Are Preoperative Systemic Immune Index and Neutrophil-to-Lymphocyte Ratio Sufficient to Predict Lymph Node Positivity and Overall Survival in Muscle-Invasive Bladder Cancer Cases?

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––––––––––––––––––––––––––––––––– Abstract –––––––––––––––––––––––––––––––––

Aim: The neutrophil-lymphocyte ratio (NLR) is a parameter that has been shown to be effective as a prognostic marker in many solid tumors. It is aimed to investigate NLR and the systemic immune-inflammation index (SII) in predicting the overall survival and lymph node positivity in bladder cancer (BC).

Methods: The retrospective study included patients that underwent radical cystoprostatectomy/radical cystectomy (RC) due to muscle-invasive bladder cancer (MIBC), high-grade T1 BC, or carcinoma *in situ* in our clinic between January 2010 and March 2020. All the patients had no history of preoperative metastasis, lymph nodes, chemotherapy, hematological malignancies, and preoperative urinary tract infection. Data on neutrophil, lymphocyte, platelet, and hemoglobin levels and total white blood cell counts were retrieved from clinical records and data on disease stage and lymph node positivity were retrieved from pathology reports. Follow-up times and survival times were recorded.

Results: The 213 patients comprised 196 (92%) men and 17 (8%) women with a mean age of 63.17±11.25 years. Lymph node positivity was detected in 49 (23%) patients. The mean overall survival time was 75.04, 63.77, and 84.4 months in all patients, patients with lymph node positivity, and patients with lymph node negativity, respectively. No significant difference was found between patients with lymph node positivity and negativity with regard to NLR and SII values (p=0.975 and p=0.745, respectively). In the receiver operating characteristics (ROC) analysis NLR and SII had no significant effect in predicting lymph node positivity [Area under the ROC curve (AUC) 0.499 (95% confidence interval (CI): 0.403-0.594) and AUC 0.485 (95% CI: 0.394-0.575), respectively] and in predicting overall survival [AUC 0.423 (95% CI: 0.346-0.501, p=0.056) and AUC 0.435 (95% CI: 0.357-0.514, p=0.107), respectively].

Conclusion: The results indicated that SII and NLR are not sufficient to predict lymph node positivity and survival in patients with organ-confined BC.

Keywords: Bladder cancer, neutrophils, lymphocytes, lymph nodes, systemic immune-inflammation index

Introduction

Bladder cancer (BC) is among the most frequently seen cancers in the world, ranking the 7th most common cancer in men and 11th in women (1). In Turkey, BC is the 4th most common cancer in men and 13th in women (2). At the time of diagnosis, 70-75% of the cases are non-muscle invasive bladder cancer (NMIBC). In the first five years after diagnosis, 50-70% of NMIBC cases will recur. On the other hand, 10-15% of NMIBC cases progress to muscle-invasive bladder cancer (MIBC) and approximately 25% of BC cases are MIBC at the time of diagnosis. The five-year survival rate in MIBC is only 50% (3,4). Radical cystectomy (RC) is the most effective treatment in MIBC. Regardless, some patients may recur. Therefore, neoadjuvant chemotherapy

is recommended particularly in patients with T2-T4a, N0M0 tumors in order to increase overall survival and disease-free survival. Nevertheless, this therapy has been shown to provide positive contributions only to overall survival (5). To our knowledge, there are no reliable indicators showing patient suitability for neoadjuvant chemotherapy and/or patient prognosis after cystectomy.

Accumulating evidence suggests that immune response cells (monocytes, lymphocytes, and neutrophils) and platelets along with their associated signaling pathways are an important component of the tumor microenvironment and that these factors can play a significant role in tumor progression and metastasis (6). In particular, the effectiveness of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein-to-albumin (CRP/ALB) ratio in predicting recurrence and life expectancy has been investigated (7-9). These studies have shown that the systemic immune-inflammation index (SII), which is calculated by multiplying the NLR ratio by the number of platelets, has a prognostic value in solid tumors such as gastric and colorectal esophageal tumors and also in BC. The role of NLR and SII in predicting the prognosis of prognosis BC is already known (10-14). Also, higher SII was shown to be related to prostate cancer with a high Gleason score (15). Moreover, lymph node positivity is known as an indicator of poor prognosis in BC (3).

In this study, we aimed to determine whether NLR and SII values are effective in predicting the overall survival and lymph node positivity in BC.

Methods

This retrospective study was approved by Erciyes University Medical School Clinical Research Ethics Committee (date: June 10, 2020; no: 220/273). Patients with complete follow-up data and who underwent radical cystoprostatectomy/RC due to MIBC, high-grade T1 BC, or carcinoma in situ in our clinic, between January 2010 and March 2020 were evaluated retrospectively. Patients whose age was between 18-85 years old, who had no solid organ and lymph node metastasis on preoperative imaging [computed tomography (CT), magnetic resonance imaging (MRI), or positron emission CT (PET-CT)], without history of bladder sparing protocol and without the indication of salvage cystectomy due to conditions such as hematuria and postrenal acute renal failure, without a known history of hematological malignancies, neoadjuvant chemotherapy within the last one month and preoperative diagnosis of cystitis/pyelonephritis were included. Having the known history of hematological malignancies and neoadjuvant chemotherapy, having indication for salvage cystectomy due to persistent symptoms of BC despite

chemotherapy performed according to the bladder-sparing protocol, being below 18 years old and above 85 years old, having preoperative diagnosis of cystitis and/or pyelonephritis were settled as exclusion criteria.

In all patients included in the study, data on neutrophil, lymphocyte, platelet, and hemoglobin levels and total white blood cell counts were retrieved from clinical records and data on disease stage and lymph node positivity were retrieved from pathology reports. NLR and SII values were calculated as previously described in the literature (14). Follow-up durations and overall survival times were calculated from follow-up data. Overall survival was defined as the time from surgery to death. The 2017 TNM classification was used for tumor staging (16). Informed consent was obtained from each patient.

Statistical Analysis

Data were analyzed using SPSS for Windows version 22 (Armonk, NY: IBM Corp.). The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean ± standard deviation median and continuous variables with nonnormal distribution were expressed as median (25th-75th percentile). Categorical variables were expressed as frequencies (%). Continuous variables with nonnormal distribution were compared using the Mann-Whitney U test. The prognostic values of NLR and SII in predicting lymph node positivity were calculated using the area under the receiver operating characteristics (ROC) curve (AUC).

Results

Of the 475 patients evaluated, 213 patients that met the inclusion criteria were included in the study. These patients comprised 196 (92%) men and 17 (8%) women with a mean age of 63.17±11.25 years. Lymph node positivity was detected in 49 (23%) patients, while no surgical margin positivity was present in any patient (Table 1).

No significant difference was found between patients with lymph node positivity and negativity with regard to NLR and SII values (p=0.975 and p=0.745, respectively). In the ROC analysis that was performed to evaluate the effectiveness of NLR and SII in predicting lymph node positivity, the AUC value for NLR and SII was 0.499 [95% confidence interval (CI): 0.403-0.594 and 0.485 95% CI: 0.394-0.575], respectively. These values indicated that NLR and SII had no effect in predicting lymph node positivity (Table 2, Figure 1).

The mean overall survival time was 75.04, 63.77, and 84.4 months in all patients, patients with lymph node positivity, and patients with lymph node negativity, respectively. No significant difference was found between patients with lymph node positivity and negativity with regard to overall survival (p=0.227). In contrast, the

Table 1. Characteristics of patients

Variables	(n=213)
Age (years)	63.17±11.25
Sex	
Male Female	17 (8%) 196 (82%)
Pathological stage (n, %)	
T0 Tis Ta T1 T2a T2b T3a T3b T4a T4b	12 (5.6%) 5 (2.3%) 7 (7.3%) 22 (10.3%) 8 (3.8%) 68 (31.9%) 38 (17.8%) 36 (36%) 14 (6.6%) 2 (0.9%)
Type of the urinary diversion applied	
Cutaneous incontinent urinary diversion Orthotopic bladder	146 (69%) 67 (31%)
Follow up in month	29.9 (12.7-78.4)*
5 year survival (n, %)	74/213 (34.7%)
Overall survival with 95% CI	75.04 (63.22-86.85)
*Median (25th-75th percentile) CI: Confidence interval	

Table 2. Comparison of SII, NLR and survivals according to lymph node status

	Lymph node positive (n=49)	Lymph node negative (n=164)	p
NLR	2.57 (1.87-3.69)*	2.67(2.04-3.52)	0.975**
SII	700 (474.9-876.5)	678.5(502.1-1025.1)	0.745**
5 year survival rate	10/49 (20.4%)	64/164 (39.0%)	0.016***
Overall survival	63.77 (29.32-98.21)	84.40 (72.13-96.66)	0.227***
*Median (25th-75th percentile) **The Mann-Whitney U test ***Chi-square, SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio,			

Figure 1. ROC curve for lymph node invasion
ROC: Receiver operating characteristics, SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio

Figure 2. ROC curve for overall survival
ROC: Receiver operating characteristics, SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio

mean five-year survival rate was 34.7%, 20.4%, and 39%, respectively, and a significant difference was found between patients with lymph node positivity and negativity (p=0.016). In the ROC analysis performed to evaluate the effectiveness of NLR and SII in predicting survival, the AUC value was 0.423 (95% CI: 0.346-0.501, p=0.056) and 0.435 (95% CI: 0.357-0.514, *p*=0.107), respectively. Accordingly, NLR and SII were found to have no significant effect in predicting survival (Figure 2,3).

Discussion

The present study investigated the effect of NLR and SII in predicting lymph node positivity, which is inflammatory indicators calculated from preoperative blood parameters, in patients who underwent RC due to clinical T1/T2 N0M0
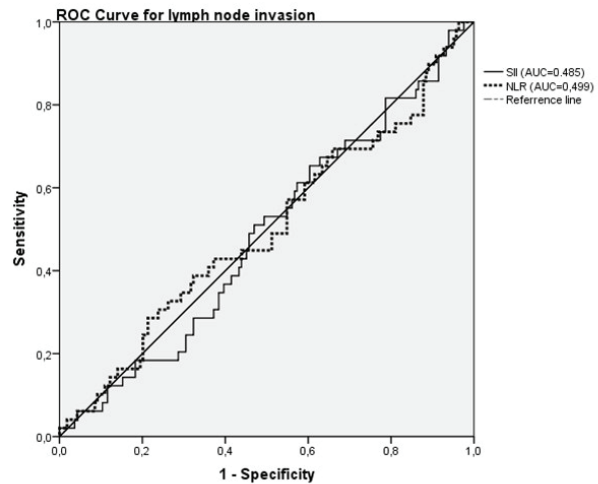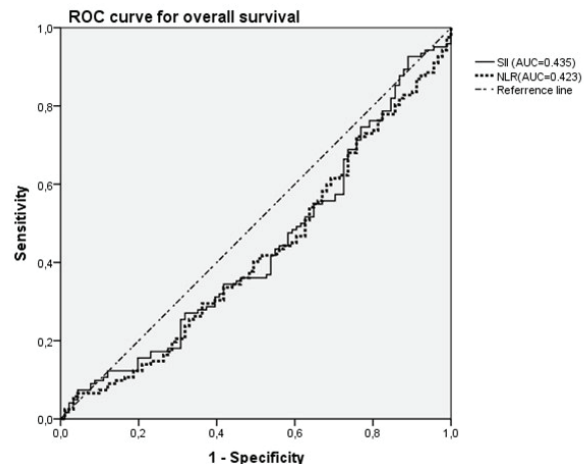
MIBC. The median follow-up period was 29.9 months. Although no significant difference was found between patients with lymph node positivity and negativity with regard to overall survival time (63.77 and 84.4 months, respectively) (p=0.227), the five-year survival rate was higher in patients with lymph node negativity (p<0.05). No significant difference was found between the two groups with regard to NLR and SII values (p=0.975 and p=0.745, respectively). Moreover, ROC analysis indicated that NLR and SII had no effect in predicting lymph node positivity and overall survival. To our knowledge, our study is the first of its kind to show that SII and NLR have no significant effect in predicting lymph node positivity in patients with MIBC.
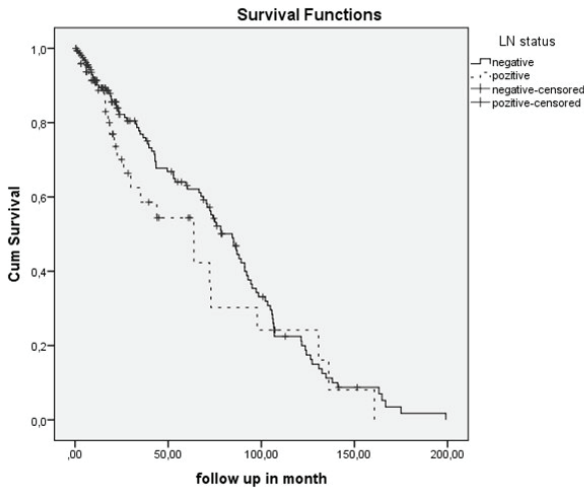
Figure 3. Overall survival according to lymph node (LN) status-Kaplan-Meier curve

Gorgel et al. (13) evaluated a cohort of 191 patients who underwent RC and reported that SII values greater than 843 were cancer-specific and indicated a poor overall survival. However, the authors did not state whether they only included organ-confined MIBC. Additionally, the authors did not perform an analysis regarding the prediction of lymph node positivity (13). Similarly, Zhang et al. (14) evaluated a patient series of 209 patients that were randomized into primary (n=139) and validation (n=70) cohorts and reported that SII is an independent factor in predicting overall survival and is more effective than NLR. However, the researchers examined the effect of SII and NLR only in predicting overall survival. Similarly, the authors did not state whether they only included organ-confined MIBC (14). Bi et al. (17) found that peripheral nutritional index (PNI) and SII are independent factors in predicting overall survival in high-risk pT1 patients. Nevertheless, the group analyzed in that study consisted of 387 patients who received intracavitary Bacillus Calmette-Guérin (BCG) treatment due to high-risk pT1, and only 42 of the patients underwent RC. Accordingly, this patient group had a better prognosis when compared to the patients evaluated in the present study (17). In a retrospective study, Peng et al. (18) evaluated 516 patients who underwent RC and reported that PNI and NLR were independent factors in predicting overall survival and progression-free survival. In that study as well, the authors did not state whether they only included patients with organ-confined MIBC, and they performed no evaluation regarding the role of the investigated indicators in predicting lymph node positivity (18).

Study Limitations

The main limitations of this study were its retrospective manner and including highly selected small group of patients. The present study only included patients with organ confined MIBC and aimed to seek an answer to the following question: "If SII and NLR are effective parameters in predicting lymph node positivity, can they be used to determine candidate patients for neoadjuvant chemotherapy?". Nonetheless, the results indicated that SII and NLR had no significant effect in predicting lymph node positivity and overall survival in this patient group. We consider that this finding could be attributed to the inclusion of a highly selected patient group in our study. However, to our knowledge, it is the first study in the literature to investigate the role of SII and NLR in predicting lymph node positivity. Also with respect to the prognosis of BC, the data about cancer specific survival could not be given in this study due to incomplete data entry about reason of death.

Conclusion

From the results obtained from this study it can be concluded that SII and NLR are not sufficient to predict lymph node positivity and survival in patients with organ-confined BC. However, these results should be confirmed in prospective studies with larger cohort.

Authorship Contributions

Concept: S.T.T., A.D., Design: S.T.T., A.D., Data Collection or Processing: S.T.T., G.S., Analysis or Interpretation: S.T.T., G.S., T.D., Literature Search: S.T.T., G.S., T.D., Writing: S.T.T., A.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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