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ORIGINAL ARTICLE

Elevated preoperative neutrophil-to-lymphocyte ratio may be associated with decreased overall survival in patients with metastatic clear cell renal cell carcinoma undergoing cytoreductive nephrectomy

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Abstract *Objective:* Inflammatory serum markers have proven to be a powerful predictive tool of patient prognosis in cancer treatment for a wide variety of solid organ malignancies, predominantly in the context of localized disease. In this study we evaluated the preoperative neutrophil-to-lymphocyte ratio (NLR) as a predictive tool in patients with metastatic clear cell renal cell carcinoma (RCC).
Methods: Sixty-four patients with metastatic clear cell RCC undergoing nephrectomy were selected. Only patients with preoperative NLR were included for survival analysis. Patients were categorized into high and low NLR score determined by plotting the NLR ROC curve. Multivariable analysis was performed.
Results: Median age was 60.8 years (38.2–81.2). Median follow-up time was 8.1 months (0.1–106.3). Fuhrman grade distribution was: 2 (3.1%) grade 1, 6 (9.4%) grade 2, 24 (37.5%) grade 3 and 32 (50.0%) grade 4. Median NLR score was 3.5 (1.4–31.0). NLR ≥ 4 was associated with decreased overall survival compared to NLR < 4 ($p = 0.017$). Multivariable survival analysis showed NLR ≥ 4 as an independent predictor of survival (Hazard ratio (HR) 2.41, 95%CI 1.05–5.50, $p = 0.03$).
Conclusion: Elevated preoperative NLR is associated with poor prognosis in patients with metastatic kidney cancer. Preoperative NLR is a useful tool, which can predict prognosis, stratify patients for postoperative surveillance, and help guide decisions for therapy.

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1. Introduction

Renal cancer is among the 10 most common cancers in the United States, with 63,920 new cases and 13,860 deaths estimated in 2014 [1]. Approximately 30% of patients with apparent localized disease will ultimately develop metastasis with a 5-year survival rate of less than 10% [2,3]. As such, there has been a tremendous, long-standing interest in accurately identifying those patients most likely to suffer from disease progression. Research in recent years has focused on the development of prognostic models to aid in surveillance strategies and patient counseling. Currently, the most commonly used tool to predict outcome in renal cell carcinoma (RCC) is the TNM staging system and nuclear grade [4]. However, there is considerable overlap in survival between stages [2], which has promoted the search for new prognostic markers to better stratify patients with expected poor outcomes.

In past years, efforts at identifying markers of disease progression in RCC have focused on the available and cost-effective preoperative laboratory blood tests. It is becoming increasingly clear that cancer progression depends on a coordinated interface between tumor biology and the host inflammatory response [5].

The systemic inflammatory response, which is usually measured by blood-based parameters, such as C-reactive protein, neutrophil or platelet count, among others has been shown to independently predict the clinical outcome of various human cancer types [6]. With the context of genitourinary malignancies elevated neutrophil-to-lymphocyte ratio (NLR) has been associated with high T stage and worse survival in a variety of tumor types including bladder and kidney cancer [7]. Of these inflammatory parameters, an increased NLR has been proposed as an easily accessible and reliable marker to predict cancer survival [6]. Increasing evidence in metastatic RCC suggests that a high NLR might represent an independent adverse prognostic factor in interferon treated [8], interleukin-2-treated [9], as well as in sunitinib-treated [10] patients. Therefore, the aim of our study is to provide further evidence of the prognostic significance of the preoperative NLR in metastatic clear cell RCC and to evaluate whether this parameter provides additional prognostic information [11].

2. Patients and methods

2.1. Patients

A total of 1871 patients underwent nephrectomy at Emory University Hospital for renal tumors between 2004 and 2014. The database contains information on the demographics, pathological findings, preoperative laboratory parameters and survival of consecutive patients. Inclusion criteria consisted of clear cell histology and radiological or histopathological evidence of distant metastases at the time of intervention, available preoperative NLR measurements, and no concomitant immunosuppression therapy. We chart reviewed the medical records of 81 patients following cytoreductive nephrectomy for confirmed metastatic RCC and all clinical records, including follow-up. Seventeen patients with non-clear cell RCC were excluded from the study. Consequently, the remaining 64 patients were included in the present study (Fig. 1). The Institutional Review Board approved the study.

2.2. Clinical and laboratory assessment

The clinical variables recorded included age, gender, race, ethnicity, date of intervention, surgical approach (open *vs.* laparoscopic), Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), obesity (BMI $\geq$ 30 kg/m^2), neutrophil count, lymphocyte count, preoperative NLR. NLR within 1 month prior to the intervention was used for analysis. All the clinicopathologic data were retrieved from medical records of the Department of Urology, as well as from the pathology reports from the Department of Pathology at Emory University Hospital.

The pathologic features studied included histologic subtype classified according to the Union for International Cancer Control, American Joint Committee on Cancer, and Heidelberg guidelines, tumor size, the 2009 primary tumor and regional lymph node classifications, nuclear grade,

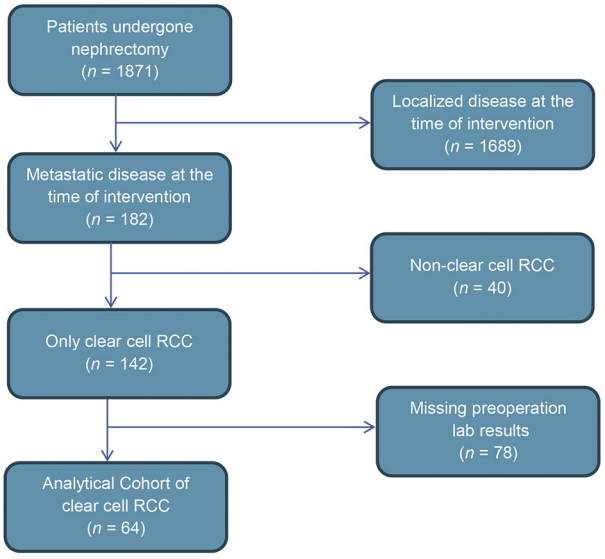

Figure 1 Flow chart of patients who met study inclusion/exclusion criteria. RCC, renal cell carcinoma.