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The prognostic utility of preoperative neutrophil-to-lymphocyte ratio in localized clear cell renal cell carcinoma

Wassim M. Bazzi, MD[1], **Amy L. Tin, MD**[2], **Daniel D. Sjoberg, MD**[2], **Melanie Bernstein, MD**[1], and **Paul Russo, MD**[1]

[1]Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[2]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, USA

Abstract

Introduction—To explore whether the association between preoperative neutrophil-to-lymphocyte ratio (NLR) elevation and worse survival is of use prognostically or merely a reflection of medical comorbidities in clear cell renal cell carcinoma (CC RCC).

Materials and methods—We identified 1970 patients treated at Memorial Sloan Kettering Cancer Center from 1998–2012 by partial or radical nephrectomy for non-metastatic CC RCC. NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count; both were obtained from preoperative complete blood count. Uni- and multivariable Cox proportional hazards regression, which included established prognostic variables, were used to test for association between NLR and recurrence-free (RFS), cancer-specific (CSS), and overall survival (OS).

Results—Univariate analysis identified elevated NLR as significantly associated with worse RFS, CSS, and OS (all $p < 0.0001$). However, upon multivariable analysis, elevated NLR was significantly associated with only worse OS ($p < 0.0001$). After adding markers of comorbidity that were significantly correlated with NLR elevation—higher American Society of Anesthesiologists class ($p = 0.013$), older age, and higher estimated glomerular filtration rate (both $p < 0.0001$)—into the multivariable model, NLR remained significantly associated with OS ($p = 0.001$). The addition of NLR into the prognostic model for OS did not increase Harrell's concordance index from 0.776.

Conclusions—In our cohort, preoperative NLR elevation is associated with worse OS, but there was no significant association with RFS or CSS on multivariable analysis. Preoperative NLR does not add unique prognostic information for patients undergoing surgical resection of renal tumors.

Keywords

kidney neoplasms; renal cell carcinoma; survival

Address correspondence to Dr. Paul Russo, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065 USA.

Introduction

Kidney cancer is the 6th most common cancer in men and 8th in women, with an estimated 65,150 new cases and 13,680 resultant deaths in the United States in 2013.[1] Numerous investigators have reported an association between chronic inflammation and malignancies.[2–4] It is estimated that 15% of worldwide malignancies have an infectious causative agent.[5] C-reactive protein (CRP), a serum marker for systemic inflammation, has been shown to correlate with oncologic outcomes in kidney cancer,[6–9] but it is not readily available for all patients because it is a unique blood assay.

With systemic inflammation there is a simultaneous rise in circulating neutrophils and a decrease in lymphocytes.[10] Preoperative neutrophil-to-lymphocyte ratio (NLR) has been investigated by numerous centers demonstrating its utility as an alternative serum marker for systemic inflammation and good prognostication of numerous malignancies including those arising from the genitourinary system.[11–14] The literature also reports NLR elevation with systemic inflammation secondary to chronic medical conditions,[15–20] and recent work by Pichler et al[21] showed NLR elevation to be associated with worse overall survival (OS), but not for recurrence-free (RFS) or cancer-specific survival (CSS) in clear cell renal cell carcinoma (CC RCC), possibly reflecting patients' comorbidities.

Numerous prognostic nomograms based on institutional databases have been published to predict renal mass pathology preoperatively,[22] RCC recurrence rates,[23,24] and RCC survival[25] outcomes. We herein explore further the association between preoperative NLR and oncologic outcomes to determine NLR's prognostic utility in a cohort of patients with localized CC RCC who were treated at Memorial Sloan Kettering Cancer Center (MSKCC).

Materials and methods

Pre-treatment laboratory complete blood count with differential, which was typically drawn less a month before surgery part of preoperative blood work per our institution's protocol, was used to calculate the NLR by dividing the absolute neutrophil count by the absolute lymphocyte count. Our initial objective was to determine the association of NLR with other predictors of recurrence—age, pathologic tumor size and Fuhrman grade—and representations of comorbidity status—American Society of Anesthesiologists (ASA) classification system and estimated glomerular filtration rate (eGFR)—in patients with CC RCC. Spearman's rank correlations were calculated between NLR and each of the predictors to summarize their relationships. We were then primarily interested in whether NLR offers predictive ability for RFS, CSS, and OS.

We identified 3874 patients who underwent partial or radical nephrectomy between 1998 and 2012. Of these patients, we omitted 257 because of incomplete preoperative labs, and we excluded 1648 patients based on their having metastatic RCC or non-CC RCC histology; therefore, our final cohort included 1970 patients. Tumors were staged according to American Joint Commission on Cancer 2010 classification.[26] eGFR was calculated using the Chronic Kidney Disease–Epidemiology Collaboration formula (CKD-Epi).[27] We used Cox proportional hazards regression to assess whether NLR was associated with recurrence

and CSS. Because of possible nonlinearity, restricted cubic splines were used to model the relationship between the novel marker and risk. We were further interested in whether NLR could be a significant prognostic factor after including known predictors of recurrence and CSS into the model. To make such a determination, we built multivariable Cox proportional hazards models and included pathologic T stage (categorized as T1A, T1B, T2, T3, T4), Fuhrman grade (categorized as FG1, FG2, FG3, FG4),[28] presentation (categorized as incidental, local, or systemic), and tumor size (entered with restricted cubic splines with knots at the tertiles); all factors were chosen based on MSKCC's postoperative CC RCC nomogram.[23]

To test the hypothesis that NLR is related to comorbidity status and a patient's overall health and survival status, we also ran the univariate and multivariable analysis with OS as the end point, then created one final model that included age, ASA(I versus II versus III versus IV) class,[29] and eGFR as markers for comorbidities. To evaluate the discriminative accuracy of the model including NLR, we calculated Harrell's concordance index after running a 10-fold cross-validation, to correct for any overfit. All statistical analyses were conducted using STATA 12.0 (StataCorp, College Station, TX, USA).

Results

Patient characteristics are listed in Table 1. The median age of patients was 61 years (interquartile range 52–70); two thirds of the cohort were men. Among the 1970 patients, 228 experienced a recurrence, 115 of whom died due to the progression of RCC. Overall, there were 313 deaths due to any cause; the median follow up time for survivors was 3.7 years. NLR was significantly correlated with tumor size and grade (both $p < 0.0001$), which are risk factors for cancer recurrence and OS. NLR also significantly correlated with additional factors associated with OS: age ($p < 0.0001$), ASA class ($p = 0.013$), and eGFR ($p < 0.0001$). Table 2 summarizes the p values testing the association between NLR and our end points for all the models created. Since nonlinear terms were used to model NLR in the Cox models, we do not report the hazard ratios. Univariate Cox regression identified NLR as significantly associated with RFS, CSS, and OS (all $p < 0.0001$). The relationship between NLR and OS is shown in Figure 1, where the risk for death, due to any cause, within 5 years of nephrectomy is calculated based on NLR values. As an example, this risk would be 17% for patients with a NLR of 4.

After multivariable analysis, NLR remained significantly associated with OS ($p < 0.0001$), but not for RFS and CSS ($p = 0.10$ and $p = 0.12$, respectively). NLR remained significantly associated with OS ($p = 0.001$) even after adding age, ASA class, and eGFR into the multivariable model. However, the addition of NLR into the prognostic model for OS (incorporating associated factors—tumor size, stage, grade, and presentation—and significantly correlated comorbidities—age, ASA class, and eGFR) did not increase the concordance index from 0.776.

Discussion

In this study, we noted that preoperative NLR is associated with RFS, CSS, and OS on univariate analysis, but only OS after multivariable analysis. Our findings are similar to Pichler's et al[21] large European validation study of pretreatment NLR prognostication of RCC findings. However, our findings are in contrast with Ohno et al,[12] who reported that in nonmetastatic RCC, clinical tumor stage and preoperative NLR higher than 2.7 were both associated with worse RFS after multivariable analysis. Ohno et al,[12] however, did not report OS data.

Because NLR level has been demonstrated to be an alternative marker of systemic inflammation with medical conditions such as renal insufficiency,[15–20] we hypothesized that the association of NLR with OS, but not RFS or CSS, is possibly a reflection of patients' comorbidities. Upon further analysis, we noted that NLR elevation correlated with advancing age, higher ASA class, and worse preoperative eGFR, and even after adjusting for these factors, preoperative NLR still predicted OS. We were not able to demonstrate that preoperative NLR in and of itself is associated with cancer-specific outcomes in CC RCC after multivariable analysis.

In this study, we analyzed NLR as a continuous variable, similar to the recently published report on non-CC RCC by DeMartino et al,[14] because this is a more powerful and informative approach than using NLR level cut offs to optimize statistical significance. The addition of NLR to the already established variables for assessing OS (tumor size, stage, Fuhrman grade, presentation, age, ASA class, and eGFR) did not increase Harrell's concordance index from 0.776. The analysis of the relationship between NLR and outcome did not show important discontinuities in risk over the range of NLR most commonly seen in the population, and because NLR provides no additional prognostic utility to the already established predictors of oncologic outcomes, we find it futile to identify cutoffs from our analyses.

Our study is limited by the fact that, as alluded to by Pichler et al,[21] NLR is not a specific disease biomarker and can be influenced by factors such as active infection, hematologic and inflammatory diseases, and stress at time of the blood draw.

Conclusions

In this large cohort of patients with nonmetastatic CC RCC, preoperative NLR elevation is significantly associated with worse OS, but not with RFS or CSS after multivariable analysis and hence does not add unique prognostic information for patients undergoing surgical resection of renal tumors.

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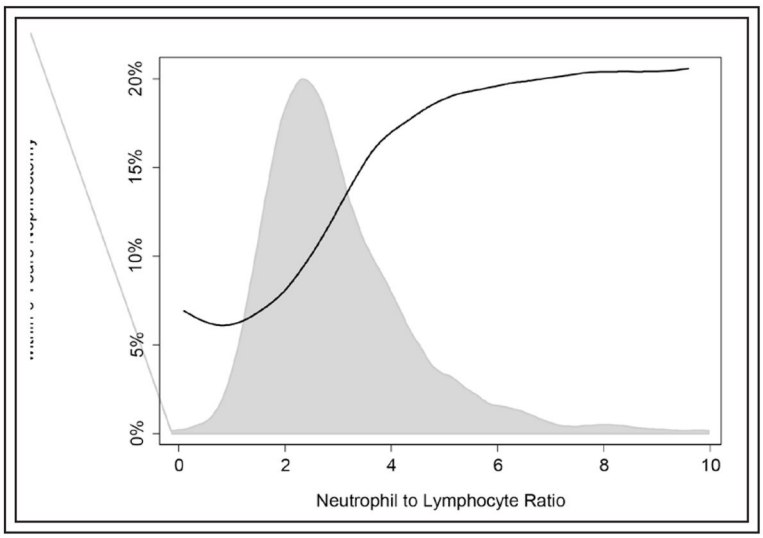

Figure 1.

Univariate risk for death (due to any cause) within 5 years of nephrectomy, calculated by locally weighted Kaplan–Meier estimates, based on NLR, overlaid on the distribution of NLR measurements.

TABLE 1

Patient characteristics (n = 1970)

Age at surgery (years)	61 (52, 70)
Male sex	1307 (66%)
Neutrophil-to-lymphocyte ratio	2.7 (2.1, 3.7)
Pathologic max tumor size (cm)	3.8 (2.5, 6.0)
Pathologic T stage	
T1A	989 (50%)
T1B	358 (18%)
T2	96 (4.9%)
T3	510 (26%)
T4	17 (0.9%)
Fuhrman grade	
FG 1	69 (3.5%)
FG 2	1048 (53%)
FG 3	719 (36%)
FG 4	125 (6.3%)
Unknown	9 (0.5%)
Presentation	
Incidental	1497 (76%)
Local	399 (20%)
Systemic	57 (2.9%)
Unknown	17 (0.9%)
ASA score	
1	83 (4.2%)
2	962 (49%)
3	896 (45%)
4	29 (1.5%)
eGFR (mL/min/1.73 m^2)	68.0 (56.2, 80.8)

All values are median (IQR) or frequency (proportion)

TABLE 2

Values testing the association between neutrophil/lymphocyte ratio and corresponding outcomes

	Univariate	Multivariable*	Multivariable†
Recurrence-free survival	p < 0.0001	p = 0.10	n/a
Cancer-specific survival	p < 0.0001	p = 0.12	n/a
Overall survival	p < 0.0001	p < 0.0001	p = 0.001†

All hazard ratios and confidence intervals were excluded because of neutrophil/lymphocyte ratio (NLR) being entered as a nonlinear term in our models.

n/a = not available because these models were not analyzed.

*adjusted for pathologic T stage, Fuhrman grade, presentation, and tumor size.

†adjusted for the base covariates, age, ASA score, and eGFR.