The neutrophil-to-lymphocyte ratio is an effective prognostic marker in localized upper urinary tract urothelial carcinoma treated with nephroureterectomy

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Abstract

Background: Recent studies have revealed that the neutrophil-to-lymphocyte ratio (NLR) is an independent prognostic factor for several types of malignancies including urological cancers. We herein evaluated the significance of NLR in localized upper urinary tract urothelial carcinoma (UUT-UC) treated with surgery.

Methods: A total of 60 patients who underwent radical nephroureterectomy at our institution from 1995 to 2015 were evaluated. The association between preoperative NLR and the prognosis was analyzed.

Results: The higher NLR (≥ 2.43) group showed a significantly poorer overall survival ($p = 0.007$) than the lower NLR group. There was no association between NLR and recurrence-free survival ($p = 0.213$). High-grade tumors tended to show higher NLRs ($p = 0.068$), which significantly correlated with the cancer grade ($p < 0.01$) and muscle invasion ($p = 0.02$). In contrast, the NLR did not correlate with lymph node metastasis ($p = 0.69$). According to a multivariate analysis, the NLR was an independent risk factor for the overall survival ($p = 0.008$, HR $= 12.194$).

Conclusions: Preoperative NLR is therefore considered to be a useful biomarker to predict the prognosis of the patients with UUT-UC treated with radical nephroureterectomy.

Abbreviations: NLR: Neutrophil to Lymphocyte Ratio, UUT-UC: Upper Urinary Tract Urothelial Carcinoma

Background

Upper urinary tract urothelial carcinoma (UUT-UC) accounts for approximately 5% of urothelial cancers [1]. Radical nephroureterectomy is the standard treatment for localized UUT-UC. However, UUT-UC correlates with a high incidence of tumor recurrence and a poor patient outcome. Although the pathological findings, including the tumor size, tumor number, tumor grade, stage, lymph node involvement, and lymphovascular invasion, are thought to be predictors of recurrence [2-5], a new marker that more precisely predicts the prognosis prior to nephroureterectomy is needed to help provide additional treatment, such as neoadjuvant systemic chemotherapy.

Previous studies have shown that inflammation is associated with cancer development and progression. In particular, C-reactive protein as a systemic inflammation marker was reported to be a poor prognostic factor in several types of cancers [6,7]. Others and we have also revealed that neutrophil-to-lymphocyte ratio (NLR) is an independent prognostic factor in various solid malignancies, including renal cell carcinoma, bladder urothelial carcinoma, and prostatic carcinoma [8-13]. Of note, NLR can be easily calculated from complete blood counts (CBCs) in the peripheral blood, and this parameter can be used both pre- and post-operatively. The aim of this study is to evaluate preoperative NLR as a prognostic marker in patients with localized UUT-UC treated with radical nephroureterectomy.

Materials and methods

Patients

A total of 60 Japanese patients treated with radical nephroureterectomy for their UUT-UC in Yokohama City University Hospital (Yokohama, Japan) from December 1998 to July 2015 were enrolled in this study. All these patients had a blood test with CBCs preoperatively. Institutional Review Board of Yokohama City University Hospital approved this study. The tumor grade was determined according to the World Health Organization guidelines 1973 and WHO/ISUP (International Society of Urological Pathology) classification. Pathological T stage was adjusted according to the TNM classification. Postoperatively, patients were followed up every 3

months for 2 years and thereafter every 6 months by both cystoscopy and computed tomography scans.

NLR was calculated using the neutrophil and lymphocyte counts in CBCs obtained a few days before surgery. We determined the cut-off points of NLR based on the sensitivity and specificity levels derived from area under receiver operator characteristic (AUROC) curves plotted for death or disease progression. None of the patients demonstrated systemic inflammation or blood disease at the time of the blood test. Disease recurrence was defined as local tumor development, including development in the lymph nodes, distant metastasis, and recurrence in the bladder. The data is listed in table 1.

Statistical analysis

The patients' characteristics and preoperative factors were analyzed by the Mann-Whitney U and chi-square tests, using the Graph Pad Prism software program (Graph Pad Software, La Jolla, CA, USA). The survival duration was defined as the time between the dates of pathological diagnosis and tumor recurrence or death. A log-rank test was performed for comparisons between higher and lower NLR groups. A multivariate analysis was performed using the SPSS software program (IBM, Chicago, IL, USA). P values of <0.05 were considered to indicate statistical significance.

Results

Patients' characteristics

The patients included 44 males and 16 females. The median age (range) was 70.5 (21-85) years, and the median follow-up duration

Table 1. Baseline patient characteristics

Variables	number (%) or (mean, median)
	all
Number of Pts.	60 (100.0%)
Age (mean, median)	67.8, 70.5
Gender	
Male	44 (73.3%)
Female	15 (35.7%)
Side	
Left	26 (43.3%)
Right	10 (16.7%)
Lymphnode metastasis	
T stage	
is	5 (8.3%)
a	7 (11.7%)
1	16 (26.7%)
2	7 (11.7%)
3	24 (49.0%)
unknown	1 (1.7%)
Low	14 (23.3%)
High	32 (53.3%)
Unknown	16 (26.7%)
Grade1	9 (15.0%)
Grade2	28 (46.7%)
Grade3	21 (35.0%)
Unknown	2 (3.3%)
Recurrence	31 (51.7%)
Bladder	19 (31.7%)
Lung	7 (11.7%)
Liver	4 (6.7%)
Lymphnode	4 (6.7%)
Bone	2 (3.3%)

(range) after surgery was 35 (1-235) months. The characteristics of the patients and the clinicopathologic data, including tumor grade, T stage, and the presence of lymph node metastasis, are summarized in Table 1. During the follow-up period, 31 (51.7%) patients had recurrence, and the median recurrence-free survival (RFS) was 32 months. Of these patients, 19 (31.7%) experienced recurrence as a bladder tumor.

NLR value and patient outcomes

Based on the AUROC curve, the NLR cut-off point was determined to be 2.43 for death (AUROC: 0.690; Figure 1) and 2.35 for recurrence (AUROC: 0.469; figure not shown). A Kaplan-Meier analysis and log-rank test revealed that higher NLR was correlated with a significantly lower overall survival (OS) rate compared with lower NLR (p=0.007; Figure 2). However, no significant differences in the NLRs were noted between the non-muscle invasive and muscle invasive groups (p=0.104 and 0.166, respectively). The association between NLR and RFS was not statistically significant (p=0.213; Figure 3). Moreover, high NLR was significantly correlated with high tumor grade (p = 0.07, low-grade vs high-grade; p < 0.001, G1 vs G2 vs G3), muscle invasion or not (p=0.02), and not significant for lymph node metastasis (p=0.69) (Fig. 4). According to a multivariate analysis, the NLR was an independent risk factor for the overall survival (p = 0.008, HR =12.194) (Table 2).

Discussion

Neutrophils play an important role in inducing cytokines to promote tumor progression or invasiveness, and an increasing number of neutrophils results in tumor progression. On the other hand, lymphocytes have a potential anti-tumor activity in the host immune system. Although the detailed mechanisms remain unclear, an increased NLR is thought to be due to the combination of upgrading of tumor progression by neutrophils and downgrading of the host immune system by lymphocytes [14-16].
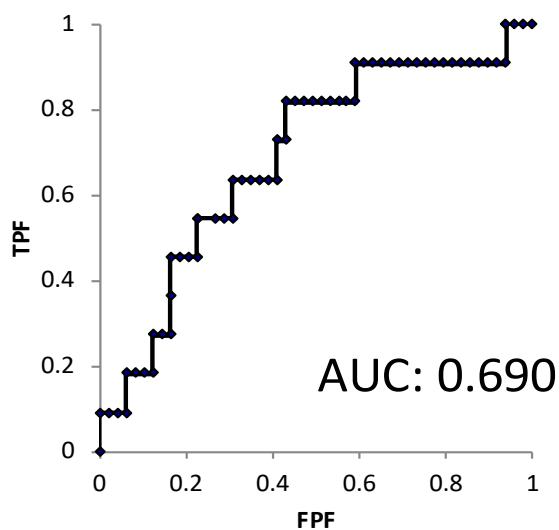
Prognostic significance of NLR in patients with a variety of solid malignancies have been studied. Some of these studies revealed correlations between NLR and prognosis of patients with UUT-UC who underwent nephroureterectomy [17-20]. In urothelial carcinoma, our previous reports showed the cut-off points as 2.38 for the patients who received radical cystectomy and the other reports in bladder cancer showed similar cut-off point (2.38 – 3.0) [11]. For UUT-UC, the cut-off points were 2.5 to 2.7 [19,20]. Our results also supported that data. Consistent with these findings, our results demonstrated that high preoperative NLR strongly correlated with worse patient outcomes. However, no correlations between NLR and tumor invasiveness or lymph node metastasis were identified.

Nephroureterectomy is the gold standard for localized UUT-UC. However, there is currently no consensus on neoadjuvant or adjuvant systemic chemotherapy. Several studies showed that adjuvant chemotherapy reduced the risk of distant metastasis or intra-bladder tumor recurrence. In contrast, there has been no evidence for neoadjuvant chemotherapy. Because of the difficulty in isolating high-risk patients, neoadjuvant chemotherapy may result in overtreatment [21,22]. Meanwhile, NLR can be calculated preoperatively, and a high preoperative NLR may therefore suggest the indication of neoadjuvant chemotherapy.

There are several limitations associated with our study. First, the study was retrospective in nature. Second, NLR may be affected by infection, systemic inflammation and medication, while none of the patients in our study had such conditions at the time of blood test before undergoing nephroureterectomy Third, the sample size was relatively small. So, large study is needed to conclude the results.
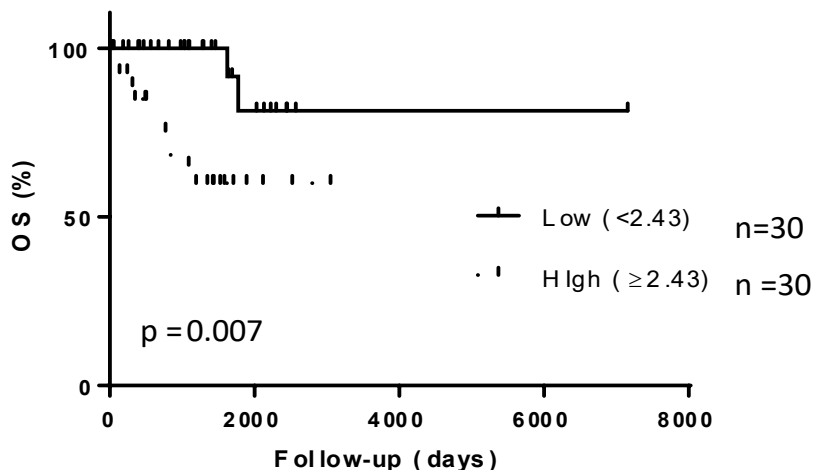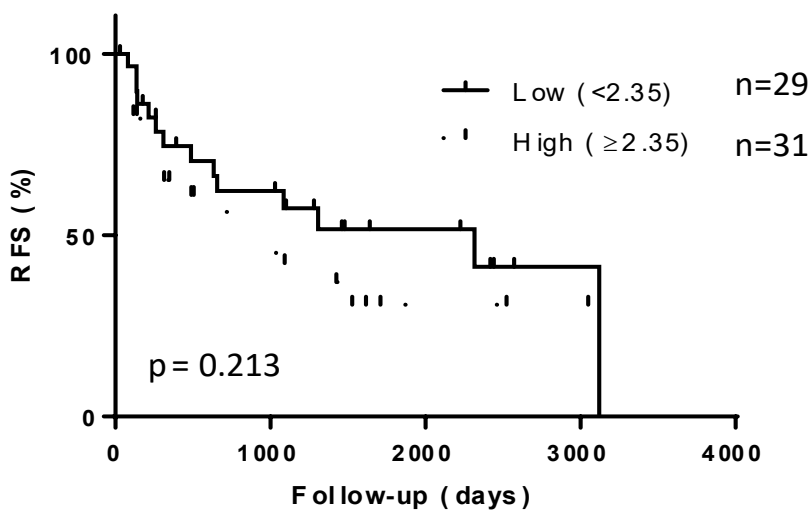
The AUROC of NLR (AUROC:0.690). The NLR cut-off point was determined to be 2.43 for death.

Figure 1. The AUROC of NLR.

The association of NLR with OS. Higher NLR was correlated with a significantly lower OS rate compared with lower NLR.

Figure 2. The association of NLR with overall survival.

The association of NLR with RFS. The association between NLR and RFS was not statistically significant.

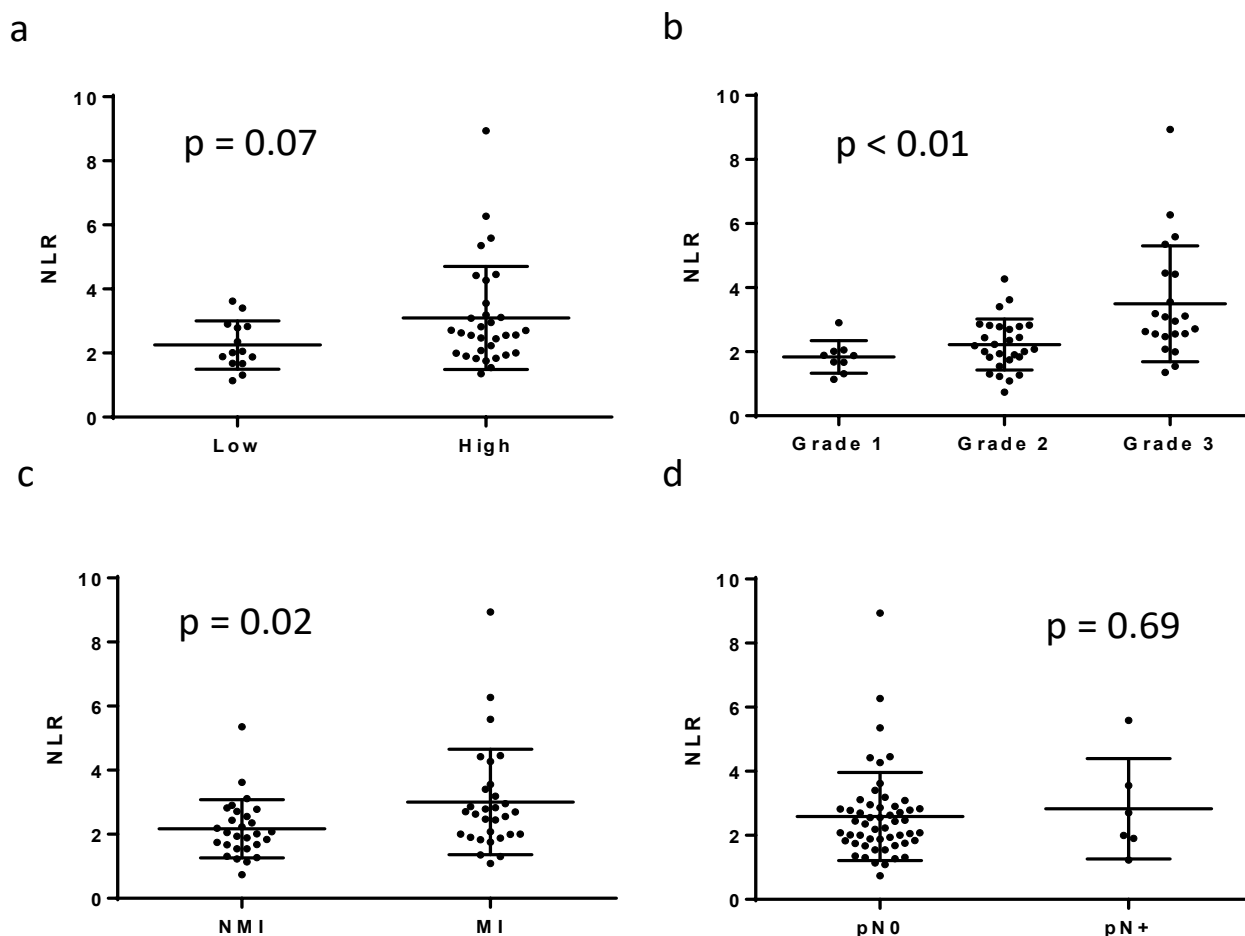**Figure 3.** The association of NLR with recurrence-free survival.

Figure 4. NLR and clinicopathological features, including tumor grade (a, b), muscle invasiveness (c), and lymph node metastasis (d).

Table 2. Multivariate analysis

	P value	HR	98%CI
Gender (male)	0.371	0.687	0.121-3.894
Age (>70)	0.050	0.190	0.036-1.000
NLR (≥2.43)	0.008	12.194	1.930-77.056
Muscle invasive	0.404	1.903	0.420-8.630
pN+	0.029	6.398	1.208-33.894

In conclusion, NLR is a potential biomarker to predict the survival in UUT-UC patients who have undergone radical nephroureterectomy. Patients with high preoperative NLR are suggested to be candidates for additional chemotherapy pre- and/or post-operatively.

Authors' contributions

Conceived and designed the experiments: MO, TK, HI, SK, MS, KM ,YY, HM, HU. Performed the experiments: TM, HI, YH, JT, YM. Wrote the paper: MO, TK, HM, MY, HU. All authors have read and approved the manuscript

Availability of supporting data

Due to ethical restrictions, the raw data underlying this paper is available upon request to the corresponding author.

Funding declaration

Institutional Review Board of Yokohama City University Hospital approved this study.

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