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Research Article

Prognostic value of systemic inflammatory markers in renal cell carcinoma with isolated lung metastases: A retrospective analysis

İzole akciğer metastazlı renal hücreli karsinomda sistemik inflamatuvar belirteçlerin prognostik önemi: Retrospektif inceleme

Nargiz Majidova*[1], Ali Kaan Güren[1], Gülhan Dinç[2], Muhammed Fatıh Kırcalı[1], Mustafa Seyyar[3], Demet Işık Bayraktar[4], Erkam Kocaaslan[1], Nadiye Sever[1], Yeşim Ağyol[1], Pınar Erel[1], Burak Paçacı[1], Mustafa Alperen Tunç[1], Abdussamet Çelebi[1], Selver Işık[1], Rukiye Arıkan[1], İbrahim Vedat Bayoğlu[1], Osman Köstek[1], Murat Sarı[1]

[1]Department of Internal Medicine, Division of Medical Oncology, Marmara University School of Medicine, Istanbul, Turkey,

[2]Department of Internal Medicine, Division of Medical Oncology, Professor Dr Cemil Tascioglu City Hospital, Istanbul, Turkey,

[3]Department of Internal Medicine, Division of Medical Oncology, Kocaeli University, Kocaeli, Turkey,

[4]Department of Internal Medicine, Division of Medical Oncology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey.

Abstract

Aim: Metastatic renal cell carcinoma (mRCC) with lung metastases is associated with poor prognosis, and there is a growing interest in systemic inflammatory markers as potential prognostic indicators. This study evaluates the prognostic significance of the Systemic Immune-Inflammation Index (SII), Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Advanced Lung Cancer Inflammation Index (ALI) in patients with mRCC.

Material and Methods: In our retrospective and multicenter study, we analyzed 76 mRCC patients with isolated lung metastases. Clinical data, including demographic characteristics, treatment details, and inflammatory markers, were collected. Patients were stratified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification. The association of clinical and laboratory parameters with progression-free survival (PFS) and overall survival (OS) was analyzed using Kaplan-Meier curves and Cox proportional hazards models.

Results: The median age of the patients was 61 years (IQR: 29-84), with the majority being male (74%) and smokers (57%). High SII, NLR, and PLR were significantly associated with poor IMDC risk classification (p=0.001, p=0.003, and p=0.001, respectively). Multivariate analysis identified age >65 years (HR 3.09, 95% CI 1.3-6.9, p=0.006) and high PLR (HR 5.9, 95% CI 2.2-15.8, p=0.001) as independent predictors of worse OS. ALI was not significantly associated with survival outcomes.

Conclusion: Systemic inflammatory markers, particularly SII, NLR and PLR are strongly associated with poor prognosis in mRCC patients with lung metastases. These markers could be integrated into existing prognostic models to improve risk stratification and guide clinical decision-making. Further research is warranted to validate these findings and explore the underlying mechanisms linking systemic inflammation to RCC progression.

Keywords: Metastatic renal cell carcinoma, Lung metastases, Systemic immune-inflammation index, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio

Corresponding author*: Nargiz Majidova, Department of Internal Medicine, Division of Medical Oncology, Marmara University School of Medicine, Istanbul, Turkey.
E-mail: nergiz.mecidova1991@gmail.com
Orcid: 0000-0002-2575-5819
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Öz

Amaç: İzole akciğer metastazlı metastatik renal hücreli karsinom (mRHK) kötü prognozla ilişkilidir ve potansiyel prognostik göstergeler olarak sistemik inflamatuar belirteçlere artan bir ilgi vardır. Bu çalışmada mRCC hastalarında Sistemik İmmün-İnflamasyon İndeksi (Sİİ), Nötrofil-Lenfosit Oranı (NLO), Trombosit-Lenfosit Oranı (PLO) ve İleri Akciğer Kanseri İnflamasyon İndeksi'nin (İAİİ) prognostik önemi değerlendirilmektedir.

Gereç ve Yöntemler: Akciğer metastazları tedavi edilen 76 mRHK hastasının retrospektif bir analizini yaptık. Demografik özellikler, tedavi ayrıntıları ve enflamatuar belirteçler dahil olmak üzere klinik veriler toplandı. Hastalar Uluslararası Metastatik Renal Hücreli Karsinom Veritabanı (IMDC) risk sınıflandırmasına göre tabakalandırıldı. Klinik ve laboratuvar parametrelerinin progresyonsuz sağkalım (PFS) ve genel sağkalım (GS) ile ilişkisi Kaplan-Meier eğrileri ve Cox orantılı tehlikeler modelleri kullanılarak analiz edilmiştir.

Bulgular: Hastaların ortanca yaşı 61 (dağılım: 29-84) olup, çoğunluğu erkek (%74) ve sigara içmektedir (%57). Yüksek SII, NLR ve PLR kötü IMDC risk sınıflandırması ile anlamlı olarak ilişkiliydi (sırasıyla p=0.001, p=0.003 ve p=0.001). Çok değişkenli analizde 65 yaş üstü (HR 3.09, %95 CI 1.3-6.9, p=0.006) ve yüksek PLR (HR 5.9, %95 CI 2.2-15.8, p=0.001) daha kötü OS için bağımsız öngörücüler olarak tanımlanmıştır. ALI ile sağkalım sonuçları arasında anlamlı bir ilişki bulunmamıştır.

Sonuç: Sistemik inflamatuvar belirteçler, özellikle SII, NLR ve PLR, akciğer metastazı olan mRCC hastalarında kötü prognoz ile güçlü bir şekilde ilişkilidir. Bu belirteçler, risk sınıflandırmasını iyileştirmek ve klinik karar verme sürecini yönlendirmek için mevcut prognostik modellere entegre edilebilir. Bu bulguları doğrulamak ve sistemik enflamasyonu RCC progresyonuna bağlayan altta yatan mekanizmaları keşfetmek için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Metastatik renal hücreli kanser, akciğer metastazı, sistemik immune-inflamatuar indeks, nötrofil lenfosit oranı, trombosit lenfosit oranı,

Introduction

Renal cell carcinoma (RCC) is one of the most prevalent malignancies of the kidney, with mRCC representing a particularly aggressive form of the disease [1]. Despite advances in targeted therapies, the prognosis for patients with mRCC, especially those with lung metastases, remains poor [2]. Identifying reliable prognostic factors is crucial for optimizing treatment strategies and improving patient outcomes.

Although combined treatments with immunotherapy are generally recommended in mRCC, in developing countries, tyrosine kinase inhibitors (TKI) are used due to financial conditions. However, TKI's have been shown to be effective after immunotherapy in advanced stages [3].

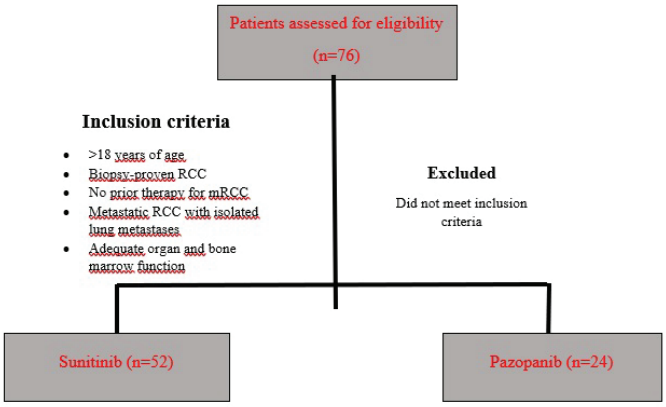
In recent years, systemic inflammatory markers such as SII, NLR, PLR and ALI have gained attention as potential prognostic indicators in various cancers, including RCC. These markers are reflective of the host's immune response and have been associated with tumor progression and survival outcomes [4], [5], [6], [7].

IMDC risk classification is a widely recognized tool for predicting prognosis in mRCC patients [8]. However, the integration of inflammatory markers with traditional risk stratification systems like the IMDC remains underexplored, particularly in patients with lung metastases. In this study, we aimed to evaluate the prognostic significance of SII, NLR, PLR and ALI in patients with mRCC and lung metastases. Additionally, we sought to assess the relationship between these inflammatory markers and the IMDC risk classification, as well as their impact on PFS and OS. Our findings provide insights into the potential role of systemic inflammation in the progression of mRCC and highlight the importance of incorporating these markers into clinical decision-making.

Material and Methods

Study Design and Patient Population

In our retrospective and multicenter (3 centers) study, we analyzed 76 mRCC patients with isolated lung metastases who were followed-up and treated between 2000 and 2022. Patients were eligible for inclusion if they were over 18 years of age, had biopsy-proven RCC, and had not received any prior therapy for mRCC. All patients received first-line treatment with either sunitinib or pazopanib (Figure 1).



Data Collection

Demographic and clinical data were collected from medical records, including age, gender, smoking status, tumor size, histological subtype, and treatment details. Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) scale. Laboratory values such as lactate dehydrogenase (LDH) levels and SII, ALI, NLR and PLR were recorded.

Systemic Inflammatory Markers

The systemic inflammatory markers were calculated as follows:

SII = Platelet count * Neutrophil count / Lymphocyte count; NLR = Neutrophil count / Lymphocyte count; PLR = Platelet count / Lymphocyte count; Body Mass Index (BMI) = kg / m 2; ALI = BMI * Serum Albumin / NLR

The receiver operating characteristic (ROC) curve analysis was used to determine the area under the curve (AUC), sensitivity, specificity, and cutoff values for pretreatment NLR, PLR, ALI and SII. Optimal cut off value, according to ROC curve analysis, was 3.1 for NLR, 193.7 for PLR, 890 for SII, and 79.1 for ALI.

These markers were categorized as high or low based on median values within the cohort. For example; SII (low <890; high ≥890). Patients were then stratified into favorable, intermediate, or poor risk groups according to the IMDC criteria (table 1) (table 2).

Statistical Analysis

PFS was defined as the time from diagnosis to disease progression or death; and OS was defined as the time from diagnosis to death from any cause. Kaplan-Meier survival curves were constructed to estimate PFS and OS, and differences between groups were assessed using the log-rank test.

Independent categorical variables were compared using the Chi-square test or Fisher exact test. Univariate and multivariate Cox proportional hazards models were used to identify predictors of OS. Variables with a p-value < 0.05 in univariate analysis were included in the multivariate model. Hazard ratios (HR) with 95% confidence intervals (CI) were reported to quantify the strength of associations (table 3).

All statistical analyses were performed using SPSS 23, and a p-value < 0.05 was considered statistically significant.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of the University of Marmara (Approval Number 08.12.2023.1551).

Table 1. Demographic and Clinical Characteristics of Patients

	Value n (%)
Age (years) (median, range)	61 (29-84)
Gender	
Female	20 (26)
Male	56 (74)
Smoker	
Yes	35 (57)
No	26 (43)
Tumor size (median, range) (cm)	9 (4-17)
Nephrectomy	
Yes	68 (90)
No	8 (10)
Histological subtype	
Clear cell	69 (91)
Non clear cell	7 (9)
Metastasis status	
Metastatic at diagnosis	30 (40)
Later developing metastasis	46 (60)
ECOG PS	
0-1	73 (96)
≥2	3 (4)
First line treatment	
Sunitinib	52 (68)
Pazopanib	24 (32)
LDH (median, range) (U/L)	195 (120-735)
Sarcomotoid features	
Yes	18 (31)
No	40 (69)
First line progression	
Yes	46 (61)
No	30 (40)
Second line treatment	
TKI	9 (28)
mTOR	2 (7)
IO	20 (65)

n: number, IQR: Interquartile Range, PS: Performance Status, LDH: Lactate Dehydrogenase, TKI: Tyrosine Kinase Inhibitor, mTOR: Target of rapamycin, IO: Immunotherapy

Table 2. Association between SII, ALI, NLR, PLR (low and high) and IMDC risk classification (favorable, intermediate, or poor risk)

		IMDC risk classification, n (%)				
		Favorable	Intermediate	Poor	Total	P
SII	High	4 (12)	8 (25)	8 (73)	20	0.001
	Low	29 (88)	24 (75)	3 (27)	56	
	Total	33 (100)	32 (100)	11 (100)	76	
ALI	High	5 (15)	8 (25)	1 (9)	14	0.4
	Low	28 (85)	24 (75)	10 (91)	62	
	Total	33 (100)	32 (100)	11 (100)	76	
NLR	High	4 (12)	8 (25)	7 (64)	19	0.003
	Low	29 (88)	24 (75)	4 (36)	57	
	Total	33 (100)	32 (100)	11 (100)	76	
PLR	High	2 (6)	5 (16)	7 (64)	14	0.001
	Low	31 (94)	27 (84)	4 (36)	62	
		33 (100)	32 (100)	11 (100)	76	

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; ALI: Advanced Lung Cancer Inflammation Index; SII: Systemic Immune Inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio

Table 3. Comparison of overall survival in the risk factors for Renal Cell Carcinoma patients with lung metastases

Variables		Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
Age (years)	<65 vs. >65	2.3 (1.08-5.03)	0.03	3.09 (1.3-6.9)	0.006
Sex	Female vs. male	0.9 (0.4-2.0)	0.80		
ECOG PS	0-1 vs. ≥2	56.9 (9.2-349)	0.001	29.4 (4.5-192.8)	0.001
Histology	Clear vs. Non-clear	1.3 (0.5-3.3)	0.50		
IMDC risk classification	Favorable vs. intermediate / poor	2.7(1.3-5.6)	0.008	2.2 (1.0-5.1)	0.04
Nephrectomy	No vs. Yes	0.78 (0.02-0.2)	0.001		
Sarcomotoid features	Yes vs. No	1.3 (0.4-3.6)	0.57		
First line treatment	Sunitinib vs. pazopanib	0.54 (0.24-1.22)	0.14		
NLR	Low vs. high	4.27 (1.9-9.6)	0.001		
PLR	Low vs. high	6.9 (2.8-17.1)	0.001	5.9 (2.2-15.8)	0.001
SII	Low vs. high	4.01 (1.7-9.1)	0.001		
ALI	Low vs. high	1.2 (0.5-2.9)	0.61		

CI: confidence interval; HR: hazard ratio; IMDC: International Metastatic renal cell cancer Database Consortium classification; ALI: Advanced Lung Cancer Inflammation Index; SII: Systemic Immune Inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio

Results

Patient Demographics and Clinical Characteristics

A total of 76 patients were assessed for eligibility (Figure 1). The median age of the patients was 61 years, ranging from 29 to 84 years. The majority of the patients were male (74%), and 57% were smokers. The median tumor size was 9 cm, with 90% of the patients having undergone nephrectomy. The most common histological subtype was clear cell carcinoma, observed in 91% of the patients. At diagnosis, 40% of the patients were metastatic, while the remaining 60% developed metastasis later. Most patients had a favorable ECOG-PS of 0-1 (96%), and the first line of treatment was predominantly sunitinib (68%) (table 1).

Association Between Systemic Inflammatory Markers and IMDC Risk Classification

The analysis of the relationship between SII, ALI, NLR, PLR, and IMDC risk classification revealed significant associations for SII, NLR, and PLR. Patients with high SII, NLR, and PLR were more likely to have a poor IMDC risk classification. Specifically, 73% of patients with high SII were classified as poor risk (p=0.001). Similarly, 64% of patients with high NLR and PLR were in the poor-risk category (p=0.003 and p=0.001, respectively). In contrast, ALI was not significantly associated with IMDC risk classification (p=0.4) (table 2).

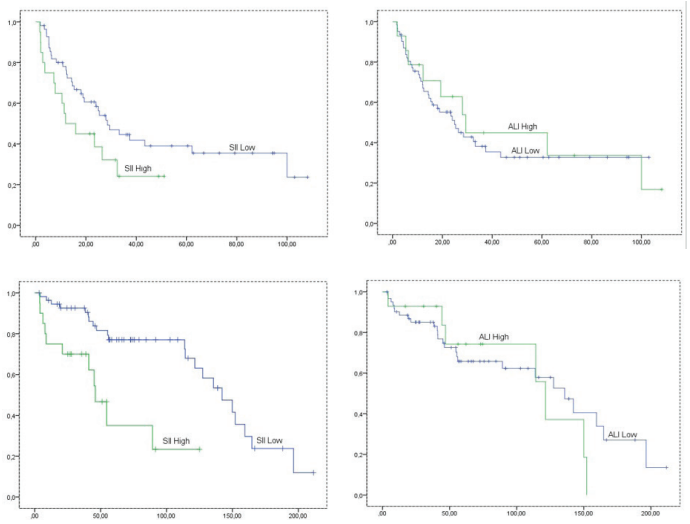
Overall Survival Analysis

Median follow-up was 75.6 months (IQR: 56.6-94.7). During follow-up, 46 (61%) patients progressed and 33 (43%) died. Median PFS was 25.3 months (95% CI, 16.1-34.5) and median OS was 127.4 months (95% CI, 101-154 months).

The univariate analysis indicated that age, ECOG PS, IMDC risk classification, nephrectomy status, NLR, PLR, and SII were significantly associated with overall survival. Patients older than 65 years had a higher risk of mortality (HR 2.3, 95% CI 1.08-5.03, p=0.03). Poor ECOG PS (≥2) was strongly associated with worse survival outcomes (HR 56.9, 95% CI 9.2-349, p=0.001). Intermediate or poor IMDC risk classification also predicted lower survival (HR 2.7, 95% CI 1.3-5.6, p=0.008). Among the inflammatory markers, high NLR, PLR, and SII were associated with worse overall survival (p=0.001 for all). However, multivariate analysis confirmed the independent prognostic significance of age, ECOG PS, IMDC risk classification, and PLR (table 3).

Progression-Free Survival and Overall Survival Based on Inflammatory Markers

Figures 2 and 3 illustrate PFS and OS of patients based on systemic immune-inflammation markers. Patients with lower SII and ALI had better PFS and OS compared to those with higher values of these markers (figure 2) (figure 3).



Discusion

This study highlights the prognostic significance of systemic inflammatory markers, including SII, ALI, NLR, PLR, in patients with mRCC and lung metastases. Our findings underscore the potential of these markers in refining prognostic stratification beyond traditional systems such as IMDC risk classification.

Prognostic Value of Inflammatory Markers

The strong association between elevated levels of SII, NLR, and PLR and poor IMDC risk classification observed in our cohort suggests that systemic inflammation plays a critical role in the progression of mRCC. Notably, patients with high SII, NLR, and PLR were more likely to be classified as having poor risk, indicating that these markers could serve as additional tools for identifying high-risk patients who may require more aggressive treatment strategies.

Our survival analysis further reinforces the prognostic relevance of these inflammatory markers. High NLR, PLR, and SII were associated with significantly worse OS, consistent with previous studies that have reported similar findings in various cancers, including RCC [9], [10], [11], [12], [13], [14], [15]. In particular, the multivariate analysis identified PLR as an independent predictor of OS, emphasizing its potential as a robust biomarker in mRCC. The lack of significant association between ALI and survival outcomes in our study, however, suggests that not all inflammatory markers may have the same prognostic utility in mRCC, warranting further investigation. Studies with ALI have mostly been conducted in primary lung cancer, but there are no similar studies in patients with lung metastases [16], [17], [18]. These parameters are being investigated not only in cancers but also in other diseases [19], [20], [21].

Implications for Clinical Practice

The integration of SII, NLR, and PLR into clinical practice could enhance the current prognostic models for mRCC, allowing for more personalized treatment approaches. For instance, patients identified as high-risk based on these markers might benefit from closer monitoring and potentially more aggressive therapeutic interventions. Furthermore, the use of these markers could help in stratifying patients for clinical trials, ensuring that those with the highest risk of progression are prioritized for novel therapies.

Limitations and Future Directions

Despite the promising findings, our study has some limitations that need to be addressed. The retrospective nature of the analysis may introduce selection bias, and the relatively small sample size could limit the generalizability of our results. Additionally, while our study focused on patients with lung metastases, the prognostic value of these markers in mRCC with other metastatic sites remains to be elucidated.

Future studies should aim to validate our findings in larger, prospective cohorts and explore the underlying biological mechanisms linking systemic inflammation to RCC progression. Understanding these pathways could lead to the identification of new therapeutic targets and the development of interventions aimed at modulating the inflammatory response in mRCC patients.

Conclusion

In conclusion, our study demonstrates that systemic inflammatory markers such as SII, NLR, and PLR are significantly associated with poor prognosis in mRCC patients with lung metastases. These markers, particularly PLR, have the potential to be incorporated into existing prognostic models to improve risk stratification and guide clinical decision-making. Further research is warranted to validate these findings and to explore the role of inflammation in RCC progression more comprehensively.

Conflicts of interest

Authors declare no conflicts of interest.

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