Prognostic Role of Neutrophil-to-lymphocyte Ratio-based Markers During Pre- and Postadjuvant Chemotherapy in Patients With Advanced Urothelial Carcinoma of Upper Urinary Tract

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Abstract

Despite the prognostic significance of neutrophil-to-lymphocyte ratio (NLR)-based markers, such as the NLR and derived NLR, in patients with various malignancies receiving systemic chemotherapy, no reports have been published on the prognostic role of these markers in late-stage urothelial carcinoma of the upper urinary tract treated with adjuvant chemotherapy. We found that a higher derived NLR after adjuvant chemotherapy was independently predictive of poor survival outcomes in patients with advanced urothelial carcinoma of the upper urinary tract receiving systemic adjuvant chemotherapy after radical nephroureterectomy.

Purpose: The aim of the present study was to assess the prognostic significance of neutrophil-to-lymphocyte ratio (NLR)-based markers before and after adjuvant chemotherapy (ACH) in patients with urothelial carcinoma of the upper urinary tract (UTUC) undergoing radical nephroureterectomy (RNU) and ACH. **Materials and Methods:** The data from 112 patients with advanced UTUC who had undergone first-line ACH after RNU from 1994 to 2012 were reviewed. After excluding 22 patients, the clinicopathologic data for 90 patients were analyzed, in particular, the NLR and derived NLR (dNLR) preoperatively and before and after ACH. Cancer-specific survival (CSS) and overall survival (OS) outcomes were measured using Kaplan-Meier analysis. To identify the predictors for the oncologic outcomes, a multivariate Cox regression model was used. **Results:** Patients with a higher preoperative NLR, pre-ACH dNLR, and post-ACH dNLR had poorer CSS and OS than their counterparts with lower values. After adjustment of various clinicopathologic factors, age at surgery ($\geq$ 65 years; hazard ratio [HR], 3.13) and higher post-ACH dNLR (HR, 3.06) remained significant predictors for CSS. Similarly, age ($\geq$ 65 years; HR, 2.90) and elevated post-ACH dNLR ($\geq$ 2.3; HR, 2.89) were also identified as predictors of OS on multivariate analysis. **Conclusion:** A higher post-ACH dNLR was independently predictive of poor CSS and OS in patients with advanced UTUC receiving systemic ACH after RNU. From the obtained data, we propose that the NLR-based marker could be a readily available and valuable biomarker for predicting oncologic outcomes after chemotherapy.

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Introduction

The incidence of upper tract urothelial carcinoma (UTUC) is relatively low, comprising only 5% to 10% of all urologic malignancies.[1] However, UTUC has been considered an immense clinical issue owing to its aggressive nature, resistance to therapy, and worse prognosis, with an approximately 20% 5-year survival rate.[2] Radical nephroureterectomy (RNU) with bladder cuff excision is the standard treatment option for patients with localized UTUC.[3] For some patients with advanced-stage UTUC, the current guidelines

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Table 1 Patient Demographics

Variable	n (%)
Patients	90
Age (y)	
Median	62
Interquartile range	54-68
Gender	
Male	67 (74.4)
Female	23 (25.6)
BMI (kg/m^2)	
Median	24.41
Interquartile range	21.92-26.35
NLR	
Preoperative	
Median	2.31
Interquartile range	1.65-3.15
Before ACH	
Median	2.17
Interquartile range	1.66-3.02
After ACH	
Median	1.63
Interquartile range	1.40-2.27
dNLR	
Preoperative	
Median	1.54
Interquartile range	1.24-2.18
Before ACH	
Median	1.46
Interquartile range	1.20-2.04
After ACH	
Median	1.26
Interquartile range	1.03-1.63
Bladder cancer history	
Absent	74 (82.2)
Previous or concurrent	16 (17.8)
Pathologic T stage	
≤pT2	10 (11.1)
≥pT3	80 (88.9)
Tumor grade	
Low	5 (5.6)
High	85 (94.4)
LVI	37 (41.1)
Concomitant CIS	11 (12.2)
Hydronephrosis	53 (58.9)
Multifocality	19 (21.1)
Tumor location	
Pelvis	36 (40.0)
Ureter	34 (37.8)
Both	20 (22.2)
Positive surgical margin	11 (12.2)
Pathologic N stage	
pNx-N0	79 (87.8)
pN1-N2	6 (6.7)
pN3	5 (5.6)
Chemotherapy regimen	
G-cisplatin	
Patients	67 (74.4)
Cycles (median; range)	4 (1-9)
G-carboplatin	
Patients	13 (14.4)
Cycles (median; range)	4 (2-6)
G-cisplatin and G-carboplatin	
Patients	4 (4.4)
Cycles (median; range)	6 (2-14)
MVAC	
Patients	2 (2.2)
Cycles	4 only
Other	
Patients	2 (2.2)
Cycles	1 only
Unknown	2 (2.2)
Intravesical recurrence	27 (30.0)
Mortality	
All cause	43 (47.8)
Disease specific	39 (43.3)

Abbreviations: ACH = adjuvant chemotherapy; BMI = body mass index; CIS = carcinoma in situ; dNLR = derived neutrophil-to-lymphocyte ratio; G = gemcitabine; LVI = lymphovascular invasion; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NLR = neutrophil-to-lymphocyte ratio.

recommend systemic adjuvant chemotherapy (ACH) to improve the long-term prognosis.[4] However, certain patients might experience disease recurrence and progression of advanced-stage UTUC to distant metastases, finally resulting in death from UTUC aggravation.[5] To achieve better oncologic outcomes, it is crucial to accurately estimate the prognosis and select appropriate patients for further salvage treatment according to the risk classification.[6]

Among the many pretreatment predictive factors, systemic inflammatory response (SIR) markers reflect a complex interplay between the tumor microenvironment and host immune defense system and have received a great amount of attention.[7] In particular, the neutrophil-to-lymphocyte ratio (NLR) in the blood has been identified as a major prognosticator in several types of malignancies. For instance, a recent meta-analysis of data from 16 studies showed that a higher pretreatment NLR was associated with poorer survival outcomes in patients with colorectal cancer.[8] For patients with hepatocellular carcinoma, a meta-analysis of 90 studies, including 20,475 patients, demonstrated that a lower baseline NLR independently predicted for better survival outcomes.[9] Moreover, UTUC patients, who underwent surgery with a higher preoperative NLR, also had poor survival outcomes compared with those with a lower NLR in the study by Dalpiaz et al.[10]

Because systemic chemotherapy can influence the host immune status by bone marrow suppression,[11] NLR status might