



The prognostic value of preoperative neutrophil-to-lymphocyte ratio in patients with upper tract urothelial carcinoma

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ABSTRACT

Background: We evaluated the prognostic impact of the preoperative neutrophil-to-lymphocyte ratio (NLR) in patients with upper tract urothelial carcinoma (UTUC) after radical nephroureterectomy treatment.

Methods: A total of 717 patients were identified between 2003 and 2016. The cutoff value of NLR was set as 2.5. Kaplan–Meier method and Cox's proportional hazards regression models were utilized to analyze the association between NLR and oncological outcomes.

Results: The median follow-up was 42 months. The results suggested that preoperative elevated NLR was associated with worse pathological features. Also, patients with $NLR \geq 2.5$ had worse survival outcomes than those with $NLR < 2.5$ (all $P < .001$). Multivariate cox analysis revealed that $NLR \geq 2.5$ was an independent predictor of worse cancer-specific survival, disease recurrence-free survival, metastasis-free survival and overall survival (HR 1.95, 95%CI: 1.42–2.69, $P < .001$; HR 1.70, 95%CI: 1.31–2.20, $P < .001$; HR 1.67, 95%CI: 1.22–2.31, $P = .002$; and HR 1.88, 95%CI: 1.42–2.50, $P < .001$; respectively). Notably, NLR was ascertained to be a useful prognostic predictor in patients with high-grade disease, but not in those with low-grade UTUC.

Conclusions: Preoperative elevated NLR was associated with worse outcomes in patients with UTUC. Subgroup analysis affirmed that NLR was a useful predictor in patients with high-grade disease, but not in those with low-grade UTUC.

1. Introduction

Upper tract urothelial carcinomas (UTUCs), which include renal pelvicalyceal and ureteric urothelial carcinoma, are uncommon urothelial carcinomas (UCs) and only account for 5–10% of UCs [1]. The incidence of UTUC is approximately 2 cases per 100,000 inhabitants in western countries but higher in Asian countries due to exposure to Chinese herbs and arsenic [1]. Although conservative management can be carried out in selected patients, radical nephroureterectomy (RNU) with bladder-cuff excision is the reference standard treatment for UTUC to date [1].

Despite the advancement of surgical techniques and benefits of neoadjuvant or early adjuvant intervention, the survival rates of patients with UTUC have not been improved significantly over time. Thus, the identification of the prognostic factors is of paramount importance to adapt treatment in time. Pathological features such as tumor stage, tumor grade, lymphovascular invasion (LVI), and lymph node invasion

have been well established as independent predictors of patients' survival, but preoperative prognostic factors are scarcely appraised.

The neutrophil-to-lymphocyte ratio (NLR) is a blood-based inflammatory marker reported in the routine blood test, and it has been proved to be an independent prognostic factor in various malignancies. An increase in NLR may be a result of increased tumor-associated neutrophils and/or decreased lymphocytes, a connection that reflects an unbalanced tumor immunity and inflammation [2], which play important roles in triggering tumor genesis, promoting and/or inhibiting tumor progression in the tumor microenvironment [3]. Recently, several studies have been performed to evaluate the association of preoperative NLR with clinicopathological features as well as oncological outcomes in UTUC patients, but their results are controversial [4–8]. According to data, only 4385 UTUC patients from nine studies were included to assess the importance of NLR on outcomes of UTUC [3, 9]. Moreover, a majority of them have < 500 patients included, and utilized different cut-off values of NLR. Meanwhile, the impacts of NLR

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on outcomes in subsets with different disease grade or stage were rarely discussed due to the small sample size. More importantly, although, since 2016, NLR has been included into the EAU guidelines on UTUC and regarded as a preoperative prognostic factor, it still has not been applied to clinical use to date [10]. Therefore, more evidence from studies with large sample size is essential and informative to confirm NLR's importance, and can further enhance its clinical application.

2. Material and methods

2.1. Patients

A total of 822 patients with UTUC who received RNU treatment from our center between 2003 and 2016 were collected with approval from our institutional review board. Patients with missing data, history of conservative surgery (such as segmental ureterectomy and endourological resection of tumor) before RNU, background of receiving neoadjuvant chemotherapy or radiotherapy before RNU, record of undergoing cystectomy prior to or concurrently with RNU, presence of concomitant tumors, as well as those with systematic diseases which could interfere NLR level at the time of RNU (such as blood malignancies, acute or chronic inflammatory diseases, active infection, or immune diseases) were excluded ($n = 105$). Lymph node dissection was not routinely performed.

All patients received standard open or laparoscopic RNU, including extrafascial dissection of the kidney with the entire span of ureter and adjacent bladder-cuff resection, which were performed by three experienced surgeons. The surgical methods were the same as to what we have previously described [11]. Briefly, the open RNU procedures were performed through a standard double-access procedure, with a loin incision followed by an iliac incision. The laparoscopic RNU procedure was performed using retroperitoneal laparoscopic nephrectomy in combination with an open iliac incision. Lymphadenectomy was not routinely performed. Only patients with suspicious enlarged lymph nodes on preoperative radiology or with intraoperative abnormal observations received regional lymphadenectomy. The extent of and the number of lymph nodes removed in the lymphadenectomy were determined by the surgeons during the surgery.

2.2. Data collection

All RNU specimens were retrospectively reviewed by 2 experienced pathologists (HX & YJ) according to standard procedures. The 2002 American Joint Committee of Cancer TNM classification and the WHO International Society of Urological Pathology consensus classification were used to evaluate the tumor stage and grade, respectively. Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls [12]. A positive surgical margin was defined as the presence of the tumor at inked areas of soft tissue on the RNU specimen [13]. Lymph node status was categorized as negative (pN0), unknown (pNx) or positive (pN+) [14]. Tumor location was categorized as the renal pelvis, ureter or involvement of both renal pelvis and ureter [15]. Multifocality means two or more tumors were found during surgery or pathological analysis. Disease recurrence was defined as local recurrence in the operating field, as well as lymph node spread and/or distant metastasis that had not been found in the preoperative examination. Specifically, the tumor found in the urinary bladder or contralateral upper urinary tract after surgery was not regarded as tumor relapse. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Preoperative serum NLR was measured within 30 days before surgery. If more than one preoperative NLR values were available, the most recent one before surgery was used. The cutoff value of NLR was defined as 2.5 by using the receiver-operating characteristic (ROC) curves and Youden Index, which were commonly used to select cutoff point for markers in clinical trials [5,

16]. Moreover, the cutoff value of white cell count was determined according to the previous study [6]. The clinicopathological data including patients' age, gender, smoking history, surgical procedures, preoperative anemia and renal function, peri-operative blood transfusion, hydronephrosis, and tumor side as well as tumor size were also collected.

2.3. Follow-up regimen

Patients were followed up every 3–4 months for the first year after surgery according to the guideline. Then, semiannually for the second and third year, and annually thereafter. Alternatively as clinically indicated with urinary cytology and excretory urography of the contralateral upper urinary tract, routine check-ups were performed that included medical history, physical examination, blood laboratory tests, and chest radiography. If clinically indicated, selective bone scan and chest/abdomen CT/MRI were carried out.

2.4. Statistical analysis

Continuous variables were analyzed using Student's *t*-test, and categorical variables were evaluated using the chi-squared test. The Kaplan–Meier method was used to calculate survival outcomes including overall survival (OS), cancer-specific survival (CSS), disease recurrence-free survival (RFS) and metastasis-free survival (MFS). The log-rank test was used to assess differences. Univariate and multivariate Cox's proportional hazards regression models were used to evaluate the relationship between variables and OS, CSS, RFS, and MFS. Risk factors with a *P* value < .1 in the univariate analysis were included in the multivariate analysis model. Hazard ratios (HRs) with their 95% CIs were used to assess the strength of the individual variables. All reported *P* values were 2-sided with statistical significance set at *P* < .05. Statistical analyses were performed using IBM SPSS Statistics ver 22.0.

3. Result

The selection flowchart of patients was shown in Fig. 1. A total of 717 patients were ultimately included in the analyses; their demographic and clinicopathological features were shown in Table 1. This study was approved by the Research Ethics Committee of West China Hospital. Informed consent was not applicable for this study.

The median age of the whole cohort was 67 (interquartile range, IQR: 59–74) y and the follow-up duration was 42 (range: 1–167; IQR: 18–76) months. The median preoperative NLR was 2.75 (IQR: 2.00–4.43), and median WBC count was 6.34 (IQR: 5.18–7.98) $\times 10^9/l$. Among them, 385 patients had a tumor in the renal pelvis, 205 had a tumor only in the ureter, and 127 had tumors in both sites. 221 patients (30.8%) were diagnosed with pTis/Ta/T1, 20.2% with pT2, 34.6% with pT3, and 14.4% with pT4. Positive lymph nodes were found in 71 (9.9%) patients (Table 1).

Three hundred and eleven patients (43.4%) were included in NLR < 2.5 group and 406 cases were included in NLR \geq 2.5 group (56.6%), respectively. There were no differences between 2 groups in age, sex, tumor side, smoking, tumor location, lymph node status, tumor size or multifocality (all *P* > .05); however, patients with elevated NLR were found to have higher rate of positive LVI (*P* < .001), worse tumor stage (*P* < .001) and high tumor grade (*P* = .021), as well as concomitant variant histology (CVH) (*P* = .040) (Table 1).

At the time of the analysis, 209 patients (29.1%) had died from UTUC, 260 patients (36.3%) had died from all causes, and 298 patients (41.6%) had developed cancer recurrence. Kaplan–Meier curves revealed that patients with elevated preoperative NLR (\geq 2.5) could be accurately predicted to develop worse CSS, RFS, MFS, and OS (all *P* < .001). The 5-year CSS, RFS, MFS, and OS were 48.4, 37.9, 52.7, and 42.6%, respectively, in cases with NLR \geq 2.5, and 73.3, 60.3, 72.1, and 67.3%, respectively, in their counterparts (Fig. 2. A–D; all

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