Systemic Inflammatory Markers Predicting the Overall Survival of Patients Using Tyrosine Kinase Inhibitors in the First-line Treatment of Metastatic Renal Cell Carcinoma

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ABSTRACT

Objective: To identify prognostic inflammatory markers in metastatic renal cell carcinoma (mRCC) patients who received anti-vascular endothelial growth factor receptor (VEGFR) agents.

Study Design: Observational study.

Place and Duration of the Study: Department of Medical Oncology, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey, between January 2015 and December 2021.

Methodology: A total of 110 patients with mRCC who received sunitinib or pazopanib for at least 3 months were enrolled. Hemogram, C-reactive protein (CRP) and albumin values of the patients, CRP to albumin ratio (CAR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), prognostic nutrition index (PNI) and systemic inflammatory response indexes (SIRI) were calculated and recorded. Progression-free survival and overall survival analyses of the patients were performed using the Kaplan-Meier method. Cox regression method was used to identify prognostic factors. Variables found to be significant in univariate analysis were enrolled in multivariate analysis.

Results: In the univariate analysis for median overall survival (mOS), whether or not surgery was applied as the primary treatment option, grade, lymphovascular invasion (LVI), International Metastatic RCC Database Consortium (IMDC) score, CAR, NLR, PLR, SII, PNI and SIRI were found to be statistically significant. Systemic inflammation markers (CAR, NLR, PLR, PNI, SII and SIRI) were found to be independent prognostic markers for mOS as a result of Cox multivariate analysis.

Conclusion: CAR, NLR, PLR, SII, PNI, and SIRI values measured before anti-VEGFR treatment in patients with mRCC may be of additional prognostic significance. These markers, which are calculated by using parameters that are always measured in routine practice, such as complete blood count (CBC), albumin, and CRP levels, are easy and inexpensive methods that give an idea about the course of the disease.

Key Words: *Sunitinib, Pazopanib, Renal cell carcinoma, Prognostic marker, Overall survival, Inflammatory.*

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INTRODUCTION

Renal cell carcinoma (RCC) is the most common of the kidney cancers. The primary treatment for localised disease is surgery, one-third of these patients develop metastases, and approximately a third of these patients have metastases at the time of first admission.[1] Systemic treatment of metastatic RCC (mRCC) has shifted from cytokines to drugs targeting angiogenesis, immunotherapy, and combinations of two agents.[2]

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The most commonly used tyrosine kinase inhibitors (TKI) in primary care are sunitinib and pazopanib. Sunitinib is a multiple-targeted tyrosine kinase inhibitor, including platelet-derived growth factor (PDGF) receptors and vascular endothelial growth factor receptors (VEGFR).[3] Pazopanib is an oral agent that inhibits the TKIs associated with VEGFR, PDGF receptor, and Kit receptor.[4] Pazopanib is not inferior to sunitinib when it comes to overall survival (OS) and progression-free survival (PFS). However, the quality of life and safety profiles were better in favour of pazopanib.[5] Tyrosine kinase inhibitor, TKI plus immuno-oncological treatment (IO), IO plus IO have become standard for the first-line mRCC treatment.

Therefore, with the increasing number of first-line treatment options in clinical practice, there is a need to develop a marker to determine which patients would benefit most from which possible treatment. Cellular effectors and mediators of inflammation are among the most important components of the local

tumour environment. Evidence suggests that the systemic inflammatory response leads to the progression of most types of cancer by enhancing tumour metastasis and angiogenesis.[6] In the literature, the prognostic and predictive importance of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), prognostic nutrition index (PNI) and systemic inflammatory response index (SIRI) in mRCC patients have been investigated.[7-10] The aim of the current study was to identify those inflammatory markers that have prognostic significance for OS in patients with mRCC who received sunitinib or pazopanib in first-line therapy.

METHODOLOGY

This observational study was conducted at the Department of Medical Oncology, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkiye, between January 2015 and December 2021. Files of patients with histopathologically confirmed mRCC who have received pazopanib or sunitinib were retrospectively reviewed. Demographic characteristics and histopathological data were obtained from patient files. One hundred and ten patients who were on pazopanib or sunitinib for mRCC in the first-line treatment, whose baseline complete blood count (CBC) parameters, albumin, and C-reactive protein (CRP) levels were available, and whose files could be accessed were included in the study. A total of fifteen patients, those who did not have CBC parameters, albumin, and CRP levels before anti-VEGFR treatment (6 patients), those who have not been using their current treatment for at least 3 months (8 patients), and those who were using these treatments other than the first-line treatment, were not included in the study. Pre-treatment lymphocytes (10^3/mL), neutrophils (10^3/mL), monocytes (10^3/mL), platelets (10^3/mL), serum albumin (g/dl), and CRP (mg/dl) values were recorded.

The CRP-albumin ratio (CAR) was calculated by dividing the CRP value by serum albumin, the PLR was calculated by dividing the platelet count by the lymphocyte count, and the NLR was calculated by dividing the neutrophil count by the lymphocyte number. The PNI was calculated by using the formula 10 x albümin level + 0.005 total lymphocyte count. The SII was calculated using the (neutrophil × platelet)/lymphocyte formula. The SIRI (neutrophil × monocytes) / lymphocyte formula was calculated.

SPSS software version 22.0 was used to perform all statistical analyses. Kaplan-Meier method was used for survival analysis and log-rank test was used for statistical comparisons. OS was expressed as the time from the start of anti-VEGFR treatment to death, while progression-free survival (PFS) was expressed as the time from the start of anti-VEGFR treatment to the first radiological evidence of progression. Univariate Cox proportional hazards regression model was used to determine the prognostic significance of variables for OS and PFS. Multivariate Cox proportional hazards regression models were used to identify independent prognostic factors. The prognostic significance of CAR, PLR, NLR, PNI, SII, and SIRI was defined by the receiver operating characteristic (ROC) Curve. A p-value of <0.05 was considered statistically significant.

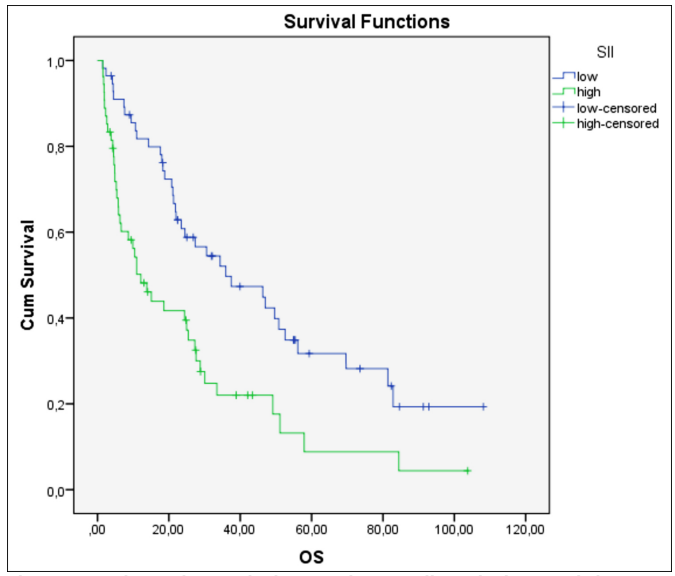

Figure 1: Kaplan meier survival curves for overall survival systemic immune-inflammation index.

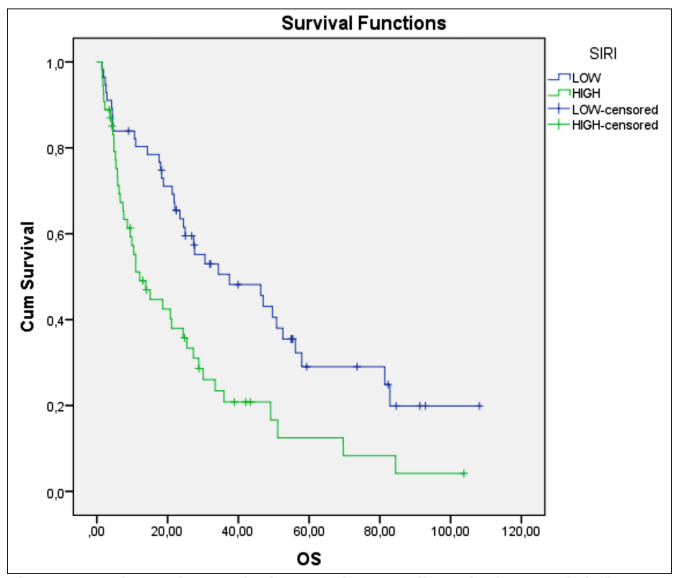

Figure 2: Kaplan meier survival curves for overall survival systemic inflammatory response index.

RESULTS

A total of 110 patients were included in the study. A total of 29 patients were excluded because they did not meet the inclusion criteria. Thirty-five (31.8%) of the patients were females and 75 (68.2%) were males. The 35 patients were older than 65 years, and 75 patients were 65 years old and younger. Fifty-seven (51.8%) of the patients did not have metastases at the time of diagnosis, while 53 (48.2%) patients had metastases. Surgery was performed on the primary tumour of 93 (84.5%) patients. Ninety-one (82.7%) patients were in clear cell histology and 19 (17.3%) patients were in non-clear cell histology. Sixty-one patients had grade 3-4 tumours, 49 patients had grade 1-2 tumours.

Table I: Multivariate and univariate analyses of overall survival in patient treated with sunitinib and pazopanib for systemic inflammatory markers.

	Univariate analyses			Multivariate analyses		
Variable	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Sex (Male/Female)	0.813	0.508-1.303	0.390			
Age (<65 / >65)	0.939	0.579-1.522	0.798			
Metastasis at the time of diagnosis (Yes / No)	1.546	0.984-2.429	0.059	1.541	0.916-2.592	0.403
Primary surgery (Yes / No)	0.558	0.311-1.000	0.050	0.851	0.434-1.668	0.639
Histological type (clear / nonclear cell)	0.879	0.484-1.598	0.672			
Grade (1-2 / 3-4)	1.692	1.068-2.681	0.025	1.499	0.860-2.614	0.153
Lymphovascular invasion (Yes / No)	1.654	1.026-2.664	0.039	1.230	0.730-2.073	0.437
Necrosis (Yes / No)	1.352	0.863-2.118	0.188			
IMDC						
Favorable	Reference	Reference	<0.001	Reference	Reference	0.001
Intermediate	0.944	0.524-1.811	0.849	0.541	0.270- 1.083	0.083
Poor	3.097	1.676-5.724	<0.001	1.543	0.710-3.352	0.274
CAR (Low / High)	1.785	1.135-2.805	0.012	2.112	1.299-3.434	0.003
NLR (Low / High)	2.068	1.305-3.278	0.002	1.967	1.221-3.170	0.005
PLR (Low / High)	1.810	1.156-2.834	0.010	1.986	1.230-3.206	0.005
PNI (Low / High)	0.538	0.337-0.858	0.009	0.500	0.307-0.813	0.005
SII (Low / High)	2.146	1.363-3.378	0.001	1.891	1.177-3.039	0.008
SIRI (Low / High)	2.090	1.327-3.290	0.001	1.783	1.083-2.933	0.023

CAR: CRP albumin ratio, International Metastatic RCC Database Consortium (IMDC), NLR: Neutrophil-lymphocyte ratio, OS: Overall survival, PFS: Progression-free survival, PLR: Platelet-lymphocyte ratio, PNI: Prognostic nutrition index, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index.

Table II: Multivariate and univariate analyzes of progression-free survival in patient treated with sunitinib and pazopanib for systemic inflammatory markers.

	Univariate analyses			Multivariate analyses		
Variable	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Sex (Male / Female)	0.810	0.446-1.470	0.487			
Age (<65 / >65)	0.053	0.990-3.975	0.053	0.547	0.268-1.113	0.096
Metastasis at the time of diagnosis (Yes / No)	2.037	1.151-3.604	0.015	2.288	1.269-4.128	0.006
Primary surgery (Yes / No)	0.638	0.283-1.437	0.278			
Histological type (clear / nonclear cell)	0.716	0.321-1.593	0.412			
Grade (1-2 / 3-4)	0.925	0.530-1.612	0.782			
Lymphovascular invasion (Yes / No)	1.380	0.767-2.481	0.282			
Necrosis (Yes / No)	1.930	1.127-3.305	0.017	2.427	1.1334-4.414	0.006
IMDC						
Favorable	Reference	Reference	0.242			
Intermediate	1.026	0.513-2.050	0.943			
Poor	1.806	0.802-4.069	0.154			
CAR (Low / High)	0.940	0.532-1.660	0.830			
NLR (Low / High)	2.135	1.196-3.810	0.010	1.199	0.587-2.449	0.618
PLR (Low / High)	2.000	1.139-3.513	0.016	2.143	1.037-4.429	0.040
PNI (Low / High)	0.702	0.400-1.234	0.219			
SII (Low / High)	1.647	0.937-2.894	0.083			
SIRI (Low / High)	1.601	0.910-2.817	0.102			

CAR: CRP albumin ratio, International Metastatic RCC Database Consortium (IMDC), NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, PNI: Prognostic nutrition index, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index.

According to the International Metastatic RCC Database Consortium (IMDC) risk scoring, the number of cases in favourable, intermediate, and poor risk groups was 26 (23.6%), 49 (44.5%) and 35 (31.8%), respectively. The metastasis site was lung in 51 (46.4%) of the patients, and 59 patients had metastases in other sites (liver, lymph node, bone, adrenal gland and brain). Out of 110 patients, 72 (65.5%) used sunitinib and 38 (34.5%) used pazopanib as first-line therapy.

Subjects were divided into 2 groups as high and low based on the cut-off values calculated by ROC analysis of CAR, LNR, PLR, PNI, SII, and SIRI. Cut-off values of these inflammatory markers CAR ≤4.73 - CAR >4.73, NLR ≤2.33 - NLR >2.33, PLR ≤161.58 - PLR >161.58, PNI ≤41.6 - PNI >41.6, SII ≤782.56 – SII >782.56 and SIRI ≤1.58 – SIRI >1.58.

The mOS was found to be 34.3 and 13.8 months in the CAR low and high groups, respectively (p=0.011). mPFS was found to be 18.5 and 29.0 months in the CAR low and high groups, respectively (p=0.830). The mOS was 37.4 and 15.0 months in the NLR low and high groups, respectively (p=0.002). The mPFS was 38.0 and 14.9 in the NLR low and high groups, respectively (p=0.009). mOS was 30.5 and 13.8 months in the PLR low and high groups, respectively (p=0.008). mPFS was 38.0 and 14.5 months in the PLR low and high groups, respectively (p=0.014). In the PNI low

group, mOS and mPFS were 18.3 and 17.1 months, respectively, while in the PNI high group, mOS and mPFS were 47.0 and 20.4 months, respectively (p=0.008 for mOS, and p=0.216 for mPFS). In the SII low and high groups, the mOS was 35.9 and 12.1 months, respectively, while the mPFS was 25.4 and 17.1 months, respectively (p=0.001 for mOS and p=0.001 for mPFS). In the SIRI low and high groups, mOS was 37.4 and 12.1 months, respectively, while mPFS was 25.4 and 14.9 months (p=0.001 for mOS, p=0.099 for mPFS).

In the univariate analysis for mOS, whether surgery was performed on the primary, grade, LVI, IMDC score, CAR, NLR, PLR, PNI, SII and SIRI were statistically significant (p=0.050, p=0.025, p=0.039, p<0.001, p=0.012, p=0.002, p=0.010, p=0.009, p<0.001 and p<0.001, respectively). In the multivariate analysis for OS, IMDCC, CAR, NLR, PLR, PNI, SII and SIRI were found to be significant markers (p<0.001, p=0.003, p=0.005, p=0.005, p=0.008, and p=0.023 respectively, Table I). As a result of Cox multivariate analysis, systemic inflammation markers (CAR, NLR, PLR, PNI, SII and SIRI) were found as independent prognostic predictors for OS.

In the univariate analysis for mPFS, the presence of metastasis at the time of diagnosis, necrosis, NLR, and PLR were statistically significant (p=0.015, p=0.017, p=0.010, and p=0.016, respectively). In the multivariate analysis for mPFS, the presence of metastasis at the time of diagnosis, necrosis, and PLR were determined as prognostic factors (p=0.006, p=0.006, and p=0.040, respectively, Table II).

DISCUSSION

In this study, CAR, PLR, NLR, PNI, SII, and SIRI were independent prognostic predictors of OS in metastatic RCC patients who received anti-VEGFR inhibitors as first-line therapy. CAR, NLR, PLR, SIRI and SII low group and PNI high group have longer OS.

Evidence for a strong relationship between cancer and inflammation has been increasing recently. Tumour progression may be the trigger of a tissue inflammatory response.[6] Inflammation may also be initiated by inflammatory cytokines secreted by a number of cells in the tumour microenvironment or by the tumour cells themselves.[11] Thus, an immunogenic environment associated with cancer is formed. Biomarker studies that indirectly show this immunogenic environment are increasing day by day. It is aimed to use these biomarkers as prognostic and predictive. Renal cancer is an immunogenic tumour and plays a role in inflammation, tumorigenesis and progression.[12] For this reason, it is a type of cancer in which inflammatory markers are frequently investigated. It has been suggested that some peripheral markers of inflammation, CRP, hemogram parameters and albumin levels are associated with prognosis in subjects with mRCC.[7,13] There are still new biomarker studies. As a reliable and sensitive prognostic parameter of systemic inflammation, CRP has been found to be important in predicting the outcome of urologic cancers, most commonly RCC. Albumin, which indicates both inflammation and nutritional status, has proven to be an independent prognostic predictor for mRCC patients. Based on these, they studied the CAR in RCC patients and reported that CAR independently predicted the OS of patients with RCC.[14] In subsequent studies, high CAR was also found to be associated with poor survival in RCC patients, and CAR before targeted therapy was an independent indicator of OS in subjects with mRCC.[14,15] The findings obtained in the current study were similar to the findings of previous studies.

NLR, which is one of the most frequently investigated parameters in all diseases, has also been studied in RCC patients. Various studies evaluating the prognostic significance of NLR have controversial results. For the first time, Gunduz *et al*. used tyrosine kinase inhibitors in 2013, it was shown that high NLR before treatment is an independent prognostic parameter in subjects with mRCC. In patients with NLR ≤2 and NLR >2, the mPFS was 23.9 versus 8.6 months.[16] Another study investigating the prognostic significance of systemic inflammatory parameters in patients with advanced RCC who had received targeted therapies revealed that high NLR was associated with worse OS and PFS than low NLR. In patients with NLR<2.6 and NLR≥2.6, mPFS was found to be 42.1 and 18.8 months, respectively.[13] A recent meta-analysis of 6461 RCC patients reported a significant association between higher pre-treatment NLR and worse OS and PFS in mRCC patients.[17] A cut-off for NLR has not been determined yet, and different values are taken on a study basis. In the current study, the authors defined the NLR cut-off as 2.33 and found the mOS to be 37.4 and 15.0 months in the low and high NLR groups, respectively. Another marker whose prognostic and predictive importance is investigated in cancer patients is the PLR. Numerous studies have been published evaluating the prognostic value of PLR in RCC patients, but the findings are controversial. A meta-analysis of 44 studies published in 2022, including a total of 15,193 patients, reported that PLR was associated with the prognosis of patients with RCC and higher PLR was associated with worse OS and PFS.[18]

Albumin is used as a marker of nutritional status and the immune system. The concept of PNI was first proposed by combining the lymphocyte count with the albumin level. It was reported in 2015 that low preoperative PNI is an independent poor prognostic predictor for long-term survival in patients with localised RCC. A potential prognostic significance of PNI in RCC patients has been

reported in later years, but its role still needs to be clarified. Numerous meta-analyses regarding PNI in RCC patients have been published in the last 1-2 years, and these studies revealed the prognostic importance of PNI. Low PNI has been shown to be associated with worse survival outcomes in RCC patients. Thus, it has been suggested that PNI can be used as a reliable prognostic marker in patients with RCC.[19] There are few studies in the literature on the clinical significance of PNI in patients receiving targeted therapy. All of these studies suggested that low PNI is an independent prognostic predictor for PFS and OS in patients with advanced RCC.[8,20]

Lolli *et al.* showed in 2016 that SII and its changes over the course of sunitinib therapy are independent prognostic predictors of patients with advanced RCC who received sunitinib as first-line therapy.[21] In a meta-analysis of 10 studies and 3180 patients, high SII has been shown to have an impact on poor survival outcomes in RCC patients, and high SII has been suggested to indicate more aggressive disease. The cut-off values of SII in the studies in this meta-analysis were between 529 and 1375, and 5 of the 10 studies investigated the efficacy of SII before TKI use.[22] SII was an independent prognostic predictor and led to significant differences in survival for the poor, intermediate, and favourable IMDC groups. Therefore, adding SII to the IMDC score may provide clinical benefit as a predictor of survival.[23] In this study, the patients with low SII also had a longer OS, and the cut-off value found in this study was 782.56. Gu *et al*. developed a SIRI based on neutrophil, lymphocyte, and monocyte counts to predict the survival of my mRCC patients after cytoreductive nephrectomy and those with low SIRI have been shown to be associated with longer survival.[10] There are limited studies investigating SIRI in patients with RCC, which included patients with RCC with tumour thrombus of the inferior vena cava undergoing surgery, patients with RCC undergoing nephrectomy, and mRCC patients treated with nivolumab. All of these studies reported that high SIRI was associated with worse survival outcomes and was prognostic.[10,24,25] The current study is the first to investigate the prognostic impact of SIRI before targeted therapy. The cut-off value for SIRI in the current study was 1.58. The mOS in the SIRI low and high groups were 37.4 and 12.1 months, respectively. The low SIRI group had an OS that was more than 3 times longer than the high SIRI group.

The current study has some limitations, such as a single-centre, retrospective design, and small sample size. The cut-off value that was determined by the statistical method is one of the limitations of this study since almost all studies in the literature have a different cut-off value for each marker and there is no standard cut-off value. However, it should be noted that the values used as this indicator are a continuous variable.

CONCLUSION

CAR, NLR, PLR, SII, PNI, and SIRI values measured before anti-VEGFR treatment in patients with mRCC may be of additional prognostic significance. These results can be used to give an idea about the prognosis of patients who will use anti-VEGFR TKI in first-line treatment with mRCC.

ETHICAL APPROVAL:
The study was approved by the Institutional Ethics Committee of Necmettin Erbakan University, Meram Faculty of Medicine (Date: 17.12.2021; No. 2021/3559).

PATIENTS' CONSENT:
Since it was designed as a retrospective study, the data were obtained from the electronic medical record system after approval of the Ethics Committee.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
MK: Conception, design, data acquisition, data analysis, manuscript drafting, interpretation, and statistical analysis.
MKE: Critical revision of the manuscript and supervision.
All the authors have approved the final version of the manuscript to be published.

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