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ORIGINAL ARTICLE

Can the neutrophil-to-lymphocyte ratio be used to predict recurrence and progression of non-muscle-invasive bladder cancer?

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Abstract The aim of our study was to evaluate whether neutrophil-to-lymphocyte ratio (NLR) is a predictor of disease progression and recurrence in patients with primary non-muscle-invasive bladder cancer (NMIBC). This was a prospective study of 86 patients with newly diagnosed NMIBC. The patients were classified by the number of points assigned by the European Organization for Research and Treatment of Cancer risk tables. The correlation between progression score, recurrence score, age, mean platelet volume, red blood cell distribution width and NLR was assessed statistically. The same parameters were compared between the risk groups. A significant difference in NLR and age values was observed between recurrence and progression risk score groups. The relationships between NLR and recurrence and progression risk scores were no longer significant after correcting for the statistical effect of age on scores. Age was significantly different between groups after adjusting for NLR. Our study revealed that NLR and age were associated with patient age and bladder tumor progression and recurrence risk scores. After correcting for age, the significant relationship with NLR was lost, in contrast to some previous studies. We recommend that patient age should be corrected to avoid misleading results in NLR studies.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

The overall incidence of urinary bladder cancer (BC) was about 429,200 cases in 2012. Most (75%) BC is non-muscle invasive (NMI) at the first diagnosis [Ta, T1, and carcinoma *in situ* (CIS)] and usually has a good prognosis. Between 30% and 80% of cases will relapse as NMI tumors and 1–45% will progress to muscle invasion (MI) within 5 years [1–3]. The difficulty of treating non-muscle-invasive bladder cancer (NMIBC) is to protect the bladder and its function for as long as possible, accepting the risk of recurrence while minimizing the possibility of progression to muscle-invasive disease. The European Organization for Research and Treatment of Cancer (EORTC) risk stratification can be used to measure these risks [1,3]. The aim has been to divide patients into risk groups of good, intermediate, and poor prognosis. After transurethral resection of bladder tumor (TURBT) and one immediate instillation of chemotherapy, treatment can be modified according to the patient's prognosis. Patients with a good prognosis receive either no more instillations or intravesical chemotherapy. The treatment of choice for poor prognosis patients is Bacillus Calmette–Guérin with maintenance. Treatments for intermediate-risk patients are controversial [4].

According to recent theories, the systemic inflammatory response induced by cancer causes relative neutrophilia and lymphocytopenia, producing a protumor inflammatory state [5]. The neutrophil-to-lymphocyte ratio (NLR), as a marker of the systemic inflammatory response, has been studied as a valuable prognostic biomarker in various types of tumors including BC [6–8]. Among patients with BC, a high NLR is related to muscle-invasive disease, extravesical disease, and poorer cancer-specific and overall survival [8–12]. Nonsteroidal anti-inflammatory drugs have been suggested to decrease the risk of evolving BC by 19%, suggesting a critical correlation between BC and inflammation [13]. Mean platelet volume (MPV) is also related with the pathophysiological characteristics of various types of cancer and inflammation [14,15]. Red blood cell distribution width (RDW) is a strong predictor of all-cause mortality, including cancer-related death and cancer progression [16,17].

The aim of our study was to evaluate whether NLR is a predictor of disease progression and recurrence in patients with primary NMIBC.

Methods

Study population

This was a prospective study of 86 patients with newly diagnosed NMIBC (72 men and 14 women) who presented consecutively at the Urology Clinic of Bozok University Research Hospital, Yozgat, Turkey. We selected patients using our laboratory information system database to retrieve data regarding NLR, RDW, hemoglobin, MPV, and age. Clinical and pathological data were recorded. The NLR ratio was calculated using the neutrophil and lymphocyte values obtained from the complete blood counts. Patients with newly diagnosed urothelial carcinoma underwent TURBT at a single institute between 2010 and 2014. These patients were followed up until September 2015. The study data were collected from 2010 to 2015. All specimens were reviewed by a pathologist, and the urothelial carcinoma of the bladder diagnosis was confirmed. Tumors were staged according to the 2002 American Joint Committee on Cancer TNM (tumor–node–metastasis) staging system [18], and graded according to the 1973 World Health Organization grading system [19].

The patients were classified by the number of points assigned by the EORTC risk tables. Patients with a progression risk score of 0, 2–6, 7–13, and $>$ 13 were categorized as Group 1, 2, 3, and 4, respectively. Furthermore, scores of 0, 2–6, and $>$ 6 were considered low, intermediate, and high risk for progression, respectively, according to the European Association of Urology (EAU) guidelines. Patients with a recurrence risk score of 0, 1–4, 5–9, and $>$ 9 were Groups 1, 2, 3, and 4, respectively. Similarly, 0, 1–9, and $>$ 9 were low, intermediate, and high risk of recurrence, respectively according to the EAU guidelines [20].

A second TURBT was routinely performed in patients who had a T1 tumor or the important risk of residual tumor after the first TURBT of Ta or G3 tumor in initial TURBT. Patients received postoperative intravesical instillations based on tumor characteristics, and according to the choice of the treating urologist. Maintenance chemotherapy or immunotherapy was administered to medium- and high-risk patients according to the selection of treating urologist. Postoperative follow-up was designed according to EAU guidelines and the selection of the treating urologist, for instance, high-risk patients underwent cystoscopy every 3 months for 2 years, and every 6 months in the following years. Low-risk patients were monitored after 3 months, and if the result was negative, the next cystoscopy was planned for 9 months and subsequently once yearly [3]. Recurrence of bladder tumor was defined as the first histologically confirmed tumor relapse in the bladder, regardless of its stage. Progression of bladder tumor was defined as an advance in T category from CIS or Ta to T1 (invasion), development of T2 or an increase in grade of tumor from low to high [21]. The study endpoints were defined as immunotherapy requirement or T2 disease. The follow-up average was 29 months.

This study was approved by the Institutional Ethics Committee of Bozok University. The correlation between progression score, recurrence score, patient age, MPV, RDW, and NLR was assessed statistically. Similar parameters were compared between the recurrence and progression risk groups.

Statistical analysis

Shapiro–Wilk's and Levene's tests were used to test for normality and homogeneity of the data. Values are expressed as frequencies and percentages, mean ± standard deviation, or median and 25–75th percentiles. Student *t* test and one way analysis of variance were used to compare parametric continuous variables, and the Mann–Whitney *U* test was used to compare nonparametric continuous variables. Categorical data were compared using the χ^2 distribution. Pearson's test was used for the correlation analysis. A multiple linear regression model was