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Predictive value of preoperative lymphocyte-to-monocyte ratio for patients with upper tract urothelial carcinoma

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ABSTRACT

Background: To determine the predictive value of preoperative lymphocyte-to-monocyte ratio (LMR) for pathological and survival outcomes in upper tract urothelial carcinoma (UTUC) after radical nephroureterectomy (RNU).
Methods: This retrospective study included 704 UTUC patients between 2008 and 2017. We used a cutoff LMR of 3.6 to evaluate its relationship with oncological outcomes after RNU, using the Kaplan–Meier method and logistic regression models.
Results: During median follow-up of 39 months, decreased preoperative LMR was an independent predictor of poor pathological outcomes. Kaplan–Meier analysis revealed that patients with low LMR (< 3.6) had poor cancer-specific survival (CSS), recurrence-free survival (RFS), and overall survival (OS); this prognostic value was ascertained for patients with high pathological grade and more advanced stage UTUC, but not for patients with low pathological features. Multivariate Cox proportional hazards model revealed that low LMR was an independent predictor of poor CSS, RFS and OS [hazard ratio (HR) = 1.42, $P = 0.02$; HR = 1.39, $P = 0.008$; HR = 1.38, $P = 0.017$, respectively].
Conclusion: Preoperative low LMR was an independent predictor of poor pathological and oncological outcomes of UTUC after RNU. Subgroup analysis confirmed that the prognostic value of LMR was confined to patients with a high pathological grade and more advanced stage tumor.

1. Introduction

Upper tract urothelial carcinoma (UTUC) is a rare malignancy that accounts for only ~5% of all urothelial cancers [1], and is more lethal and aggressive than urothelial carcinoma of bladder [2,3]. Radical nephroureterectomy (RNU) with bladder cuff excision remains the gold-standard treatment for clinically localized UTUC. However, the high incidence rates of recurrence and poor prognosis after RNU have not improved despite significant advances in medical technology [4,5]. The European Association of Urology (EAU) guidelines currently recommend cisplatin-based adjuvant chemotherapy to improve oncological outcomes, especially in patients with high recurrence rates [1,6,7]. Additionally, neoadjuvant chemotherapy was demonstrated as a promising approach in pathological downstaging, although long-term survival rates remain unknown [1,7,8]. Thus, accurate identification of the optimal indications of these therapies and prediction of oncological outcomes are paramount, given the associated high treatment costs and impaired potency [8,9].

Currently, neither computed tomography (CT) nor magnetic resonance imaging (MRI) has achieved sufficient preoperative diagnostic accuracy to guide individualized therapy [5]. The most important pathological parameters, including tumor grade and stage, lymphovascular invasion (LVI), and tumor necrosis, are also inadequate, as they cannot be determined until RNU [3,10].

Conversely, numerous studies have revealed the association of various preoperative blood-based markers with pathological features and oncological outcomes in various malignancies, including UTUC [3,11–14]. For example, the EAU guidelines recommend the neutrophil-to-lymphocyte ratio (NLR) as a preoperative indicator for UTUC, although it has not yet been applied to clinical practice [6,11]. Several studies have also revealed that the lymphocyte-to-monocyte ratio (LMR), another blood marker, has a better prognostic value than NLR [8,15]. However, few studies have investigated the prognostic value of LMR in patients with UTUC.

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The purpose of our study was to determine the predictive value of preoperative LMR for pathological and oncological outcomes in patients with UTUC.

2. Materials and methods

2.1. Patient selection

This retrospective study was approved by the Research Ethics Committee of West China Hospital, and included 789 UTUC patients who received RNU between 2008 and 2017. Eighty-five patients who met the following criteria were excluded from the analysis: missing data; loss to follow-up; neoadjuvant chemotherapy or radiotherapy before RNU; presence of concomitant tumors; and concomitant systemic diseases that could interfere with LMR, including immune disorders, active infection, and acute or chronic inflammatory diseases. RNU, including dissection of the kidney with the entire ureter and adjacent bladder-cuff resection, was performed with standard open or laparoscopic procedures. The exact surgical approach was mainly determined according to the experience of the patient's urologist in each case. Regional lymphadenectomy was performed only in patients with suspicious enlarged lymph nodes on preoperative CT/MRI, or in those with abnormal intraoperative findings. All procedures were performed by three experienced urologists, and the exact number and extent of lymph node excision were determined by the attending surgeon.

2.2. Data collection

Clinical patient data including age, sex, smoking history, body mass index (BMI), tumor side and size, hydronephrosis, surgical procedures, and other oncological features were extracted from the hospital information system, and the missing data were supplemented during follow-up visits. LMR was defined as the absolute lymphocyte count divided by the absolute monocyte count. Preoperative LMR was collected within 30 days before surgery, and the most recent value was selected if multiple preoperative data were available.

Pathological grade and stage were identified by the WHO International Society of Urological Pathology consensus classification (2004) and the American Joint Committee of Cancer TNM classification (2017, 8th version), respectively. Multifocality, LVI, positive surgical margins (PSMs), and tumor architecture were determined by two experienced urological pathologists. Concomitant variant histology (CVH) was defined as urothelial carcinomas with aberrant histological differentiation such as micropapillary, squamous cell, lymphoepithelioma, and sarcomatoid carcinoma.

2.3. Follow-up strategy

In accord with the guidelines, patients were followed every 3–4 months during the first year, 6-monthly for the second year, and annually thereafter. Medical history, physical examination, laboratory blood tests, and routine urinalysis were obtained conventionally. Chest radiography, chest/abdominal CT/MRI, cystoscopy, and bone scans were obtained depending on the follow-up strategy, or in cases of suspicious disease recurrence or metastasis.

2.4. Statistical analysis

The receiver operating characteristic (ROC) curve analysis was performed to evaluate the optimal LMR cutoff value for predicting survival, according to the maximum sensitivity and specificity points [16–18].

Continuous and categorical variables were analyzed by Student's *t*-test and chi-squared test, respectively. Cancer-specific survival (CSS), recurrence-free survival (RFS), and overall survival (OS) were calculated using the Kaplan–Meier method, with the log-rank test to compare

Table 1
Baseline characteristics of patients with upper tract urothelial carcinoma after radical nephroureterectomy.

Variables	Total (n = 704)	LMR < 3.6 (n = 320)	LMR ≥ 3.6 (n = 384)	P
Age (mean ± SD, yr.)	66 ± 11.4	66 ± 11.4	66 ± 11.3	0.521
Gender, n (%)				0.004
Male	401 (57.0)	201 (62.8)	200 (52.1)	
Female	303 (43.0)	119 (37.2))	184 (47.9)	
Smoking status, n (%)				0.028
No	504 (71.6)	216 (67.5)	288 (75.0)	
Yes	200 (28.4)	104 (32.5)	96 (25.0)	
BMI	22.73 ± 14.45	23.44 ± 20.51	22.14 ± 5.56	0.263
Tumor side, n (%)				0.720
Left	360 (51.1)	166 (51.9)	194 (50.5)	
Right	344 (48.9)	154 (48.1)	190 (49.5)	
Hydronephrosis, n (%)				0.006
No	267 (37.9)	139 (43.4)	128 (33.3)	
Yes	437 (62.1)	181 (56.6)	256 (66.7)	
Tumor location, n (%)				0.337
Pelvicalyceal	375 (53.3)	177 (55.3)	198 (51.6)	
Ureteric	202 (28.7)	83 (25.9)	119 (31.0)	
Both	127 (18.0)	60 (18.8)	67 (17.4)	
Multifocality, n (%)				0.868
No	587 (83.4)	266 (83.1)	321 (83.6)	
Yes	117 (16.6)	54 (16.9)	63 (16.4)	
Surgical approach, n (%)				0.930
Open RNU	474 (67.3)	216 (67.5)	258 (67.2)	
Laparoscopic RNU	230 (32.7)	104 (32.5)	126 (32.8)	
Tumor grade, n (%)				0.038
Low	185 (26.3)	72 (22.5)	113 (29.4)	
High	519 (73.7)	248 (77.5)	271 (70.6)	
Pathological T stage, n (%)				0.006
≤ pT2	359 (51.0)	145 (45.3)	214 (55.7)	
≥ pT3	345 (49.0)	175 (54.7)	170 (44.3)	
Lymph node status, n (%)				0.502
pN0/x	635 (90.2)	286 (89.4)	349 (90.9)	
pN+	69 (9.8)	34 (10.6)	35 (9.1)	
LVI, n (%)				0.180
No	597 (84.8)	265 (82.8)	332 (86.5)	
Yes	107 (15.2)	55 (17.2)	52 (13.5)	
Tumor size (cm), n (%)				0.606
≤ 3	227 (32.2)	100 (31.3)	127 (33.1)	
> 3	477 (67.8)	220 (68.8)	257 (66.9)	
PSM, n (%)				0.317
No	646 (91.8)	290 (90.6)	356 (92.7)	
Yes	58 (8.2)	30 (9.4)	28 (7.3)	
Tumor architecture, n (%)				0.336
Papillary	222 (31.5)	95 (29.7)	127 (33.1)	
Sessile	482 (68.5)	225 (70.3)	257 (66.9)	
CVH, n (%)				0.948
No	542 (77.0)	246 (76.9)	296 (77.1)	
Yes	162 (23.0)	74 (23.1)	88 (22.9)	
Adjuvant Chemotherapy, n (%)				0.441
No	418 (59.4)	195 (60.9)	223 (58.1)	
Yes	286 (40.6)	125 (39.1)	161 (41.9)	
AGR	1.71 ± 7.13	1.96 ± 10.57	1.50 ± 0.28	0.071

Note: RNU, radical nephroureterectomy; BMI, body mass index; LVI, lymphovascular invasion; CVH, concomitant variant histology; PSM, positive surgical margins; AGR, albumin to globulin ratio; LMR, lymphocyte-to-monocyte ratio.

differences. Additional subgroup analyses were performed according to pathological grade and stage. Logistic regression analysis was performed to investigate the relationship between LMR and adverse
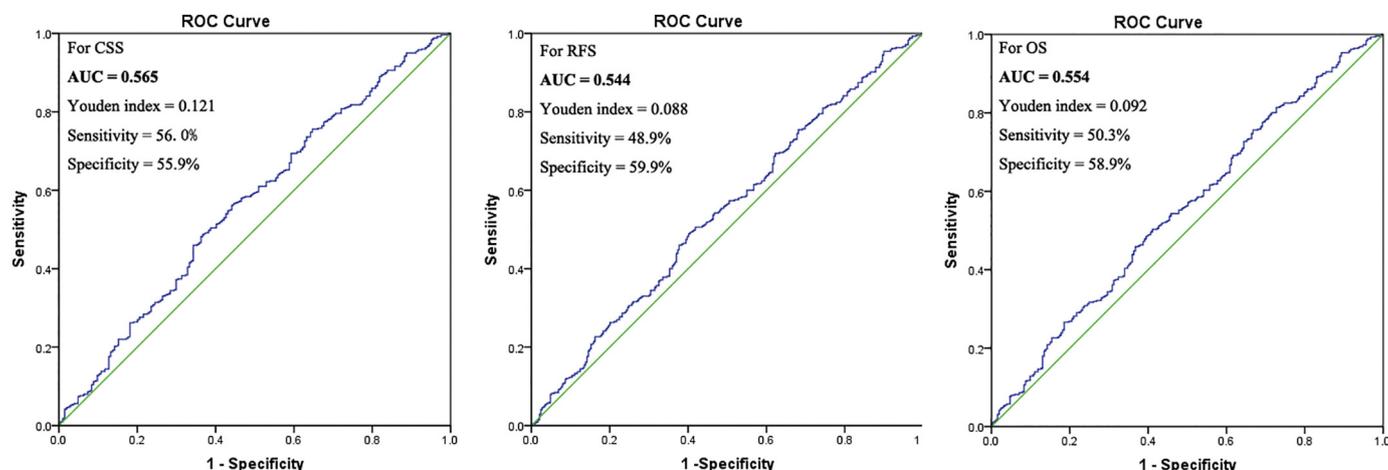
Fig. 1. ROC curve analysis of LMR for survival outcomes in 704 UTUC patients after radical nephroureterectomy. CSS revealed the largest AUC (0.565), while LMR cutoff was set at 3.6 for the largest Youden Index (0.121) obtained (sensitivity, 56.0%; specificity, 55.9%). CSS, cancer-specific survival; RFS, recurrence-free survival; OS, overall survival; LMR, lymphocyte-to-monocyte ratio. AUC, area under the ROC curve.

Table 2
Logistic regression analysis of low lymphocyte-to-monocyte ratio and its predictive value for adverse pathological outcomes.

Adverse pathological outcomes	Adjusted OR[a]	95% CI	P value
High-grade disease	1.58	1.11–2.25	0.011
High tumor stage (≥ pT3)	1.70	1.24–2.33	0.001
Lymph node involvement	1.29	0.77–2.16	0.328
LVI	1.35	0.89–2.06	0.159
Sessile carcinoma	1.28	0.92–1.78	0.147
CVH	1.07	0.74–1.53	0.724
PSM	1.64	0.94–2.88	0.084

[a] Adjusting for age, gender, smoking status, body mass index, hydronephrosis, tumor side, tumor location and multifocality. LVI, lymphovascular invasion; CVH, concomitant variant histology; PSM, positive surgical margins; OR, odds ratios; CI, confidence interval.

pathological features. Cox proportional hazards regression models were used to identify independent predictors of CSS, RFS and OS. Risk factors with $P < 0.1$ in univariate analysis were selected for multivariate analyses, and hazard ratios (HRs) with 95% confidence intervals (CIs) were chosen to evaluate the strength of individual variables. All statistical analyses were performed using SPSS version 22.0 (IBM SPSS, Chicago, IL, USA).

3. Results

3.1. Patient characteristics

After strict screening, 704 patients (401 male and 303 female) with complete follow-up data were included in the final analysis. Mean age at the time of surgery was 66 ± 11.4 years, and median follow-up duration was 39 (interquartile range [IQR]: 34–43) months. Two hundred patients (28.4%) admitted to a smoking history, and 437 (62.1%) suffered from hydronephrosis. In addition, 519 patients (73.7%) were diagnosed with high-grade urothelial carcinoma, 345 (49.0%) had high-stage tumor (≥ pT3), and 69 (9.8%) had lymph node invasion. The demographic and pathological characteristics of the patients are shown in Table 1.

3.2. Low LMR is a predictor of adverse pathological features

The areas under the ROC curves (AUCs) were 0.565, 0.544 and 0.554 for CSS, RFS and OS, respectively. The largest AUC of 0.565 obtained for CSS was used to set a cutoff LMR of 3.6, which achieved maximum sensitivity (56.0%) and specificity (55.9%). According to the threshold of LMR, 320 patients (45.5%) with LMR < 3.6 were categorized into the low LMR group, whereas the remaining 384 patients (54.5%) with an LMR ≥ 3.6 were assigned to the high LMR group.
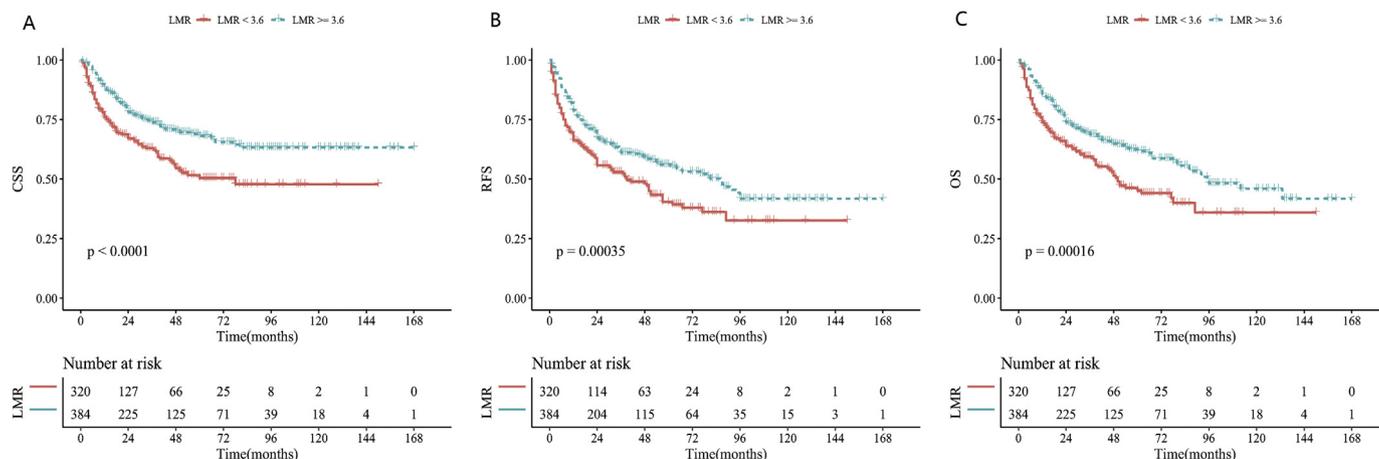

Fig. 2. Kaplan–Meier curves for CSS (A), RFS (B), and OS (C) which was stratified according to LMR value (LMR < 3.6 vs. LMR ≥ 3.6) for UTUC patients receiving RNU. The difference was evaluated by log-rank tests.
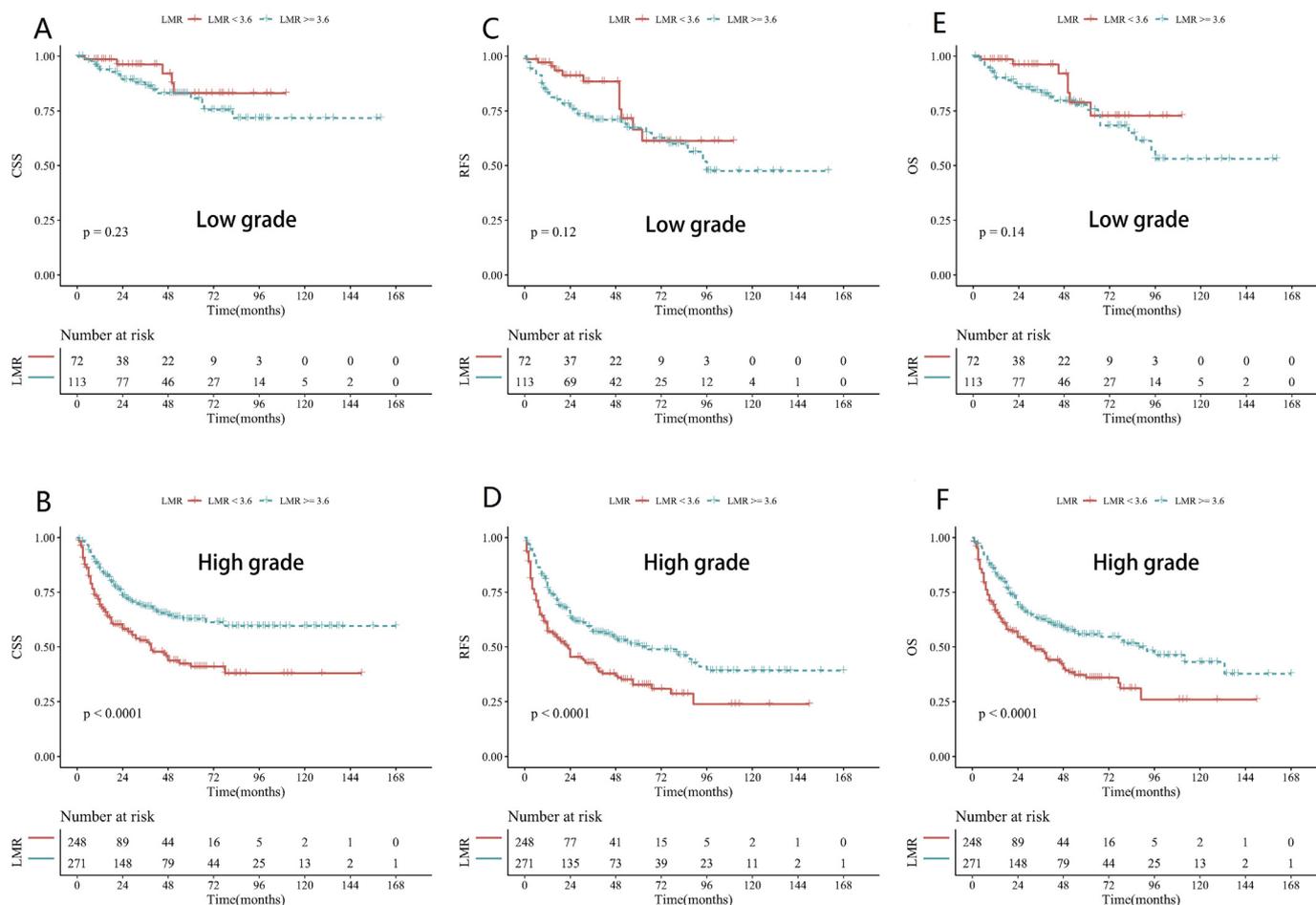
Fig. 3. Subgroup analysis based on tumor pathologic grade, Kaplan–Meier curves for CSS (A and B), RFS (C and D), and OS (E and F) which was stratified according to LMR value (LMR < 3.6 vs. LMR ≥ 3.6) for UTUC patients receiving RNU. The difference was evaluated by log-rank tests.

There were no significant differences in age, BMI, tumor side, tumor location, multifocality, surgical approach, lymph node status, LVI, tumor size, PSM, tumor architecture, CVH, adjuvant chemotherapy, and albumin to globulin ratio (AGR) between the two groups. However, low LMR was significantly more frequent in male patients ($P = 0.004$) as well as those with a history of smoking ($P = 0.028$), worse tumor grade ($P = 0.038$) and advanced stage ($\geq$ pT3) ($P = 0.006$), (Fig. 1, Table 1). In addition, multivariate logistic regression analysis revealed that low LMR independently predicted high tumor grade (odds ratio [OR] 1.58, $P = 0.011$) and stage (OR 1.70, 95%, $P = 0.001$) (Table 2).

3.3. Low LMR is associated with poor CSS, RFS and OS

At the time of analysis, the rates of UTUC-related mortality, cancer recurrence, and all-cause mortality were 29% ($n = 204$), 41.1% ($n = 289$), and 35.9% ($n = 253$), respectively.

3.3.1. LMR and CSS

The 5-year CSS was 50.3% and 68.1% for the low and high LMR groups, respectively. By Kaplan–Meier analysis, the CSS was worse in the low LMR group compared with the high LMR group ($P < 0.0001$) (Fig. 2). In subgroup analysis according to the tumor grade and stage, low LMR was associated with worse CSS for patients with higher grade ($P < 0.0001$) and more advanced stage ($P = 0.00035$) tumors; however, no significant difference in CSS was observed for those with lower grade ($P = 0.23$) and less advanced stage ($\leq$ pT2) ($P = 0.27$) tumors (Figs. 3 and 4). In addition, univariate analysis revealed that low LMR was associated with low CSS (HR = 1.77, $P < 0.0001$) (Table 3). By

multivariate analysis, low LMR (HR = 1.42, $P = 0.02$), tumor size $\geq$ 3 cm, high tumor grade, advanced tumor stage ($\geq$ pT3), lymph node invasion, tumor architecture, CVH, and AGR were significant predictors for worse CSS (Table 4).

3.3.2. LMR and RFS

The 5-year RFS rates were 40.3% and 55.3% for the low and high LMR groups, respectively. The Kaplan–Meier analysis revealed that patients with a low preoperative LMR (< 3.6) exhibited worse RFS ($P = 0.00035$) (Fig. 2). Similarly, by subgroup analysis, high grade ($P < 0.0001$) and more advanced stage ($P = 0.00032$) of tumor were predictors for worse RFS in patients with UTUC, which was not observed for low pathological grade ($P = 0.12$) and less advanced stage ($P = 0.81$) (Figs. 3 and 4). Univariate Cox regression analysis showed that low LMR was an independent predictor of worse RFS (HR = 1.52, $P < 0.0001$) (Table 3). Furthermore, low LMR (HR = 1.39, $P = 0.008$), in combination with tumor size $\geq$ 3 cm, high tumor stage, lymph node invasion, CVH, and AGR were corrected with decreased RFS in multivariable analysis (Table 4).

3.3.3. LMR and OS

The 5-year OS rates were 45.2%, and 61.7% for the low and high LMR groups, respectively. Kaplan–Meier analysis exhibited that OS was poorer in the low LMR group ($P = 0.00016$) (Fig. 2). By subgroup analysis, low LMR predicted decreased OS in patients with high grade ($P < 0.0001$) and more advanced stage ($P = 0.0013$) tumors, which was not observed in patients with low grade and less advanced stage tumors ($P = 0.14$, $P = 0.31$, respectively) (Figs. 3 and 4). Low LMR was
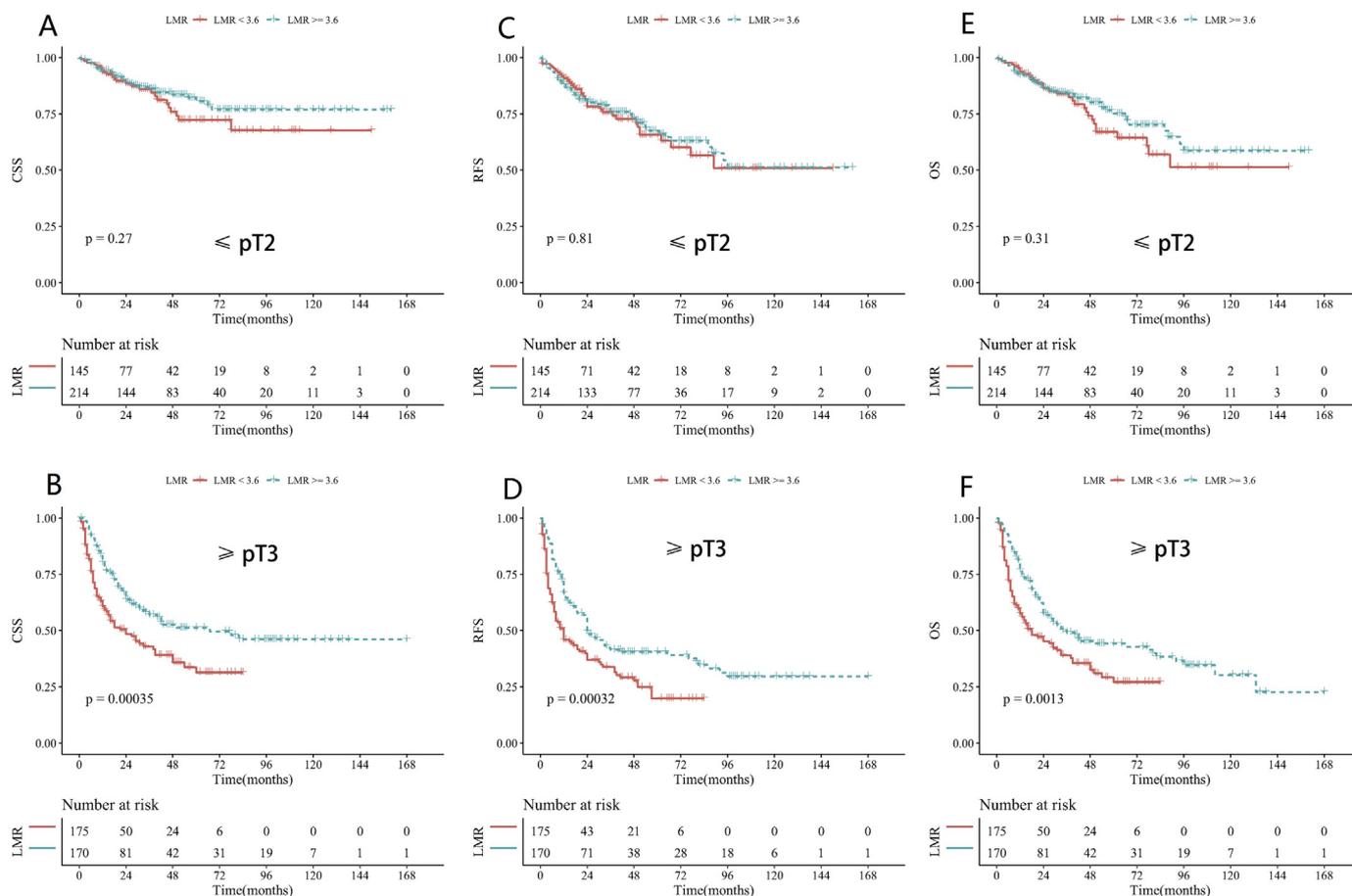
Fig. 4. Subgroup analysis based on tumor pathologic stage, Kaplan–Meier curves for CSS (A and B), RFS (C and D), and OS (E and F) which was stratified according to LMR value (LMR < 3.6 vs. LMR ≥ 3.6) for UTUC patients receiving RNU. The difference was evaluated by log-rank tests.

Table 3
Univariable Cox regression analyses to predict survival outcomes for upper tract urothelial carcinoma.

Variables	Cancer-specific survival		Recurrence-free survival		Overall survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥ 65 years vs < 65 years)	0.82 (0.62–1.08)	0.159	0.85 (0.67–1.07)	0.163	0.94 (0.73–1.21)	0.617
Gender (male vs female)	0.80 (0.61–1.06)	0.115	1.18 (0.93–1.48)	0.169	0.87 (0.68–1.12)	0.278
Smoking status (yes vs no)	0.81 (0.59–1.12)	0.196	0.86 (0.66–1.12)	0.275	0.87 (0.65–1.15)	0.329
BMI	0.98 (0.96–1.01)	0.227	0.99 (0.98–1.01)	0.425	0.99 (0.97–1.01)	0.400
Tumor side (right vs left)	1.10 (0.84–1.45)	0.502	1.05 (0.84–1.33)	0.660	1.06 (0.83–1.35)	0.655
Hydronephrosis (yes vs no)	1.28 (0.96–1.71)	0.095	1.40 (1.10–1.80)	0.007	1.36 (1.05–1.77)	0.021
Tumor location		0.505		0.497		0.681
Ureteric vs Pelvicalyceal	1.03 (0.75–1.42)	0.862	0.98 (0.74–1.28)	0.277	0.97 (0.72–1.29)	0.816
Both vs Pelvicalyceal	1.24 (0.86–1.79)	0.249	1.19 (0.87–1.62)	0.285	1.14 (0.81–1.59)	0.458
Multifocality (yes vs no)	1.02 (0.71–1.48)	0.906	0.98 (0.71–1.34)	0.883	0.94 (0.67–1.33)	0.730
Surgical approach (Laparoscopic vs Open)	0.69 (0.50–0.95)	0.025	0.85 (0.66–1.11)	0.226	0.73 (0.54–0.98)	0.034
Tumor grade (high vs low)	3.56 (2.30–5.49)	< 0.0001	2.31 (1.69–3.15)	< 0.0001	2.94 (2.05–4.23)	< 0.0001
pT stage (≥ pT3 vs ≤ pT2)	3.94 (2.89–5.37)	< 0.0001	3.13 (2.45–4.01)	< 0.0001	3.47 (2.65–4.55)	< 0.0001
Lymph node status (pN+ vs pN0/x)	4.18 (2.99–5.84)	< 0.0001	3.84 (2.85–5.20)	< 0.0001	3.73 (2.72–5.12)	< 0.0001
LVI (yes vs no)	2.70 (1.98–3.70)	< 0.0001	2.23 (1.69–2.94)	< 0.0001	2.49 (1.87–3.32)	< 0.0001
Tumor size (≥ 3 cm vs < 3 cm)	2.00 (1.45–2.76)	< 0.0001	1.86 (1.43–2.42)	< 0.0001	1.96 (1.47–2.60)	< 0.0001
PSM (yes vs no)	2.39 (1.60–3.57)	< 0.0001	1.93 (1.34–2.78)	< 0.0001	2.17 (1.50–3.15)	< 0.0001
Tumor architecture (Sessile vs Papillary)	3.85 (2.59–5.74)	< 0.0001	2.55 (1.91–3.41)	< 0.0001	3.04 (2.19–4.22)	< 0.0001
CVH (yes vs no)	2.45 (1.83–3.26)	< 0.0001	2.13 (1.66–2.72)	< 0.0001	2.30 (1.77–2.98)	< 0.0001
Adjuvant Chemotherapy (yes vs no)	1.06 (0.81–1.40)	0.664	0.95 (0.85–1.07)	0.390	1.15 (0.90–1.47)	0.278
AGR	0.18 (0.12–0.29)	< 0.0001	0.31 (0.21–0.46)	< 0.0001	0.24 (0.16–0.36)	< 0.0001
LMR (< 3.6 vs ≥ 3.6)	1.77 (1.34–2.33)	< 0.0001	1.52 (1.20–1.91)	< 0.0001	1.60 (1.25–2.06)	< 0.0001

Note: BMI, body mass index; LVI, lymphovascular invasion; CVH, concomitant variant histology; PSM, positive surgical margins; AGR, albumin to globulin ratio; LMR, lymphocyte-to-monocyte ratio; HR, hazard ratio.

Table 4
Multivariable Cox regression models to predict survival outcomes for upper tract urothelial carcinoma.

Variables	Cancer-specific survival		Recurrence-free survival		Overall survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Hydronephrosis (yes vs no)	0.99 (0.73–1.33)	0.933	1.12 (0.87–1.45)	0.391	1.08 (0.82–1.42)	0.579
Tumor size(≥ 3 vs < 3 cm)	1.57 (1.12–2.19)	0.009	1.52 (1.16–2.00)	0.003	1.56 (1.16–2.09)	0.004
Surgical approach (Laparoscopic vs Open)	0.84 (0.60–1.17)	0.289	1.02 (0.78–1.34)	0.861	0.86 (0.64–1.17)	0.338
Tumor grade (high vs low)	1.72 (1.08–2.75)	0.023	1.35 (0.96–1.90)	0.084	1.61 (1.08–2.38)	0.018
Pathological T stage (≥ pT3 vs ≤ pT2)	1.86 (1.29–2.67)	0.001	1.83 (1.37–2.44)	< 0.0001	1.81 (1.32–2.49)	< 0.0001
Lymph node status (pN + vs pN0/x)	2.01 (1.39–2.88)	< 0.0001	2.22 (1.59–3.09)	< 0.0001	1.88 (1.33–2.65)	< 0.0001
LVI (yes vs no)	1.17 (0.82–1.66)	0.395	1.06 (0.77–1.44)	0.735	1.15 (0.84–1.59)	0.381
PSM (yes vs no)	1.24 (0.81–1.89)	0.319	1.12 (0.76–1.64)	0.580	1.18 (0.80–1.75)	0.403
Tumor architecture (Sessile vs Papillary)	1.77 (1.14–2.75)	0.011	1.39 (1.00–1.93)	0.052	1.51 (1.04–2.18)	0.03
CVH (yes vs no)	1.45 (1.07–1.96)	0.017	1.37 (1.05–1.78)	0.021	1.44 (1.09–1.90)	0.009
AGR	0.33 (0.20–0.55)	< 0.0001	0.54 (0.35–0.83)	0.005	0.42 (0.27–0.68)	< 0.0001
LMR (< 3.6 vs ≥ 3.6)	1.42 (1.06–1.90)	0.02	1.39 (1.09–1.77)	0.008	1.38 (1.06–1.79)	0.017

Note: LVI, lymphovascular invasion; CVH, concomitant variant histology; PSM, positive surgical margins; AGR, albumin to globulin ratio; LMR, lymphocyte-to-monocyte ratio; HR, hazard ratio.

associated with decreased OS by univariate (HR = 1.60, $P < 0.0001$) and multivariate (HR 1.38, $P = 0.017$) analyses (Tables 3 and 4). Moreover, tumor size ≥3 cm, high tumor grade, more advanced stage, lymph node invasion, tumor architecture, CVH, and AGR were associated with worse OS (Table 4).

4. Discussion

Increasing evidence indicates that host inflammatory responses play essential roles in tumorigenesis. These responses also contribute to changes in parameters related to circulating leukocytes, such as LMR, NLR, platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) level [16,19]. Strong associations have been found between changes in these parameters and the development and progression of malignancies [8,11,12,15,16,20]. Recent studies have focused on the elucidation of these relationships [4,6,9–11], and aimed at utilizing their advantages for universally available, easily accessible, cost-effective, and reproducible biomarkers.

A study by Stotz et al. was the first to report the predictive value of preoperative LMR in colon cancer, showing that low LMR was an indicator of shorter time to recurrence and worse OS [17]. Since this first report, the prognostic value of LMR has been reported for various malignancies including: gastric and esophagogastric junction adenocarcinoma; colorectal, pancreatic, lung, and ovarian cancers [3,12,16,18,20]; and bladder carcinoma [8,15]. Some studies have also investigated the relationship between preoperative LMR and UTUC, and have concluded that low LMR was an independent predictor of poor OS. However, those studies were limited by small sample sizes, and other survival outcomes such as CSS and RFS were not analyzed [3,21].

In the current study, a cohort of 704 patients with UTUC who received RNU was analyzed retrospectively. Final analyses confirmed that low LMR (< 3.6) was an independent predictor for poor CSS, RFS and OS. Low LMR was also associated with higher pathological grade and more advanced stage of tumor. Pathological features are considered as important factors for risk stratification according to EAU guidelines [6]. Therefore, we performed further subgroup analyses that revealed that LMR was an independent predictor only for UTUC patients with high pathological grade and more advanced stage of tumor.

The studies that investigated LMR and UTUC were limited by small sample size [3,21]. The current study with a relatively large cohort confirmed that LMR was a valuable predictor for oncological progression of UTUC, and provided further information on its utility in risk stratification. However, similar to the well-studied NLR [6], the precise value of LMR in a clinical setting requires further investigation. For example, a prognostic model based on preoperative factors including LMR, NLR, PLR, CRP and AGR might be utilized to guide further

therapeutic strategies such as adjuvant or neoadjuvant chemotherapy or radiotherapy; however, this requires more clinical evidence.

Malignancy is known to trigger systemic inflammatory responses and alter the number of circulating lymphocytes and monocytes, which play different roles in tumor growth, maturation and differentiation [16,19]. Lymphocytes have essential roles in antitumor immunity and induce apoptosis of tumor cells by several mechanisms; they also exert antitumor effects as mediators of antibody-dependent and cell-mediated cytotoxicity [20,22]. It has been shown that patients with invasive bladder tumor have reduced numbers of T and natural killer cells [23], whereas reactivity of lymphocytes to mitogens, CD4/CD8 ratio, and activity of natural killer cells are inhibited in invasive disease [24]. It is speculated that a decline in lymphocytes was responsible for a weak and insufficient immunological response to tumorigenesis, which predicted negative prognostic outcomes [25].

Conversely, as a representative source of multiple chemokines/cytokines, monocytes can induce inflammation and immune dysfunction [26], which promote cancer progression by immunosuppression and induction of tumor neovascularization [27]. Tumor-associated macrophages have been shown to inhibit antitumor responses by promoting tumor-associated angiogenesis and inducing tumor cell invasion, intravasation and migration [28]. Moreover, increased macrophage density is associated with poor clinical outcomes in various malignancies [29], while induction of M2 macrophages by tumor cells is reported to accelerate progression of pancreatic cancer [30].

Because of a reduction in lymphocytes or an increase in monocytes, low LMR resulting from cancer-associated systemic inflammatory response is an independent predictor of poor oncological outcomes in patients with UTUC after RNU.

Several limitations to our study should be acknowledged. First, this single-center, retrospective study might have had selection bias. Second, CRP and some of the other inflammatory parameters were not evaluated routinely; therefore, their prognostic value could not be analyzed. Third, adjuvant chemotherapy was not included in the analyses because of incomplete data, which might have affected the findings of the study. Fourth, due to the relatively short follow-up duration, the results from subgroup analysis with low pathological features remain to be identified. Finally, the previously reported cutoff LMR values were controversial, and the LMR cutoff used in the current study was limited as a result of the low AUC, sensitivity and specificity. Future studies with larger samples size and longer follow-up are necessary to validate the prognostic value of LMR in UTUC.

5. Conclusions

Low preoperative LMR was an independent predictor of advanced

pathological and oncological features of patients with UTUC after RNU. Those with low LMR (< 3.6) were more likely to have poor CSS, RFS and OS. Additionally, low LMR exhibited a prognostic value only for patients with high pathological grade and more advanced stage tumors, but not for those with low pathological grade and less advanced stage tumors. As an easily accessible and low-cost method, the application of preoperative LMR to predict the oncological progression of UTUC patients is promising.

Declarations of interest

None.

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