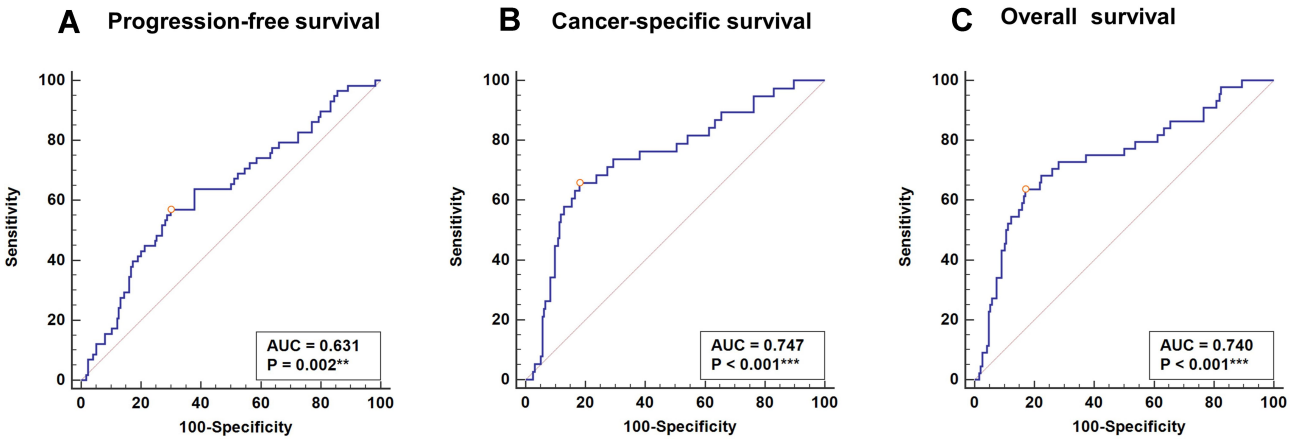

Figure 3 ROC curves predicting disease progression, cancer-specific survival, and overall survival according to preoperative NLR: (**A**) Progression-free survival; (**B**) Cancer-specific survival; (**C**) Overall survival. **P < 0.01; ***P < 0.001.

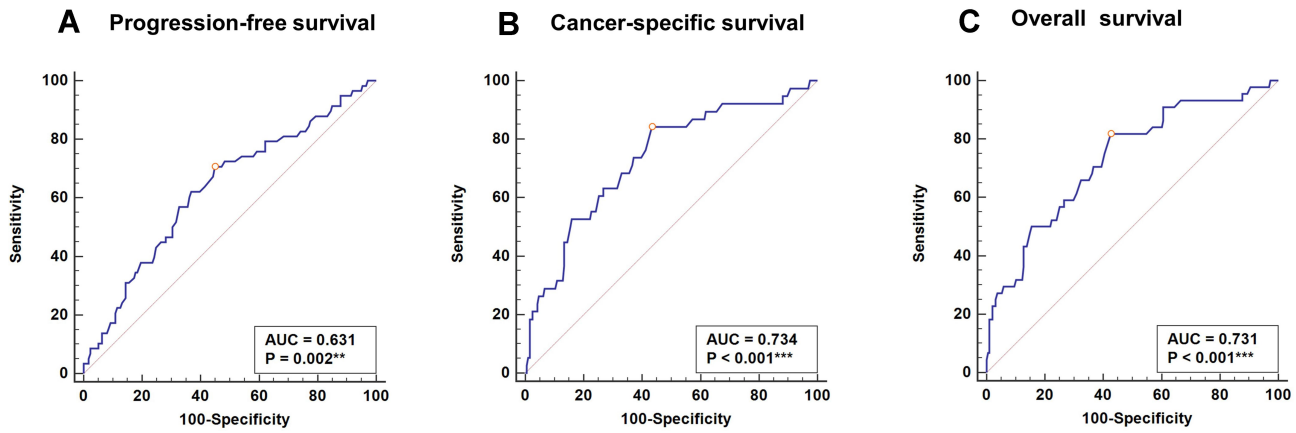

Figure 4 ROC curves predicting disease progression, cancer-specific survival, and overall survival according to preoperative ALB: (**A**) Progression-free survival; (**B**) Cancer-specific survival; (**C**) Overall survival. **P < 0.01; ***P < 0.001.

grade, but only rarely determine the tumor stage.[12] In addition, preoperative imaging studies are often inaccurate for staging. The poor accuracy of clinical staging inhibits our capacity to classify high-risk patients who are most likely to deteriorate and possibly benefit from NAC.

Due to limited studies on UTUC, the NAC for UTUC is derived from that used to treat bladder cancer.[13] Compared to immediate cystectomy in muscle-invasive bladder cancer, platinum-based neoadjuvant therapies have shown significant survival benefits.[14] Because RNU will cause nephron loss, patients may have difficulty with cisplatin-based adjuvant chemotherapy after surgery. Therefore, NAC may be more suitable for high-risk patients with UTUC than adjuvant chemotherapy. Several retrospective studies have evaluated the use of NAC to improve the survival of patients with UTUC.[15,16] Ongoing Phase II and Phase III clinical trials of NAC and adjuvant therapy applied to patients with UTUC will provide sounder guidance.

Meanwhile, it is important to determine the most suitable patients for NAC to increase the pathological downgrading rate and to improve survival outcomes.[17]

Table 4 Chi-Square and One-Way ANOVA Tests for Clinicopathological Features in Different Risk Groups

	All Patients	Low-Risk Group	Intermediate-Risk Group	High-Risk Group	P-value
Number of patients (%)	232 (100%)	99 (42.7%)	89 (38.4%)	44 (19.0%)	–
Gender, Male, n (%)	156 (67.2%)	68 (68.7%)	61 (68.5%)	27 (61.4%)	0.653
Age at UTUC (yrs.), median (range)	68.5 (36–87)	67.0 (43–85)	70.0 (36–87)	69.5 (42–85)	0.101
pT-stage, > T2, n (%)	105 (45.3%)	34 (34.3%)	40 (44.9%)	31 (70.5%)	0.000†
v	15 (6.5%)	2 (2.0%)	7 (7.9%)	6 (13.6%)	0.026†
Tumor grade, High, n (%)	200 (86.2%)	83 (83.8%)	76 (85.4%)	41 (93.2%)	0.314
Tumor size, > 3.5 cm, n (%)	97 (41.8%)	29 (29.3%)	40 (44.9%)	28 (63.6%)	0.000†
Location, n (%)					0.990
Pelvis	111 (47.8%)	49 (49.5%)	41 (46.1%)	21 (47.7%)	
Ureter	98 (42.2%)	40 (40.4%)	39 (43.8%)	19 (43.2%)	
Both	23 (9.9%)	10 (10.1%)	9 (10.1%)	4 (9.1%)	
Multifocality, n (%)	35 (15.1%)	10 (10.1%)	18 (20.2%)	7 (15.9%)	0.151
LVI present, n (%)	40 (17.2%)	12 (12.1%)	15 (16.9%)	13 (29.5%)	0.039†
Surgical margin: positive, n (%)	15 (6.5%)	3 (3.0%)	7 (7.9%)	5 (11.4%)	0.138
Papillary: present, n (%)	194 (83.6%)	88 (88.9%)	73 (82.0%)	33 (75.0%)	0.102
Progression, n (%)	58 (25.0%)	14 (14.1%)	24 (27.0%)	20 (45.5%)	0.000†
Cancer-specific mortality, n (%)	38 (16.4%)	2 (2.0%)	15 (16.9%)	21 (47.7%)	0.000†
Overall mortality, n (%)	44 (19.0%)	4 (4.0%)	16 (18.0%)	24 (54.5%)	0.000†

Note: †Statistically significant.
Abbreviation: LVI, lymphovascular invasion.

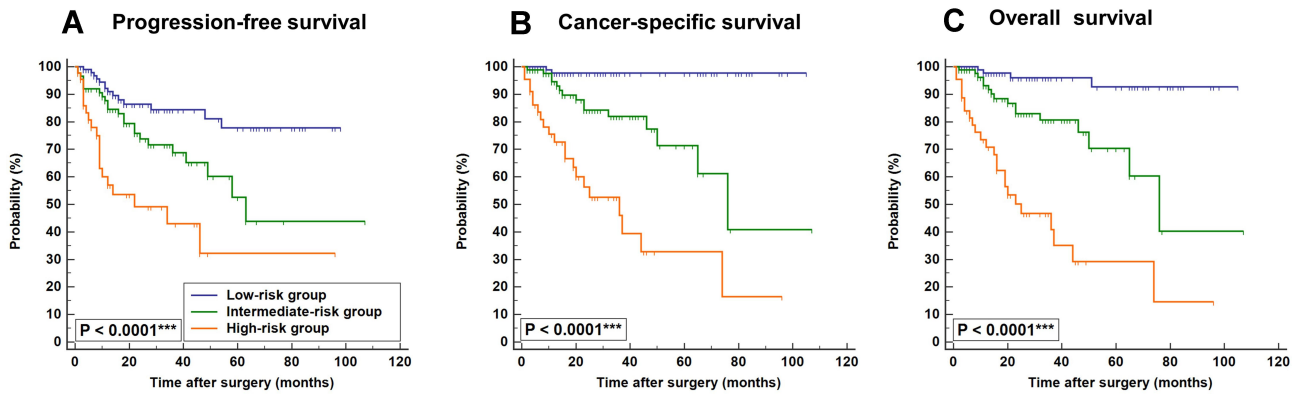

Figure 5 Kaplan–Meier estimates of progression-free survival, cancer-specific survival, and overall survival rates according to different risk groups: (**A**) Progression-free survival; (**B**) Cancer-specific survival; (**C**) Overall survival. ***P < 0.001.

If the patient's tumor stage decreases after receiving NAC, the treatment plan may be re-evaluated according to the tumor stage. Therefore, it is important to identify risk stratification factors for UTUC patients before surgery. Several prognostic models have been reported, including the use of clinical and pathological variables to predict survival outcomes after RNU, but none have been validated externally.[18] The limitation of these models is that they mainly include postoperative variables, and therefore cannot be used for preoperative risk stratification. It has been reported that some preoperative biomarkers, including molecular markers assessed by immunohistochemistry on preoperative tumor biopsy tissue, can increase the accuracy of prognostication of UTUC.[19] However, these molecular markers require special tests to be performed and they require a certain amount of intact tissue for evaluation.

There is increasing evidence that preoperative blood-based biomarkers can serve as prognostic indicators for UTUC.[20,21] The European Association of Urology guidelines updated in 2017 has suggested preoperative NLR as a prognostic factor for CSS in UTUC.[3] Patients with UTUC routinely undergo laboratory tests, including blood tests and biochemical tests, before surgery. Therefore, using these laboratory parameters in a prognostic model could provide potentially prognostic information without increasing costs. In this research, we retrospectively analyzed data from 232 UTUC patients who underwent RNU to explore the prognostic significance of preoperative serum biomarkers: NLR, ALB, AGR and PLT. Although univariate Cox regression analysis showed that GLB, AGR and PLT were associated with CSS and OS, NLR and ALB were the most significant and were also related to PFS. Moreover, according to the results of the Kaplan–Meier and ROC curve

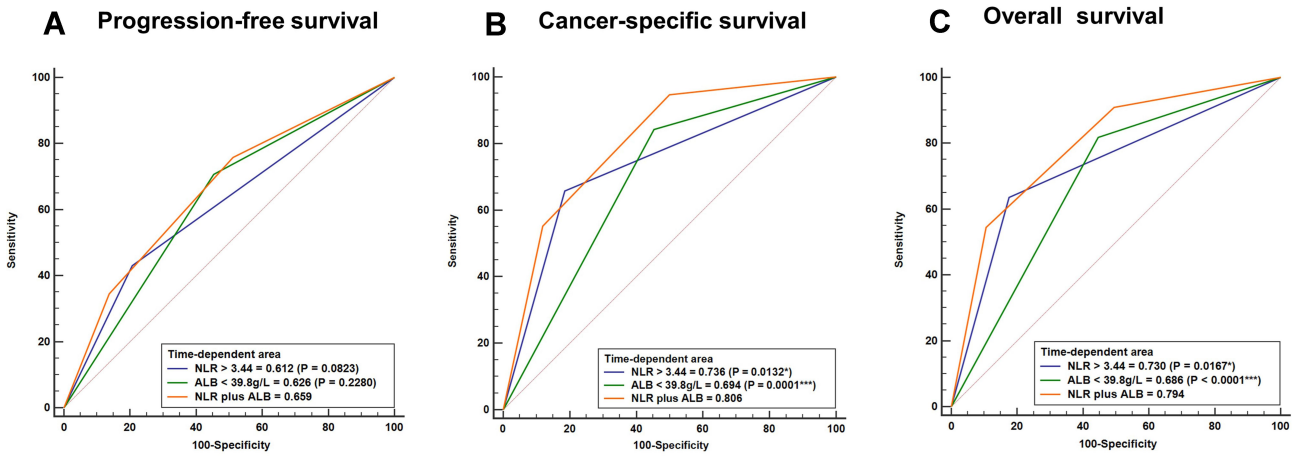

Figure 6 ROC curves predicting progression-free survival, cancer-specific survival, and overall survival according to NLR plus ALB: (**A**) Progression-free survival; (**B**) Cancer-specific survival; (**C**) Overall survival. *P < 0.05; ***P < 0.001.

analyses, preoperative NLR and ALB are significant predictors of PFS, CSS, and OS in UTUC patients after RNU. Thus, we developed a preoperative risk classification model for patients with UTUC using preoperative NLR and ALB.

Kaplan–Meier analysis showed that the high-risk group had significantly worse PFS, CSS and OS than the other groups. The ROC curve analysis also showed that NLR plus ALB had a greater diagnostic value than NLR or ALB alone regarding CSS and OS. Considering the differences in 5-year survival rates among the different groups, the treatment options for patients in these different risk groups should be individualized. For the low-risk group, since the patients have a 5-year survival rate greater than 90%, adjuvant chemotherapy may not be needed to avoid overtreatment. For the high-risk group, these patients may have higher staging and poor survival outcomes, so they may benefit more from NAC.[17] For the intermediate-risk group, the treatment options should be considered comprehensively. Therefore, this preoperative risk classification model using NLR and ALB will be a valuable tool for predicting survival outcomes and for guiding treatment options in UTUC patients.

In this study, the results raised the question of how preoperative elevated NLR and decreased ALB are related to the survival outcomes of UTUC after RNU. There is increasing evidence that chronic inflammation may be associated with the occurrence and progression of malignant tumors through multiple inflammatory signaling pathways.[22] However, the best biomarkers have not yet been found. The NLR has been considered as an accurate, simple, cheap, standardized and widely available index of systemic inflammation, and it is associated with a worse prognosis of several types of cancers, including UTUC.[23] An elevated NLR may imply an increase in tumor-associated neutrophils and/or a decrease in lymphocytes, which reflects the imbalance of tumor immunity and inflammation.[24] Studies have shown that tumor-associated neutrophils have a pivotal role in the tumor microenvironment, promoting extracellular matrix modification and further activation of epithelial-mesenchymal transformation.[25,26] Moreover, lymphopenia has been reported as an independent predictor of poor survival in several carcinomas, and the increase of tumor-infiltrating lymphocytes is related to cytotoxic treatment and an improved prognosis of cancer patients.[27]

ALB is mainly manufactured by the liver and is not only considered as a nutritional marker, is but also used to assess the inflammatory status of patients.[28] Low levels of albumin, also called hypoalbuminemia, might due to the increases of catabolism, inflammatory responses and chronic malnutrition.[29] A deficiency of nutritional status is often correlated with impaired immune responses, including a decrease in cell-mediated immunity and reduced complement system components. Therefore, a few studies have suggested that low serum albumin independently predicts poor oncology outcomes for UTUC after RNU.[30]

It is reasonable to believe that systemic inflammation has a pivotal role in the survival outcomes of UTUC patients after RNU. Although there is increasing evidence of an association between systemic inflammation and poor oncological outcomes in patients with various malignancies, the underlying mechanisms of these phenomena have not been fully elucidated. One possible explanation is that the tumor inflammatory microenvironment may be critical for cancer development and progression. The inflammatory tumor microenvironment enables tumor cells to avoid immune responses, facilitates the production of cytokines, and promotes tumor development and metastasis. Inflammation is also thought to be a pivotal event in the early development of cancer.[31] Both NLR and ALB are good indicators of inflammation, and the combination of NLR and ALB can more comprehensively reflect the inflammatory status of UTUC patients, which helps us to judge the prognosis of patients more accurately.

The present study also had several limitations. First, it is a retrospective study with a limited number of cases from a single center, which may cause various biases. Second, the operating techniques (open vs laparoscopic surgery vs robotic assisted laparoscopic surgery, lymphadenectomy or not) differed among the patients. Third, other inflammatory factors were not calculated, including the levels of CRP, fibrinogen, and inflammatory cytokines.

Conclusions

Elevated preoperative NLR and decreased ALB were identified as independent prognostic factors of oncological outcomes in UTUC patients who underwent RNU. The addition of ALB improved the prognostic significance of NLR alone. Thus, we recommend a sample risk classification model based on NLR and ALB, which may be routinely used in clinical practice to provide an objective preoperative prognostic assessment. Our research requires more validation, such as additional data from multicenter and prospective studies.

Data Sharing Statement

The datasets analyzed during the current study are not publicly available as the Ethics Committee of Nanjing Drum Tower Hospital does not have permission to provide the data of individual participants, but they are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The present study was approved by the Ethics Committee of Nanjing Drum Tower Hospital in accordance with the Declaration of Helsinki. As the present study collected only retrospective clinical data and offered no risk to the participants, written informed consent was not required.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed on the journal to which the article will be submitted; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (81772727 and 81772710), the General Financial Grant from the China Postdoctoral Foundation (2016M591831) and the Nanjing Science and Technology Development Project (YKK16073).

Disclosure

All authors declare that they have no competing interests for this work.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65(1):5–29. doi:10.3322/caac.21254
2. Zigeuner R, Pummer K. Urothelial carcinoma of the upper urinary tract: surgical approach and prognostic factors. *Eur Urol*. 2008;53(4):720–731. doi:10.1016/j.eururo.2008.01.006
3. Rouprêt M, Babjuk M, Compérat E, et al. European association of urology guidelines on upper urinary tract urothelial carcinoma: 2017 update. *Eur Urol*. 2018;73(1):111–122. doi:10.1016/j.eururo.2017.07.036
4. Ku JH, Byun -S-S, Jeong H, Kwak C, Kim HH, Lee SE. Lymphovascular invasion as a prognostic factor in the upper urinary tract urothelial carcinoma: a systematic review and meta-analysis. *Eur J Cancer*. 2013;49(12):2665–2680. doi:10.1016/j.ejca.2013.04.016
5. Laird BJ, Kaasa S, McMillan DC, et al. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. *Clin Cancer Res*. 2013;19(19):5456–5464. doi:10.1158/1078-0432.CCR-13-1066
6. Crumley AB, Stuart RC, McKernan M, McMillan DC. Is hypoalbuminemia an independent prognostic factor in patients with gastric cancer? *World J Surg*. 2010;34(10):2393–2398. doi:10.1007/s00268-010-0641-y
7. Niwa N, Matsumoto K, Ide H, Nagata H, Oya M. Prognostic value of pretreatment albumin-to-globulin ratio in patients with non–muscle-invasive bladder cancer. *Clin Genitourin Cancer*. 2018;16(3):e655–e661. doi:10.1016/j.clgc.2017.12.013
8. Todenhofer T, Renninger M, Schwentner C, Stenzl A, Gakis G. A new prognostic model for cancer-specific survival after radical cystectomy including pretreatment thrombocytosis and standard pathological risk factors. *BJU Int*. 2012;110(11Pt B):E533–E540. doi:10.1111/j.1464-410X.2012.11231.x
9. Vartolomei MD, Porav-Hodade D, Ferro M, et al. Prognostic role of pretreatment neutrophil-to-lymphocyte ratio (NLR) in patients with non–muscle-invasive bladder cancer (NMIBC): a systematic review and meta-analysis. Paper presented at: Urologic Oncology: Seminars and Original Investigations; 2018.
10. Tamalunas A, Buchner A, Kretschmer A, et al. Impact of routine laboratory parameters in patients undergoing radical cystectomy for urothelial carcinoma of the bladder: a long-term follow-up. *Urol Int*. 2020;104(7–8):551–558. doi:10.1159/000506263
11. Sobin L, Wittekind C. *In TNM Classification of Malignant Tumors*. 6th ed. New York: Wiley-Liss; 2002.
12. Sheth KR, Haddad AQ, Ashorobi OS, et al. Prognostic serum markers in patients with high-grade upper tract urothelial carcinoma. *Urol Oncol*. 2016;34(9):418 e419–418 e416. doi:10.1016/j.urolonc.2016.04.009
13. Gayed BA, Thoreson GR, Margulis V. The role of systemic chemotherapy in management of upper tract urothelial cancer. *Curr Urol Rep*. 2013;14(2):94–101. doi:10.1007/s11934-013-0307-z
14. Vale C. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data: advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol*. 2005;48(2):202–206.
15. Porten S, Siefker-Radtke AO, Xiao L, et al. Neoadjuvant chemotherapy improves survival of patients with upper tract urothelial carcinoma. *Cancer*. 2014;120(12):1794–1799. doi:10.1002/cncr.28655
16. Matin SF, Margulis V, Kamat A, et al. Incidence of downstaging and complete remission after neoadjuvant chemotherapy for high-risk upper tract transitional cell carcinoma. *Cancer*. 2010;116(13):3127–3134. doi:10.1002/cncr.25050
17. Leow JJ, Martin-Doyle W, Fay AP, Choueiri TK, Chang SL, Bellmunt J. A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma. *Eur Urol*. 2014;66(3):529–541. doi:10.1016/j.eururo.2014.03.003
18. Xylinas E, Kluth L, Mangal S, Roupret M, Karakiewicz PI, Shariat SF. Predictive tools for clinical decision-making and counseling of patients with upper tract urothelial carcinoma. *World J Urol*. 2013;31(1):31–36. doi:10.1007/s00345-012-0947-5
19. Bagrodia A, Youssef RF, Kapur P, et al. Prospective evaluation of molecular markers for the staging and prognosis of upper tract urothelial carcinoma. *Eur Urol*. 2012;62(1):e27–e29. doi:10.1016/j.eururo.2012.04.031
20. Tanaka N, Kikuchi E, Kanao K, et al. A multi-institutional validation of the prognostic value of the neutrophil-to-lymphocyte ratio for upper tract urothelial carcinoma treated with radical nephroureterectomy. *Ann Surg Oncol*. 2014;21(12):4041–4048. doi:10.1245/s10434-014-3830-3

21. Xu H, Tan P, Ai J, et al. Prognostic impact of preoperative albumin-globulin ratio on oncologic outcomes in upper tract urothelial carcinoma treated with radical nephroureterectomy. *Clin Genitourin Cancer*. 2018;16(5):e1059–e1068. doi:10.1016/j.clgc.2018.06.003
22. Aggarwal BB, Vijayalekshmi R, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. *Clin Cancer Res*. 2009;15(2):425–430. doi:10.1158/1078-0432.CCR-08-0149
23. Tan P, Xu H, Liu L, et al. The prognostic value of preoperative neutrophil-to-lymphocyte ratio in patients with upper tract urothelial carcinoma. *Clin Chim Acta*. 2018;485:26–32. doi:10.1016/j.cca.2018.06.019
24. Yin X, Xiao Y, Li F, Qi S, Yin Z, Gao J. Prognostic role of neutrophil-to-lymphocyte ratio in prostate cancer: a systematic review and meta-analysis. *Medicine*. 2016;95(3):e2544. doi:10.1097/MD.0000000000002544
25. Azab B, Bhatt VR, Phookan J, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. *Ann Surg Oncol*. 2012;19(1):217–224. doi:10.1245/s10434-011-1814-0
26. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883–899. doi:10.1016/j.cell.2010.01.025
27. Saroha S, Uzzo RG, Plimack ER, Ruth K, Al-Saleem T. Lymphopenia is an independent predictor of inferior outcome in clear cell renal carcinoma. *J Urol*. 2013;189(2):454–461. doi:10.1016/j.juro.2012.09.166
28. McMillan DC, Watson WS, O'Gorman P, Preston T, Scott HR, McArdle CS. Albumin concentrations are primarily determined by the body cell mass and the systemic inflammatory response in cancer patients with weight loss. *Nutr Cancer*. 2001;39(2):210–213. doi:10.1207/S15327914nc392_8
29. Al-Shaiba R, McMillan D, Angerson W, Leen E, McArdle C, Horgan P. The relationship between hypoalbuminaemia, tumour volume and the systemic inflammatory response in patients with colorectal liver metastases. *Br J Cancer*. 2004;91(2):205–207. doi:10.1038/sj.bjc.6601886
30. Ku JH, Kim M, Choi WS, Kwak C, Kim HH. Preoperative serum albumin as a prognostic factor in patients with upper urinary tract urothelial carcinoma. *Int Braz J Urol*. 2014;40(6):753–762. doi:10.1590/S1677-5538.IBJU.2014.06.06
31. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. *Mol Cancer Res*. 2006;4(4):221–233. doi:10.1158/1541-7786.MCR-05-0261

Cancer Management and Research Dovepress

Publish your work in this journal

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient.

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/cancer-management-and-research-journal