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Association between pretreatment neutrophil-to-lymphocyte ratio and outcome of patients with metastatic renal cell carcinoma treated with nivolumab

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Abstract

Background—Biomarkers to guide treatment in metastatic renal cell carcinoma (mRCC) are lacking. We aimed to investigate the association between pretreatment neutrophil-to-lymphocyte ratio (NLR) and outcome of patients with mRCC receiving nivolumab.

Methods—Through retrospective chart review, we identified 38 patients with mRCC treated with standard of care nivolumab between 2015 – 2016 at Winship Cancer Institute of Emory University. NLR was determined from complete blood count collected prior to starting treatment and imaging was performed to assess progression. The NLR cutoff value of 5.5 was determined by log rank test, and the univariate association with overall survival (OS) or progress free survival (PFS) was assessed by Cox proportional hazard model and Kaplan-Meier method.

Results—The 38 patients had a median age of 68.5 years. The PFS and OS for all patients at 12 months was 54% and 69%, respectively. The median PFS was 2.6 months in the high NLR group but not reached in the low NLR group. Low NLR was strongly associated with increased PFS with hazard ratio of 0.20 (95%CI 0.07–0.64; p=0.006). The median OS was 2.7 months in the high NLR group but not reached in the low NLR group. Low NLR was significantly associated with a prolonged OS with hazard ratio of 0.06 (95% CI 0.01–0.55; p=0.012).

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Conclusion—Pre-treatment NLR less than 5.5 is associated with superior PFS and OS. NLR is a biomarker that can inform prognosis for patients with mRCC and should be further validated in larger cohorts and in prospective studies.

1. Introduction

Therapeutic options for metastatic renal cell carcinoma (mRCC) have expanded in recent years; patients now have several treatment options with proven clinical benefit (1). Immune-checkpoint inhibition is a novel approach for cancer therapy, which has recently advanced our treatment options in mRCC. In particular, PD1/PDL1 inhibitors, which target inhibitory pathways on T cells, have been approved in several advanced malignancies, including mRCC (2–4). The landmark trial of nivolumab showed an increase in overall survival (OS) benefit, leading to its FDA approval in 2015 for the treatment of mRCC (4).

Given the array of treatment options in mRCC from anti-VEGF TKIs, MTOR inhibitors, and now, PD/PDL1 inhibitors; there has been great interest in identifying biomarkers to guide treatment decisions. The neutrophil-to-lymphocyte ratio (NLR) is a measure of systemic inflammation that has been reported as a prognostic factor for several solid tumors (5). A systematic review and meta-analysis of 100 studies of the association of NLR with outcome in solid tumors found that high NLR is associated with poor OS across all tumor subtypes studied, including renal cell carcinoma (5). The association of elevated systemic inflammatory markers such as CRP and NLR with worse prognosis is well-established in mRCC patients receiving targeted therapy. Previous studies have shown that NLR predicts prognosis in mRCC patients receiving targeted therapy, such as sorafenib or sunitinib (5, 7). In this study, we aimed to investigate the association between pretreatment NLR and outcome in patients with mRCC receiving standard of care nivolumab.

2. Methods

Patient data

Through retrospective chart review of the Emory electronic health record, we identified 38 patients with mRCC who were treated with nivolumab as standard of care during the period of November 2015 through December 2016 at Winship Cancer Institute of Emory University. Patient demographic data, treatment history, and laboratory data were obtained from review of progress notes and other records. All patients had complete blood count (CBC) collected on the date of initial clinic visit or within 7 days prior to starting nivolumab. All blood samples and laboratory tests were collected at the same facility, within our institution.

Response assessment and endpoints

Computed tomography or magnetic resonance imaging was performed at baseline, and repeated approximately every 8–12 weeks at the discretion of the treating physician. All radiographs were read in the Department of Radiology and Imaging Science at Emory University and reviewed in our clinic. Clinical tumor response was determined during the time of treatment by using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 according to the patient's medical record (8). We defined clinical benefit as complete

response (CR) or partial response (PR) or stable disease (SD) of greater than 4 months. Progression-free survival (PFS) was defined as time from nivolumab initiation to date of progression, hospice enrollment, or death from any cause, whichever was earlier. Overall survival (OS) was defined as time from nivolumab initiation to death or hospice enrollment.

Statistical analysis

Statistical analysis was conducted using SAS Version 9.4, and SAS macros developed by the Biostatistics and Bioinformatics Shared Resource at the Winship Cancer Institute (9). The significance level was set at $p< 0.05$. The cutoff value of NLR 5.5 was determined by a bias adjusted log rank test after searching all possible cuts (see Supplemental Methods) (10). Throughout this article we refer to NLR ≤5.5 as "low NLR" and NLR >5.5 as "high NLR". The univariate association of each covariate with NLR (≤5.5 vs. > 5.5) was assessed using the chi-square test for categorical covariates and ANOVA for numerical covariates. The univariate association of each covariate with OS or PFS was tested by Cox proportional hazard model with hazard ratio (HR) and its 95% confidence interval (CI) being reported. In the multivariable analysis, we initially considered several variables in addition to NLR: age, gender, race, tumor histology, baseline albumin, ECOG, MSKCC score, baseline platelets > ULN, and prior nephrectomy. The multivariable model was built by backward elimination process; a criterion of $p > 0.2$ was specified to remove variables that were not significantly predictive. The MSKCC risk score, age, race, ECOG, baseline platelets, prior nephrectomy were not predictive of OS or PFS at the pre-specified level, and therefore were dropped as co-variates. The final multivariable analysis included the covariates that had a value $p <0.2$ which are gender, tumor histology, and baseline albumin. Kaplan-Meier plot along with log-rank test was used to plot OS and PFS stratified by low versus high NLR.

3. Results

Patient and tumor characteristics

The characteristics of 38 patients with mRCC are shown in Table 1. Patients had a median age of 68.5 years, 29 (76%) were men and 9 (24%) were women. Within the cohort, tumor histology includes 20 (53%) non-clear cell and 18 (48%) clear cell. Nephrectomy prior to nivolumab was common, seen in 30 (79%) patients. Thirty-five patients (92%) received prior VEGF inhibitor; however, two patients (5%) received treatment other than VEGF inhibitor (mTOR inhibitor and IL2), and one patient (3%) received no prior medical therapy. The majority of patients (45%) had KPS score of 80–100. MSKCC score within the cohort showed 4 (10%) patients with good prognosis, 20 (53%) patients with intermediate prognosis, and 14 (37%) with poor prognosis.

Response was evaluable for 32 patients; the other six patients did not complete two cycles (8 weeks) of treatment. One patient experienced CR, one patient had PR, and 15 patients (40%) experienced SD. Among those 15 patients with SD, 12 patients (80%) had stable disease for greater than 4 months. In our cohort, a total of 17 patients (53%) had clinical benefit after nivolumab treatment.

Baseline NLR and clinical benefit

The majority of patients (66%) had low NLR at baseline. According to univariate analysis, baseline low NLR is associated with good (ECOG 0–1) performance status (p=0.029) but not with any other factors (Supplemental Table 1). The univariate analysis of clinical benefit from nivolumab showed a significant association with treatment initiation less than one year (p=0.016), but not with any other of the factors studied, including baseline NLR (p=0.314) (Supplemental Table 2).

Progression free survival

The PFS rate at 12 months was 54% in our cohort. The median PFS was 2.6 months in patients with high NLR, but was not reached for patients with low NLR. The Kaplan-Meier curve for PFS is shown in Figure 1A. In univariate analysis, low baseline NLR was significantly associated with longer PFS with a hazard ratio of 0.26 (95% CI 0.09–0.74; p=0.012) (Table 2). No other variables were significantly associated with PFS. The multivariable analysis showed an adjusted hazard ratio of 0.20 (95% CI 0.07–0.64; p=0.006) for low baseline NLR relative to high NLR patients (Table 3).

Overall survival

The OS rate at 12 months was 69% in our cohort. The median OS was 2.7 months in patients with high NLR, but was not reached for patients with low NLR. The Kaplan-Meier curve for OS is shown in Figure 1B. In the univariate analysis, low NLR was significantly associated with prolonged OS with a hazard ratio of 0.06 (95% CI 0.01–0.049; p=0.009) (Table 4). In other words, the chance of being alive was 94% among patients with low NLR (≤5.5). Multivariable analysis similarly showed a significant association between NLR and OS, with an adjusted hazard ratio of 0.06 (95% CI 0.01–0.55, p=0.012) for low NLR comparing to high NLR patients (Table 5).

4. Discussion

The treatment of metastatic RCC has advanced in recent years with the addition of new therapeutic options, most recently immune checkpoint inhibitors such as nivolumab. Consequently, it has become important to develop strategies to determine which patients will benefit from treatment with immunotherapy agents. Biomarkers that correlate with disease activity and prognosis are of high interest and have high clinical value; however, a marker to guide treatment for patients with mRCC is lacking. In our study, we demonstrate that a baseline NLR of ≤5.5 prior to nivolumab treatment was significantly associated with superior PFS and OS among patients with mRCC treated with nivolumab.

Many studies have shown that inflammatory markers such as CRP, albumin, and NLR have prognostic value in mRCC (7, 11). In a recent study, authors monitored CRP before and during sunitinib therapy and found that elevated CRP at baseline was associated with decreased PFS and OS (12). Furthermore, patients whose CRP normalized during treatment had greater PFS and OS compared to patients whose CRP did not normalize (12). While limited in scope due to small cohorts, such studies show that biomarkers have potential for clinical application. Our group recently reported a prognostic risk assessment model, which

includes CRP and albumin for patients with mRCC (13). In this study, multiple measurements of the inflammatory markers during the course of treatment allowed for risk stratification not only at baseline, but at any time during the course of treatment (13).

NLR is an attractive, cost-effective biomarker that is easily calculated from routine laboratory data. The utility of NLR in RCC was previously reported in several studies. A 2015 meta-analysis of 15 cohorts containing over 3000 patients with RCC showed that elevated NLR indicates poorer prognosis (14). Another study from 2015 showed high NLR prior to nephrectomy for metastatic RCC was associated with decreased OS (11). In 2016, Zhang et al. reported that low NLR predicted greater OS and PFS in patients receiving targeted therapy (7). Recently, Jeyakumar et al. reported that NLR >4 predicted shorter OS and PFS in 57 patients receiving immune checkpoint inhibitors for RCC and urothelial cancer (15).

Importantly, the cutoff value defining elevated NLR is different in each of these studies. The NLR values of the individual study cohorts ranged from 2.5 – 4.41 in the 2015 meta-analysis by Hu et al (13). The authors suggested that studies with NLR≥3 as the cutoff had a superior prognostic role; however, it should be noted that the patients in the study cohorts were post-nephrectomy or receiving targeted therapy (13). Whether the NLR≥3 cutoff value is relevant for immune checkpoint inhibitors is not known. In our cohort, we chose the cut off value 5.5 based on statistical analysis (see Supplemental Methods). Since these cutoff values were derived statistically from each cohort, it is likely that differences in patient characteristics and treatment factors among cohorts may be responsible for the different cutoff values observed.

The main limitations to our study are the small cohort size and retrospective design, which are susceptible to selection bias in data analysis. However, our results are consistent with previously reported studies in that low NLR values are associated with greater OS and PFS. Our study examined initial NLR prior to nivolumab therapy as a prognostic factor. Future studies tracking NLR over the course of treatment would be valuable to assess whether NLR changes in response to treatment. Given the multiple retrospective studies showing the prognostic value of NLR for treatment with different agents, it is important to incorporate NLR into a prospective trial to validate its utility in the treatment of advanced RCC.

In conclusion, we demonstrated that low baseline NLR was associated with superior PFS and OS in patients with metastatic RCC who received nivolumab therapy. These results suggest that NLR can be used as a biomarker for prognosis in patients with mRCC and should be further validated in larger cohorts and in prospective studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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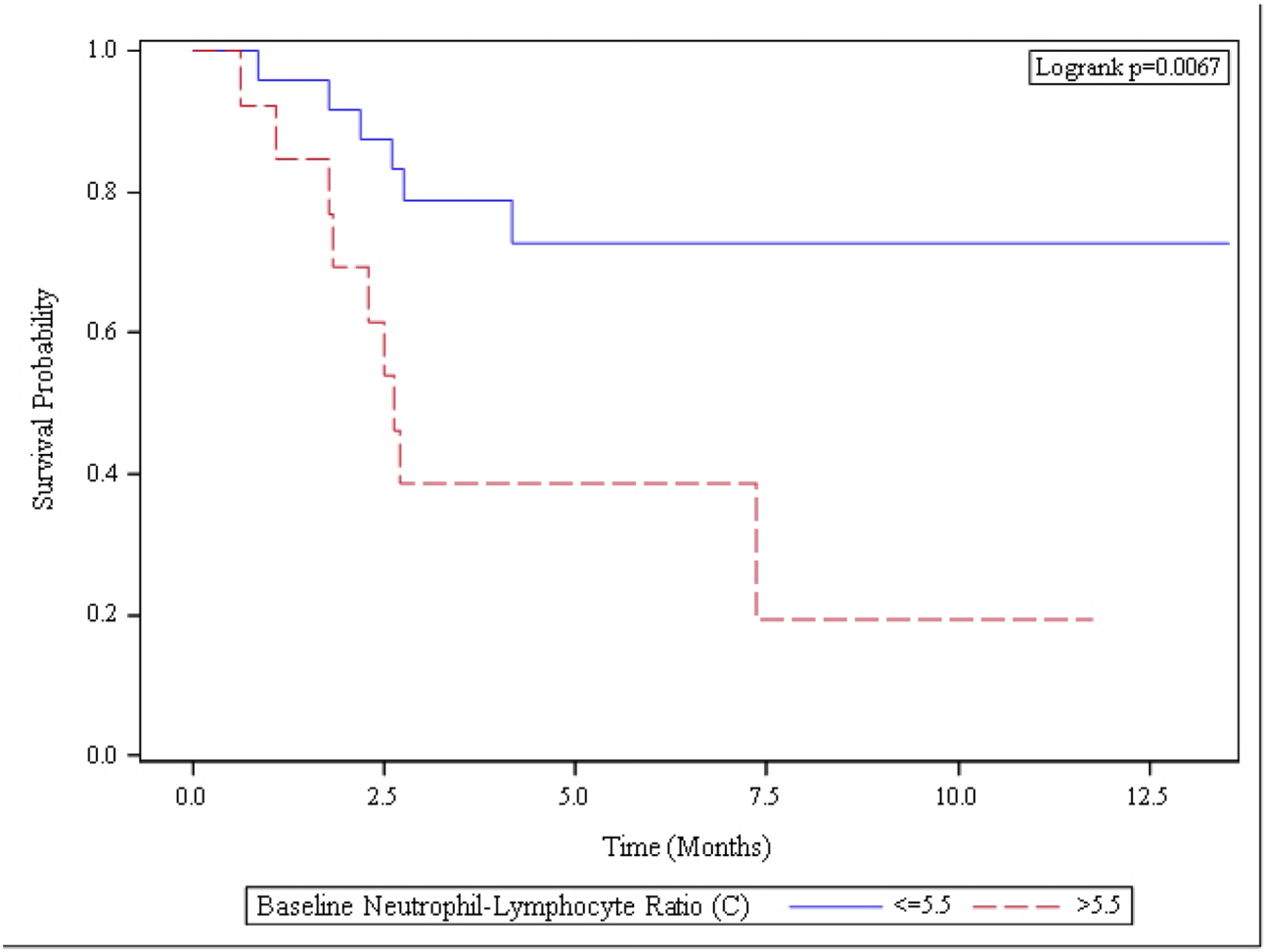
Clinical Practice Summary

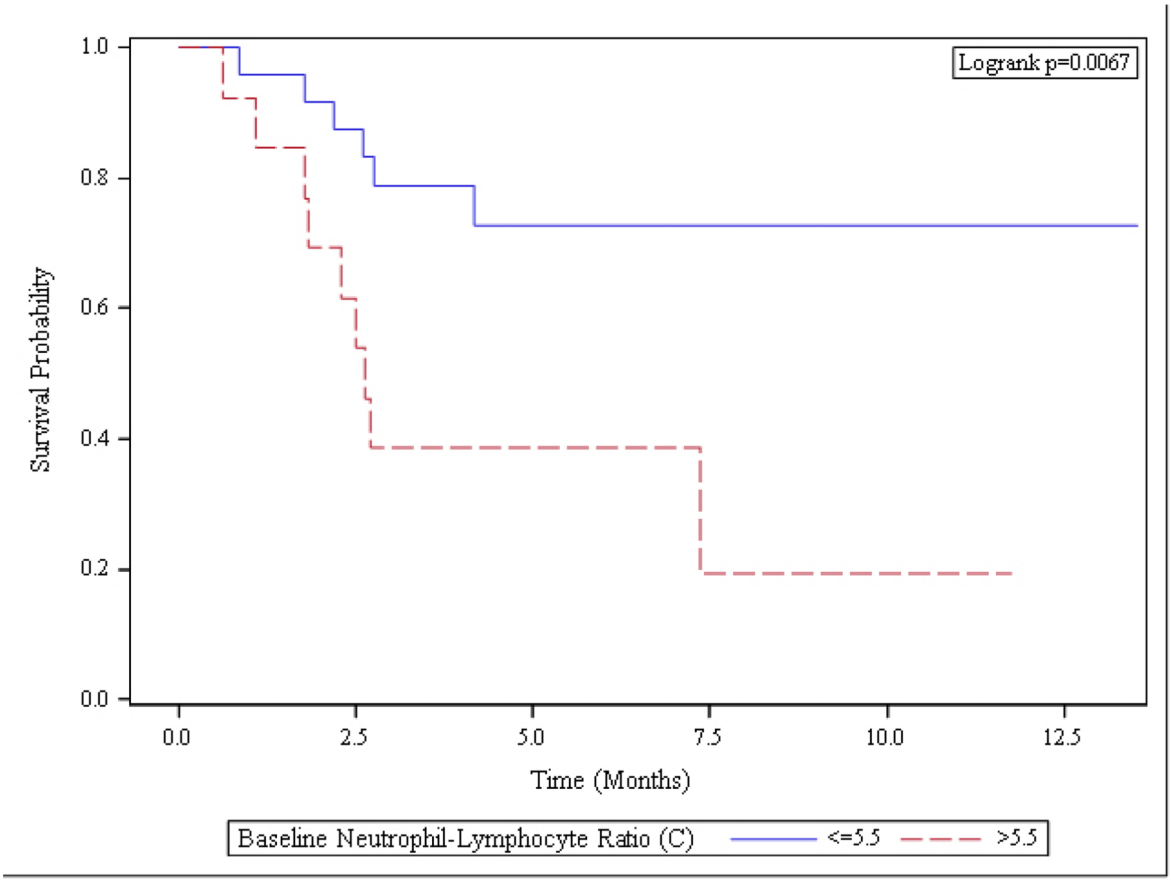
- NLR is an attractive, cost-effective biomarker that is easily calculated from routine laboratory data.
- We show that in patients treated with nivolumab, a pre-treatment NLR less than 5.5 is associated with superior PFS and OS.
- Biomarkers such as NLR may help clinical decisions about prognosis in mRCC.
- These results should be further validated in larger cohorts and in prospective studies.

A.



Baseline Neutrophil-Lymphocyte-Ratio (C)	Number of Subjects	Median Survival (95% CI)
≤5.5	25	NA (4.2, NA)
>5.5	13	2.6 (1.8, NA)

B.



Baseline Neutrophil-Lymphocyte Ratio (C)	Number of Subjects	Median Survival (95% CI)
≤5.5	25	NA (NA, NA)
>5.5	13	2.7 (1.8, NA)

Figure 1.

A. Kaplan-Meier Curve of Progression Free Survival

B. Kaplan-Meier Curve of Overall Survival

Table 1

Descriptive Statistics

Variable	Level	N (%) = 38
Age	Median (range)	69 (24–80)
Gender	F	9 (23.7)
	M	29 (76.3)
Race	Non-White	5 (13.2)
	White	33 (86.8)
Histology	None Clear Cell	20 (52.6)
	Clear Cell	18 (47.4)
ECOG	0–1	21 (55.3)
	2–4	17 (44.7)
Prior Nephrectomy	N	8 (21.1)
	Y	30 (78.9)
KPS	30–60	10 (26.3)
	70	11 (28.9)
	80–100	17 (44.7)
MSKCC Risk	Good	4 (10.5)
	High	14 (36.8)
	Intermediate	20 (52.6)
Best Response	CR	1 (2.6)
	IE	6 (15.8)
	PD	15 (39.5)
	PR	1 (2.6)
	SD	15 (39.5)
Clinical Benefit	No	15 (39.4)
	Yes	17 (44.7)
	IE	6 (15.9)
Baseline Neutrophil-Lymphocyte Ratio	≤5.5	25 (65.8)
	>5.5	13 (34.2)
Baseline Albumin	Median (range)	3.5 (2.3–4.3)
Baseline Calcium	Median (range)	9.2 (7.3–11.4)
Baseline Neutrophil count	Median (range)	4.4 (1.5–9.3)
Baseline Lymphocyte count	Median (range)	1.2 (0.3–3.2)
Baseline Neutrophil-Lymphocyte Ratio	Median (range)	4.1 (0.7–21.7)

ECOG: Eastern Cooperative Oncology Group, KPS: Karnofsky Performance Scale CR: Complete response, PR: Partial response, PD: Progressive disease. SD: Stable disease, IE: Inevaluable

Table 2

Univariate Association with Neutrophil-Lymphocyte ratio

			Baseline Neutrophil-Lymphocyte Ratio (C)		
Covariate	**Statistics**	**Level**	**≤5.5 N=25**	**>5.5 N=13**	**P-value***
Gender	N (%)	F	7 (28)	2 (15.38)	0.456
	N (%)	M	18 (72)	11 (84.62)	
Race	N (%)	Non-White	4 (16)	1 (7.69)	0.643
	N (%)	White	21 (84)	12 (92.31)	
Histology	N (%)	None Clear Cell	13 (52)	7 (53.85)	0.914
	N (%)	Clear Cell	12 (48)	6 (46.15)	
ECOG	N (%)	0–1	17 (68)	4 (30.77)	**0.029**
	N (%)	2–4	8 (32)	9 (69.23)	
Prior Nephrectomy	N (%)	N	4 (16)	4 (30.77)	0.407
	N (%)	Y	21 (84)	9 (69.23)	
KPS	N (%)	30–60	5 (20)	5 (38.46)	0.158
	N (%)	70	6 (24)	5 (38.46)	
	N (%)	80–100	14 (56)	3 (23.08)	
Baseline PLT > ULN	N (%)	N	22 (88)	12 (92.31)	1.000
	N (%)	Y	3 (12)	1 (7.69)	
Initiation of Tx < 1 year	N (%)	N	12 (48)	3 (23.08)	0.136
	N (%)	Y	13 (52)	10 (76.92)	
Baseline Low Hb	N (%)	N	11 (44)	2 (15.38)	0.148
	N (%)	Y	14 (56)	11 (84.62)	
Baseline Elevated LDH	N (%)	N	16 (64)	9 (69.23)	0.888
	N (%)	Unknown	3 (12)	2 (15.38)	
	N (%)	Y	6 (24)	2 (15.38)	
MSKCC Risk	N (%)	Good	4 (16)	0 (0)	0.340
	N (%)	High	8 (32)	6 (46.15)	
	N (%)	Intermediate	13 (52)	7 (53.85)	
Age	N		25	13	0.426

Covariate	Statistics	Level	Baseline Neutrophil-Lymphocyte Ratio (C) ≤5.5 N=25	Baseline Neutrophil-Lymphocyte Ratio (C) >5.5 N=13	P-value*
	Median (Min – Max)		67 (24–78)	70 (49–80)	
Baseline Ca	N		25	13	0.935
	Median (Min – Max)		9.2 (8.2 –11.2)	9.3 (7.3–11.4)	
Baseline albumin	N		25	13	0.124
	Median (Min – Max)		3.6 (2.4–4.3)	3.3 (2.3–3.9)	

*The p-value is calculated by ANOVA for numerical covariates; and chi-square test or Fisher's exact for categorical covariates, where appropriate.

ECOG: Eastern Cooperative Oncology Group, KPS: Karnofsky Performance Scale, Tx: Treatment, Hb: Hemoglobin, LDH: Lactate Dehydrogenase, Ca: Calcium

Table 3

Univariate association with PFS

			Time to progress, death, or hospice (Months)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Baseline Neutrophil-Lymphocyte Ratio	≤5.5	25	0.26 (0.09–0.74)	**0.012**	**0.012**
	>5.5	13	-	-	
Gender	F	9	1.44 (0.46–4.53)	0.536	0.536
	M	29	-	-	
Race	Non-White	5	0.49 (0.06–3.75)	0.492	0.492
	White	33	-	-	
Histology	None Clear Cell	20	0.50 (0.18–1.41)	0.191	0.191
	Clear Cell	18	-	-	
ECOG	0–1	21	0.46 (0.16–1.31)	0.146	0.146
	2–4	17	-	-	
Prior Nephrectomy	N	8	0.99 (0.28–3.52)	0.990	0.990
	Y	30	-	-	
KPS	30–60	10	1.90 (0.47–7.63)	0.364	0.183
	70	11	3.20 (0.92–11.06)	0.066	
	80–100	17	-	-	
Baseline PLT > ULN	N	34	0.78 (0.18–3.45)	0.742	0.742
	Y	4	-	-	
Initiation of Tx < 1 year	N	15	0.28 (0.08–1.00)	0.051	0.051
	Y	23	-	-	

ECOG: Eastern Cooperative Oncology Group, KPS: Karnofsky Performance Scale, PLT: Platelet, Tx: Treatment

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Table 4

Multivariable Survival Analysis of PFS

			Time to PFS (Months)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Baseline Neutrophil-Lymphocyte Ratio	≤5.5	25	0.20 (0.07–0.64)	**0.006**	**0.006**
	>5.5	13	-	-	
Gender	F	9	2.64 (0.69–10.02)	0.155	0.155
	M	29	-	-	
Race	Non-White	5	0.06 (0.00–1.04)	0.053	0.053
	White	33	-	-	
Histology	None Clear Cell	20	0.35 (0.12–1.05)	0.060	0.060
	Clear Cell	18	-	-	
Baseline albumin		38	0.39 (0.11–1.39)	0.145	0.145

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Table 5

Univariate association with Overall Survival

			Time to OS (Months)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Baseline Neutrophil-Lymphocyte Ratio	≤5.5	25	0.06 (0.01–0.49)	**0.009**	**0.009**
	>5.5	13	-	-	
Gender	F	9	0.55 (0.07–4.50)	0.580	0.580
	M	29	-	-	
Race	Non-White	5	0.00 (0.00-.)	0.996	0.996
	White	33	-	-	
Histology	None Clear Cell	20	0.27 (0.05–1.32)	0.106	0.106
	Clear Cell	18	-	-	
ECOG	0–1	21	0.42 (0.10–1.74)	0.229	0.229
	2–4	17	-	-	
Prior Nephrectomy	N	8	1.36 (0.27–6.75)	0.705	0.705
	Y	30	-	-	
KPS	30–60	10	3.96 (0.36–43.74)	0.261	0.118
	70	11	8.93 (1.04–76.62)	**0.046**	
	80–100	17	-	-	
Baseline PLT > ULN	N	34	0.78 (0.10–6.39)	0.821	0.821
	Y	4	-	-	
Initiation of Tx < 1 year	N	15	0.19 (0.02–1.54)	0.120	0.120
	Y	23	-	-	

ECOG: Eastern Cooperative Oncology Group, KPS: Karnofsky Performance Scale, PLT: Platelet, Tx: Treatment,

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Table 6

Multivariable Survival Analysis of OS

			Time to OS (Months)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Baseline Neutrophil-Lymphocyte Ratio	≤5.5	25	0.06 (0.01–0.55)	**0.012**	**0.012**
	>5.5	13	-	-	
Gender	F	9	0.11 (0.01–1.94)	0.133	0.133
	M	29	-	-	
Histology	None Clear Cell	20	0.23 (0.04–1.30)	0.097	0.097
	Clear Cell	18	-	-	
Baseline albumin		38	0.21 (0.02–1.97)	0.171	0.171

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