Preoperative Low Lymphocyte-to-Monocyte Ratio Predicts Poor Clinical Outcomes for Patients with Urothelial Carcinoma of the Upper Urinary Tract

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Purpose: Urothelial carcinoma of the upper urinary tract (UUTUC) is a rare genitourinary tumor. Pre-operative lymphocyte-to-monocyte ratio (LMR) is associated with worse outcome in several malignancies. The aim of this study was to determine the prognostic value of pre-operative LMR in UUTUC.

Materials and Methods: A historical cohort of 100 UUTUC patients was recruited from January 1990 to June 2011. The counts of peripheral lymphocyte and monocyte were retrieved, and the LMR was calculated by dividing lymphocyte count by monocyte count. Receiver operating characteristic curve (ROC) analysis, Log-rank test and Cox proportional hazards regression models were used for univariate and multivariate analyses to evaluate the associations of LMR with overall survival (OS) and disease-free survival (DFS).

Result: Univariate analysis revealed that low level of LMR (≤ 3.0) was significantly associated with worse OS ($P = .024$) but not DFS ($P = .993$). Multivariate Cox proportional hazard analysis showed that low level of LMR was a significantly independent predictor for worse OS (hazard ratio = 0.366, 95% confident interval: 0.180-0.744). Based on the results of multivariate analysis, the rates of OS at 5 years developed by the prognostic model were as follows: low risk, 88.0%, intermediate risk, 44.0%, and high risk, 13.0%, respectively.

Conclusion: The pre-operative LMR serves an independent prognostic biomarker in UUTUC. The prognostic model based on the LMR and pathologic factors can be available in selection of high risk patients for further aggressive therapy.

Keywords: urothelial carcinoma; lymphocyte-to-monocyte ratio; prognostic; biomarker; overall survival; disease-free survival

INTRODUCTION

Upper urinary tract urothelial carcinoma (UUTUC) is a rare urological disease, and easily appears to a propensity for local relapse, multifocality and distant metastasis[1]. It represents approximately 10% of renal tumors and 5% of urothelial neoplasms[2,3]. Because of the high rate of recurrence ranging from 30% to 75%, radical nephroureterectomy (RNU) with an excision of bladder cuff remains to be the golden standard for UUTUC treatment[3-5]. Several studies have shown that pathological parameters, including pathological T stage, tumor grade, tumor necrosis, lymph node invasion, existence of lymphovascular invasion (LVI) and DNA ploidy are of prognostic value in UUTUC[6,7]. These factors are useful for selection of patients for adjuvant chemotherapy. Meanwhile, prognostic value of pre-operative markers consisting of lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) for UUTUC were also clinical significance[8,9]. These factors are associated with metabolism and the corresponding inhibitors of LDH and ALP could be applied in clinical practice in the future[10,11].

Recent researches indicate that systemic inflammatory response plays a critical role in tumor aggressiveness and migration[12]. Tumor-associated lymphoid cells consisted of neutrophils, monocytes and macrophages facilitate tumor development by changing the extracellular matrix and stimulating tumor cell invasion and metastasis[13]. On the other hand, the cytokines and their mediators secreted by inflammatory cells can further facilitate angiogenesis and cells migration[14,15]. Although peripheral blood draws taken can reflect inflammatory status within the tumor tissues when the tumor was diagnosed and treated, very few blood-based biomarkers were identified in UUTUC. Prior literatures have reported that elevating C-reactive protein (CRP) level, high alkaline phosphatase (ALP) level, white blood cell count and elevated lactate dehydrogenase (LDH) have been reported to be of adverse prognostic significances in patients with UUTUC[8,9,16].

The circulating blood lymphocyte-to-monocyte ratio (LMR) is an easily examined, economic and reproducible indicator to reflect systemic inflammation. Recent researches showed that the absolute count of lymphocyte was independently correlated with the survival of

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Table1. Correlation between the LMR and clinicopathological features in 100 patients with UUTUC.

		LMR		
	All cases	**≤ 3.0**	**> 3.0**	***P* value**
Gender				.949
Female	21	10 (47.6%)	11 (52.4%)	
Male	79	37 (46.8%)	42 (53.2%)	
Age at diagnosis (years)				.106
< 60	49	19 (38.8%)	30 (61.2%)	
≥60	51	28 (54.9%)	23 (45.1%)	
Pathological stage				.305
pTa-pT1	48	20 (41.7%)	28 (58.3%)	
pT2-pT4	52	27 (51.9%)	25 (48.1%)	
Lymph node status				.423
pNx/pN0	80	36 (45.0%)	44 (55.0%)	
pN1-pN3	20	11 (55.0%)	9 (45.0%)	
Subsequent bladder tumor				.723
No	62	30 (48.4%)	32 (51.6%)	
Yes	38	17 (44.7%)	21 (55.3%)	
Tumor diameter, cm				.542
≤ 3	35	15 (42.9%)	20 (57.1%)	
>3	65	32 (49.2%)	33 (50.8%)	
Tumor grade				.358
Low	21	8 (38.1%)	13 (61.9%)	
High	79	39 (49.4%)	40 (50.6%)	
Tumor site				.371
Pelvic	57	29 (50.9%)	28 (49.1%)	
Ureteric	43	18 (41.9%)	25 (58.1%)	
Multifocality				.609
No	58	26 (44.8%)	32 (55.2%)	
Yes	42	21 (50.0%)	21 (50.0%)	
Vascular invasive				.292
No	69	30 (43.5%)	39 (56.5%)	
Yes	31	17 (54.8%)	14 (45.2%)	
Tumor necrosis				.168
No	52	21(40.4%)	31 (59.6%)	
Yes	48	26 (54.2%)	22 (45.8%)	
Achitecture				.259
Papillary	57	24 (42.1%)	33 (57.9%)	
Non-papillary	43	23 (53.5%)	20 (46.5%)	

Abbreviations: LMR:lymphocyte-to-monocyte ratio; UUTUC: Urothelial carcinoma of the upper urinary tract

patients with several malignancies, including gastric cancer, oropharyngeal cancer and acute lymphoblastic leukemia[17-19]. Other studies demonstrated that patients with low LMR had a worse overall survival in bladder cancer and pancreatic cancer[20,21]. A recent study showed that the European patients with preoperative elevated LMR had the longer OS in UUTUC, and suggested the prognostic model including LMR would be better to predict clinical outcome[22]. Another study found that low LMR with UUTUC patients had a worse DFS and progression-free survival (PFS) in Chinese, but not mentioned OS[23]. In this study, we aimed to evaluate the prognostic implication of the preoperative LMR in Chinese UUTUC, also we tried to provide the prognostic model including LMR to predict the clinical outcome for future clinical management of the UUTUC patients.

PATIENTS AND METHODS

Patients

A total of 100 patients with upper urinary tract urothelial carcinoma (UUTUC) underwent radical nephroureterectomy with bladder cuff excision were recruited from Sun Yat-sen University Cancer Center (SYSUCC) from January 1990 to June 2011. The use of tissues for this study has been approved by the Institute Research Medical Ethics Committee of SYSUCC. The patient demographics and follow-up data were obtained from the medical record with approval of the Institutional Review Board. The pathological finding, including tumor necrosis, vascular invasion, tumor grade, tumor location and TNM classification, were noted from the pathology reports. Additional clinical information, such as preoperative laboratory data, was recorded from patients' charts. The counts of lymphocyte and monocyte were achieved in two weeks before surgical resection. Lymphocyte-to-monocyte ratio (LMR) was served as the ratio of the absolute count of lymphocyte and the monocyte count. Patients without blood draw data and patients with pre-operative infection, fever and blood diseases, or received neoadjuvant chemotherapy were excluded[24]. No informed consent (written or verbal) was obtained for the use of retrospective tissue samples from the patients, part of whom were deceased, because this was deemed unnecessary by the ethics committee. All samples were anonymous. The recruited patients were observed by physical examination consisted of computerized tomography (CT), magnetic resonance imaging (MRI), cystoscopy and ureteroscopy. The patients were observed every 3 months for the first 3 years after surgery, every 3-6 months in the next year and every 6-12 mouths from the 5thyear, and annually thereafter (starting from the 6th year). Overall survival (OS) as the date of surgery to the date of death from any cause, or to the last follow-up date if the patient was alive and disease-free survival (DFS) as the length of time from the date of surgery on the primary tumor to local, regional, or distant recurrence or death from

Table 2. Univariate and multivariate analyses of overall survival in UUTUC

Variable	All cases	Univariate analysis HR (95% CI)	*P* value	Multivariate analysis HR (95% CI)	*P* value
Gender			.790		
Female	21	Reference			
Male	79	0.894 (0.391-2.042)			
Age at diagnosis (years)			.112		
< 60	49	Reference			
≥ 60	51	1.705 (0.883-3.292)			
Pathological stage			<.001	4.854 (1.806-13.044)	.002
pTa-pT1	48	Reference			
pT2-pT4	52	6.342 (2.636-15.259)			
Lymph node status			.004	1.291 (0.750-2.220)	.357
pN0	46	Reference			
pNx	34	0.903 (0.391-2.087)			
pN1-pN3	20	1.852 (1.267-2.708)			
Subsequent bladder tumor			.005	2.966 (1.428-6.163)	.004
No	62	Reference			
Yes	38	2.537 (1.322-4.871)			
Tumor diameter, cm			.835		
≤ 3	35	Reference			
> 3	65	0.930 (0.471-1.837)			
Tumor grade			.010	2.933 (0.252-34.119)	.390
Low	21	Reference			
High	79	15.204 (1.937-119.344)			
Tumor site			.063		
Pelvic	57	Reference			
Ureteric	43	1.852 (0.968-3.541)			
Multifocality			.022	2.070 (1.039-4.123)	.039
No	58	Reference			
Yes	42	2.143 (1.116-4.114)			
Vascular invasion			<.001	0.857 (0.319-2.302)	.760
No	69	Reference			
Yes	31	3.273 (1.693-6.327)			
Tumor necrosis			<.001	3.773 (1.460-9.751)	.006
No	52	Reference			
Yes	48	7.445 (3.090-17.936)			
Architecture			.001	2.217 (1.067-4.607)	.033
Papillary	57	Reference			
Non-papillary	43	3.096 (1.581- 6.064)			
LMR			.028	0.366 (0.180-0.744)	.005
≤ 3.0	46	Reference			
>3.0	54	0.478 (0.248-0.924)			

Abbreviations: LMR, lymphocyte-to-monocyte ratio; UUTUC, upper urinary tract urothelial carcinoma; HR, Hazard ratio; CI, Confident interval.

any cause.

Selection of Cut-off Value

Sensitivity and specificity for LMR cut-off were calculated with receiver operating characteristic (ROC) curve. ROC analysis was plotted to investigate optimal cut-off values that maximized sensitivity and specificity[25]. The cut-off value of LMR was corresponding with the largest sensitivity and specificity on the ROC curve. The valueless lower than or equal to cut-off value was considered as low level of LMR, and more than the cut-off value was determined as high level of LMR.

Risk Factor Classification for OS and DFS

A prior study has described the method of risk factor classification[24]. Overall survival distributions for groups classified according to the number of independent clinical risk factors are shown in the result section.

Statistical Analysis

Statistical analysis was performed with SPSS software, version 16.0 (SPSS, Chicago, USA). The suitable cut-off value of the diverse LMR was analyzed with ROC curve. The association of LMR with other clinicopathological factors was analyzed by Chi-square test. Survival curve were plotted for both high and low level of LMR with the Kaplan–Meier method. Univariate analysis was performed to identify the impact of clinicopathological factors on survival. Multivariate analysis was used to explore the independent prognostic factors for survival. The evaluation of hazard ratios (HRs) was served as relative risks with corresponding 95% confidence intervals (CIs). All data tests were 2-sided, with statistical significant set as $P < .050$.

RESULTS

The clinical and pathological characteristics of 100 patients with UUTUC are detailed in **Table 1**. The average age was 60.3 years (range from 30 to 85 years). Seventy-nine (79%) patients were male and 21 (21%) were female (male to female ratio 3.8:1). The average follow-up interval was 45.83 months (range from 1 to 151 months). The median overall survival (OS) was 37.0 months. The rates of OS at 2nd and 5thyears after surgery were 83% and 70%, respectively. The median DFS was 32.0 months. The rates of DFS at 2ndand 5th years after surgery were 80% and 66%, respectively.
To select an optimal cut-off value for LMR, the ROC

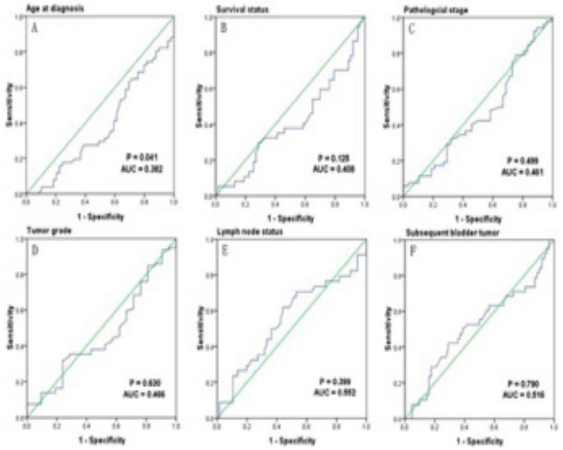

Figure 1. ROC curve analysis was conducted to determine the cut-off value for LMR. The sensitivity and specificity of each outcome were plotted for LMR: Age at diagnosis, sensitivity = 0.627, specificity = 0.305, likelihood ration positive and negative = 90.3% and 81.8%, 95% confidence intervals = 0.272-0.491 **(A),** survival status, sensitivity = 0.297, specificity = 0.714, likelihood ration positive and negative = 103.8% and 101.6%, 95% confidence intervals = 0.290-0.526 **(B),** pathological stage, sensitivity = 0.923, specificity = 0.125, likelihood ration positive and negative = 105.5% and 162.3%, 95% confidence intervals = 0.346-0.575 **(C),** tumor grade, sensitivity = 0.316, specificity = 0.762, likelihood ration positive and negative = 132.8% and 111.4%, 95% confidence intervals = 0.329-0.602 **(D)**, lymph node status, sensitivity = 0.618, specificity = 0.561, likelihood ration positive and negative = 140.8% and 146.9%, 95% confidence intervals = 0.426-0.677 **(E),** subsequent bladder tumor, sensitivity = 0.421, specificity = 0.710, likelihood ration positive and negative = 145.2% and 122.6%, 95% confidence intervals = 0.395-0.637 **(F)**

curves were used. Results showed that the area under the curve (AUC) for age at diagnosis variable had the biggest area (AUC = 0.382, P = .041, 95% confident interval: 0.272-0.491). LMR value of 3.0 had the largest sensitivity and specificity on the ROC curve (**Figure 1**). As a result, the value of 3.0 was chosen as the cut-off value of LMR for survival analysis. Patients were divided into two groups: low level of LMR ($\leq$ 3.0) and high level of LMR (> 3.0). No significant correlation was found between LMR and pathological variables, including gender, age, vascular invasion, pathological stage, lymph node status, subsequent bladder tumor, tumor site, tumor diameter, tumor grade, multifocality, tumor necrosis and architecture (**Table 1**).

In univariate analysis, LMR, along with a series of well-known clinicopathological prognostic factors (pathological stage, lymph node status, subsequent bladder tumor, tumor grade, vascular invasion, multifocality, tumor necrosis, architecture), was significantly associated with OS in patients with UUTUC (**Table 2**). Furthermore, in multivariate analysis, LMR retained independent significance in patients with UUTUC for OS (P = .005, **Table 2**). Kaplan-Meier analysis revealed that patients with low LMR level had a significantly poorer survival (5-year OS, 48.0%), compared with patients with high LMR level (5-year OS, 68.0%) (P = .024, **Figure 2**) but not DFS (P = .993, **Figure 2**).

Risk Factor Classification for OS

Multivariate analysis revealed that pathological stage, subsequent bladder tumor, multifocality, tumor necrosis, architecture and LMR (a total of 6 risk factors) were of independent significance in patients with UUTUC for OS (**Table 2**). Accordingly, the 100 patients were divided into seven groups through 0 to 6 risk factors. Survival analysis showed that there were no significant differences for OS among the groups simultaneously harboring the 0, 1 or 2 risk factors. However, there were inversely statistical differences for OS between above mentioned three groups (simultaneously harboring the 0, 1 or 2 risk factors) and other groups including simultaneously harboring 3, 4, 5 or 6 risk factors (P < .001). Therefore, these groups simultaneously harboring the 0, 1 or 2 risk factors was categorized into low risk groups. Similarly, univarite analysis showed that there were no significant differences for OS between the groups simultaneously harboring 3 and 4 risk factors, but OS of both of groups as one variable had closely statistical differences comparing with that of simultaneously harboring 5 or 6 risk factors (P = .008, data no shown). Thus, the groups simultaneously harboring 3 or 4 risk factors was served as intermediate risk group, and correspondingly the groups simultaneously harboring 5 or 6 risk factors was considered as high risk group. The median OS and the 5-year OS rate was 151.0 months and 88.0% in low risk group (50 patients), while the

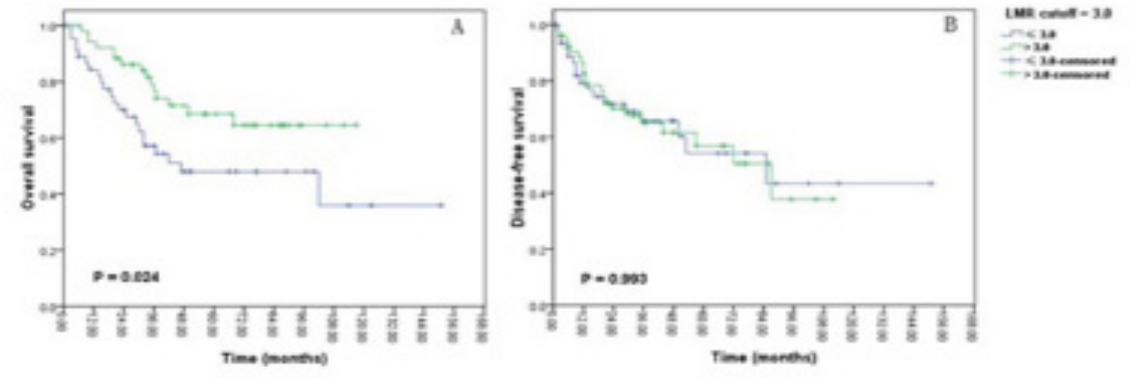

Figure 2. The association of LMR with UUTUC patients' survival (log-rank test).Kaplan-Meier survival analysis of LMR for overall survival **(A)** and disease-free survival **(B)**

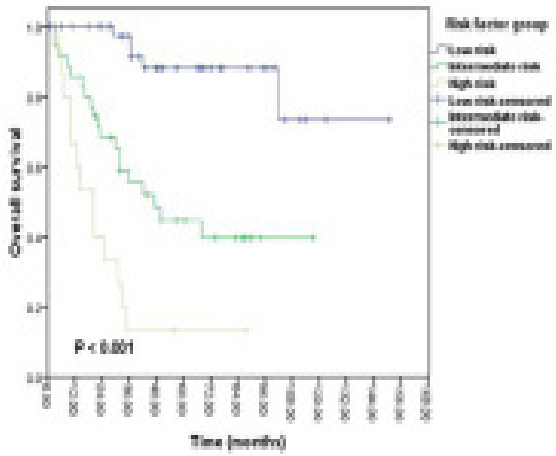

Figure 3. Kaplan-Meier analysis for overall survival each risk factor group.

corresponding values were 47.5 and 44.0% in intermediate risk group (35 patients), and 20.3 and 13.0% in high risk group (15 patients). Kaplan-Meier analysis showed a distinct prognostic pattern among the three groups (**Figure 3**).

DISCUSSIONS

The inflammatory cells response stimulated by tumors could lead to the increase of various cytokines and inflammatory mediators, further resulting in the upregulation of capability for invasion and migration[12,14]. Inflammatory responses are very important with respect to the tumor and outcome of patients by chronic cellular injury and oxidative stress, which will facilitate tumor initiation and progression[26], more importantly, the procession of tumor-recruited lymphocytes interacting with tumor cells might induce tumor progression by secreting diverse cytokines. Herein, we have made an investigation on UUTUC to evaluate the critically prognostic significances of circulating lymphocyte-to-monocyte ratio (LMR) and other clinical parameters. Recent much advancement for the molecular and genetic alterations has been demonstrated in UUTUC[27], however, the conventional clinicopathological parameters are still applied to assess the prognosis of patients with UUTUC. At the same time, blood-based markers, including the count of lymphocyte, neutrophil and the variable of LMR, maybe used to estimate the relative risks in the patients with UUTUC. Recently, an elevated pre-treatment neutrophil-to-lymphocyte ratio (NLR) was demonstrated as an adverse prognostic biomarker for different human neoplasms, including soft tissue sarcoma[28], nasopharyngeal carcinoma[29], renal cell carcinoma[30], lung cancer[31], and UUTUC[24]. Regarding the LMR, so far, the prognostic value has been investigated only in nasopharyngeal carcinoma [32], diffuse large B-cell lymphoma[33] and soft tissue sarcoma[34]. Recently, two publications reported that low LMR was closely associated with the poor prognosis of UUTUC[22,23]. Hutterer GC et al.[22] reported that UUTUC patients with preoperative low LMR had a worse overall survival in European, and Song X et al.[23] showed that UUTUC patients with preoperative low LMR had a worse DFS and PFS but without OS information in Chinese population. In our study, we found a statistically significant association of low LMR with poor OS in UUTUC patients in univariate as well as multivariate analysis. Together with the Kaplan-Meier analysis result, we demonstrated for the first time that a decreased LMR represents a novel independent poor prognostic marker in UUTUC patient in Chinese, and we timely provided the prognostic models, which including LMR (pathological stage, subsequent bladder tumor, multifocality, tumor necrosis and LMR). We demonstrated that UUTUC patients with high risk factor, intermediate risk factor and low risk factor had significantly statistical differences for the prediction of OS.

Monocytes constitute about 5% of the circulating leukocytes and play an important role in innate immunity. Derive from circulating monocytes, tumor-associated macrophages (TAMs) selectively recruited to the tumor microenvironment by locally secreted cytokines and chemokines, such as monocyte chemoattractant protein-1 (MCP-1), TNF-α and others. The interaction between TAMs and tumor cells is believed to have substantial effects in tumor initiation and progression. Paik KY et al. have found that absolute monocyte count was associated with clinical outcomes in colorectal cancers patients[35] and Lenz G et al. have demonstrated that the infiltrated monocytes in tumor tissue had abilities to promote tumor invasion and cell growth in large B-cell lymphoma[36]. The predictive value of preoperative monocytes count in other solid tumor was also reported[37]. The exact role of monocytes in tumor development has not yet been well identified. One possibility is the soluble factors released by infiltrative monocytes, including interleukin (IL)-1, IL-6, IL-10 and TGF-α, which have been well studied to enhance neo-angiogenesis, invasion and migration, and are associated with worse prognosis in various malignances [38]. Furthermore, monocytes can inhibit mitogen and antigen-induced lymphocytes proliferative response, impair the host defense anti-tumor role by lymphocytes, resulting in suppression of anti-cancer immunity in cancers[39]. This was demonstrated by our study from another aspect. In other words, when the circumstances of high monocytes in combination with low lymphocytes or low LMR were appeared, these patients had a worse OS. Therefore, inhibition of this pathway of decreased lymphocytes inducing by monocytes could be the newly therapeutic target. To the best of our knowledge, this is the first study indicating that preoperative LMR is an independent prognostic factor in Chinese UUTUC patients for OS. This finding was partial in agreement with that of two other studies[22,23]. Our study and two other studies had a certain degree of similarities. Firstly, Hutterer GC et al.[22] reported that UUTUC patients with preoperative low LMR had a worse OS in European, which was consistent with that of our study, and in our study, we firstly revealed the same conclusion in Chinese UUTUC patients. Meanwhile, they also believed that this parameter should be considered in future prognostic models. However, they did not accomplish this work, and we timely provided the prognostic models, which including LMR (pathological stage, subsequent bladder tumor, multifocality, tumor necrosis and LMR). We further demonstrated that UUTUC patients with high, intermediate and low risk factor had significantly statistical differences for the prediction of overall survival. Therefore, our results verified their specula-

tion and the model based on the LMR and pathologic factors can be available in clinical practice, especially in selection of high risk patients for further aggressive therapy.

The limitation of our study was that small patients were recruited. Therefore, large-scale prospective studies in multicenter are necessary to validate these conclusions. Taken together, we firstly demonstrated that pretreatment peripheral LMR is an independent biomarker for predicting OS of Chinese UUTUC patients. Additionally, we firstly provided the prognostic model, which including LMR (pathological stage, subsequent bladder tumor, multifocality, tumor necrosis and LMR). In this prognostic model, we demonstrated that UUTUC patients with high risk factor, intermediate risk factor and low risk factor had significantly statistical differences for the prediction of OS. Technically, our study is directly derived from routine blood test and easily applied in clinical practice. Large-scale prospective studies in multicenter are warranted to advanced validate our findings.

CONCULUSIONS

Our analysis has showed the pre-operative LMR serves as an independent prognostic biomarker in UUTUC. The prognostic model based on the LMR and pathologic factors can be available in selection of high risk patients for further aggressive therapy.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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