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Prognostic and Predictive Role of Neutrophil/Lymphocyte Ratio in Egyptian Patients with Metastatic Renal Cell Carcinoma (mRCC)

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Abstract

Background: Treatment and prognosis of patients with mRCC have been improved by understanding molecular pathogenesis. Several prognostic models based on the data of patients treated with targeted therapy and immunotherapy have been useful in clinical practice. Serum blood markers related to inflammatory response have been reported to be associated with their prognosis or prediction of therapeutic efficacy. **Study design and Methodology:** Neutrophil/lymphocyte ratio (NLR) was estimated in thirty-two patients with pathological confirmed mRCC as baseline and after two months of systemic therapy. NLR failure was defined as an increase of 3 or more compared to baseline NLR. **Results:** Thirty-two patients were enrolled with a mean age 62.7 years and male gender predominance (81.2%). Twenty-seven patients had clear cell pathological subtype. Neutrophil/lymphocyte ratio (NLR) mean value baseline was 3.17 and after 2 months of treatment was 5.88. Pazopanib was the commonest received treatment (50%). Six patient (18.8%) had progressed after 2 months of first line of treatment. By the end of the study, only 2 patients were still alive. Mean disease-free survival (DFS) for patients presented with non-metastatic disease 16 months. Mean overall survival (OS) for all patients was 18 months. NPL difference change before and after 2 months of treatment, revealed that patients with lower NLR change had a statistically significant better OS than patients with high NLR change ($p < 0.0001$). Cutoff value of NLR 3.6. **Conclusion:** NLR is a prognostic marker in patients with mRCC with predictive role in response to treatment on survival rate.

Keywords

Renal Cell Carcinoma, Neutrophil/Lymphocyte Ratio, Prognosis.

INTRODUCTION

According to the 2018 GLOBLE data, 403,000 individuals were diagnosed with kidney cancer each year, accounting for 2.2% of all cancers worldwide [1]. It is the sixth most common type of cancer among males and the ninth among females [2]. Approximately one-third of patients with RCC have experienced metastasis by the time of diagnosis [3].

Metastatic renal cell carcinoma (mRCC) is an incurable malignancy, characterized by its resistance to traditional chemotherapy, radiation, and hormonal therapy [4]. There

are several globally prognostic models regarding the survival of patients with mRCC [5]. Treatment prediction and prognosis of patients with mRCC have been significantly improved by advances in understanding of its molecular pathogenesis; this understanding has led to the development of targeted therapeutics agents like antivasular endothelial growth factor (VEGF), immune checkpoint inhibitors, (PDL-1) or the mammalian target of rapamycin (mTOR) pathways [6].

In recent years, it has become clear that tumor-related inflammatory responses, such as local and systemic inflammation has a major role in the development and progression of malignancies [7]. The alteration of peripheral blood

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biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) can represent the systemic inflammatory response in patients. Several studies have demonstrated that the NLR is a potent prognostic biomarker related to worse overall survival (OS) in several tumor types, including mRCC in the pre-immunotherapy era [8]. Normal NLR values in an adult population in good health are between 0.78 and 3.53. NLR failure was defined as an increase of 3 or more compared to baseline NLR [9].

Study Design and Methodology

In this study neutrophil/lymphocyte ratio (NLR) was estimated as a laboratory predictive and prognostic marker in thirty-two patients with mRCC baseline and after two months of systemic therapy. All patients enrolled retrospectively at clinical oncology department at Ain Shams University hospital and El-Araby international Hospital from January 2016 till December 2021. All enrolled patients had assigned a medical consent for research before data collection

Inclusion Criteria

- Pathologically confirmed renal cell carcinoma
- Clinical and radiological proved metastatic disease
- Any age and gender

Exclusion Criteria

- Uncontrolled comorbid disease or another malignancy.
- Any immune related disorders or medications (e.g. immunosuppressant)
- Known family history of RCC or other cancer type

All continuous data summarized in terms of mean and standard deviation, while categorical data were summarized in terms of frequencies and percentages. ROC curve was used to estimate the optimal cutoff point that differentiate progressed and non-progressed patients. Also, we used Kaplan-Meier estimator to calculate the overall survival and disease-free survival. Log-rank test was used for comparison. The R software version 4.1.1.was used in this analysis.

Results

Thirty-two patients with mRCC were enrolled in the study with a mean age 62.7 years with male gender predominance (81.2%). Thirty patients had no family history of renal cell carcinoma with 2 unknown information about their family history. Only 14 patients were cigarette smokers. Fifty percent of patients had ECOG performance status 1 at presentation time. Unfortunately, only two patients are still alive by the end of the study (Table 1).

Table 1: Clinic-pathological Descriptive Analysis of Studied Patients' Data.

	N=32
Age. Mean±SO	62.7±4.15
Sex: N (%);	
F	6 (18.8%)
M	26 (81.2%)
Smoking, N	
No	18 (56.2%)
Yes	14 (43.8%)
Family History, N (%):	
No	30 (93.8%)
unkown	2 (6.25%)
Comorbid Disease, N (%):	
COPD	1 (3.12%)
DM	3 (9.38%)
HTN	6 (18.8%)
HTN, COPD	1 (3.12%)
HTN, DM	6 (18.8%)
HTN, DM, IHD	1 (3.12%)
HTN, IHD	2 (6.25%)
No	12 (37.5%)
Pathological Type, N (%):	
chromophobe	1 (3.12%)
Clear cell	27 (84.4%)
medullary	1 (3.12%)
papillary	3 (9.38%)
Stage at Presentation, N (%):	
1	5 (15.6%)
2	7 (21.9%)
3	13 (40.6%)
4	7 (21.9%)
Performance Status, N (%)	
1	16 (50.0%)
2	14 (43.8%)
3	2 (6.25%)

Twenty-seven patients developed clear cell pathological subtype representing (84.4%) of all patients.

Stage III was the most common presentation stage (40.6%) and equally presented stage II and Stage IV (21.9%).

Twenty percent of patients had a single metastatic site, and the commonest site of metastasis was lungs (22 patients) (Table 1)

Pazopanib was the commonest received treatment (50%). Regarding patients' response after 2 months, 19

patients had partial response (59%), 7 patients with stable disease (21.9%) and 6 patients had progressive disease (18.8%). The NLR mean baseline was 3.17 and after 2 months of treatment was 5.88. Six patient (18.8%) had progressed after 2 months of first line of treatment (Table 2).

Table 2: Laboratory, Radiological and Treatment-related Descriptive Analysis of Studied Patients' Data.

Treatment Received, N (%):	
afinitor	5 (15.6%)
sutent	11 (34.4%)
votrient	16 (50.0%)
Baseline NLR, Mean±SD	3.17±1.07
Difference NLR (baseline and after 2 m), Mean±SD	2.70±1.23
After 2 mon NLR, Mean±SD	5.88±2.06
Number of Metastatic Sites, N (%):	
1	20 (62.5%)
2	11 (34.4%)
3	1 (3.12%)
Organs, N (%):	
Locoregional	1 (3.12%)
liver	6 (18.8%)
liver and bone	1 (3.12%)
liver and local	1 (3.12%)
bone and locoregional	1 (3.12%)
lung	13 (40.6%)
lung and bone	1 (3.12%)
lung and brain	1 (3.12%)
lung and liver	5 (15.6%)
lung and liver and bone	1 (3.12%)
lung and local	1 (3.12%)
Response to Treatment after 2 Months, N (%):	
PR	19 (59.4%)
progress	6 (18.8%)
SD	7 (21.9%)
Response, N (%):	
Not progressed	26 (81.2%)
Progressed	6 (18.8%)
Survival, N (%):	
Alive	2 (6.25%)
Dead	30 (93.8%)

After estimating the difference between neutrophil-to-lymphocyte ratio (NLR) before and after 2 months of treatment, cutoff value of NLR with highest sensitivity and specificity was (3.6). The median overall survival (OS) for all studied patients was 18 months (figure 1) but it

was 26 months for patients presented with non-metastatic disease (figure 2). Regarding disease-free survival (DFS) for patients presented with non-metastatic disease, the estimated median DFS was 16 months (figure 3).

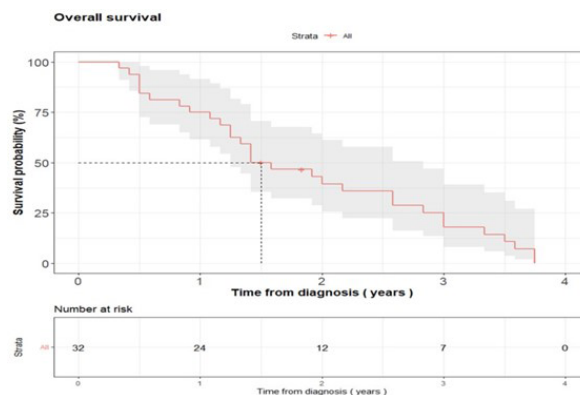


Figure 1: OS for All Studied Patients with Metastatic RCC

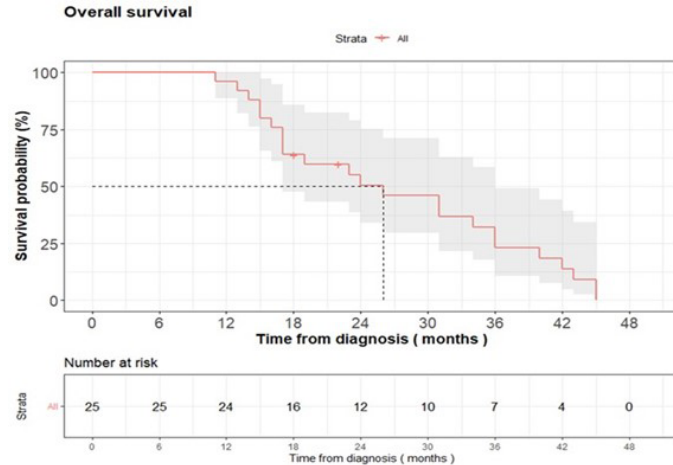


Figure 2: OS for Patients Presented with Non-metastatic RCC

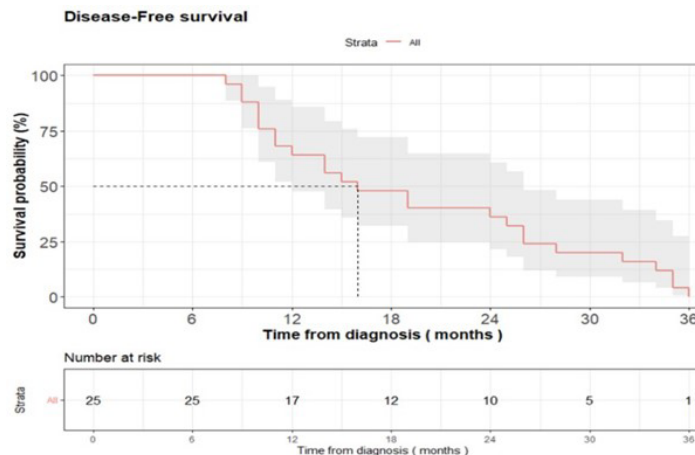
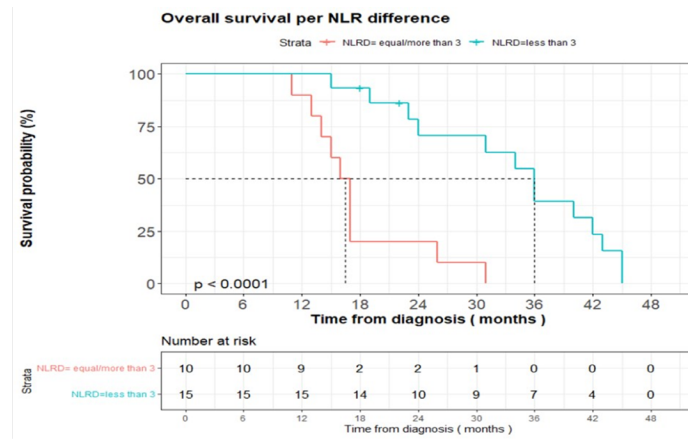


Figure 3: DFS for Patient Presented with Non-metastatic Disease

According to NLR failure definition as increased by 3 or more, patients with lower NLR change had a statistically significant better overall survival than patients with NLR change ($p < 0.0001$) (figure 4).



NLRD= equal/more than 3							
time	n.risk	n.event	survival	std.err	lower	95% CI upper	95% CI
1	9	7	0.562	0.1240	0.3651	0.867	
2	2	7	0.125	0.0827	0.0342	0.457	

NLRD=less than 3							
time	n.risk	n.event	survival	std.err	lower	95% CI upper	95% CI
1	15	1	0.938	0.0605	0.826	1.000	
2	10	4	0.661	0.1246	0.457	0.956	
3	7	4	0.367	0.1295	0.184	0.733	

Figure 4: Impact of Difference NLR between Baseline and Post-treatment on OS in Metastatic RCC

Also in this study, Patients presented with non-metastatic disease with lower NLR change had a statistically significant better DFS than patients with high NLR change

after being metastatic after 2 months of treatment ($p < 0.0003$) (figure 5).

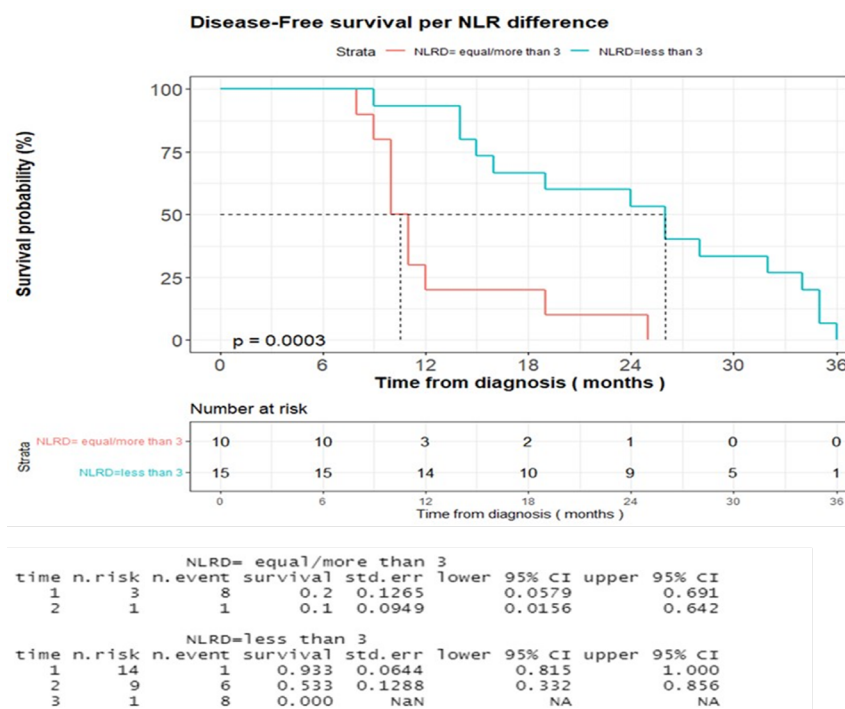


Figure 5: Impact of Difference NLR between Baseline and Post-treatment on DFS in Previously Nonmetastatic RCC

Discussion

The neutrophil/lymphocyte ratio (NLR) is an easily measurable and inexpensive serum inflammatory marker with many types of malignancies have been correlated to it [10]. In this study

neutrophil/lymphocyte ratio (NLR) was estimated as a laboratory predictive and prognostic marker in 32 Egyptian patients were diagnosed as metastatic renal cell carcinoma (either presented with metastatic disease or with early stages and developed metastasis later during the study).

The results of a Chinese meta-analytical study revealed that a high NLR at baseline or pre-therapy was associated with a poor OS (HR, 2.23; 95% CI, 1.84–2.70; $p < 0.001$). During treatment, a decrease in the NLR was associated with a significantly longer OS (HR, 0.34; 95% CI, 0.20–0.56; $p < 0.001$) [11]. Dana Farber Cancer Institute (Boston, MA) receiving IO based therapies were included. The NLR was examined at baseline and 6 weeks later. Higher NLR at baseline and at 6-weeks showed a trend to reduced worse OS and NLR at 6-weeks ($p < 0.001$) was a stronger prognostic than baseline values and the changed value between baseline and 6 weeks of treatment ($p = 0.008$). These results coincide with our results as patients with lower NLR change had a statistically significant better OS than patients with higher NLR change after 2 months

of treatment ($p < 0.0001$).

In March 2014, a meta-analysis was performed to generate a combination of HRs with 95% CIs for overall survival (OS) and recurrence-free/progress-free survival (RFS/PFS). Results of 15 cohorts containing 3357 patients were included indicated that elevated NLR predicted poorer OS (HR=1.82, 95% CI 1.51 to 2.19) and RFS/PFS (HR=2.18, 95% CI 1.75 to 2.71) in patients with RCC. These findings were different when stratified by study region, sample size, therapeutic intervention, types of RCC and study quality. However, it differed significantly by assessment of the cut-off value defining the 'elevated NLR' in RFS/PFS ($p = 0.004$) [12].

Conclusion

Elevated NLR indicates a poorer prognosis for patients with mRCC and should be monitored in patients for risk stratification and predictor for treatment response.

Strength and Limitations of the Study

The study gives new issues regards treatment choice and response expectations related to immunotherapy in metastatic renal cell carcinoma with further recommendation related to immune-related oncogenesis. The limited number of the enrolled patients affects significance of results, more studies on large number of patients with meta-analysis will give more reliable

results that can have a great impact on treatment decision

Ethics Approval

Oncology ethical committee of Faculty of Medicine Ain Shams University approval available on demand

Patient Consent

Not available for most of patients as it is a retrospective study.

Availability of Data and Materials

Available on demand.

Competing Interests

The author has declared no conflict of interest and no risk of bias as the study is retrospective enrolled patients presented in a certain period during era of immune-related cancer studies

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Authors Contribution

Single author.

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