Cerrahpaşa Med J 2026; 50: 1-8

ORIGINAL ARTICLE

Prognostic Value of Baseline Endothelial Activation and Stress Index in Metastatic Renal Cell Carcinoma Treated with First-Line Tyrosine Kinase Inhibitors

Murat Günaltılı, Ebru Çiçek, Murad Guliyev, Zeliha Birsin, Emir Çerme, Vali Aliyev, Hamza Abbasov, Selin Cebeci, Özkan Alan, Nebi Serkan Demirci

Division of Medical Oncology, Department of Internal Medicine, Istanbul University-Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye

Cite this article as: Günaltılı M, Çiçek E, Guliyev M, et al. Prognostic value of baseline endothelial activation and stress index in metastatic renal cell carcinoma treated with first-line tyrosine kinase inhibitors. *Cerrahpaşa Med J*. 2026, 50, 0053, doi: 10.5152/cjm.2026.26053.

What is already known on this topic?

- *The International Metastatic RCC Database Consortium model is the standard prognostic tool in metastatic renal cell carcinoma, but may not fully reflect underlying biological processes such as endothelial dysfunction.*
- *Inflammatory and laboratory-based indices have shown prognostic relevance in metastatic renal cell carcinoma, highlighting the importance of tumor–host interactions.*
- *The endothelial activation and stress index (EASIX) score has been linked to survival outcomes in both hematologic cancers and certain solid tumors.*

What this study adds on this topic?

- *To the best of the authors' knowledge, there has been no previous research that has directly assessed the prognostic significance of baseline EASIX in cases of metastatic renal cell carcinoma.*
- *Higher EASIX scores were independently correlated with reduced progression-free and overall survival in patients receiving first-line tyrosine kinase inhibitor therapy.*
- *EASIX could act as an easily accessible biomarker that enhances current risk stratification models.*

Abstract

Objective: In this research, the influence of the initial endothelial activation and stress index (EASIX) on the prognosis of patients with metastatic renal cell carcinoma (mRCC) undergoing first-line treatment with tyrosine kinase inhibitors (TKIs) was examined.

Methods: This study, conducted retrospectively at a single center, included patients with mRCC who received first-line TKI therapy. The EASIX score was determined from serum lactate dehydrogenase, creatinine, and platelet count measurements taken within 15 days before starting treatment. Patients were divided into low and high EASIX groups according to the cohort's median score. Survival outcomes, including progression-free survival (PFS) and overall survival (OS), were evaluated using the Kaplan–Meier method, and prognostic factors were identified through Cox regression analyses.

Results: A total of 99 patients were included in the study. The median PFS was 11.5 months, while the median OS was 34.3 months. Those with elevated EASIX scores had notably reduced PFS and OS, with PFS at 8.6 months compared to 19.1 months ($P < .001$) and OS at 24.8 months versus 61.9 months ($P = .003$). In multivariate analyses, high EASIX remained an independent predictor of shorter PFS (hazard ratio [HR] = 2.77, 95% CI: 1.60-4.79; $P < .001$) and OS (HR = 2.53, 95% CI: 1.32-4.84; $P = .005$).

Conclusion: Baseline EASIX was independently associated with survival outcomes in patients with mRCC undergoing first-line TKI treatment. As a simple and readily accessible biomarker, EASIX may provide additional prognostic information beyond conventional risk models. Prospective validation is warranted, particularly in the context of contemporary treatment strategies.

Keywords: Biomarkers, endothelium, prognosis, renal cell carcinoma, tyrosine kinase inhibitors

Introduction

Renal cell carcinoma (RCC) continues to be a major health issue globally, representing about 4% of all newly diagnosed cancer cases around the world. At the time of diagnosis, around 15% of patients have metastatic disease, and numerous others experience distant relapse during subsequent follow-up.[1] Although the introduction of tyrosine kinase inhibitors (TKIs) aimed at vascular endothelial growth factor has significantly improved clinical results, there remains a notable fluctuation in survival rates among patients with metastatic RCC (mRCC). Recently, combinations of TKIs with immune checkpoint inhibitors have expanded first-line therapeutic options; however, marked heterogeneity in treatment response persists across patient subgroups.[2] This variability highlights the need for biologically informative prognostic markers that can enhance risk stratification and better support treatment selection in routine clinical practice.

In clinical settings, the prognostic tool most frequently employed for patients undergoing targeted treatments or immunotherapy is the International Metastatic RCC Database Consortium (IMDC)

Received: March 23, 2026 **Revision Requested:** May 28, 2026 **Last Revision Received:** June 9, 2026 **Accepted:** June 16, 2026 **Publication Date:** August 31, 2026
Corresponding author: Murat Günaltılı, Division of Medical Oncology, Department of Internal Medicine, İstanbul University-Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye **e-mail:** muratgunaltili@gmail.com
DOI: 10.5152/cjm.2026.26053

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

model. Its components allow practical and reproducible risk stratification; however, the IMDC may not adequately reflect the biological heterogeneity of metastatic RCC. Previous studies have suggested that IMDC categories may insufficiently reflect tumor–host interactions, inflammatory signaling, and endothelial dysfunction, all of which influence disease progression and treatment response.[3-5] These limitations have prompted increasing interest in complementary biomarkers that offer additional biological insights beyond conventional clinical scoring systems.

There is a growing body of evidence indicating that markers related to systemic inflammation and immune response, which are obtained from standard blood tests, hold prognostic significance in RCC and various other solid tumors. These markers include the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, pan-immune-inflammation value, and, more recently, the glucose-to-lymphocyte ratio. These markers are thought to reflect the interaction between inflammatory activity, metabolic stress, and immune competence, all of which contribute to tumor growth, angiogenesis, and metastatic progression.[6-12] Alongside these findings, increasing attention has been paid to the role of endothelial dysfunction, a process that promotes tumor cell intravasation, facilitates metastatic dissemination, and shapes the tumor microenvironment through inflammatory and prothrombotic signaling.[13-15]

The endothelial activation and stress index (EASIX) was initially introduced as an indirect indicator of endothelial damage in the context of allogeneic hematopoietic stem cell transplantation. This index is derived from measurements of lactate dehydrogenase, creatinine, and platelet count.[16] Its prognostic value has been demonstrated in several hematologic cancers such as multiple myeloma and lymphoma, where elevated EASIX scores correlate with impaired microvascular integrity and adverse clinical outcomes.[17-19] Beyond hematologic disorders, the applicability of EASIX has also been explored in solid tumors, with emerging studies in upper tract urothelial carcinoma, small cell lung cancer, and pancreatic cancer suggesting a potential association between elevated EASIX levels and poorer survival.[20-22] Considering the vascular characteristics of RCC and the importance of vascular endothelial growth factor (VEGF)-targeted treatments, assessing an endothelial stress indicator like EASIX could be especially pertinent. However, its prognostic significance in RCC remains unexamined.

This study sought to determine whether baseline EASIX scores were associated with clinical outcomes in patients with metastatic RCC undergoing first-line treatment with TKIs.

Methods

Patients

In this retrospective cohort study, patients diagnosed with mRCC who were treated at the institution between September 2007 and February 2024 were examined. The study included adult patients (aged 18 years or older) with a histological confirmation of renal cell carcinoma who began first-line therapy with TKIs for their metastatic condition. As part of the inclusion criteria, patients were required to have baseline laboratory measurements of serum lactate dehydrogenase (LDH), creatinine, and platelet count obtained within 15 days before starting first-line TKI therapy. Patients with missing baseline laboratory or clinical data, insufficient radiologic documentation, concurrent active malignancies, or inadequate follow-up were excluded.

Data Collection and Endothelial Activation and Stress Index Assessment

Data on demographic, clinical, pathological, and treatment-related factors were extracted from electronic medical records and, when needed, confirmed with archived patient charts. These factors encompassed age at the time of metastatic diagnosis, sex, comorbidity status, Eastern Cooperative Oncology Group (ECOG) performance score, histologic subtype, presence of sarcomatoid differentiation, history of nephrectomy, IMDC risk category, metastatic locations (lung, liver, bone, soft tissue/lymph nodes), and the count of metastatic sites.

Blood tests conducted within 15 days prior to starting first-line TKI therapy provided the baseline laboratory parameters. These tests measured serum LDH, creatinine, platelet count, hemoglobin, albumin, C-reactive protein, and calcium levels.

The EASIX score was calculated according to its original definition as follows: LDH (U/L) × creatinine (mg/dL) / platelet count (10^9/L).

Because no biologically or clinically validated cut-off has been established for EASIX in metastatic RCC, the cohort was dichotomized using the median EASIX value to form low and high EASIX groups.

Definition of Survival Outcomes

Progression-free survival (PFS) refers to the time span beginning with the initiation of first-line TKI treatment and ending with either radiologically confirmed disease progression or death from any cause, depending on which happens first. Patients who neither showed documented progression nor died were censored at the date of their most recent follow-up.

Overall survival (OS) was measured from the start of first-line TKI treatment to death from any cause. Patients who were still alive at the last follow-up were censored at the date of their most recent follow-up.

Ethical Considerations

The study adhered to the principles outlined in the Declaration of Helsinki. The Ethics Committee of İstanbul University-Cerrahpaşa granted ethical approval (Approval no.: E-83460662-050.04-1560873, Date: January 7, 2026). As the study was retrospective, the Ethics Committee waived the need for informed consent, following national regulations.

Statistical Analysis

IBM SPSS Statistics software version 27.0 (IBM SPSS Corp.; Armonk, NY, USA) was utilized for conducting statistical analyses. To evaluate the normality of continuous variables, the Shapiro–Wilk test was applied. Variables exhibiting a normal distribution are reported as means and SDs, and their comparisons were made using the independent samples *t*-test. Conversely, variables not adhering to a normal distribution are summarized as medians with interquartile ranges and examined through the Mann–Whitney *U*-test. Categorical variables are shown as frequencies and percentages, with comparisons between groups conducted using either the chi-square test or Fisher's exact test, depending on suitability.

The Kaplan–Meier method was used to evaluate PFS and OS, and differences between the groups were assessed using the log-rank test. Univariate Cox proportional hazards regression analyses were performed on all predefined clinical, pathological, and laboratory variables to identify prognostic factors associated with survival outcomes. Variables with a *P*-value below .10 in the univariate analyses were incorporated into multivariate Cox regression

models. The findings were reported with adjusted hazard ratios (HRs) and 95% CIs. A 2-sided *P*-value of less than .05 was considered statistically significant.

Results

Baseline Clinical and Demographic Characteristics

The analysis included 99 patients with metastatic RCC. With a median EASIX value of 0.72 (interquartile range [IQR] = 0.61), patients were categorized into low and high EASIX groups based on this median threshold. Overall, 66.7% of the cohort was male, and the median age was 59 years (IQR = 12). Most patients (67.7%) had an ECOG performance status of ≥1. Clear-cell histology was the predominant subtype (88.3%), and 76.8% of patients had undergone nephrectomy.

Baseline characteristics were generally comparable between low and high EASIX groups. Age distribution, sex, comorbidity burden, ECOG performance status, histologic subtype, and nephrectomy history did not differ significantly between the groups. In the high EASIX group, sarcomatoid differentiation appeared more frequently, occurring in 24.0% of cases compared with 8.2% in the low EASIX group; however, this difference did not reach statistical significance (*P* = .094). The distribution of IMDC risk categories was comparable between the groups (*P* = .525).

Patterns of metastatic involvement were also well balanced between groups. Similarly, there were no significant differences in the number of metastatic sites or the type of first-line therapy. Overall, baseline demographic and clinical features demonstrated no statistically significant disparities between low and high EASIX groups. All baseline characteristics are presented in Table 1.

Table 1. Baseline Clinical and Demographic Characteristics of the Study Population According to Endothelial Activation and Stress Index Groups

	All Patients N = 99 (%)	Low EASIX n = 49 (%)	High EASIX n = 50 (%)	*P*
Age (years), median (IQR)	59.0 (12)	59.0 (16)	59.5 (13)	.543
Age category (years)				.299
<65	70 (70.7)	37 (75.5)	33 (66)	
≥65	29 (29.3)	12 (24.5)	17 (34)	
Gender				.477
Female	33 (33.3)	18 (36.7)	15 (30)	
Male	66 (66.7)	31 (63.3)	35 (70)	
Comorbidity (DM or HT)				.269
Absent	41 (41.4)	23 (46.9)	18 (36)	
Present	58 (58.6)	26 (53.1)	32 (64)	
ECOG PS				.174
0	32 (32.3)	19 (38.8)	13 (26)	
≥1	67 (67.7)	30 (61.2)	37 (74)	
Histology				.093
Clear cell	83 (88.3)	45 (93.8)	38 (82.6)	
Non-clear	11 (11.7)	3 (6.3)	8 (17.4)	
Nephrectomy				.442
Yes	76 (76.8)	36 (73.5)	40 (80)	
No	23 (23.2)	13 (26.5)	10 (20)	
Sarcomatoid differentiation				.094
Absent	73 (73.7)	39 (79.6)	34 (68)	
Present	16 (16.2)	4 (8.2)	12 (24)	
Unknown	10 (10.1)	6 (12.2)	4 (8)	
IMDC risk group				.525
Favorable	21 (21.2)	9 (18.4)	12 (24)	
Intermediate	58 (58.6)	28 (57.1)	30 (60)	
Poor	20 (20.2)	12 (24.5)	8 (16)	
Metastatic sites				
Lung metastasis	68 (68.7)	32 (65.3)	36 (72)	.473
Liver metastasis	17 (17.2)	8 (16.3)	9 (18)	.825
Bone metastasis	32 (32.3)	18 (36.7)	14 (28)	.353
Soft tissue/lymph node metastasis	52 (52.5)	28 (57.1)	24 (48)	.362
Number of metastatic sites				.702
≤2 sites	71 (71.7)	36 (73.5)	35 (70)	
>2 sites	28 (28.3)	13 (26.5)	15 (30)	
First-line therapy				.185
Sunitinib	80 (80.8)	37 (75.5)	43 (86)	
Others*	19 (19.2)	12 (24.5)	7 (14)	

DM, diabetes mellitus; EASIX, endothelial activation and stress index; ECOG PS, Eastern Cooperative Oncology Group performance status; HT, hypertension; IMDC, International Metastatic RCC Database Consortium; IQR, interquartile range; RCC, renal cell carcinoma.
*Others include pazopanib, cabozantinib, sorafenib, and axitinib.

Survival Outcomes

The median duration of follow-up for the cohort was 67.6 months (95% CI, 62.1-73.1). During this period, 78 of 99 patients (78.8%) experienced disease progression, while 21 patients (21.2%) were censored at their last documented visit.

Across the whole group, the median PFS was 11.5 months, with a 95% CI ranging from 7.6 to 15.4 months. In terms of EASIX categories, patients with a low EASIX score had a median PFS of 19.1 months (95% CI: 12.0-26.3). In contrast, patients with a high EASIX score experienced a markedly shorter median PFS of 8.6 months (95% CI: 4.6-12.6). This difference was statistically significant (*P* < .001) (Figure 1).

In univariate Cox regression analyses for PFS, several clinical factors were associated with shorter PFS, including sarcomatoid differentiation, the presence of more than 2 metastatic sites, and IMDC risk category. Compared with the favorable-risk group, both intermediate and poor-risk patients demonstrated worse outcomes. High EASIX scores were also significantly associated with reduced PFS. Other baseline characteristics were not significantly associated with PFS.

Within the multivariate model, a high EASIX score continued to independently predict a reduced PFS (HR = 2.77, 95% CI: 1.60-4.79; *P* < .001). The IMDC classification also preserved its prognostic value, with both intermediate-risk and poor-risk groups showing significantly worse outcomes compared with the favorable-risk group. While sarcomatoid differentiation and the number of metastatic sites appeared to be associated with worse PFS, these factors were not statistically significant in the final model. Table 2 presents a summary of the univariate and multivariate Cox analyses.

During the follow-up period, 61 out of 99 patients (61.6%) died, and 38 patients (38.4%) were censored at their most recent follow-up. The median OS for the entire group was 34.3 months (95% CI: 24.8-43.7). When categorized by EASIX, patients with low EASIX had a median OS of 61.9 months (95% CI: 21.6-102.2), while the high EASIX group experienced a significantly shorter median OS of 24.8 months (95% CI: 18.1-31.5). This difference was statistically significant (*P* = .003) (Figure 2).

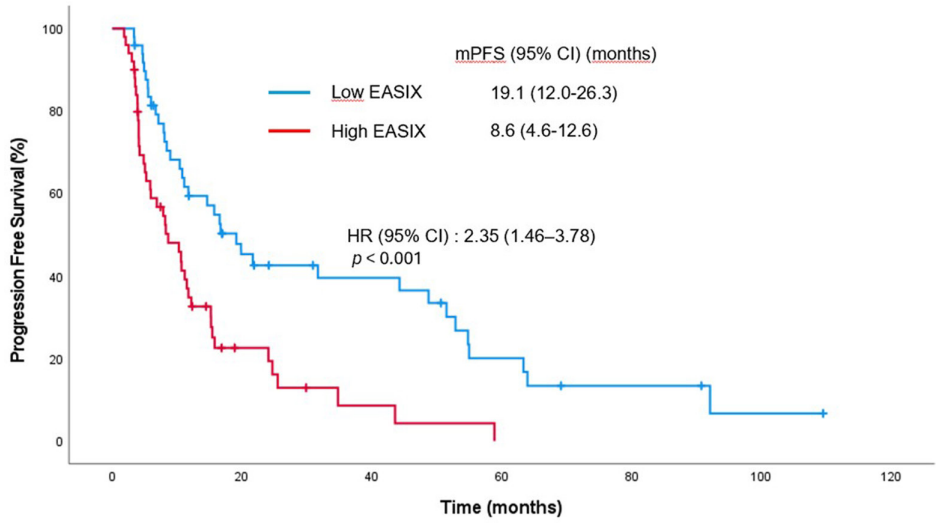

Figure 1. The Kaplan–Meier curve illustrates PFS based on EASIX group classification in individuals with metastatic renal cell carcinoma. EASIX, endothelial activation and stress index; PFS, progression-free survival.

In univariate Cox regression analyses for OS, several baseline factors were associated with worse survival outcomes, including ECOG performance status ≥1, sarcomatoid differentiation, the presence of lung metastasis, and having 3 or more metastatic sites. The IMDC risk classification also demonstrated a clear prognostic gradient. High EASIX scores were significantly associated with shorter OS. Other factors did not show a significant association with OS.

Table 2. Univariate and Multivariate Cox Regression Analyses for Progression-Free Survival

	Univariate Analyses		Multivariate Analyses	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, years (≥65 vs. <65)	1.22 (0.72-2.04)	.450		
Sex (male vs. female)	0.97 (0.61-1.55)	.895		
ECOG PS (≥1 vs. 0)	1.46 (0.90-2.37)	.122		
Comorbidity (absent vs. present)	0.72 (0.46-1.21)	.145		
Histology (non-clear vs. clear)	1.65 (0.81-3.35)	.169		
Sarcomatoid features (present vs. absent)	1.96 (1.05-3.66)	.035	1.66 (0.87-3.19)	.125
Nephrectomy (yes vs. no)	0.82 (0.63-1.07)	.142		
Lung metastasis (present vs. absent)	1.13 (0.88-1.43)	.329		
Liver metastasis (present vs. absent)	1.09 (0.82-1.45)	.550		
Bone metastasis (present vs. absent)	1.04 (0.82-1.32)	.756		
Soft-tissue/lymph node metastasis (present vs. absent)	1.13 (0.91-1.42)	.272		
Number of metastatic sites (>2 vs. ≤2)	2.04 (1.24-3.33)	.005	1.74 (0.98-3.08)	.057
IMDC risk category (overall)		.005		<.001
Intermediate vs. favorable	2.01 (1.10-3.67)	.024	1.98 (1.03-3.80)	.040
Poor vs. favorable	3.30 (1.60-6.81)	.001	5.51 (2.42-12.52)	<.001
First-line treatment (sunitinib vs. others)	1.03 (0.60-1.78)	.902		
EASIX (high vs. low)	2.35 (1.46-3.78)	<.001	2.77 (1.60-4.79)	<.001

DM, diabetes mellitus; EASIX, endothelial activation and stress index; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; HT, hypertension; IMDC, International Metastatic RCC Database Consortium; IQR, interquartile range; PFS, progression-free survival; RCC, renal cell carcinoma.

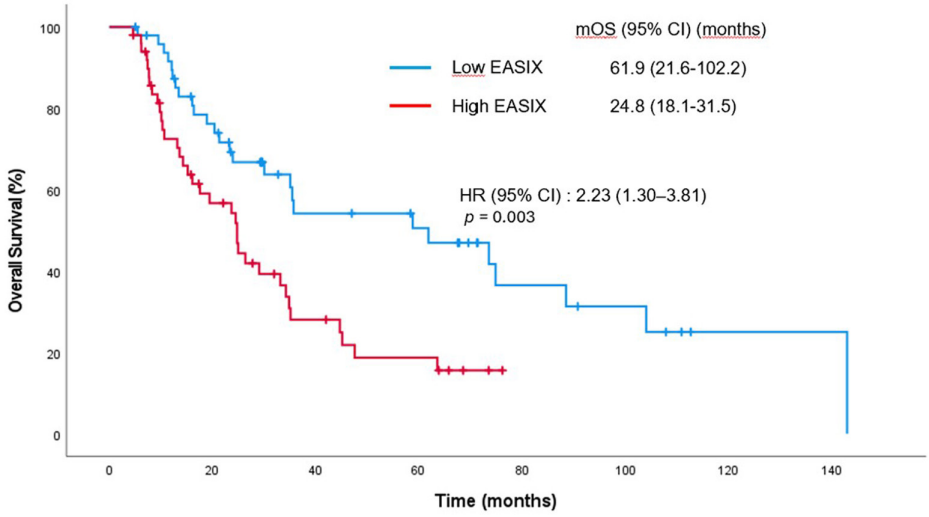

Figure 2. The Kaplan–Meier curve illustrates OS based on EASIX group classification in individuals with metastatic renal cell carcinoma. EASIX, endothelial activation and stress index; OS, overall survival.

In the multivariate model, a high EASIX score remained an independent predictor of shorter OS (HR = 2.53, 95% CI: 1.32-4.84; *P* = .005). Lung metastasis (HR = 2.99, 95% CI: 1.38-6.46; *P* = .005), sarcomatoid features (HR = 3.46, 95% CI: 1.71-6.98; *P* < .001), and IMDC risk groups retained strong prognostic significance. The number of metastatic sites showed a trend toward poorer OS but did not reach statistical significance (*P* = .087). Detailed results of the univariate and multivariate Cox analyses for OS are presented in Table 3.

Table 3. Univariate and Multivariate Cox Regression Analyses for Overall Survival

	Univariate Analyses		Multivariate Analyses	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, years (≥65 vs. <65)	1.45 (0.82-2.54)	.200		
Sex (male vs. female)	1.07 (0.62-1.83)	.806		
ECOG PS (≥1 vs. 0)	2.23 (1.23-4.03)	.008	1.68 (0.84-3.36)	.146
Comorbidity (absent vs. present)	1.01 (0.60-1.69)	.981		
Histology (non-clear vs. clear)	1.60 (0.78-3.31)	.202		
Sarcomatoid features (present vs. absent)	2.71 (1.44-5.11)	.002	3.46 (1.71-6.98)	<.001
Nephrectomy (yes vs. no)	0.71 (0.52-0.96)	.026	0.85 (0.40-1.80)	.666
Lung metastasis (present vs. absent)	1.44 (1.07-1.95)	.018	2.99 (1.38-6.46)	.005
Liver metastasis (present vs. absent)	1.08 (0.78-1.50)	.654		
Bone metastasis (present vs. absent)	1.23 (0.94-1.62)	.132		
Soft-tissue/lymph node metastasis (present vs. absent)	1.17 (0.91-1.51)	.226		
Number of metastatic sites (>2 vs. ≤2)	2.38 (1.36-4.17)	.002	1.87 (0.91-3.81)	.087
IMDC risk category (overall)		<.001		<.001
Intermediate vs. favorable	2.83 (1.31-6.11)	.008	3.02 (1.30-7.04)	.010
Poor vs. favorable	6.71 (2.75-16.39)	<.001	8.37 (2.87-24.43)	<.001
First-line treatment (sunitinib vs. others)	1.01 (0.54-1.91)	.964		
EASIX (high vs. low)	2.23 (1.30-3.81)	.003	2.53 (1.32-4.84)	.005

DM, diabetes mellitus; EASIX, endothelial activation and stress index; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; HT, hypertension; IMDC, International Metastatic RCC Database Consortium; IQR, interquartile range; OS, overall survival; RCC, renal cell carcinoma.

Discussion

In the present study, elevated baseline EASIX scores were associated with poorer PFS and OS in patients with metastatic RCC receiving first-line TKI treatment. Notably, this association persisted even after controlling for established prognostic factors, including the IMDC risk classification, suggesting that EASIX offers prognostic insights beyond those provided by traditional clinical risk models. Data regarding the prognostic relevance of EASIX in RCC are currently lacking. The present findings therefore, provide initial clinical evidence indicating a potential prognostic role for EASIX in metastatic RCC, a disease characterized by marked vascular involvement and biological heterogeneity.

Beyond its composite structure, the biological plausibility of EASIX in metastatic RCC can be appreciated by considering the prognostic relevance of its components. Serum LDH is widely regarded as a surrogate marker of tumor aggressiveness in RCC and is incorporated into established prognostic models. Previous evidence has linked elevated LDH levels to worse survival outcomes, likely reflecting increased tumor burden, hypoxia-driven metabolic adaptation, and enhanced proliferative activity.[23,24]

Platelet count represents another clinically relevant component of the EASIX score. Thrombocytosis has been associated with adverse outcomes in metastatic RCC, independent of conventional clinical and laboratory factors. Available evidence suggests that elevated platelet levels may contribute to tumor progression through proangiogenic signaling, facilitation of tumor–endothelial interactions, and modulation of the immune microenvironment.[25,26]

Although serum creatinine primarily reflects renal function, Aktepe et al[27] reported that impaired kidney function was associated with poorer survival in patients with metastatic RCC receiving targeted therapy. Życzkowski et al[28] identified baseline creatinine levels among routine laboratory parameters associated with long-term survival in an RCC cohort with extended follow-up, suggesting that renal function may carry prognostic information at baseline rather than serving solely as a treatment-related factor.

Collectively, the integration of LDH, platelet count, and creatinine within the EASIX framework provides a composite measure that captures complementary aspects of tumor aggressiveness, endothelial stress, and overall patient vulnerability, offering a biologically coherent rationale for its prognostic relevance in patients with metastatic RCC.

Several solid tumor contexts, marked by significant vascular and microenvironmental disturbances, have also documented the prognostic significance of EASIX. According to Gu et al,[20] elevated EASIX scores were independently associated with poorer survival outcomes in patients with upper tract urothelial carcinoma who underwent radical nephroureterectomy. This finding reinforces the idea that endothelial stress might play a role in the aggressive nature of urothelial cancers.[20] Similarly, Go et al[21] reported that higher EASIX values were associated with inferior PFS and OS in small cell lung cancer, suggesting that endothelial dysfunction retains prognostic relevance even in tumors dominated by rapid proliferation and chemosensitivity. More recently, Cavdar et al[22] evaluated EASIX in metastatic pancreatic cancer and observed significantly shorter survival among patients with elevated EASIX scores, further reinforcing the concept that endothelial stress and vascular injury represent biologically meaningful determinants of clinical outcomes across distinct solid tumor types.

These observations suggest that EASIX reflects tumor–host interactions that extend beyond histology-specific mechanisms. In contrast, despite the well-established vascular dependence of RCC and the central role of angiogenesis-targeted therapies, the prognostic relevance of EASIX in RCC has not previously been explored, underscoring the importance of the present findings.

Although the IMDC risk model remains the cornerstone of prognostic stratification in metastatic RCC, it primarily integrates clinical and laboratory variables that reflect tumor burden and general host conditions rather than specific biological processes, such as endothelial stress or vascular injury.[3] In contrast, RCC is a prototypical angiogenesis-driven malignancy in which dysregulation of hypoxia-inducible signaling leads to sustained VEGF activation, aberrant neovascularization, and chronic endothelial activation. These processes are accompanied by structural and functional alterations in the tumor vasculature, including increased permeability, impaired nitric oxide signaling, inflammatory cytokine release, and a pro-thrombotic endothelial phenotype.[29,30]

Beyond its role in tumor angiogenesis, endothelial dysfunction contributes to disease progression through interconnected mechanisms, such as hypoxia amplification, facilitation of tumor cell intravasation, and modulation of the tumor microenvironment via inflammatory and coagulation pathways. Although anti-VEGF–based therapies are designed to inhibit tumor angiogenesis, they may also disrupt endothelial homeostasis, highlighting the importance of vascular stress in the clinical course of mRCC. Within this biological framework, biomarkers that capture endothelial activation and vascular injury may provide clinically relevant information that extends beyond the conventional prognostic models.[31,32]

The independent prognostic significance of EASIX, even after accounting for IMDC risk categories, reinforces the idea that endothelial stress constitutes a unique biological aspect not entirely captured by existing clinical stratification methods. Rather than serving as a substitute for IMDC, EASIX may offer complementary insights by integrating signals related to vascular injury, systemic stress, and host susceptibility in a disease that is fundamentally driven by angiogenic dysregulation.

The potential role of EASIX in patients receiving immune checkpoint inhibitor–based treatment also deserves consideration. Although the present cohort was limited to patients treated with first-line TKI monotherapy, several studies in mRCC have shown that inflammation-based indices are associated with clinical outcomes in patients receiving nivolumab or other immune checkpoint inhibitor–based regimens.[4-6] These findings suggest that host-related inflammatory and vascular factors may remain clinically relevant in the immunotherapy era. However, the prognostic value of EASIX in contemporary immune checkpoint inhibitor–based treatment cohorts has not yet been established and should be evaluated in future studies.

It is important to recognize certain limitations. Firstly, the retrospective, single-center design may have introduced selection bias and limited the generalizability of the findings. Secondly, all patients in this cohort were treated with first-line TKI monotherapy. Given that the current standard first-line treatment for metastatic RCC increasingly involves immune checkpoint inhibitor–based combinations, the applicability of the present findings to contemporary treatment paradigms warrants further investigation. Third, EASIX was assessed only at baseline, and dynamic changes during or after anti-VEGF–based therapy were not evaluated. Therefore, the potential prognostic implications of longitudinal endothelial stress modulation could not be assessed. Finally, no RCC-specific, biologically validated cut-off value for EASIX has been established, and patient stratification based on the median value may limit direct clinical translation. Despite these limitations, the present study provides biologically grounded real-world evidence supporting the prognostic relevance of EASIX in metastatic RCC and

underscores the need for prospective validation in larger, multicenter cohorts, particularly in the context of contemporary combination therapies.

Baseline EASIX was identified as an independent prognostic marker for patients with metastatic RCC receiving first-line TKI treatment. Given its reliance on routinely accessible laboratory parameters, EASIX represents a practical biomarker for prognostic stratification within this population. Further prospective studies are needed to validate these findings and to define its role within contemporary treatment strategies.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstanbul University-Cerrahpaşa (Approval No.: E-83460662-050.04-1560873; Date: January 7, 2026).

Informed Consent: The requirement for informed consent was waived by the Ethics Committee owing to the retrospective design of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.G.; Design – M.G., N.S.D., Ö.A.; Supervision – N.S.D., Ö.A.; Materials – M.G., E.Ç., M.Gul, Z.B.; Data Collection and/or Processing – M.G., E.Ç., M.Gul, Z.B., E.Çe., V.A., H.A., S.C.; Analysis and/or Interpretation – M.G., M.Gul; Literature Search – M.G., E.Ç.; Writing Manuscript – M.G.; Critical Review – N.S.D., Ö.A.

Declaration of Interests: Murad Guliyev is a Section Editor for Medical Oncology at Cerrahpaşa Medical Journal; however, his involvement in the peer review process was solely as an author. The other authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

References

1. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. National Cancer Institute. Accessed March 2, 2026. https://seer.cancer.gov/statfacts/html/kidrp.html.
2. Bosma NA, Warkentin MT, Gan CL, et al. Efficacy and safety of first-line systemic therapy for metastatic renal cell carcinoma: a systematic review and network meta-analysis. *Eur Urol Open Sci*. 2022;37:14-26. [CrossRef]
3. Ernst MS, Navani V, Wells JC, et al. Outcomes for international metastatic renal cell carcinoma database consortium prognostic groups in contemporary first-line combination therapies for metastatic renal cell carcinoma. *Eur Urol*. 2023;84(1):109-116. [CrossRef]
4. Martini DJ, Liu Y, Shabto JM, et al. Novel risk scoring system for patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors. *Oncologist*. 2020;25(3):e484-e491. [CrossRef]
5. Rebuzzi SE, Signori A, Banna GL, et al. Inflammatory indices and clinical factors in metastatic renal cell carcinoma patients treated with nivolumab: the development of a novel prognostic score (Meet-URO 15 study). *Ther Adv Med Oncol*. 2021;13:17588359211019642. [CrossRef]
6. Yildirim A, Wei M, Liu Y, et al. Association of baseline inflammatory biomarkers and clinical outcomes in patients with advanced renal cell carcinoma treated with immune checkpoint inhibitors. *Ther Adv Med Oncol*. 2025;17:17588359251316243. [CrossRef]
7. Yasar HA, Bir Yucel K, Arslan C, et al. The relationship between prognostic nutritional index and treatment response in patients with metastatic renal cell cancer. *J Oncol Pharm Pract*. 2020;26(5):1110-1116. [CrossRef]
8. Iinuma K, Enomoto T, Kawada K, et al. Utility of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune inflammation index as prognostic, predictive biomarkers in patients with metastatic renal cell carcinoma treated with nivolumab and ipilimumab. *J Clin Med*. 2021;10(22):5325. [CrossRef]
9. Xu J, Chen P, Cao S, Hu X, Li X. Prognostic value of systemic immune-inflammation index in patients with metastatic renal cell carcinoma treated with systemic therapy: a meta-analysis. *Front Oncol*. 2024;14:1404753. [CrossRef]
10. Bolek H, Kuzu OF, Sertesen Camoz E, et al. Evaluating the prognostic role of glucose-to-lymphocyte ratio in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors in first line: a study by the Turkish Oncology Group Kidney Cancer Consortium (TKCC). *Clin Transl Oncol*. 2025;27(7):3110-3120. [CrossRef]
11. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. *Oncotarget*. 2017;8(43):75381-75388. [CrossRef]
12. Hibino S, Kawazoe T, Kasahara H, et al. Inflammation-induced tumorigenesis and metastasis. *Int J Mol Sci*. 2021;22(11):5421. [CrossRef]
13. Kruk L, Mamtimin M, Braun A, et al. Inflammatory networks in renal cell carcinoma. *Cancers (Basel)*. 2023;15(8):2212. [CrossRef]
14. Follain G, Osmani N, Gensbittel V, et al. Impairing flow-mediated endothelial remodeling reduces extravasation of tumor cells. *Sci Rep*. 2021;11(1):13144. [CrossRef]
15. Monjaras-Avila CU, Lorenzo-Leal AC, Luque-Badillo AC, D'Costa N, Chavez-Muñoz C, Bach H. The tumor immune microenvironment in clear cell renal cell carcinoma. *Int J Mol Sci*. 2023;24(9):7946. [CrossRef]
16. Penack O, Luft T, Peczynski C, et al. Endothelial Activation and Stress Index (EASIX) to predict mortality after allogeneic stem cell transplantation: a prospective study. *J Immunother Cancer*. 2024;12(1):e007635. [CrossRef]
17. Song GY, Jung SH, Kim K, et al. Endothelial activation and stress index (EASIX) is a reliable predictor for overall survival in patients with multiple myeloma. *BMC Cancer*. 2020;20(1):803. [CrossRef]
18. Park S, Go SI, Lee GW. The Endothelial Activation and Stress Index (EASIX) score is an independent prognostic factor in patients with diffuse large B-cell lymphoma. *BMC Cancer*. 2022;22(1):816. [CrossRef]
19. Li M, Chen H, Gao L, et al. Endothelial activation and stress index (EASIX) as a predictive biomarker for survival in patients with T-cell lymphoma. *Hematology*. 2025;30(1):2519974. [CrossRef]
20. Gu JS, Ryu JW, Yu SH, et al. Prognostic value of the endothelial activation and stress index in patients with upper tract urothelial cancer undergoing radical nephroureterectomy. *Investig Clin Urol*. 2022;63(6):623-630. [CrossRef]
21. Go SI, Park S, Kang MH, et al. Endothelial activation and stress index (EASIX) as a predictive biomarker in small cell lung cancer. *Cancer Biomark*. 2022;35(2):217-225. [CrossRef].
22. Cavdar VC, Gokmen Y, Aric M, et al. The prognostic value of the EASIX score in patients with metastatic pancreatic cancer. *Diagnostics (Basel)*. 2025;15(14):1740. [CrossRef]
23. Zhang N, Zhang H, Zhu D, et al. Prognostic role of pretreatment lactate dehydrogenase in patients with metastatic renal cell carcinoma: a systematic review and meta-analysis. *Int J Surg*. 2020;79:66-73. [CrossRef]
24. Shen J, Chen Z, Zhuang Q, et al. Prognostic value of serum lactate dehydrogenase in renal cell carcinoma: a systematic review and meta-analysis. *PLOS One*. 2016;11(11):e0166482. [CrossRef]
25. Gu L, Li H, Gao Y, et al. The association of platelet count with clinicopathological significance and prognosis in renal cell carcinoma: a systematic review and meta-analysis. *PLOS One*. 2015;10(5):e0125538. [CrossRef]
26. Suppiah R, Shaheen PE, Elson P, et al. Thrombocytosis as a prognostic factor for survival in patients with metastatic renal cell carcinoma. *Cancer*. 2006;107(8):1793-1800. [CrossRef]
27. Aktepe OH, Arslan AM, Yetginoglu O, et al. Prognostic impact of glomerular filtration rate decline on survival outcomes in metastatic renal cell carcinoma treated with targeted therapy. *Medicina (Kaunas)*. 2025;61(9):1574. [CrossRef]
28. Życzkowski M, Prokopowicz G, Taborowski P, et al. Basic parameters of blood count, serum sodium, and creatinine as prognostic factors for renal cell carcinoma at five-year follow-up. *Med Sci Monit*. 2018;24:3895-3902. [CrossRef]

29. Franczyk B, Rysz J, Ławiński J, Ciałkowska-Rysz A, Gluba-Brzózka A. Cardiotoxicity of selected vascular endothelial growth factor receptor tyrosine kinase inhibitors in patients with renal cell carcinoma. *Biomedicines*. 2023;11(1):181. [CrossRef]
30. Uyl TJJ, Ngo A, Pratt D, et al. Mechanisms of anti-VEGF therapy-induced kidney injury: current insights and future perspectives in combination with immune checkpoint inhibitors. *Am J Physiol Ren Physiol*. 2025;329(2):F284-F299. [CrossRef]
31. Chehrazi-Raffle A, Meza L, Alcantara M, et al. Circulating cytokines associated with clinical response to systemic therapy in metastatic renal cell carcinoma. *J Immunother Cancer*. 2021;9(3):e002009. [CrossRef]
32. Ndiaye PD, Dufies M, Giuliano S, et al. VEGFC acts as a double-edged sword in renal cell carcinoma aggressiveness. *Theranostics*. 2019;9(3):661-675. [CrossRef]