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Original article

Preoperative neutrophil-lymphocyte ratio predicts death among patients with localized clear cell renal carcinoma undergoing nephrectomy

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Abstract

Objectives: The neutrophil-lymphocyte ratio (NLR) is an indicator of the systemic inflammatory response. An increased pretreatment NLR has been associated with adverse outcomes in other malignancies, but its role in localized (M0) clear cell renal cell carcinoma (ccRCC) remains unclear. As such, we evaluated the ability of preoperative NLR to predict oncologic outcomes in patients with M0 ccRCC undergoing radical nephrectomy (RN).

Methods and materials: From 1995 to 2008, 952 patients underwent RN for M0 ccRCC. Of these, 827 (87%) had pretreatment NLR collected within 90 days before RN. Metastasis-free, cancer-specific, and overall survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate models were used to analyze the association of NLR with clinicopathologic outcomes.

Results: At a median follow-up of 9.3 years, 302, 233, and 436 patients had distant metastasis, death from ccRCC, and all-cause mortality, respectively. Higher NLR was associated with larger tumor size, higher nuclear grade, histologic tumor necrosis, and sarcomatoid differentiation (all, $P < 0.001$). A NLR ≥ 4.0 was significantly associated with worse 5-year cancer-specific (66% vs. 85%) and overall survival (66% vs. 85%). Finally, after controlling for clinicopathologic features, NLR remained independently associated with risks of death from ccRCC and all-cause mortality (hazard ratio for 1-unit increase: 1.02, $P < 0.01$).

Conclusions: Our results suggest that NLR is independently associated with increased risks of cancer-specific and all-cause mortality among patients with M0 ccRCC undergoing RN. Accordingly, NLR, an easily obtained marker of biologically aggressive ccRCC, may be useful in preoperative patient risk stratification.

Keywords: Neutrophil-lymphocyte ratio; Clear cell; Nonmetastatic; Renal cancer; Radical nephrectomy

1. Introduction

There has been an increase in the incidence of renal cell carcinoma (RCC) in the last 3 decades [1] with most patients with RCC (>80%) presenting with the clear cell (cc) histologic subtype [2]. Although surgical resection remains the "gold standard" treatment for patients with clinically localized disease, approximately 10% to 60% of such patients develop recurrence following surgical extirpation [3], and of these patients, a significant proportion die of their disease [4]. Therefore, advancements in patient risk stratification are needed to appropriately identify patients at highest risk of cancer-related mortality who may be candidates for adjuvant therapy trial enrollment.

One significant challenge in the identification of the patients at highest risk is the limited pretreatment risk data that are available for patients presenting with a solid renal mass. Not surprisingly, then, most current predictive models rely almost exclusively on postoperative pathologic analysis of the surgical specimen with minimal consideration for associated patient-related variables [5–7]. As such, the

Take-Home Message: Pretreatment NLR is independently associated with an increased risk of cancer-specific and all-cause mortality among patients with clinically localized ccRCC undergoing RN. Accordingly, NLR, an easily obtained marker of biologically aggressive ccRCC, may be useful in preoperative patient risk stratification.

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potential exists that the prognostic accuracy of these models may be significantly improved with the addition of inflammatory and molecular tumor biomarkers [8]. Nevertheless, a paucity of preoperative data exists to facilitate appropriate patient counseling and guide clinic trial enrollment, and thereby there remains a need to identify biomarkers that will incrementally improve preoperative risk stratification.

The neutrophil-lymphocyte ratio (NLR) represents an easily measured, reproducible, and inexpensive marker of systemic inflammation that has been associated with oncologic outcomes in multiple malignancies, including colorectal and gastric cancers [9,10]. It has been hypothesized that the synthesis of inflammatory cytokines triggered by the tumor microenvironment alters acute phase reactants and hematological components including serum neutrophil and lymphocyte counts [11,12]. Evaluation of NLR in ccRCC might be particularly relevant as inflammation has been correlated with tumor stage, grade, and proliferative index and, moreover, has been associated with disease-free and overall survival as well [13,14]. Indeed, ccRCC is currently one of the few malignancies in which immunotherapy has been employed, in some cases (high-dose IL-2), with remarkable responses. In fact, both lymphocytosis and C-reactive protein have been observed to be predictive of oncologic outcomes in patients treated for advanced RCC [15,16].

For those with RCC undergoing curative resection, lymphocytopenia and an elevated CRP have been associated with worse cancer-related outcomes, suggesting a correlation between inflammation and disease biology [17,18]. Nevertheless, limited data exist regarding the potential prognostic value of NLR in nonmetastatic (M0) ccRCC [19–21]. Moreover, these studies have been limited by relatively small patient numbers, heterogeneous histologic subtypes, short-term follow-up, and differing clinical end points.

We hypothesize that a greater preoperative NLR is associated with adverse outcomes among patients treated for RCC. Accordingly, we sought to determine the association between pretreatment NLR and oncologic outcomes in a large cohort of patients with M0 ccRCC treated with radical nephrectomy (RN) with long-term follow-up.

2. Materials and methods

Following institutional review board approval, we reviewed the Mayo Clinic Nephrectomy Registry to identify 952 patients treated with RN for sporadic, unilateral, noncystic M0 ccRCC at our institution between 1995 and 2008.

The clinic variables recorded included age, sex, year of RN, surgical approach (open vs. laparoscopic), symptoms at presentation, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, Charlson comorbidity index, body mass index (BMI), obesity (defined as BMI $\geq$ 30), neutrophil count, lymphocyte count, pretreatment NLR, estimated blood loss during RN, and units of blood transfused during surgery or hospitalization. Patients with a palpable flank or abdominal mass, discomfort, gross hematuria, acute-onset varicocele, or constitutional symptoms including rash, sweats, weight loss, fatigue, early satiety, and anorexia were considered symptomatic. Neutrophil and lymphocyte counts closest to RN, but within 3 months before, were used for analysis. When multiple values existed for a patient, the values closest to the date of RN were utilized.

The pathologic features studied included histologic subtype classified according to the Union Internationale Contre le Cancer, American Joint Committee on Cancer, and Heidelberg guidelines, tumor size, the 2009 primary tumor and regional lymph node classifications, nuclear grade, coagulative tumor necrosis, and sarcomatoid differentiation. One genitourinary pathologist (J.C.C.) re-reviewed the microscopic slides from all specimens without knowledge of patient outcome. The primary tumor stage, size, nuclear grade, and coagulative tumor necrosis characteristics were combined to calculate the Stage, Size, Grade, and Necrosis (SSIGN) score [5]. The SSIGN score was developed at our institution to stratify cancer-specific survival in patients with ccRCC undergoing nephrectomy. Lymph node dissection was performed at the discretion of the treating surgeon at the time of RN. At our institution, follow-up after RN was generally done quarterly for the first 2 years, semiannually for the next 2 years, and annually thereafter for patients without evidence of recurrent disease. For survival end points, vital status was identified from death certificates or physician correspondence. For patients followed up elsewhere, the Nephrectomy Registry monitors outcomes annually by correspondence with the patient and the local treating physician.

Comparisons of clinicopathologic features and presurgical NLR were performed using the Wilcoxon rank sum, chi-square, Fisher exact, and Cochran-Armitage trend tests, as appropriate. Metastasis-free, cancer-specific, and overall survivals were estimated as the time from RN to event, or last follow-up, using the Kaplan-Meier method and compared with the log-rank test. A visual assessment of the association of NLR with patient outcome (i.e., a plot of martingale residuals from a null Cox model against NLR) indicated that this association was fairly linear, with an optimal cutpoint for increased risk of metastases or death from ccRCC occurring at a NLR of approximately 4.0. As such, associations of NLR with patient outcome were evaluated using NLR as a continuous variable and using a cutpoint $\geq$4.0. Cox proportional hazard regression models were used to evaluate the association of NLR with outcomes, controlling for clinicopathologic variables. A $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC).