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Original article

Prognostic significance of markers of systemic inflammatory response in patients with non–muscle-invasive bladder cancer

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Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) and the C-reactive protein (CRP) are markers of systemic inflammatory response, which have been associated with the prognosis of multiple malignancies, but their relationships with oncologic outcomes of non–muscle-invasive bladder cancer (NMIBC) have not been well studied yet.

Patients and methods: We retrospectively reviewed the medical records of 1,117 patients with NMIBC who underwent a transurethral resection of the bladder. Univariable and multivariable competing risk regression models were used to assess the association of preoperative NLR and CRP with disease recurrence and progression to muscle-invasive disease. The median follow-up was 64 months.

Results: In total, 360 patients (32.2%) had a high NLR ($\geq$2.5) and 145 (13.0%) had a high CRP ($\geq$5 mg/l). On multivariable analyses, a high NLR was associated with both disease recurrence (subhazard ratio [SHR] = 1.27, P = 0.013) and progression (SHR = 1.72, P = 0.007), and high CRP was associated with disease progression (SHR = 1.72, P = 0.031). Adding NLR and CRP to the multivariable model predicting disease progression lead to a relevant change in discrimination (+2.0%). In a subgroup analysis of 300 patients treated with bacillus Calmette-Guerin, both high NLR and high CRP were associated with disease progression (SHR = 2.80, P = 0.026 and SHR = 3.51, P = 0.021, respectively), and NLR was associated with disease recurrence (SHR = 1.46, P = 0.046). There was also an increase in the discrimination of the model predicting progression after bacillus Calmette-Guerin following the inclusion of both markers (+2.4%).

Conclusion: In patients with NMIBC, markers of systemic inflammation response are associated with disease recurrence and progression. The inclusion of such markers in prognostic models does enhance their accuracy. © 2016 Published by Elsevier Inc.

Keywords: Biomarker; Prediction; Prognosis; BCG; Guideline; Response; Progression

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1. Introduction

Approximately 75% of patients with newly diagnosed bladder cancer have non–muscle-invasive disease (NMIBC) [1] are usually treated with transurethral resection of the bladder (TURB) and instillation therapies according to guidelines [2]. However, more than half of patients experience disease recurrence and up to 45% experience disease progression to a muscle-invasive stage within a 5-year period [3–6]. Several prognostic models have been proposed to guide management and follow-up of patients with NMIBC [3,7,8]; however, these tools have a limited accuracy for predicting both disease recurrence and progression [9]. Therefore, there is a need for improving the accuracy of these models by incorporating valuable prognostic and predictive biomarkers.

The role of the immune system and inflammatory response against cancer has been widely investigated. Through the secretion of various cytokines such as tumor necrosis factor alpha and interleukin 6, tumors modulate their environment to enable their growth and proliferation [10,11]. The local and systemic inflammatory response can be monitored by cheap and routinely used biomarkers such as the C-reactive protein (CRP) and the differential blood cell count. Among these factors, several studies have demonstrated that a high neutrophil-to-lymphocyte ratio (NLR) is significantly associated with outcomes of various types of cancers [12–14]. In NMIBC, a small retrospective study showed that NLR may be an independent prognostic factor for disease recurrence and progression [15]; it was, however, hampered by its small number of patients. Likewise, a high CRP has been associated with worse clinical outcomes in bladder cancer [16]. Taken together, both NLR and CRP could be useful biomarkers for improving the risk stratification of NMIBC, thereby potentially facilitating adequate patient care. The aim of this study was to evaluate the association between NLR and CRP with oncologic outcomes in a multicenter cohort of patients with NMIBC.

2. Material and methods

2.1. Patient selection and collection of data

A total of 4 international institutions were involved in this retrospective IRB-approved study. We screened 1,578 patients who underwent a TURB between 1996 and 2007 for NMIBC for study inclusion. Patients who had a concomitant malignancy ($n = 21$), hematological disorders ($n = 17$), a history of radiation ($n = 8$), a concomitant infection or chronic inflammatory diseases ($n = 137$), a missing preoperative differential blood cell count and/or a missing CRP ($n = 207$), a preoperative differential blood cell count and/or CRP performed more than 7 days before surgery ($n = 28$) or patients with missing data on stage and grade ($n = 43$) were excluded. A total of 1,117 patients were finally analyzed (Fig. 1).

The following data were collected by medical record review and entered into a database: age, sex, smoking status, number of prior TURB, tumor stage, grade, numbers of tumors, tumor size, NLR, CRP, recurrence-free survival (RFS), and progression-free survival (PFS). A computerized database was generated at each center. After merging the datasets, reports were created for each variable and inconsistencies and data integrity problems were resolved before analysis.

2.2. Management

All patients had a complete TURB according to guideline recommendations. A second-look TURB was not routinely performed. Intravesical therapy was administered at the discretion of the treating physician. A total of 145 patients (13.0%) received single immediate postoperative instillation of mitomycin C, 48 (4.2%) received adjuvant mitomycin C, and 300 (26.9%) received adjuvant bacillus Calmette-Guerin (BCG). Patients generally received their first adjuvant instillation between 7 and 21 days after TURB, and repeat once a week for 6 weeks.

The postoperative follow-up was institution dependent and usually included a physical examination, a urinary cytology and a cystoscopy every 3 months in the first 2 years after surgery, then every 6 months for 3 years, and then annually. Upper urinary tract imaging was performed once a year after diagnosis. Patients who had a positive urinary cytology without bladder lesion at the cystoscopy also underwent an upper urinary tract imaging combined with mapping bladder biopsies and prostatic urethra resections. Patients with suspected disease recurrence underwent a new TURB. Disease recurrence was defined as the first tumor relapse in the bladder regardless of tumor stage. Disease progression to muscle-invasive bladder cancer (MIBC) was defined as tumor relapse at tumor stage T2 or higher. Upper urinary tract tumors were considered as new primary tumors, not as recurrence. The cause of death was determined by the treating physician or medical record review and confirmed by death certificates [17].

2.3. Pathological evaluation

All surgical specimens were processed according to standard pathologic procedures by genitourinary pathologists in each participating institution. Pathological stage was assigned according to the 2009 American Joint Committee on Cancer TNM staging system [18] and tumor grade according to the 1973 World Health Organization grading system [19].

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