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Research Article

Comparison of a Novel Blood-Based Hemato-Immune Response Score (HIRS) with IMDC and MSKCC Models in Metastatic Renal Cell Carcinoma

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Abstract

Objectives: Current prognostic models for metastatic renal cell carcinoma (mRCC), such as IMDC and MSKCC, may inadequately capture immune–inflammatory dynamics. This study evaluated the predictive and prognostic utility of a novel Hemato-Immune Response Score (HIRS) in comparison with established models.

Methods: We retrospectively analyzed 35 patients (69 treatment episodes) with mRCC treated with tyrosine kinase inhibitors, immune checkpoint inhibitors, or mTOR inhibitors between 2015 and 2024. HIRS was derived from routine hematologic and biochemical parameters, including neutrophil, lymphocyte, monocyte, and platelet counts, hemoglobin, albumin, C-reactive protein, glucose, lactate dehydrogenase, and derived inflammatory indices, and categorized into low- and high-HIRS groups using ROC/Youden analysis (cut-off: 0.11). Associations with objective response rate (ORR) and progression-free survival (PFS) were assessed using logistic and Cox regression analyses.

Results: High HIRS was independently associated with lower ORR (OR=0.31, 95% CI 0.12–0.78; p=0.018) and shorter PFS (HR=1.89, 95% CI 1.11–3.21; p=0.019). Median PFS was 11.1 months in the low-HIRS group and 5.3 months in the high-HIRS group (p=0.009). HIRS outperformed IMDC and MSKCC (0.70 vs 0.63 and 0.61), while the combined IMDC + HIRS model performed best (0.74).

Conclusion: HIRS showed independent predictive and prognostic value in mRCC and improved risk discrimination when integrated with established clinical models.

Keywords: Immunotherapy, Renal Cell Carcinoma, Treatment Outcome

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Among adult cancers, renal cell carcinoma (RCC) stands out as the primary renal malignancy, accounting for approximately 3% to 5% of all cases globally.[1] Despite progress in detection and treatment, metastatic disease is detected at initial diagnosis in roughly one-third of patients, while post-nephrectomy metastasis occurs in nearly 40% of those with localized tumors.[2] In the last ten years, the treatment algorithm for metastatic RCC (mRCC) has evolved dramatically, moving away from cytokine-based approaches toward targeted agents and, more recently, immune checkpoint inhibitors (ICIs) combined with other therapies.[3] However, clinical outcomes remain heterogeneous, necessitating reliable prognostic markers to guide personalized therapy.[4]

Risk stratification in mRCC currently relies heavily on established prognostic systems, most notably the Memorial Sloan

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Kettering Cancer Center (MSKCC) and International Metastatic RCC Database Consortium (IMDC) models.[5] These risk models utilize a combination of clinical factors and laboratory values, including performance status, time from diagnosis to treatment, hemoglobin, calcium, and lactate dehydrogenase (LDH) levels.[6] Although these models are essential tools for risk stratification, they primarily reflect tumor burden and patient performance rather than the underlying immune-inflammatory status. Consequently, patients within the same risk category frequently exhibit markedly different treatment responses, underscoring the limited ability of these conventional scores to capture biological heterogeneity.[7]

Accumulating evidence indicates that systemic inflammation and immune dysregulation play pivotal roles in RCC tumorigenesis and progression.[8] Peripheral blood markers such as neutrophils, monocytes, platelets, and C-reactive protein (CRP) serve as accessible surrogates of systemic inflammation, while lymphocyte and albumin levels reflect host immune competence and nutritional status.[9] Composite indices such as the neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and CRP/albumin ratio (CAR) have been associated with survival outcomes in RCC. Nevertheless, these parameters often evaluate only isolated aspects of the complex immune-metabolic interplay, and their prognostic consistency varies across studies.[10]

To address these limitations, we designed the Hemato-Immune Response Score (HIRS), a composite index derived entirely from routine peripheral blood tests. HIRS integrates hematologic and biochemical variables—including neutrophil, lymphocyte, monocyte, and platelet counts, as well as hemoglobin, albumin, glucose, CRP, and LDH—into a single standardized score. This multidimensional approach aims to capture the host's immune-inflammatory, metabolic, and nutritional status simultaneously. We hypothesized that a higher HIRS would correlate with inferior treatment response and shorter progression-free survival (PFS). Therefore, this multicenter retrospective study aims to evaluate the predictive and prognostic performance of HIRS in patients with mRCC and to determine whether incorporating HIRS into established models enhances predictive discrimination.

Methods

Study Design and Patient Selection

Data were retrospectively reviewed from three tertiary oncology centers, covering mRCC cases treated systemically between January 2015 and December 2024. To be included, patients had to demonstrate histopathologically confirmed RCC and possess at least one measurable metastatic lesion consistent with RECIST v1.1 guidelines. Patients were excluded if they had a concurrent second malignancy, received treatment at outside facilities, or lacked essential baseline laboratory records. A total of 35 patients (corresponding to 69 treatment episodes) meeting the inclusion criteria were included in the final analysis. Each treatment episode was considered an independent event corresponding to a specific line of systemic therapy (first, second, or subsequent lines).

Data Collection

Demographic, clinical, and laboratory data were retrieved from electronic medical records and institutional databases. Hematologic and biochemical indices were derived from laboratory parameters measured within the two-week window preceding the start of therapy. For each treatment episode, the following variables were recorded: age, sex, histologic subtype, history of nephrectomy, Eastern Cooperative Oncology Group (ECOG) performance status, treatment line, type of systemic therapy [tyrosine kinase inhibitor (TKI), ICI, or mTOR inhibitor], and clinical outcomes. Treatment response was classified as either complete (CR) or partial (PR) based on RECIST v1.1 standards. We defined PFS as the duration from the onset of systemic therapy until death or documented radiological progression.

Definition and Calculation of HIRS

HIRS was designed to integrate parameters reflecting systemic inflammation, immune surveillance, and metabolic–nutritional status. The score was constructed using standardized (z-scored) logarithmic transformations of the following parameters: neutrophil count, lymphocyte count, monocyte count, platelet count, hemoglobin, albumin, CRP, glucose, and LDH. Additionally, derived inflammatory indices—including the SII, systemic inflammation response index (SIRI), pan-immune-inflammation value (PIV), CAR, and glucose/lymphocyte ratio (GLR)—were incorporated into the composite formula. Variables associated with an adverse inflammatory or metabolic profile, including neutrophil count, monocyte count, platelet count, CRP, glucose, LDH, SII, SIRI, PIV, CAR, and GLR, were oriented so that higher values increased HIRS, whereas variables reflecting more favorable immune competence or nutritional status, including lymphocyte count, hemoglobin, and albumin, were oriented in the opposite direction, so that lower values contributed to a higher HIRS. The continuous HIRS value was derived from the mean of these z-transformed components. Patients were then dichotomized into "low" and "high" HIRS groups according to the optimal threshold identified by ROC analysis using the Youden index for objective response prediction (cut-off: 0.11).

Risk Classification and Comparative Models

Prognostic risk classification for each treatment episode was performed using both the IMDC and MSKCC criteria.

The IMDC risk model utilized six factors: hemoglobin < lower limit of normal (LLN), corrected calcium > upper limit of normal (ULN), neutrophil count > ULN, platelet count > ULN, Karnofsky performance status < 80%, and time from diagnosis to treatment < 1 year. The MSKCC model was based on hemoglobin, corrected calcium, LDH, performance status, and time from diagnosis to treatment. The predictive performance of HIRS was compared against IMDC, MSKCC, and a combined "IMDC + HIRS" model to evaluate incremental prognostic value.

Statistical Analysis

Statistical computations were performed utilizing IBM SPSS Statistics (v29.0) and R (v4.3.2). For continuous data, we reported medians and interquartile ranges (IQR), whereas categorical variables were summarized as frequencies and percentages. Differences between groups were assessed via the chi-square (χ^2) test or Mann-Whitney U test, depending on the data type. ROC curve analysis was performed to evaluate the discriminative ability of HIRS, IMDC, MSKCC, and the combined model for objective response; the area under the curve (AUC) values were compared using the DeLong test. The optimal cut-off point for HIRS was determined using the Youden index. The Kaplan–Meier method was employed to generate PFS survival curves, with differences analyzed using the log-rank test. Cox proportional hazards regression models were utilized to estimate hazard ratios (HR) and 95% confidence intervals (CI). We evaluated the discriminative performance of the models using Harrell's concordance index (C-index). Comparisons between models were conducted using the rcorr.cens function in R, and a two-sided p-value of < 0.05 was defined as statistically significant.

Ethical Approval

This study was conducted in strict accordance with the Declaration of Helsinki. The study protocol was approved by the Bezmiâlem Foundation University Scientific Research Ethics Committee at its meeting dated 26 November 2025 (Meeting No: 18; Approval No: 2025/440). Due to the retrospective nature of the study and the anonymization of patient data, the requirement for informed consent was waived.

Results

Patient and Treatment Characteristics

The final analysis included 69 treatment episodes from 35 patients with metastatic RCC. The median age was 62 years (IQR: 54–69), and the majority of the cohort was male (74%). Clear-cell RCC was the predominant histologic subtype (86%). Regarding prior and ongoing treatments, 49% of episodes corresponded to first-line therapy, while 36% and 15% represented second-line and third-line or later therapies, respectively. The systemic treatments administered included TKIs in 49% of episodes, ICIs in 35%, and mTOR inhibitors in 16%. Risk stratification based on the IMDC criteria categorized 20% of episodes as favorable, 55% as intermediate, and 25% as poor risk, with a similar distribution observed using the MSKCC model. The overall objective response rate (ORR) was 33.3%, consisting of three complete responses (CR) and twenty partial responses (PR). Baseline demographic and clinical characteristics are summarized in Table 1.

Table 1. Baseline characteristics of treatment episodes (n=69)

Variable	n (%) or Median (IQR)
Age (years)	62 (54 – 69)
Sex	
Male	26 (74%)
Female	9 (26%)
Histology	
Clear-cell RCC	59 (86%)
Non-clear cell	10 (14%)
Nephrectomy prior to systemic therapy	23 (66%)
ECOG performance status	
0	9 (13%)
1	20 (29%)
2	6 (9%)
Treatment line	
1st line	34 (49%)
2nd line	25 (36%)
≥3rd line	10 (15%)
Treatment type	
TKI	34 (49%)
ICI	24 (35%)
mTOR inhibitor	11 (16%)
IMDC risk groups	
Favorable	14 (20%)
Intermediate	38 (55%)
Poor	17 (25%)
Median follow-up (months)	21 (12 – 34)
Median PFS (months)	8.2 (6.5 – 9.9)
Objective response rate (ORR)	33.3% (3 CR + 20 PR)

RCC: Renal cell carcinoma; ECOG: Eastern Cooperative Oncology Group; TKI: Tyrosine kinase inhibitor; ICI: Immune checkpoint inhibitor; IMDC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; PFS: Progression-free survival; CR: Complete response; PR: Partial response; IQR: Interquartile range.

Predictive Performance of HIRS for Treatment Response

Receiver operating characteristic (ROC) curve analysis demonstrated that HIRS had meaningful discriminative ability in predicting objective response, yielding an AUC of 0.70 (95% CI: 0.66–0.88). HIRS demonstrated greater discriminative ability compared with IMDC (AUC=0.63, 95% CI: 0.49–0.77) and MSKCC (AUC=0.61, 95% CI: 0.47–0.75). The combined IMDC + HIRS model provided the highest predictive performance (AUC=0.74, 95% CI: 0.61–0.87), indicating incremental value beyond conventional clinical models (Fig. 1).

Based on the optimal threshold identified by ROC analysis using the Youden index (cut-off: 0.11), patients were stratified into low and high HIRS categories. In multivariable logistic regression analysis (Table 2), high HIRS emerged as an independent predictor of reduced treatment responsiveness. Patients with high HIRS had a significantly lower likelihood of achieving an objective response compared with those in the low-HIRS group (OR=0.31, 95% CI: 0.12–0.78; p=0.018). Neither the line of therapy nor the class of treatment (ICI vs. TKI) showed a significant association with ORR, indicating that the immune–inflammatory state captured by HIRS was a stronger determinant of response than treatment modality.

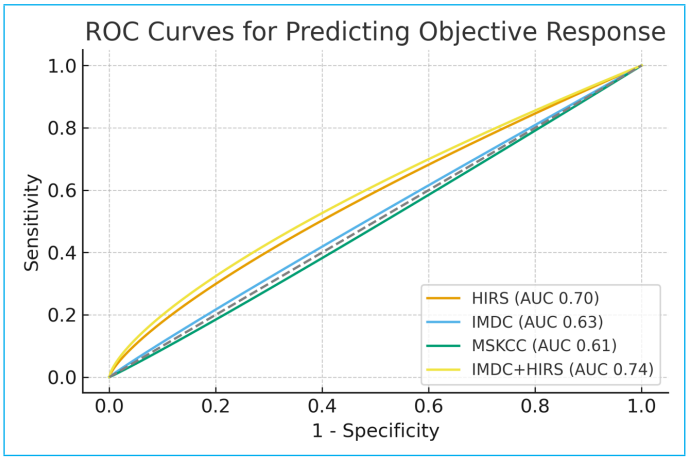

Figure 1. Receiver operating characteristic (ROC) curves for predicting objective response. The Hemato-Immune Response Score (HIRS) demonstrated superior discriminative ability (AUC = 0.70, 95% CI: 0.66–0.88) compared with the IMDC model (AUC = 0.63, 95% CI: 0.49–0.77) and the MSKCC model (AUC = 0.61, 95% CI: 0.47–0.75). The combined "IMDC + HIRS" model provided the highest predictive performance (AUC = 0.74, 95% CI: 0.61–0.87), indicating incremental prognostic value. (Abbreviations: AUC, area under the curve; IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center).

Table 2. Multivariable logistic regression for predictors of objective response

Variable	Odds ratio (95% CI)	p
HIRS (High vs. Low)	**0.31 (0.12 – 0.78)**	**0.018**
Treatment line (≥ 2 vs. 1)	0.64 (0.29 – 1.41)	0.26
Regimen type (ICI vs. TKI)	1.12 (0.52 – 2.43)	0.77

Model performance: AUC=0.77 (95% CI: 0.66–0.88). HIRS: Hemato-immune response score; CI: Confidence interval; ICI: Immune checkpoint inhibitor; TKI: Tyrosine kinase inhibitor; AUC: Area under the curve.

Prognostic Impact of HIRS on PFS

PFS analysis revealed a clear separation between HIRS groups. Patients with low HIRS achieved a median PFS of 11.1 months (95% CI: 6.4–15.8), whereas those with high HIRS had a substantially shorter median PFS of 5.3 months (95% CI: 3.4–7.2) (log-rank p=0.009) (Fig. 2). In the multivariable Cox proportional hazards model (Table 3), high HIRS was

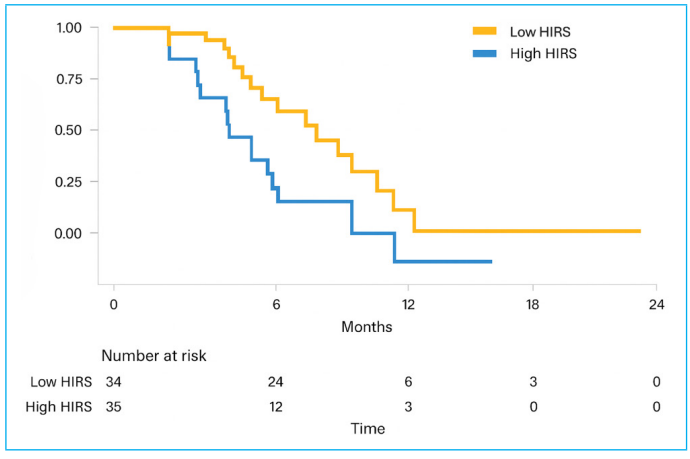

Figure 2. Kaplan–Meier curves for progression-free survival (PFS) according to HIRS status. Patients stratified into the "Low HIRS" group (blue line) achieved a significantly longer median PFS (11.1 months, 95% CI: 6.4–15.8) compared with those in the "High HIRS" group (red line, 5.3 months, 95% CI: 3.4–7.2). The difference was statistically significant (Log-rank test, p=0.009).

Table 3. Comparative prognostic performance for progression-free survival (PFS)

Model	Hazard ratio (95% CI)	p	C-index
HIRS (High vs. Low)	**1.89 (1.11 – 3.21)**	**0.019**	**0.70**
IMDC model	–	–	0.63
MSKCC model	–	–	0.61
Combined (IMDC + HIRS)	–	0.02*	**0.74**

**p value indicates the significance of the improvement in C-index (ΔC-index =+0.11 vs IMDC).* Note: Median PFS was 11.1 months in the HIRS-low group versus 5.3 months in the HIRS-high group (log-rank p=0.009). HIRS: Hemato-immune response score; IMDC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; CI: Confidence interval.

independently associated with a nearly two-fold increase in the risk of progression or death (HR=1.89, 95% CI: 1.11–3.21; p=0.019). These findings confirm the prognostic relevance of systemic immune–inflammatory status in mRCC.

Comparison with Established Risk Models

To benchmark the performance of HIRS against established prognostic systems, we compared its discriminative accuracy with the IMDC and MSKCC models using Harrell's C-index. HIRS alone achieved a C-index of 0.70, outperforming IMDC (0.63) and MSKCC (0.61). The combined IMDC + HIRS model demonstrated the highest prognostic accuracy, with a C-index of 0.74, representing a significant improvement over IMDC alone (ΔC-index =+0.11; p=0.02). These results indicate that integrating immune–inflammatory markers with traditional clinical predictors enhances risk stratification in mRCC (Table 3).

Discussion

The present study evaluated the clinical utility of a novel HIRS in patients with metastatic RCC (mRCC) treated with contemporary systemic therapies, including TKIs, ICIs, and mTOR inhibitors. Our results demonstrated that higher baseline HIRS values were independently associated with poorer objective response rates and shorter PFS. When compared with established prognostic models such as IMDC and MSKCC, HIRS showed comparable discriminative performance, and importantly, its combination with IMDC further improved model accuracy. These findings suggest that systemic immune and inflammatory status—quantified through routine peripheral blood parameters—provides complementary prognostic information beyond conventional clinical risk factors in mRCC.

Biologically, HIRS was developed to integrate multiple hematological and biochemical parameters reflecting the host immune-inflammatory balance, metabolic status, and nutritional condition. The score incorporates neutrophil, lymphocyte, monocyte, and platelet counts, as well as CRP, albumin, glucose, and LDH levels—each known to influence cancer progression through distinct but interconnected pathways.[11] Elevated neutrophil and platelet counts are known to promote tumor progression by secreting vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), and transforming growth factor-β (TGF-β), which facilitate angiogenesis and immune evasion.[12] Conversely, lymphopenia reflects impaired cytotoxic and helper T cell–mediated immune surveillance, an adverse host factor repeatedly correlated with poor immunotherapy response. Therefore, composite indices such as NLR, SII, and SIRI serve as surrogates for systemic inflammation, integrating both protumor and antitumor immune components.[13] Additionally, elevated CRP levels reflect the hepatic acute-phase response driven by IL-6 signaling, while hypoalbuminemia indicates a catabolic state and nutritional decline.[14] Collectively, these variables form a multidimensional representation of the "immune-metabolic phenotype" of the host, supporting the concept that chronic inflammation and metabolic dysregulation drive treatment resistance.

The IMDC and MSKCC scoring systems currently serve as the primary standards for risk assessment in mRCC clinical practice. Nevertheless, these models were established prior to the widespread use of immunotherapy and depend largely on tumor burden, performance status, and routine biochemical markers. While they maintain prognostic value, they do not directly capture the host immune dynamics that are critical in the era of checkpoint inhibitors.[15] Consequently, patients with similar IMDC risk scores often demonstrate markedly different clinical outcomes.[16] In our cohort, HIRS alone achieved a C-index comparable to IMDC and MSKCC; more importantly, the combined "IMDC + HIRS" model yielded a meaningful improvement in predictive performance (ΔC-index = +0.11). This supports the hypothesis that immune-inflammatory markers can refine risk stratification, potentially aiding in the identification of patients who may require early treatment intensification or closer monitoring.

From a practical perspective, HIRS offers significant advantages, as it can be easily computed from standard laboratory data without additional cost. As mRCC treatment increasingly shifts toward precision medicine, baseline HIRS could serve as a dynamic biomarker to identify patients at risk of poor response to ICIs. Moreover, HIRS could be prospectively evaluated as a stratification variable in future clinical trials to ensure a balanced distribution of host inflammatory burden between study arms.

Our findings suggest that HIRS may complement, rather than replace, established prognostic models such as IMDC and MSKCC by capturing the host inflammatory, immune, and metabolic milieu through routinely available laboratory variables. Whereas IMDC and MSKCC are widely used and externally recognized clinical models, HIRS may provide additional biologic information relevant to both treatment response and PFS. The strengths of the present study include the use of accessible laboratory parameters and the direct head-to-head comparison with conventional risk models within the same dataset. These findings support the potential additive value of HIRS, while warranting further validation in larger prospective cohorts.

Despite these promising findings, several limitations should be acknowledged. The retrospective design and relatively small sample size limit the generalizability of the results. In addition, several established prognostic factors

in metastatic RCC, such as IMDC risk score, ECOG performance status, histologic subtype, and metastatic burden, were not fully adjusted for in the multivariate logistic regression model. Owing to the limited sample size and event number, inclusion of a larger number of covariates was not feasible without increasing the risk of model overfitting. Furthermore, the analysis was performed at the level of treatment episodes rather than exclusively at the patient level; therefore, repeated treatment lines from the same patient may have introduced intra-patient correlation and may have affected the assumption of independence. In addition, a first-line-restricted subgroup analysis was not performed, which should be considered another limitation of the present study. Accordingly, the present findings should be interpreted as hypothesis-generating and require validation in larger prospective cohorts, ideally using patient-level or first-line-restricted analyses.

Conclusion

The HIRS represents a simple, cost-effective, blood-based biomarker that integrates systemic inflammation, immune response, and metabolic–nutritional status in metastatic RCC. In this study, high baseline HIRS values were independently associated with lower objective response rates and shorter progression-free survival. Notably, while the predictive performance of HIRS alone was comparable to that of established risk models, its integration with the IMDC score significantly enhanced prognostic discrimination. Given its accessibility and biologic rationale, HIRS serves as a promising adjunct to conventional clinical scores for improved patient stratification and treatment optimization in mRCC. Future prospective multicenter studies are warranted to validate its clinical utility and to explore its role in guiding personalized treatment strategies.

Disclosures

Ethics Committee Approval: The study was approved by the Bezmiâlem Foundation University Scientific Research Ethics Committee at its meeting dated 26 November 2025 (Meeting No: 18; Approval No: 2025/440) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Patient consent was waived due to the retrospective and anonymized nature of the study.

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