RUNNING HEAD: NLR as a predictor of overall survival in patients with RCC-Widz et al.

Preoperative neutrophil-lymphocyte ratio as a predictor of overall survival in patients with localized renal cell carcinoma.

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ABSTRACT

Purpose: The neutrophil-to-lymphocyte ratio (NLR), as an indicator of the systemic inflammatory response, predicts adverse outcomes in many malignancies. We investigated its prognostic significance in patients with non-metastatic renal cell carcinoma.

Materials and Methods: We retrospectively evaluated data of 196 consecutive non-metastatic RCC patients who underwent radical or partial nephrectomy between 2010 and 2012 at a single center. Overall survival (OS) was assessed using the Kaplan-Meier method and compared using the log-rank test. We applied univariate and multivariate Cox regression models to evaluate the prognostic value of dichotomized NLR for OS.

Results: At a median follow up of 68 months, high NLR (≥ 2,69) correlated with worse survival outcome (P = .006 in log-rank test) and higher tumor stage (P = .035). Univariate and multivariate analysis identified elevated NLR (P = .039), as well as age (P = .002), high Fuhrmann grade (P = .002) and high pathologic T stage (P < .001), as significantly associated with overall survival.

Conclusions: In our cohort, an elevated neutrophil-to-lymphocyte ratio is significantly associated with worse OS on univariate and multivariate analysis. Consequently, the NLR is an easily acquired biomarker, which may be useful in pretreatment patient risk stratification.

INTRODUCTION

Renal cell carcinoma, representing 2–3% of malignancies worldwide[1], has increased in incidence over the last two decades. This medical condition is often identified in Western countries, but the frequency of its occurrence in western Europe has been stabilized[2]. Also, due to the wide-spread use of ultrasound (US) and computed tomography (CT) many newly diagnosed renal tumors occur as incidental findings, and are therefore smaller and of lower stage [3, 4, 5].

Kidney cancer therapy is a subject of continuous verification and incremental modification to improve oncological outcome while reducing the negative implications of surgical or systemic treatment [6, 7, 8].

Researchers are constantly attempting to determine prognostic factors that can accurately predict clinical outcomes of RCC patients. These features are derived from anatomical, histological, clinical and molecular data and are combined into prognostic systems and nomograms [9, 10, 11, 12, 13].

This constant effort to uncover new factors has focused attention on cancer-associated inflammation, which has an established role in cancer development and progression. Pre-operative measurement of inflammatory response markers, such as elevated C-reactive protein levels, hypoalbuminemia or increased white cell, neutrophil and platelet counts, allows the prediction of patients' survival in many cancers [14, 15]. The neutrophil to lymphocyte ratio (NLR) is a cheap and easily acquired inflammatory marker widely investigated as a prognostic factor in a number of cancers [14, 16], including urologic tumors [17]. The aim of our study was to evaluate the prognostic significance of preoperative NLR in non-metastatic RCC. This is one of the first cohort studies in this field in our region.

MATERIALS AND METHODS

Study population

A total of 196 consecutive patients with non-metastatic RCC who had undergone a curative radical or partial nephrectomy at the Department of Urology at the Medical University of Lublin between January 2010 and September 2012 were included in this historical cohort study. Patients suspected of bone marrow disease (1 case) or lost from follow-up (3 cases) were not involved in the study.

Study design and Evaluations

The research was reviewed and approved by Medical University of Lublin Ethics Committee. Data regarding age, sex, body mass index (BMI), history of hypertension and diabetes were retrieved from medical records of the Department of Urology, clinicopathological parameters including histological RCC subtype, tumor grade (Fuhrmann grade), presence or absence (not quantitatively assessed) of histologic tumor necrosis (TN), and tumor size were obtained from the pathology reports from the Department of Pathology at Lublin University Hospital. Laboratory tests, including peripheral blood cell counts, were performed at 1–7 days before surgery.

Overall survival was calculated based on the dates of individuals' surgery and death from any cause. Dates of death were obtained from the registry of the Polish Ministry of Digital Affairs.

The objective of the present study was to examine the relationship between pretreatment NLR and the clinicopathological features of RCC in patients who had received radical surgery, as well as the potential effect of NLR on overall survival.

NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Statistical Analysis

The cutoff value for the dichotomization of NLR was calculated using a receiver – operating characteristic curve with survival (death) as a gold standard. The proposed and finally accepted cut-off point was determined to be 2.69.

Categorical variables were reported as frequencies and percentages. Continuous variables were reported as medians and ranges, and then dichotomized according to approximate optimal cutoff points. The relationship between NLR and the clinicopathologic parameters was evaluated by non-parametric tests - Pearson's χ^2 tests. Linear correlation analysis was used to determine the association between prognosis and NLR values. The time of overall survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Cox's proportional hazard regression model was used to assess the influence on overall survival (OS) of age, gender, Fuhrmann grade, histologic subtypes of RCC, pathologic T (tumor) stage, tumor size. We decided on a multivariate analysis with variables significant in univariate analysis, as well as including histological subtype, due to its acknowledged role as prognostic factor.

All statistical analyses were performed using STATA software version 13. $P < .05$ was considered to be statistically significant.

RESULTS

Overall, 196 RCC patients, median age 61 years (interquartile range 24-85), were treated with partial nephrectomy – 46 (23.5%) or nephrectomy – 150 (76.5%). Among all the cases, 165 (84.2%) had clear cells, 14 (7.1%) had papillary, 6 (3.1%) had chromophobe, 4 (2%) had cystic, 1 (0.5%) had collecting duct RCC and 6 (3.1%) were not specified. Pathologic T stage was T1a in 67 (34.2%), T1b in 52 (26.5%), T2a in 7 (3.6%), T2b in 2 (1%), T3a in 58 (29.6%), T3b in 7 (3.6%) and T4 in 3 (0.2%) patients. Tumor

Fuhrmann grading was Grade 1 in 11 cases (5.6%), Grade 2 in 103 (52.6%), Grade 3 in 55 (28.1%), Grade 4 in 24 (12.2%) and in 3 (1.5%) cases not specified. Histologic tumor necrosis was reported in 52 (26.5%) patients. The mean neutrophil count was 4.94 ± 1.66, mean lymphocyte count was 1.74 ± 0.64 and mean NLR was 3.18 ± 1.66. Using an ROC curve we determined the cutoff NLR value of 2.69 to be optimal to differentiate patients' overall survival and define low (< 2.69) and high NLR (≥ 2.69). Overall, there were 101 (51.5%) patients with a low NLR and 95 (48.5%) patients with a high NLR. A High NLR was significantly associated with an advanced tumor stage ($P < .05$) but not with any other tested clinicopathological feature (Table 1).

Total median follow-up time was 68 months (interquartile range (IQR) 44.5–78). Overall, there were 64 deaths from all causes. The prognosis of patients was significantly associated with NLR values ($P < .001$) (Figure 1). Kaplan–Meier curves for survival probability shown on Figure 2 revealed that a high NLR correlates with poor prognosis in RCC patients ($P = .006$ in log-rank test).

For further investigations to determine the prognostic significance of NLR for OS, univariate and multivariate Cox proportional hazard analyses were performed. Age (≥ 65 *vs* < 65 years, $P = .003$), gender (male *vs* female, $P = .004$), high tumor Fuhrmann grade (3+4 *vs* 1+2, $P < .001$), high pathologic T stage (T3–T4 *vs* T1–T2, $P < .001$), large tumor size (> 7 cm *vs* ≤ 7 cm, $P < .001$) and a high NLR (≥ 2.69 *vs* < 2.69, $P = .007$) were identified as predictors of poorer outcomes (Table 2). In multivariable analyses, after adjusting all the variables, NLR remained significantly associated with OS ($P = .039$), as well as age, gender, high Fuhrmann grade, high pathologic T stage, but not tumor size (Table 3).

DISCUSSION

The challenge presented by the personalized management of patient care requires constant research for more accurate biomarkers characterizing particular tumors. Continuously updated scientific reports on kidney cancer focus to a large extent on molecular research [18]. The complexity of molecular alterations in RCC, as well as the intratumor heterogeneity of its genomic landscape, results in time-consuming analyses and is thus associated with high costs [18, 19]. As a consequence, none of the markers are available for routine testing.

NLR is relatively easy to estimate from regularly used blood – based counts, making it an attractive prognostic factor for further evaluation and treatment of RCC patients.

NLR has been widely evaluated as an adverse factor for different human cancers, including colorectal, gastric, esophageal, pancreatic, liver, urological and gynecological cancers [1], as well as in non – neoplastic conditions, such as cardiovascular diseases [20, 21]. Graeme J.K. Guthrie demonstrated that, regardless of the type of cancer or required treatment approach, NLR was elevated in patients with more advanced or aggressive disease manifested by increased tumor stage, nodal involvement or a higher number of metastatic lesions [14].

You Luo, in his publication dedicated to urologic tumors defined as renal cell carcinoma, upper tract urothelial carcinoma, bladder cancer and prostate cancer, indicated that patients with a higher NLR had a higher all-cause mortality risk in all the mentioned groups. In terms of cancer specific survival (CSS) outcome, results showed significant differences, with inferiority of a high NLR, in upper tract urothelial carcinoma and bladder cancer but not in RCC, and no data in prostate cancer [22].

Renewed interest in the role of NLR as a prognostic factor in RCC patients has developed as a result of new scientific reports. Boissier et al. (2017) reviewed the available literature in August 2016 and found that NLR has a prognostic value for all stages of localized or metastatic RCC, including prediction of the response to systemic treatments or cytoreductive nephrectomy in metastatic kidney cancer [22]. Another study on patients with advanced disease (locally and metastatic) performed by Fox et al. showed that the addition of inflammatory markers into prognostic models based on MSKCC allows a more accurate prediction of patient survival time. According to this improved classification 25.8% of patients were more appropriately classified. The markers of systemic inflammation used in the study were elevated neutrophil counts, elevated platelet counts and high NLR, defined as > 3 [23].

There are incoming evidence on the potential benefits of adjuvant systemic therapy in advanced kidney cancer [24, 25]. Due to the fact of a possible toxicity of such treatment, the search for markers enabling proper qualification of patients is underway. Motzer et al. showed in their study that nlr may contribute in this field. According to their analysis from the S-TRAC trial, patients with NLR<3 experienced longer disease free survival with adjuvant sunitinib compared to placebo [24, 25]. Determining the basis of this relation requires further inquiry.

The value of NLR in patients with non-metastatic RCC remains under investigation. Some studies have already been published, with conflicting results reported.

In this cohort study, we found that preoperative NLR is significantly associated with OS in univariate and multivariable analyses. We demonstrated that an increased NLR > 2.7 was an independent predictor of poor prognosis. Our findings are in agreement with the large European validation study of Pichler et al (2013), where they investigated a group

of 678 patients with non – metastatic clear cell RCC and reported that NLR was an independent negative predictor for OS. They did not find the same relation to CSS or metastatic free survival [26]. Their research is in contrast to another prior study by Ohno et al (2010) on a smaller cohort of 192 patients with a mean follow-up of 93 months, where they reported that an increased NLR was an independent predictor for recurrence-free survival [27]. In his analyses Ohno omitted variables such as tumor stage, size, grade or presence of necrosis which has been proven to be highly predictive of tumor recurrence [28]. Moreover, their study did not include OS data.

Other research projects also do not provide an unambiguous answer about the prognostic role of NLR. Using a group of 827 non-metastatic clear cell RCC patients, Boyd et al (2014) demonstrated that NLR is an independent predictor of cancer-specific and all-cause mortality. In contrast to many previous studies, and ours, their multivariable analysis is based on continuous NLR [29]. This approach, perceived by the authors to be an advantage of the analysis, allows the avoidance of inaccurate setting of the cut-off value and receiving misleading results. However, everyday clinical practice usually requires the establishing of a certain point by which a clinician can identify significant abnormality in a diagnostic test. Combination of information received from analyses based on continuous NLR with tests on dichotomized NLR would make it possible to identify a group of patients with a worse prognosis and gradation of their risk.

Lastly, Bazzi et al (2016) evaluated 1970 patients undergoing partial or radical nephrectomy for localized clear cell RCC and found that NLR, as a continuous variable, was significantly associated with worse recurrence free survival (RFS), CSS, and OS; however, in contrast to Boyd's research NLR independently predicted only worse OS [30].

Attempts to explain the relationship between NLR and prognosis, on a pathophysiological basis, lead to the role of inflammation. The interaction between inflammation and carcinogenesis has been studied over the past decades. Through various mechanisms, inflammation is involved in oncogenesis. A tumor is not merely a line of cancer cells dividing in an uncontrolled manner. On the contrary, there are many accompanying cells, including those derived from the immune system, influencing tumor behavior. Cancer-associated inflammation induces the up-regulation of the innate immune response. It is manifested as a heightened neutrophil dependent reaction, increased tumor macrophage infiltration with concomitant suppression of lymphocytes. Elevated proinflammatory cytokines modify the tumor microenvironment, allowing its intense growth and overcoming consecutive barriers in tumor expansion, promoting aggressive tumor behavior [31, 32]. An elevated neutrophil–lymphocyte ratio reflects, in part, the increased role of the innate immune system; moreover, it is often associated with higher values of proinflammatory cytokines [33, 34].

Our study, as being the historical cohort, is limited by its non-randomized character. No data were available about the cause of death. Moreover, NLR is not a disease-specific biomarker and may be influenced by many factors interacting with the immune system. The NLR cut-off point used in our study differs slightly from those used in previous research, as it is always set for a certain evaluated cohort.

CONCLUSIONS

Nevertheless, considering the limitations, our data show that elevated NLR may be recognized as an independent prognostic factor for OS in non-metastatic RCC patients undergoing surgical resection of tumors. The NLR might be an easily available and inexpensive biomarker predicting clinical outcomes of RCC patients. However, to

establish an accurate NLR value, useful for clinical practice, further prospective research is needed.

CONFLICT OF INTEREST

None declared.

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Table 1. Clinicopathological characteristics of the cohort stratified by preoperative NLR.

Clinicopathological features	**NLR <2,69**	**NLR ≥2,69**	
			***P*-value** [a]
	n (%)	**n (%)**	
Age (years)			0.44
< 65	65 (64,4)	56 (58,9)	
≥ 65	36 (35,6)	39 (41,1)	
Gender			0.95
Male	60 (59,4)	56 (58,9)	
Female	41 (40,6)	39 (41,1)	
BMI			0.29
< 25	25 (24,75)	30 (31,6)	
≥ 25	76 (75,25)	65 (68,4)	
Hypertension			0.15
No	48 (47,5)	55 (57,9)	
Yes	53 (52,5)	40 (42,1)	
Tumor size			0.21
< 7	83 (82,2)	71 (74,7)	
≥ 7	18 (17,8)	24 (25,3)	
Histologic subtypes			0.18
Clear cell			
Non-clear cell	88 (87,1)	76 (80)	
	13 (12,9)	19 (20)	
pT stage			0.04
$T_1 – T_2$	73 (72,3)	55 (57,9)	
$T_3 – T_4$	28 (27,7)	40 (42,1)	
Fuhrman grade			0.74
1 – 2	61 (60,4)	54 (58,1)	
3 – 4	40 (39,6)	39 (41,9)	
Type of surgery			0.27
NSS	27 (26,7)	19 (20)	
Nephrectomy	74 (73,3)	76 (80)	
Tumor necrosis			0,80
No	75 (74,3)	69 (72,6)	
Yes	25 (26,7)	26 (27,4)	

[a] The χ^2-test

Abbreviations: BMI – body mass index, NLR – neutrophil-lymphocyte ratio, NSS – nephron-sparing surgery, pT stage – pathological tumor stage

Table 2. Univariate analysis of clinicopathological parameters for the prediction of overall survival in patients with RCC.

Features	**Overall survival**		
	HR	**95% CI**	***P*-value**
Gender (Male vs Female)	2.287	1.298-4.029	0.004
Age (≥ 65 vs < 65)	2.105	1.286-3.445	0.003
The histologic subtypes (Clear cell vs Non-clear cell)	1.008	0.955-1.064	0.77
pT stage (T3 -T4 vs T1 - T2)	5.375	3.200-9.028	0.000
NLR (≥ 2,69 vs < 2,69)	2.009	1.211-3.334	0,007
Tumor size (> 7 cm vs ≤ 7 cm)	3.924	2.380-6.473	0.000
Fuhrman grade (3 - 4 vs 1 - 2)	3.377	2.015-5.658	0.000

Abbreviations: BMI – body mass index, NLR – neutrophil-lymphocyte ratio, pT stage – pathological tumor stage

Table 3. Multivariable analysis of clinicopathological parameters for the prediction of overall survival in patients with RCC.

Features	**Overall survival**		
	HR	**95% CI**	***P*-value**
Gender (Male vs Female)	1.755	0.988-3.116	0.06
Age (≥ 65 vs < 65)	2.187	1.325-3.611	0.002
The histologic subtypes (Clear cell vs Non-clear cell)	1.058	0.995-1.125	0.07
pT stage (T3 -T4 vs T1 - T2)	4.817	2.568-9.035	0.00
NLR (≥ 2,69 vs < 2,69)	1.718	1.027-2.874	0,04
Tumor size (> 7 cm vs ≤ 7 cm)	1.435	0.819-2.514	0.21
Fuhrman grade (3-4 vs 1-2)	2.230	1.343-3.938	0.002

Abbreviations: BMI – body mass index, NLR – neutrophil-lymphocyte ratio, pT stage – pathological tumor stage

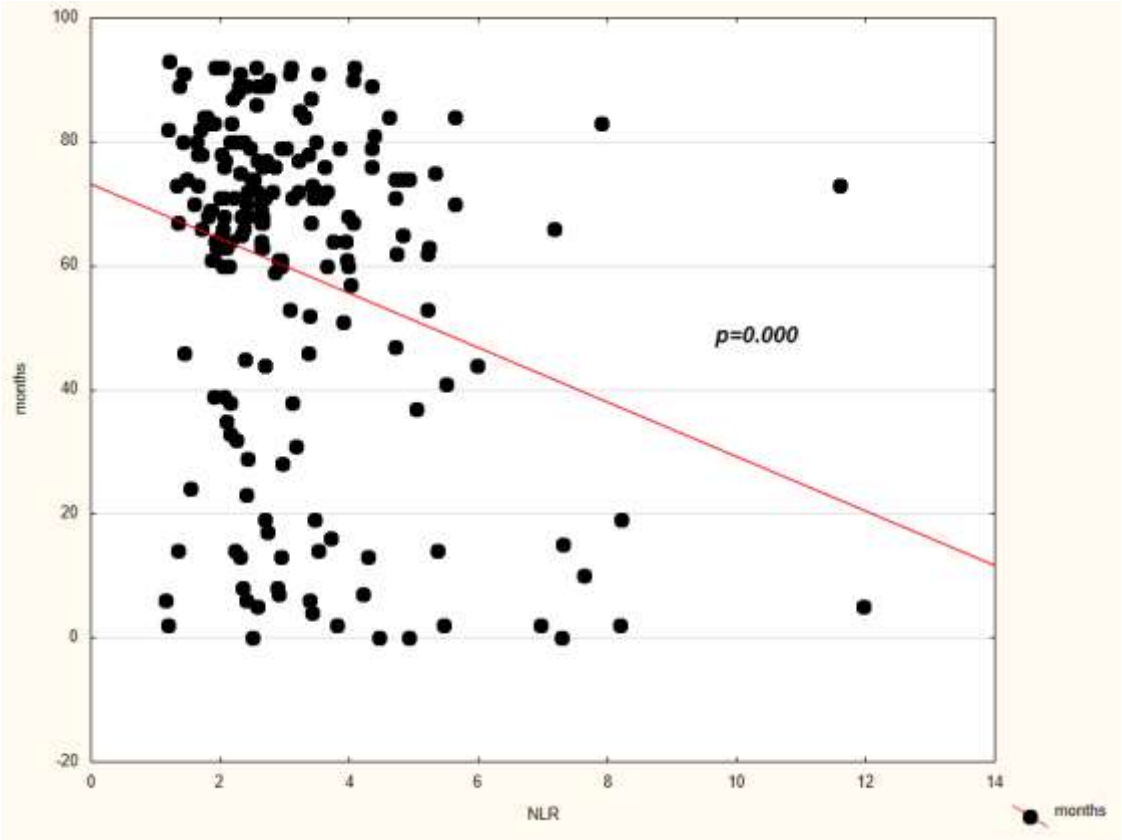

Figure 1. Linear correlation analysis of the association between prognosis and NLR values.

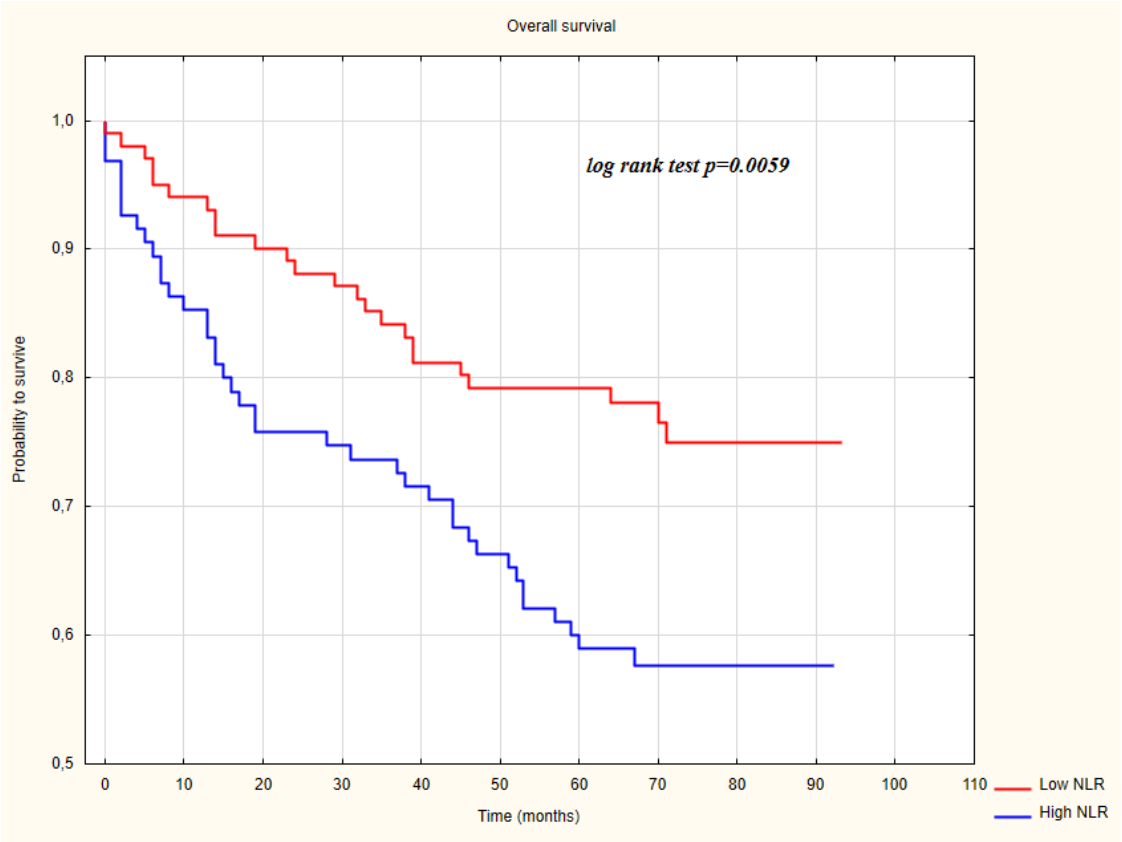

Figure 2. Kaplan–Meier curves for overall survival in renal cell carcinoma patients categorized by the neutrophil–lymphocyte ratio (low NLR < 2,69; high NLR ≥ 2,69).