

The prognostic role of preoperative neutrophil-to-lymphocyte ratio in upper tract urothelial carcinoma

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ABSTRACT

Introduction: The blood-based inflammatory marker, neutrophil-to-lymphocyte ratio (NLR), is a reliable prognostic biomarker for several cancers. Although the literature supports the correlation between preoperative NLR, clinicopathological characteristics, and oncological outcomes in upper tract urothelial carcinoma (UTUC), the cutoff of NLR is still debated. This study aimed to determine the prognostic value of NLR in patients with UTUC.

Methods: This was a retrospective analysis of prospectively collected data from July 2012 to December 2022 evaluating patients with UTUC who underwent radical nephroureterectomy (RNU). NLR was calculated using the neutrophil and lymphocyte counts obtained a day before the surgery and the cutoff value was set as 2.5. Kaplan–Meier and Cox’s proportional hazards regression were used to analyze the association between NLR and the oncological outcomes.

Results: The study included 91 patients (78 males, 13 females) in the final analysis with a median follow-up of 49 months (8–130). The mean age of the patients with NLR <2.5 and NLR ≥2.5 was 56.88 years and 56.35 years, respectively, and the pathological stage was pT1 in 48%, pT2 in 20.88%, pT3 in 27.47%, and pT4 in 3.30% of the patients. Multivariable Cox regression analysis showed that the preoperative NLR ≥2.5 was significantly associated (Hz = 7.17) with higher T stage, lymphovascular invasion, necrosis, nodal involvement, adjuvant chemotherapy, and worse overall survival (OS) (Hz = 9.87). The Kaplan–Meier analysis revealed an improved OS in patients with NLR <2.5, but a statistically significant difference in the recurrence-free survival was not found.

Conclusions: Preoperative NLR is an easily available, inexpensive, and important prognostic biomarker of survival in patients with UTUC and has a potential role in risk stratification by predicting adverse clinicopathological characteristics.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) of the renal pelvis and ureter are rare tumors comprising of up to 5% of all the urothelial tumors.^[1] Up to 10% of all the renal tumors are urothelial tumors.^[2] The majority of the literature on UTUC is from the Western countries and the data from the Indian subcontinent is limited. As per the Western literature, most of these tumors present early and at a lower stage.^[3,4] However, in our geographical region, most of these patients present at a higher stage and have worse outcomes than their Western

counterparts.^[2] UTUC is an aggressive tumor and is frequently diagnosed as an invasive disease (pT3) in up to 60% of the cases, in contrast, only 15%–20% of the cases of carcinoma urinary bladder present as an invasive disease.^[5] The treatment of UTUC varies from renal preserving endoscopic resection to radical nephroureterectomy (RNU) with bladder cuff excision depending on the grade and the stage of the disease. The prognostic significance of T stage and grade on the cancer-specific survival and recurrence-free survival has been well established in the literature.

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The neutrophil-to-lymphocyte ratio (NLR) is a blood-based inflammatory marker. The prognostic value of NLR has been established for several cancers. An increase in the tumor-associated neutrophils and a decrease in the lymphocytes leads to a higher NLR. An elevated NLR suggests an imbalance between inflammation and tumor immunity, potentially leading to the development of tumors and influencing their progression within the tumor microenvironment. Furthermore, several reports suggest a correlation between the preoperative NLR and the oncological outcomes in patients with UTUC. However, the cutoff of NLR that predicts the oncological outcomes is still controversial.^[6-12] This retrospective study was designed to assess the prognostic significance of preoperative NLR in patients with UTUC, who underwent RNU with bladder cuff excision.

MATERIALS AND METHODS

This was a retrospective analysis of prospectively maintained database of 109 patients who underwent RNU with bladder cuff excision between July 2012 and December 2022 for UTUC at our center. All these patients underwent routine blood tests with a complete hemogram preoperatively. The tumor grade was determined according to the World Health Organization 1973 guidelines and the International Society of Urological Pathology classification. The pathological “T” stage was adjusted according to the tumor, node, metastasis (TNM) classification. Postoperatively, the patients were followed-up at 3 monthly intervals for 2 years and 6 monthly thereafter with cystoscopy, routine blood test, and ultrasound of the abdomen. At six-months, a contrast-enhanced computed tomography of the abdomen and pelvis with urogram was obtained in patients with pT2 or higher disease. Data collected for analysis included age, gender, clinical presentation, TNM stage, tumor size and location, preoperative complete hemogram, postoperative histopathology, N stage, adjuvant treatment, recurrence and survival. NLR was calculated from the neutrophil and lymphocyte counts reported on the routine hemogram obtained a day before the surgery. None of the patients had systemic inflammation or blood disease at the time of the blood test. “Disease recurrence” was defined as local tumor recurrence in the bladder or lymph nodal recurrence or distant metastasis. The association of NLR with variables was assessed using the Chi-square test and the Kaplan–Meier survival was used to calculate the overall survival (OS) and recurrence-free survival (RFS). Univariable and multivariable Cox regression models were used to analyze the association with NLR. Age-adjusted logistic regression was used to assess the association of NLR with the other predictive factors. All “*P*” values were two sided, and *P* < 0.05 was used to indicate statistical significance. Stata 14.0 was utilized for all the statistical testing and analysis (Stata Corp., College Station, TX, USA).

RESULTS

During the study period, from July 2012 to December 2022, 109 patients underwent RNU at our center. However, the follow-up data was lacking for 18 patients, so 91 patients were finally considered for the analysis. Among the 91 patients, 78 were males and the median follow-up duration was 49 months (Range: 8–130 months). In our analysis, 34 patients had a preoperative NLR <2.5 (28 males, 6 females), and 57 patients had a preoperative NLR ≥2.5 (50 males, 7 females). The demographic characteristics of the patients, the clinicopathologic data, including tumor grade, T stage, the presence of lymph node metastasis, and histopathology parameters are summarized in Table 1. The mean age of the patients with NLR <2.5 and NLR ≥2.5 was 56.88 years and 56.35 years, respectively. The most common presentation was hematuria, followed by flank pain. 59.34% (*n* = 54) of the patients were smokers. The most common location of the tumor was the ureter (71.43% [*n* = 65]) and 30.77% (*n* = 28) of the patients had a synchronous bladder cancer. 59 patients underwent open RNU, 31 underwent lap RNU, and only one underwent robotic RNU. The clinicopathological characteristics and their association with preoperative NLR is summarized in Table 2. 71.43% (*n* = 65) of all the tumors were high grade and 82.46% (*n* = 47) of the patients in the NLR ≥2.5 group had high-grade tumors in comparison to 17.54% (*n* = 10) of the patients in the NLR <2.5 group. 50.88% of the patients (*n* = 29) had lymphovascular invasion (LVI) in the NLR ≥2.5 group (*P* = 0.010). 47.37% (*n* = 27) of the patient had necrosis on the histopathology (*P* = 0.004) in the NLR ≥2.5 group. 31.57% (*n* = 18) of the patients in the NLR ≥2.5 group received adjuvant chemotherapy (*P* = 0.073) in comparison to 14.71% (*n* = 5) patients in the NLR <2.5 group. 24.56% (*n* = 14) of the patients had recurrence in the NLR ≥2.5 group (*P* = 0.138) compared to 11.76% (*n* = 4) of the patients in the NLR < 2.5 group. 29.82% (*n* = 17) of the patients died during the course of the disease in the NLR ≥2.5 group (*P* = 0.002) compared to 2.94% (*n* = 1) in the NLR < 2.5 group. On the multivariable analysis, NLR ≥2.5 was associated with higher tumor grade, lymph node involvement, higher T stage, presence of LVI, and presence of necrosis in comparison with the NLR <2.5 group [Table 3]. After age-adjustment, the logistic regression analysis found a significant association between preoperative NLR and worse outcomes (*Hz* = 9.87) [Table 3]. Kaplan–Meier survival analysis showed superior OS in patients with NLR <2.5 than those with NLR ≥2.5 [Figure 1]. These findings suggest that higher levels of preoperative NLR are linked to more aggressive pathological features. On the multivariate analysis, preoperative NLR ≥2.5 was found to be an independent risk factor for the OS (*P* = 0.03, hazard ratio [HR] = 9.87) [Table 3] but the association with RFS was not statistically significant (*P* = 0.82, HR = 1.14) [Table 4]. Kaplan–Meier survival analysis showed a superior RFS in patients with NLR <2.5 than those with NLR ≥2.5, but it

Parameters	NLR <2.5 (n=34), n (%)		NLR ≥2.5 (n=57), n (%)		Total (n=91)
Age	56.88 years (mean)		56.35 (mean)		
Sex	Male (n=28; 82.35%)	Female (n=6; 17.65%)	Male (n=50; 87.72%)	Female (n=7; 12.28%)	91
Parameters	No	Yes	No	Yes	P
Hematuria	1 (2.94)	33 (97.06)	8 (14.04)	49 (85.96)	0.08
Flank pain	30 (88.24)	4 (11.76)	43 (75.44)	14 (24.56)	0.46
No comorbidity	14 (41.18)	20 (58.82)	24 (42.11)	33 (57.89)	0.93
Tobacco exposure	18 (52.94)	16 (47.06)	19 (33.33)	38 (66.67)	0.06
Multifocal tumor	26 (76.47)	8 (23.52)	39 (68.42)	18 (31.57)	0.41
Associated bladder cancer	25 (73.52)	9 (26.47)	38 (66.67)	19 (33.33)	0.49
LVI	26 (76.47)	8 (23.53)	28 (49.12)	29 (50.87)	0.010
Necrosis	28 (82.35)	6 (17.64)	30 (52.63)	27 (47.37)	0.004
Adjuvant chemotherapy	29 (85.29)	5 (14.71)	39 (68.42)	18 (31.58)	0.073
Recurrence	30 (88.23)	4 (11.76)	43 (75.44)	14 (24.56)	0.138
Survival	1 (2.94)	33 (97.06)	17 (29.82)	40 (70.17)	0.002
Histopathology T stage	Number of patients (n=91)			Percentage	
pT1	44			48.35	
pT2	19			20.88	
pT3	25			27.47	
pT4	3			3.30	
Low-grade tumor	26			28.57	
High-grade tumor	65			71.43	
Presence of LVI	37			40.66	
Presence of necrosis	33			36.26	

LVI=Lymphovascular invasion, NLR=Neutrophil-to-lymphocyte ratio

Table 2: Association of preoperative neutrophil-to-lymphocyte ratio and clinicopathological characteristics in upper tract urothelial carcinoma patients treated with radical nephroureterectomy

Parameters	NLR <2.5 (n=34), n (%)	NLR ≥2.5 (n=57), n (%)	P
T stage			
pT1	23 (67.64)	21 (36.84)	0.02
pT2	6 (17.65)	13 (22.81)	
pT3	5 (14.71)	20 (35.09)	
pT4	0	3 (5.26)	
Presence of LVI	8 (8.79)	29 (31.87)	0.010
Presence of necrosis	6 (6.59)	27 (29.67)	0.004
Nodal stage			
N0	34 (100)	46 (80.70)	0.02
N1	0	7 (12.28)	
N2	0	4 (7.02)	
Grade			
LG	16 (47.06)	10 (17.54)	0.003
HG	18 (52.94)	47 (82.46)	
Urine cytology			
Negative	11 (32.35)	15 (26.32)	0.33
Positive	23 (67.64)	42 (73.68)	

LVI=Lymphovascular invasion, NLR=Neutrophil-to-lymphocyte ratio, LG=Low grade, HG=High grade

was not statistically significant [Figure 1]. Age-adjusted multivariable analysis failed to show a statistically significant association of higher tumor grade, presence of LVI, presence of necrosis, lymph node involvement, and preoperative NLR with the RFS [Table 4]. Multivariable Cox regression analysis found that only the higher stage of the disease was associated with the higher risk of recurrence (HR = 7.90 [95% confidence interval = 1.95–31.91]) ($P = 0.004$) [Table 4].

DISCUSSION

UTUC is a rare neoplasm with aggressive potential. There has been a stage migration at presentation, from higher stages to lower stages, because of the improvements in imaging and access to health care.^[3,13] However, due to lack of awareness, patients often present late in our subcontinent.^[2] In the Western literature, the incidence of early tumors, i.e. Ta-T1, is 50%–70%, whereas the reported incidence of early tumors in the Indian population is 11%.^[2] The incidence of early tumors in the current series was higher comprising up to 48.35% and is consistent with the Western literature. The previous literature on UTUC from the Indian subcontinent, however, was published a decade ago. This difference in the presentation, noted in our series, may be explained by the greater awareness for health care among the population and the ease of access to radiological imaging.

UTUC affects people in their 6th–7th decade of life,^[2] and this was seen in our study as well, with the median age being 60 years. Male predominance is seen in urothelial cancer with a ratio of 3:1,^[14] but in our study, the number of males was 78 (85.71%), and 13 (14.29%) patients were females. This can be attributed to differential attitudes toward seeking health care. This can also be attributed to the higher incidence of smoking in men. A history of smoking was present in 59.34% of the patients in the current study. In the present study, ureteral involvement was the most common site of involvement in 65 (71.43%) cases, and multifocal tumors were found in 26 (28.57%) cases. This is consistent with the results of other studies.^[15] Bladder recurrence was observed in 18 patients, whereas two patients

Table 3: Multivariable Cox regression analysis and age-adjusted multivariable logistic regression analysis for prediction of overall survival in upper tract urothelial carcinoma patients treated with radical nephroureterectomy

Parameters	HZ	SE	Z	P> z	95% CI
Multivariable Cox regression analysis for prediction of overall survival					
Preoperative NLR	7.177	7.535	1.88	0.060	0.9169505–56.18896
Stage	1.699	0.5338	1.69	0.091	0.9184038–3.145606
LVI	1.479	0.8940	0.65	0.517	0.4525942–4.83627
Necrosis	1.176	0.6741	0.28	0.777	0.3823692–3.617066
LN stage	0.9458	0.7870	-0.07	0.947	0.1851863–4.831332
Adjuvant chemotherapy	1.228	0.8509	0.30	0.766	0.3160664–4.775373
Age-adjusted multivariable logistic regression analysis for prediction of overall survival					
Age	0.9998	0.0256	-0.00	0.996	0.95077–1.0515
Preoperative NLR	9.877	10.676	2.12	0.034	1.1873–82.169
Stage	1.744	0.6606	1.47	0.142	0.83023–3.6643
LVI	1.704	1.279	0.71	0.478	0.39117–7.4260
Necrosis	0.09562	0.7227	-0.06	0.953	0.21736–4.2064
LN stage	0.7920	0.8044	-0.23	0.818	0.10819–5.7983
Adjuvant chemotherapy	1.164	0.9893	0.18	0.857	0.22052–6.1541

LVI=Lymphovascular invasion, NLR=Neutrophil-to-lymphocyte ratio, SE=Standard error, LN=Lymph node, CI=Confidence interval

Table 4: Univariable and multivariable analysis for prediction of recurrence-free survival in upper tract urothelial carcinoma patients treated with radical nephroureterectomy

Parameters	HZ	SE	Z	P> z	95% CI
Univariable analysis for prediction of recurrence-free survival					
Grade	7.35877	7.572945	1.94	0.052	0.9791062–55.30708
LVI	1.988172	0.9437812	1.45	0.148	0.784134–5.04101
Necrosis	2.235655	1.06078	1.70	0.090	0.8821133–5.666113
LN stage	2.283259	2.375785	0.79	0.428	0.2970709–17.54892
NLR	1.146245	0.6938082	0.23	0.822	0.34999–3.754044
Multivariable Cox regression analysis for prediction of recurrence-free survival					
NLR	1.146	0.6938	0.23	0.822	0.34999–3.75404
Stage < pT2	2.800	2.352	1.23	0.220	0.5394253–14.53597
Stage ≥ pT2	7.907	5.629	2.90	0.004	1.958935–31.91596
Necrosis	1.061	0.5368	0.12	0.907	0.3936858–2.860355
Adjuvant chemotherapy	2.259	1.170	1.57	0.116	0.8186167–6.238356

SE=Standard error, NLR=Neutrophil-to-lymphocyte ratio, LN=Lymph node, CI=Confidence interval

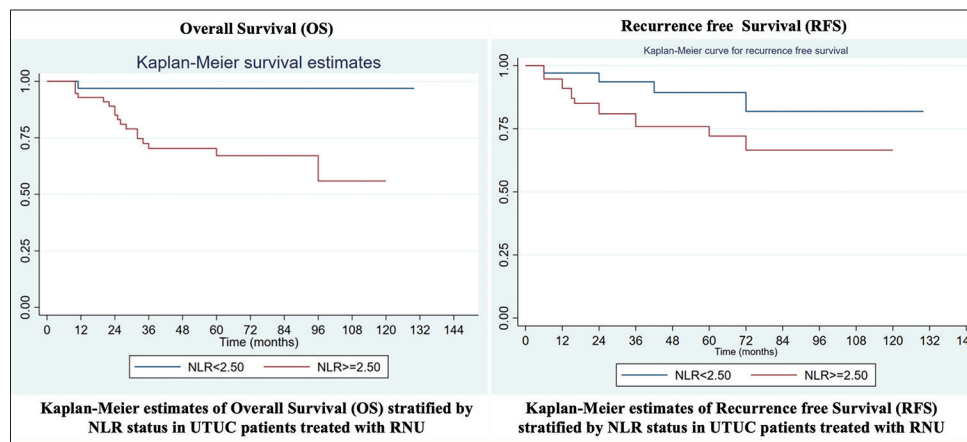


Figure 1: Kaplan–Meier estimates of overall survival and recurrence-free survival stratified by neutrophil-to-lymphocyte ratio in patients with UTUC treated with radical nephroureterectomy. RFS = Recurrence-free survival, OS = Overall survival, NLR = Neutrophil-to-lymphocyte ratio, RNU = Radical nephroureterectomy

had metastatic disease. Both these patients had T2 disease at the presentation and did not receive adjuvant chemotherapy. Bladder recurrences were treated as per the protocol for carcinoma of the urinary bladder.

In our study, 28 (30.76%) patients had a concomitant urinary bladder cancer (pT2 stage) which required concomitant radical cystectomy along with RNU. The incidence of concomitant bladder cancer was higher in

our study as compared to that reported in the Western literature.^[16]

In a similar study, synchronous bladder cancers along with UTUC were reported in 10%, 18%, and 33% of the patients with primary UTUC of the renal pelvis, upper ureter, and lower ureter, respectively. This suggests that a lower ureteric involvement has a higher risk for concomitant bladder cancer. Most of the patients in our series had a high-grade disease, comprising 71.43% of all the cases. This is consistent with another published study by Lughezzani *G et al.* where the high-grade disease was seen in 70% of the patients^[17] and can be explained by the fact that currently, a larger proportion of low-grade, and low-risk patients are being managed by nephron-sparing approaches such as endoscopic resection, ablation, percutaneous ablation, segmental ureteral resection, chemo ablation, and distal ureterectomy with ureteroneocystostomy, as recommended by the EAU Guidelines. In our series, the majority of the patients had high-risk disease and hence were managed with RNU with bladder cuff excision.

The stage of the disease has been shown to be a strong predictor of recurrence in multiple studies and this was also reflected in the present study. The postoperative histopathology in our series was as follows: T1 – 44 cases (48.35%), T2 – 19 cases (20.88%), T3 – 25 cases (27.47%), and T4 in 3 cases (3.30%). Previous literature has reported that a higher “T” stage, being a predictor of advanced disease, can predict the recurrence.^[13,18] In the present study, a higher T stage was significantly associated with a higher NLR ≥ 2.5 ($P = 0.02$). The majority of the cases in our series, 71.43% ($n = 65$), were high grade at presentation. This is in contrast with the Western literature.^[3,4,13] A total of 23 patients (25.27%) received adjuvant chemotherapy, among which three patients had T4 disease, 12 patients had T3 disease, three patients had T2 disease, and five patients had T1 disease. In our study, the rate of LVI was 40.65% ($n = 37$). The presence of LVI was found to have a significant association with NLR ≥ 2.5 ($P = 0.010$). A correlation between LVI and cancer-specific survival has been previously established.^[19,20] Tumor necrosis also significantly correlated with the NLR ≥ 2.5 ($P = 0.004$). In the present study, high preoperative NLR ≥ 2.5 was associated with higher grade of the tumor ($P = 0.003$), lymph nodal stage ($P = 0.02$), higher T stage ($P = 0.02$), presence of LVI ($P = 0.010$), necrosis ($P = 0.004$), and death of the patient ($P = 0.002$).

Researchers have investigated the potential prognostic value of NLR in patients with a wide range of solid malignancies. In patients with upper tract urothelial malignancy, some studies have established the association between NLR and prognosis.^[21-24] It is postulated that tumor progression leads to an increase in the neutrophils, which play crucial role in inducing cytokines that promote tumor progression

or invasiveness. On the other hand, lymphocytes have anti-tumor action, as part of the host immune system. Although the exact mechanism is not clearly understood, it is believed that an elevated NLR is a result of heightened neutrophil activity, which promotes tumor growth, and a reduction in the lymphocytes, which compromises the host's immune system.^[25-27]

A cutoff of 2.38 has been reported for NLR in the published literature for patients with urothelial carcinoma who underwent radical cystectomy, and a similar NLR cutoff (2.38–3.0) has also been reported for patients with bladder cancer.^[24] A cutoff of 2.5–2.7 has been suggested for upper tract urothelial carcinoma.^[23,24] The most effective treatment for localized UTUC is nephroureterectomy and adjuvant chemotherapy has been shown to decrease the likelihood of distant metastasis or recurrence within the bladder in multiple studies. However, the role of neoadjuvant chemotherapy has not been supported by evidence. Previous studies have shown that perioperative chemotherapy improves the OS in patients with pT3/pT4 and pN+ disease but it reduces the CSS for those with pT1 and OS for those with pT2 disease.^[28] Hence, perioperative chemotherapy may be an overkill in patients with low-risk disease, and hence, identifying high-risk patients with a preoperative NLR might help in reducing the over treatment with chemotherapy. Future research might explore the role of NLR as a factor to stratify high-risk patients and to identify those who can benefit from neoadjuvant chemotherapy.

Limitation of our study

There are few limitations of the current study:

- The study was retrospective in design which has its inherent limitations
- NLR may be affected by infection, systemic inflammation, and medication. However, none of the patients in our study had such conditions at the time of the blood test before undergoing a nephroureterectomy
- The sample size was relatively small.

CONCLUSIONS

UTUC is a rare but aggressive tumor of old age with varying presentation and multitude of treatment options depending on the stage and grade of the disease. The pathological factors such as T stage, LVI, and tumor necrosis are independent predictors of survival. Preoperative NLR is an easily available, inexpensive, and a reliable marker in predicting the high-risk disease and correlates with a higher stage, tumor necrosis, presence of LVI, lymph nodal involvement, and requirement of adjuvant chemotherapy. The present study shows the impact of preoperative NLR on the prognosis of patients with UTUC and incorporating NLR in the current risk stratification parameters may help in superior risk stratification as well as management of patients with UTUC.

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