



Bladder Cancer

The Neutrophil-to-lymphocyte Ratio as a Prognostic Factor for Patients with Urothelial Carcinoma of the Bladder Following Radical Cystectomy: Validation and Meta-analysis

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Article info

Article history:

Accepted March 12, 2015

Associate Editor:

James Catto

Keywords:

Neutrophil-to-lymphocyte ratio
Radical cystectomy
Urothelial carcinoma of the bladder
Meta-analysis
Survival

Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) as a marker of systemic inflammatory response has been proposed as a prognostic factor for patients with urothelial carcinoma of the bladder (UCB) following radical cystectomy (RC).

Objective: To validate NLR as a prognostic biomarker and to perform a pooled meta-analysis. **Design, setting, and participants:** The NLR was assessed in 4061 patients within 30 days before RC. A systematic review of the literature was undertaken using electronic databases.

Outcome measurements and statistical analysis: Associations with overall survival (OS) and cancer-specific survival (CSS) were evaluated using Cox models. Hazard ratios (HRs) were pooled in a meta-analysis using random-effects modeling.

Results and limitations: A high NLR (≥ 2.7) was associated with advanced pathological tumor stages ($p < 0.001$), lymph node involvement ($p < 0.001$), lymphovascular invasion ($p = 0.008$), and positive soft tissue surgical margins ($p = 0.001$). In multivariate analyses, a high NLR was independently associated with both OS (HR 1.11, 95% confidence interval [CI] 1.01–1.22; $p = 0.029$) and cancer-specific survival (CSS) (HR 1.21, 95% CI 1.07–1.37, $p = 0.003$). The discrimination of the multivariate models increased by 0.2% on inclusion of NLR. Five studies were included in the meta-analysis. The HR for NLR greater than the cutoff was 1.46 (95% CI 1.01–1.92) for OS and 1.51 (95% CI 1.17–1.85) for CSS. Limitations include the retrospective study design and the lack of standardized follow-up.

Conclusion: In patients with UCB treated with RC, a high preoperative NLR is associated with more advanced tumor stage, lymph node metastasis, and worse prognosis. The NLR may be a readily available and useful biomarker for preoperative prognostic stratification.

Patient summary: We investigated the neutrophil-to-lymphocyte ratio (NLR) as a prognostic marker in patients with bladder cancer treated with radical cystectomy. We found that a high NLR is associated with worse oncologic outcomes, suggesting it could play a role in risk stratification.

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1. Introduction

Radical cystectomy (RC) is the treatment of choice for patients with muscle-invasive urothelial carcinoma of the bladder (UCB) and no evidence of metastasis [1]. Despite aggressive surgical treatment and improvements in perioperative chemotherapy, survival has not improved over the past decades. In recent large series, the 5-yr overall survival (OS) rate was between 40% and 60%, and cancer-specific survival rates approached 30–50% [2,3]. Extravesical extension, positive lymph nodes, positive surgical margins, lymphovascular invasion (LVI), and gender are the main prognostic factors after RC [2,4]. Multivariate prognostic models have been proposed based on these criteria and may help in stratifying patients into risk groups with regard to prognosis after surgery [5–7]. However, their accuracy in predicting outcomes remains suboptimal [8–10], probably because they do not capture the entire biologic potential of host-tumor interactions.

Numerous studies have reported on potential new biomarkers detected in peripheral blood or tissue that increase the accuracy of established prognostic factors, yet none is routinely used in clinical practice for assessment of prognosis. Inflammation plays a pivotal role in the development and progression of many malignancies, including UCB [11,12]. Triggered by the tumor microenvironment, cytokines lead to an inflammatory response that may be associated with systemic inflammation [13]. Readily available routine blood parameters that reflect the systemic inflammatory response include C-reactive protein, albumin, and leukocytes and their subtypes [14–16]. Neutrophils and lymphocytes have been combined in the neutrophil-to-lymphocyte ratio (NLR), and a high NLR has been recognized as a poor prognostic factor for many solid tumors [17]. UCB studies have indicated that a high NLR before RC may be associated with more advanced tumor stage and poorer prognosis [18–21]; however, the magnitude of the prognostic impact of NLR remains unclear.

The aim of this study was to validate the value of preoperative NLR as a prognostic factor for patients with UCB following RC in a large multicenter cohort. We also performed a meta-analysis to assess the literature on this question.

2. Patients and methods

2.1. Retrospective observational study

2.1.1. Patient population

For this study, participating sites obtained institutional review board approval and provided the necessary data-sharing agreements before study initiation. Our initial study cohort consisted of 4335 patients for whom data on preoperative NLR were available and who underwent RC with bilateral pelvic lymph node dissection (PLND) at ten international academic institutions between 1979 and 2012. The indications for RC were muscle-invasive UCB or non-muscle-invasive UCB refractory to transurethral resection with intravesical instillation therapy. We excluded patients with diseases interfering with the NLR such as leukemia, lymphoma, chronic inflammatory diseases, and autoimmune diseases ($n = 228$), as well as patients with missing postoperative follow-up

($n = 46$), leaving 4061 patients as the principal study cohort. No patient received neoadjuvant chemotherapy and no patient had distant metastases at the time of RC.

2.1.2. Treatment and follow-up

All patients underwent RC with standard bilateral PLND. An extended PLND approach was performed at the surgeon's discretion. The mean number of nodes removed was 23.6 (median 18, standard deviation [SD] 18), and the mean number of positive nodes in the 1089 patients with N+ disease was 4.9 (median 2, SD 8.3). Adjuvant chemotherapy was administered in 963 patients (23.7%).

Postoperative follow-up and imaging depended on the institution and physician. In general, patients were seen at least every 3–4 mo in year 1, every 6 mo in year 2, and annually thereafter. Follow-up visits generally consisted of a physical examination and serum chemistry evaluation. Diagnostic imaging was performed at the discretion of the treating physician. In the case of death, the cause of death was determined by the treating physician from chart review, death certificate, or the clinical history.

2.1.3. Study variables

Recorded database variables included age, sex, categorically coded preoperative NLR according to the previously identified cutoff of 2.7 [21], pathologic tumor and lymph node stage, total number of lymph nodes removed, number of positive lymph nodes, surgical margin status, LVI, and receipt of adjuvant chemotherapy. A computerized database was generated at each center. After the data sets were merged, reports were created for each variable, and inconsistencies and data integrity problems were resolved before analysis. The database was frozen on October 14, 2014 and the final data set was produced.

For pathologic staging, specimens were processed according to standard procedures by a small group of experienced pathologists at each institution according to international standards, as previously described [22]. Tumors were staged according to the 2002 TNM classification. Tumor grade was assigned according to the 1973 World Health Organization grading system. LVI was defined as the presence of nests of tumor cells within an endothelium-lined space [23]. A positive soft-tissue surgical margin was defined as the presence of tumor in stained areas of soft tissue in RC specimens [24].

2.1.4. Statistical analysis

Data for categorical variables are presented as number and percentage, and data for continuous variables as mean and SD. Group differences for categorical and continuous variables were analyzed using χ^2 and Mann-Whitney tests, respectively. The endpoints of the study were overall survival (OS) and cancer-specific survival (CSS), which were calculated from the date of RC to the date of death/death from UCB or the date of last follow-up, respectively. Kaplan-Meier survival curves were used to estimate univariate survivor functions, which were compared using the log-rank test. A multivariable Cox proportional hazards model was fitted to identify independent significant prognostic factors. Discrimination was evaluated using Harrell's concordance index. Statistical testing was two-sided and a value of $p < 0.05$ was considered statistically significant. Analyses were conducted using STATA 13 (College Station, TX, USA).

2.2. Systematic review and meta-analysis

A systematic literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. An electronic search of the Medline, Embase, and Web of Science databases was undertaken using the term [bladder cancer AND cystectomy AND ratio AND (prognosis OR survival)]. The search was not restricted by year or language. The last search was conducted on October 14, 2014.

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