Original Article

# Validation of the Pretreatment Neutrophil-to-Lymphocyte Ratio as a Prognostic Factor in a Large Cohort of Chinese Patients with Upper Tract Urothelial Carcinoma

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## Abstract

**Background:** The pretreatment neutrophil-to-lymphocyte ratio (NLR) has been reported to be a prognostic factor in various types of carcinomas. The aim of this study was to investigate the prognostic value of pretreatment NLR in a large cohort of Chinese patients with upper tract urothelial carcinoma (UTUC).

**Methods:** We retrospectively analyzed the medical data of 656 UTUC patients who underwent radical nephroureterectomy (RNU) from 2001 to 2011 at Peking University First Hospital. Receiver operating characteristic (ROC) curve analysis was performed to calculate the optimal cutoff point of pretreatment NLR. Uni- and multi-variate analyses were used to identify the prognostic factors for cancer-specific survival (CSS) and intravesical recurrence-free survival (IVRFS).

**Results:** The optimal cutoff point of pretreatment NLR was 2.40 by ROC curves, by which patients with high NLR (NLR ≥2.40) and low NLR (NLR <2.40) accounted for 314 (47.9%) and 342 (52.1%) patients, respectively. Patients with a high pretreatment NLR tended to have high tumor grades ($\chi^2 = 15.725$, $P < 0.001$), high tumor stages ($\chi^2 = 25.416$, $P < 0.001$), tumor sizes >5 cm ($\chi^2 = 8.213$, $P = 0.005$), ipsilateral hydronephrosis ($\chi^2 = 4.624$, $P = 0.033$), and concomitant carcinoma *in situ* (CIS) ($\chi^2 = 9.517$, $P = 0.003$). A high pretreatment NLR (hazard ratio [*HR*] = 1.820, $P = 0.001$), main tumor diameter >5 cm (*HR* = 1.789, $P = 0.009$), lymph node metastasis (*HR* = 1.863, $P = 0.024$), and high tumor stage (*HR* = 1.745, $P < 0.001$) independently predicted poor CSS after surgery, while only concomitant carcinoma *in situ* (CIS) (*HR* = 2.164, $P = 0.034$), ureteroscopy before surgery (*HR* = 1.701, $P = 0.015$), and high tumor grade (*HR* = 1.645, $P = 0.018$) were independent predictors of IVRFS after RNU.

**Conclusions:** The pretreatment NLR was related to some adverse clinicopathological features and was an independent predictor of CSS, although not IVRFS, in Chinese UTUC patients.

**Key words:** Neutrophil-to-Lymphocyte Ratio; Prognosis; Upper Tract Urothelial Carcinoma

## Introduction

Upper tract urothelial carcinoma (UTUC) is a rare malignant tumor with an incidence of 1–4 cases per 100,000 individuals per year throughout the world.[1,2] However, in populations with a high risk of exposure to aristolochic acid, which is an important carcinogen causing UTUC in China and the Balkan region, the incidence is relatively high.[3-5] Previous studies have suggested that differences existed in the etiologies, characteristics, predictors, and oncologic outcomes among populations.[6-8] Radical nephroureterectomy (RNU) is the standard treatment for UTUC patients. However, the outcome is far from satisfactory due to the high risk of postoperative systemic recurrence.[9,10]

The pretreatment neutrophil-to-lymphocyte ratio (NLR), an index of systemic inflammation, is reported to be of prognostic value in UTUC patients in studies of European cohorts and some Asian cohorts.[11-15] Among the former, NLR was found to be an independent predictor for

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cancer-specific survival (CSS), while among the latter, it was found to be an independent predictor for intravesical recurrence-free survival (IVRFS) as well. However, the prognostic value of pretreatment NLR for UTUC patients in the Chinese population remains unclear.

We conducted this study at one of the largest urological centers in China to investigate the prognostic value of pretreatment NLR for UTUC patients in the Chinese population.

## Methods

### Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee and Review Board of Peking University First Hospital. Informed consent was obtained from all patients prior to their enrollment in the study.

### Patient selection and follow-up

We retrospectively evaluated data from patients who underwent RNU for UTUC between January 2001 and December 2011 at Peking University First Hospital. Among the 740 patients pathologically diagnosed with UTUC, 84 patients were excluded from the study due to unavailable pretreatment blood reports, concomitant bladder cancer, loss to follow-up, or receipt of neoadjuvant/adjuvant chemotherapy during follow-up. Thus, 656 patients were included in this study.

Clinical data of all patients were collected from the medical records library of Peking University First Hospital. Pretreatment NLRs were drawn from blood reports one week before surgery. However, for patients with infectious disease, we collected the data after the infection was controlled. All pathological specimens were re-reviewed by two dedicated genitourinary pathologists (Dr. Qun He and Dr. Xin-Yu Yang) to recheck the reproducibility of the diagnosis. Tumor stage was assessed according to the 2002 Union for International Cancer Control tumor/node/metastasis classification of malignant tumors, and tumor grade was assessed according to the World Health Organization classification of 1973.[3] Tumor architecture was defined as papillary or sessile by examination of the final specimen. Tumor location was divided into renal pelvis and ureter based on the site of the dominant lesion. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed macroscopic tumors in any location.

All the patients were followed up until 2013, with a median follow-up time of 46 months. For most patients, routine follow-up consisted of physical examination, routine urinalysis, cystoscopy, ultrasound, computed tomography or magnetic resonance imaging, and urine cytology or urine fluorescence *in situ* hybridization every 3 months in the first 2 years and once a year thereafter. Biopsies were conducted for the conformation of recurrence, and informed consent was obtained prior to surgery and during follow-up.

### Statistical analysis

All statistical tests were performed using SPSS 20.0 (IBM Corp., Armonk, New York, USA). The cutoff of pretreatment NLR was determined by receiver operating characteristic analysis [Figure 1], based on which pretreatment NLR ≥2.40 was defined as high and pretreatment NLR <2.40 was defined as low. The relationship between pretreatment NLR and clinicopathological variables was analyzed by Chi-square test, and Kaplan-Meier graphs were used to estimate survival outcomes. Log-rank test was used for pairwise comparison. Meanwhile, uni- and multi-variate analyses were used to identify prognosticators. A two-sided $P < 0.05$ was considered statistically significant for all the analyses.

## Results

### Patient characteristics

The clinicopathological characteristics of the two groups stratified by pretreatment NLR are summarized in Table 1. The study population comprised 290 men (44.2%) and 366 women (55.8%), and the median age was 68 years (range: 39–88 years). The pretreatment NLR was high in 314 (47.9%) patients and low in 342 (52.1%) patients. Ipsilateral hydronephrosis was found in 379 (57.8%) patients. A total of 85 (13.0%) tumors had a major diameter ≥5 cm. Additionally, 20 (3%), 354 (54%), and 282 (43%) tumors were identified as G1, G2, and G3, respectively. Positive lymph nodes were found in 47 (7.2%) patients. The number of patients with T1, T2, T3, and T4 stage tumors was 234 (35.7%), 229 (34.9%), 181 (27.6%), and 12 (1.8%), respectively.

### Correlation between pretreatment neutrophil-to-lymphocyte ratio and clinicopathological variables

Patients with a high pretreatment NLR tended to have high tumor grades ($P < 0.001$), high tumor stages ($P < 0.001$), a tumor size > 5 cm ($P = 0.005$), ipsilateral hydronephrosis ($P = 0.033$), and concomitant

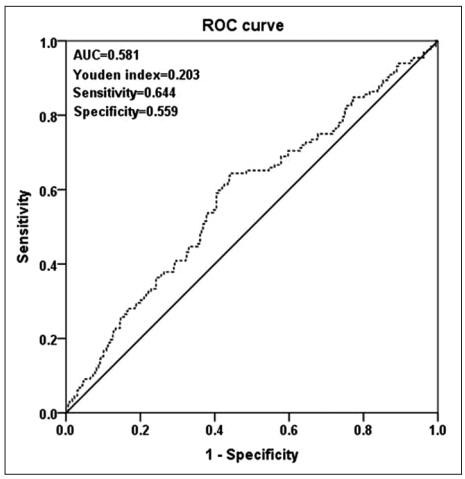


**Figure 1:** Receiver operating characteristic curve determining the optimal cutoff point of the pretreatment neutrophil-to-lymphocyte ratio.

**Table 1: Comparison of baseline clinical characteristics of 656 UTUC patients grouped by pretreatment NLR levels**

| Parameters | Pretreatment NLR (*n*) | | $\chi^2$ | *P* |
|---|---|---|---|---|
| | <2.40 (*n* = 342; 52.1%) | ≥2.40 (*n* = 314; 47.9%) | | |
| Age | | | | |
| ≥60 years | 256 | 240 | 0.221 | 0.650 |
| <60 years | 86 | 74 | | |
| Gender | | | | |
| Male | 140 | 150 | 3.101 | 0.084 |
| Female | 202 | 164 | | |
| Tobacco consumption | | | | |
| Yes | 62 | 56 | 0.010 | 0.502 |
| No | 280 | 258 | | |
| Ipsilateral hydronephrosis | | | | |
| Yes | 184 | 195 | 4.624 | 0.033 |
| No | 158 | 119 | | |
| Multifocal tumor | | | | |
| Yes | 106 | 89 | 0.550 | 0.494 |
| No | 236 | 225 | | |
| Tumor size (cm) | | | | |
| >5 | 32 | 53 | 8.213 | 0.005 |
| ≤5 | 310 | 261 | | |
| Concomitant CIS | | | | |
| Yes | 4 | 17 | 9.517 | 0.003 |
| No | 338 | 297 | | |
| Tumor grade | | | | |
| G1 | 11 | 9 | 15.725 | <0.001 |
| G2 | 209 | 145 | | |
| G3 | 122 | 160 | | |
| Tumor stage | | | | |
| T1 | 144 | 90 | 25.416 | <0.001 |
| T2 | 117 | 112 | | |
| T3 | 81 | 100 | | |
| T4 | 0 | 12 | | |
| Node | | | | |
| Positive | 14 | 33 | 10.131 | 0.001 |
| Negative | 328 | 281 | | |
| Distant metastasis | | | | |
| Yes | 6 | 15 | 4.827 | 0.023 |
| No | 336 | 299 | | |

CIS: Carcinoma *in situ*; UTUS: Upper tract urothelial carcinoma; NLR: Neutrophil-to-lymphocyte ratio.

CIS ($P = 0.003$). High pretreatment NLRs were also significantly associated with muscle invasive tumor ($P < 0.001$).

## Prognostic value

The median follow-up period was 46 months (range: 12–144). Overall, 132 (20.1%) patients died of UTUC, with a median survival time of 31 months (range: 4–104), 139 patients (21.2%) experienced intravesical recurrence, and 21 (3.2%) patients developed distant metastasis.

Uni- and multi-variate analyses of CSS and IVRFS are detailed in Tables 2 and 3. Among male patients (hazard ratio [*HR*] = 1.666, $P = 0.004$), larger tumor diameter (*HR* = 2.643, $P < 0.001$), high tumor stage (*HR* = 1.874, $P < 0.001$), high tumor grade (*HR* = 1.645, $P = 0.004$), lymph node metastasis (*HR* = 2.910, $P < 0.001$), and high pretreatment NLR (*HR* = 2.240, $P < 0.001$) were significantly associated with poor CSS in univariate analysis [Figure 2]. However, only high pretreatment NLR (*HR* = 1.820, $P = 0.001$), main tumor diameter >5 cm (*HR* = 1.789, $P = 0.009$), lymph node metastasis (*HR* = 1.863, $P = 0.024$), and higher tumor stage (*HR* = 1.745, $P < 0.001$) independently predicted poor CSS after surgery in multivariate analysis.

In addition, higher tumor grade (*HR* = 1.580, $P = 0.012$), lymph node metastasis (*HR* = 0.311, $P = 0.045$), ureteroscopy before surgery (*HR* = 1.787, $P = 0.005$), and concomitant CIS (*HR* = 2.042, $P = 0.039$) were significantly associated with IVRFS after RNU in univariate analysis. Meanwhile, only higher tumor grade (*HR* = 1.645, $P = 0.018$), ureteroscopy before surgery (*HR* = 1.701, $P = 0.015$), and concomitant CIS (*HR* = 2.164, $P = 0.034$) were associated

**Table 2: Uni- and multi-variate analyses predicting CSS in 656 patients with UTUC**

| Items | CSS | | | | | |
|---|---|---|---|---|---|---|
| | Univariate analysis | | | Multivariate analysis | | |
| | *HR* | 95% *CI* | *P* | *HR* | 95% *CI* | *P* |
| Age (<60 years vs. ≥60 years) | 1.282 | 0.845–1.947 | 0.243 | 1.303 | 0.845–2.010 | 0.230 |
| Gender (male vs. female) | 1.666 | 1.182–2.347 | 0.004 | 1.347 | 0.925–1.961 | 0.120 |
| Tobacco consumption | 1.126 | 0.733–1.729 | 0.588 | 0.945 | 0.592–1.507 | 0.812 |
| Ipsilateral hydronephrosis | 1.434 | 1.003–2.049 | 0.048 | 1.344 | 0.884–2.043 | 0.167 |
| Pretreatment NLR (≥2.40) | 2.240 | 1.570–3.197 | <0.001 | 1.820 | 1.259–2.631 | 0.001 |
| Main tumor location (pelvis/ureter) | 1.281 | 0.910–1.803 | 0.155 | 1.361 | 0.901–2.055 | 0.143 |
| Multifocality | 0.860 | 0.592–1.251 | 0.430 | 0.822 | 0.562–1.203 | 0.314 |
| Main tumor diameter (>5 cm vs. ≤5 cm) | 2.643 | 1.753–3.984 | <0.001 | 1.789 | 1.157–2.767 | 0.009 |
| Tumor stage (per stage increase) | 1.874 | 1.518–2.314 | <0.001 | 1.745 | 1.350–2.257 | <0.001 |
| Tumor grade (G3 vs. G1 or G2) | 1.645 | 1.168–2.317 | 0.004 | 0.840 | 0.554–1.275 | 0.413 |
| N status (N+ vs. N0 or pN0) | 2.910 | 1.765–4.797 | <0.001 | 1.863 | 1.086–3.194 | 0.024 |
| CIS | 1.010 | 0.413–2.470 | 0.982 | 0.882 | 0.355–2.196 | 0.788 |
| Ureteroscopy before surgery | 0.576 | 0.318–1.042 | 0.068 | 0.585 | 0.318–1.076 | 0.084 |

CIS: Carcinoma *in situ*; *HR*: Hazard ratio; *CI*: Confidence interval; CSS: Cancer-specific survival; UTUS: Upper tract urothelial carcinoma; NLR: Neutrophil-to-lymphocyte ratio.

**Table 3: Uni- and multi-variate analyses predicting IVRFS in 656 patients with UTUC**

| Items | IVRFS | | | | | |
|---|---|---|---|---|---|---|
| | Univariate analysis | | | Multivariate analysis | | |
| | *HR* | 95% *CI* | *P* | *HR* | 95% *CI* | *P* |
| Age (<60 years vs. ≥60 years) | 0.743 | 0.516–1.070 | 0.111 | 0.777 | 0.535–1.129 | 0.184 |
| Gender (male vs. female) | 1.056 | 0.755–1.477 | 0.750 | 1.019 | 0.699–1.485 | 0.924 |
| Tobacco consumption | 1.218 | 0.809–1.834 | 0.345 | 1.161 | 0.733–1.839 | 0.524 |
| Ipsilateral hydronephrosis | 1.125 | 0.802–1.577 | 0.497 | 1.213 | 0.829–1.776 | 0.320 |
| Pretreatment NLR (≥2.40) | 1.025 | 0.734–1.432 | 0.885 | 1.037 | 0.734–1.467 | 0.835 |
| Main tumor location (pelvis/ureter) | 1.052 | 0.754–1.469 | 0.764 | 0.946 | 0.644–1.389 | 0.776 |
| Multifocality | 1.360 | 0.965–1.916 | 0.079 | 1.358 | 0.959–1.925 | 0.085 |
| Main tumor diameter (>5 cm vs. ≤5 cm) | 0.835 | 0.480–1.451 | 0.522 | 0.836 | 0.471–1.482 | 0.539 |
| Tumor stage (per stage increase) | 0.941 | 0.768–1.152 | 0.556 | 1.108 | 0.875–1.403 | 0.395 |
| Tumor grade (G3 vs. G1 or G2) | 0.633 | 0.444–0.903 | 0.012 | 0.608 | 0.403–0.917 | 0.018 |
| N status (N+ vs. N0 or pN0) | 0.311 | 0.099–0.977 | 0.045 | 0.370 | 0.116–1.185 | 0.094 |
| CIS | 2.042 | 1.038–4.015 | 0.039 | 2.164 | 1.061–4.413 | 0.034 |
| Ureteroscopy before surgery | 1.787 | 1.187–2.691 | 0.005 | 1.701 | 1.108–2.612 | 0.015 |

CIS: Carcinoma *in situ*; IVRFS: Intravesical recurrence-free survival; *HR*: Hazard ratio; *CI*: Confidence interval; NLR: Neutrophil-to-lymphocyte ratio; UTUS: Upper tract urothelial carcinoma.

with high risk of IVRFS after RNU in multivariate analysis. No significant correlation was found between pretreatment NLR and IVRFS [Figure 3]. Moreover, pretreatment NLR was also significantly associated with distant metastasis after surgery ($P = 0.023$).

## Discussion

Pretreatment NLR has been investigated in various types of carcinomas. Although different thresholds were used, its sensitivity in predicting patients' survival was generally accepted. Its low cost and easy application made it a convenient clinical tool to predict the prognosis of carcinoma patients. It is important to validate the prognostic value and identify a standard threshold for better use of the pretreatment NLR.

In this study, the cutoff of pretreatment NLR was set at 2.40, which is similar to that used in some previous studies.[11,13-15] We reconfirmed that a high NLR independently led to poor outcomes in patients with UTUC in China. However, unlike studies from Japan,[13,14,16] we did not find any statistically significant association between the pretreatment NLR and IVRFS in univariate analysis. It is not clear whether the consumption of herbs containing aristolochic acid may cause some of the differences in the findings. It is well known that these herbs are commonly used and are considered an important risk factor for the development of UTUC in China.[4] However, no articles in the current literature have focused on the impact of aristolochic acid on systemic inflammation. As more techniques have been used to precisely detect aristolochic acid exposure,[17,18] we believe that the underlying mechanisms should be investigated in future studies.

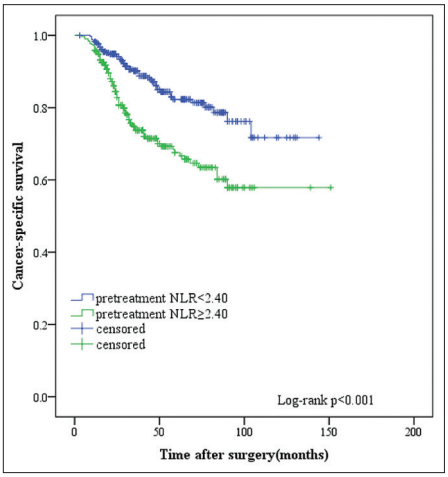


**Figure 2:** Kaplan-Meier curves of cancer-specific survival stratified by high (≥2.40) and low (<2.40) pretreatment neutrophil-to-lymphocyte ratio.

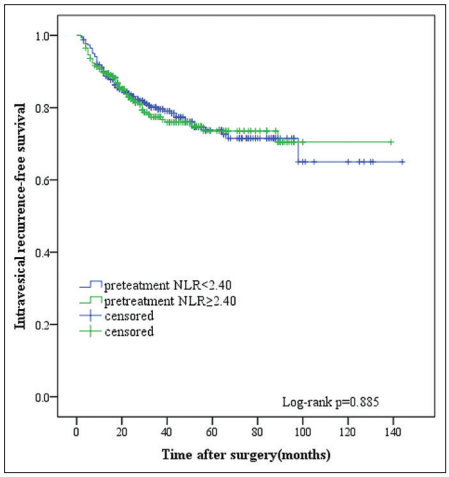


**Figure 3:** Kaplan-Meier curves of intravesical recurrence-free survival stratified by high (≥2.40) and low (<2.40) pretreatment neutrophil-to-lymphocyte ratio.

It is interesting that a high pretreatment NLR was significantly associated with distant metastasis. This is the first report to our knowledge to propose the relationship between pretreatment NLR and distant metastasis of UTUC. However, due to the limited number of cases of distant metastasis (21 patients) and the unavailability of the exact metastasis time, this phenomenon deserves further investigation, and more studies are required for further validation.

The present study demonstrated that a high pretreatment NLR is significantly associated with high tumor grade (G3) and high tumor stage (T3 and/or T4). This may be because high tumor grade indicates high heterogeneity and aggressive biological behavior such as sessile growing patterns, which is more likely to stimulate the immune system and cause systemic inflammation. High-stage UTUCs consistently mean deeper and large tumor invasion, which ultimately leads to systemic inflammation and poor outcome.

In addition, high pretreatment NLR was significantly associated with large tumor size (≥5 cm) and ipsilateral hydronephrosis. This may be because a larger tumor is more likely to develop hydronephrosis by obstructing the urinary tract, and hydronephrosis could cause various levels of systemic inflammation in the human body due to poor drainage of urine, which eventually leads to poor outcomes.[19]

We also found that the pretreatment NLR was significantly associated with concomitant CIS. A possible explanation of this finding is that CIS is associated with high tumor grade in urothelial carcinoma,[20] and high tumor grades cause systemic inflammation. To our knowledge, bladder cancer with concomitant CIS predicts a high recurrence rate and poor outcomes,[21,22] which requires aggressive treatment. Although for UTUC, concomitant CIS predicts lower recurrence rate,[23] we found that concomitant CIS was still an independent predictor for IVRFS. This may somehow reflect the homogeneity of bladder urothelial carcinoma and UTUC and may further support the hypothesis that urothelial carcinoma is more likely to develop systemic recurrence.

This study had some limitations. First, some unknown biases were unavoidable due to the inherent nature of the retrospective study. Second, the lack of some clinicopathological parameters of the study cohort such as accurate information on aristolochic acid medication history, surgical margin status, and lymphovascular invasion status which may reduce the strength of this study. However, the large sample size, single laboratory examination standard, and central pathological review could reduce the biases. Meanwhile, it should be acknowledged that further multicenter studies should be conducted for further validation.

This study demonstrated that the pretreatment NLR was an independent predictor of poor CSS in patients with UTUC, yet pretreatment NLR failed to effectively predict IVRFS in this cohort of UTUC patients. Our findings are not entirely in line with the recently published data and thus should be investigated in a prospective study to obtain a definitive statement regarding this issue.

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## Conflicts of interest

There are no conflicts of interest.

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