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Proceeding Paper

Relevance of the IMDC Risk Model in a Real World Setting: A Single Institution Experience †

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Abstract

This single-centre retrospective study evaluated outcomes in 112 patients with metastatic renal cell carcinoma (mRCC) treated with first-line VEGF-TKIs or immune checkpoint inhibitor (IO)-based combinations. The primary objective of this study was to evaluate survival outcomes of mRCC patients according to IMDC risk stratification in the modern systemic treatment era. A secondary aim was to assess whether prior nephrectomy provides an independent prognostic advantage when adjusted for an IMDC risk category. This study highlights that the IMDC risk classification remains a strong and reliable prognostic tool for predicting survival outcomes in mRCC patients treated with modern VEGF TKI and IO-based therapies, with median overall survival (OS) of 87, 36, and 9 months in favourable-, intermediate-, and poor-risk patients, respectively. Prior nephrectomy appeared to improve OS (55 vs. 21 months) and progression-free survival (29 vs. 10.9 months) on unadjusted analysis; however, this association was attenuated and no longer statistically significant after adjusting for IMDC risk groups, reflecting strong baseline imbalances and indicating that any true independent benefit is uncertain and requires confirmation in larger cohorts.

Keywords: renal cancer; IMDC risk group; cytoreductive nephrectomy; immunotherapy

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1. Introduction

Over the past two decades, there have been major advancements in the treatment of metastatic renal cell carcinoma (mRCC). Prior to the vascular endothelial growth factor tyrosine kinase inhibitors era (VEGF TKI), patients were treated with cytokine therapies like interleukin-2 and interferon-alpha, which offered limited effectiveness and were often poorly tolerated [1]. The introduction of VEGF TKIs such as sunitinib and pazopanib in the mid-2000s represented a significant improvement by slowing disease progression through the inhibition of angiogenesis in tumours. Despite this, long-term responses were uncommon. There has been a significant shift in the treatment paradigm with the emergence of immune checkpoint inhibitors like nivolumab, which not only improved survival but also had a more favourable safety profile, marking the beginning of the immunotherapy era. More recently, combination treatments—either pairing two immunotherapy agents (IO–IO) or combining immunotherapy with VEGF-TKIs (IO–TKI)—have become the preferred first-line approach. This was supported by data from landmark studies such as CheckMate 214, KEYNOTE-426, and CLEAR and these combinations have shown superior survival and response outcomes compared to single-agent VEGF TKI therapy [2–5].

The International Metastatic RCC Database Consortium (IMDC) risk model remains an essential prognostic tool for patients with metastatic renal cell carcinoma (mRCC), even in the era of IO combination therapies [6]. Originally developed during the VEGF-targeted therapy era, the IMDC model uses six clinical and laboratory parameters to categorise patients into favourable-, intermediate-, or poor-risk groups. As treatment has evolved to include immune checkpoint inhibitors and IO-based combination, such as IO–IO and IO–VEGF TKI regimens, the IMDC framework continues to offer meaningful prognostic value. Recent studies confirm its ability to stratify survival outcomes and guide treatment selection in both clinical trials and real-world practice. This enduring relevance of the IMDC model supports its ongoing use in optimising patient management and therapeutic strategies in the modern mRCC landscape [7].

Furthermore, the impact of previous nephrectomy (either radical or partial) in metastatic renal cell carcinoma (mRCC) has been a subject of ongoing research, especially in the era of targeted and immunotherapy-based treatments [8,9].

The role of previous nephrectomy, whether partial or radical, in metastatic renal cell carcinoma (mRCC) has evolved with changing treatment strategies. In the era of cytokine therapy, cytoreductive nephrectomy was shown to improve overall survival, supported by landmark trials such as SWOG 8949 and EORTC 30947 [10,11]. This benefit continued into the VEGF-TKI era, where selected patients with good performance status and limited metastatic burden had improved outcomes following surgery. However, the introduction of immune checkpoint inhibitors and IO-based combination therapies has led to a more nuanced approach. The CARMENA trial challenged the routine use of upfront nephrectomy, showing no significant survival advantage in intermediate- and poor-risk patients treated with nephrectomy followed by sunitinib compared to sunitinib alone [12]. In the current IO era, nephrectomy may still offer benefits in selected patients, particularly those with favourable-risk profiles, low-volume disease, or symptomatic primary tumours. For patients with aggressive or high-burden disease, immediate systemic therapy without surgery is often preferred [13,14]. Overall, nephrectomy remains a valuable option, but its use should be individualised based on patient characteristics, disease burden, and treatment goals.

The purpose of this analysis was two-fold: firstly, to assess whether the IMDC prognostic model continues to discriminate clinical outcomes in mRCC patients treated in the contemporary immunotherapy era; and secondly, to evaluate whether prior nephrectomy confers additional prognostic value beyond IMDC risk classification. As real-world treatment pathways have shifted from TKI-only therapy to IO-based and sequential TKI followed by IO approaches, this study aims to clarify prognostic relevance within a heterogeneous treatment landscape reflective of routine NHS practice.

2. Materials and Methods

This retrospective study, conducted at a single centre, involved 112 patients with metastatic renal cell carcinoma (mRCC) who received first-line systemic therapy between January 2018 and March 2022 (Table 1). Progression-free survival (PFS) and overall survival (OS) were evaluated using descriptive statistical methods and Kaplan–Meier survival analysis.

Patients treated with VEGF-TKI monotherapy were included because treatment between 2018 and 2020 at our centre still commonly followed a sequential pathway (TKI first-line followed by IO later-line). Therefore, although IMDC has been historically validated in TKI-treated cohorts, this study reflects real-world practice in the IO era, including patients who later received checkpoint inhibition. This differs from original IMDC publications which contained no IO-exposed patients.

Patient data was collected on variables including age, gender, performance status, IMDC risk classification, history of nephrectomy, initial pattern of metastatic spread, and the number of therapy lines received.

Table 1. Baseline clinical characteristics (n = 112).

Characteristics	n (%)
Median Age (range)	66 (35–85) [1]
Sex-Male	77 (68.8)
Histology–clear cell	88 (78.6)
Sarcomatoid features	7 (6.2)
Sites of metastasis	
Lung	67 (59.8)
Bone	31 (27.7)
Liver	15 (13.4)
Adrenal	12 (10.7)
Nodal metastatis	57 (50.9)
Prior nephrectomy	54 (48.2)
IMDC risk group	
Favourable	27 (24.1)
Intermediate	61 (54.5)
Poor	24 (21.4)

[1] Age range.

3. Results

Most patients were male (68.8%) with a median age of 66 years (35–85). Prior nephrectomy was performed in just under half of the patients (48.2%). Clear cell histology was the most prevalent subtype (78.6%), with a smaller proportion presenting with papillary or other rare variants. Sarcomatoid features were noted in 6.2% of cases. Lung metastases were the most frequent sites of metastases (59.8%), followed by bone (27.7%), liver (13.4%), and adrenal involvement (10.7%). Nodal metastases were present in about half of the cohort (50.9%) (Table 1).

Pazopanib (29.5%) and nivolumab plus ipilimumab (23.2%) were the most commonly used first line systemic treatments, followed by sunitinib (20.5%), tivozanib (17.9%), and axitinib plus avelumab (7.1%). The majority (58%) went on to receive second-line therapy, commonly with nivolumab (40%), cabozantinib (33.8%), or other VEGF inhibitors.

Treatment continuation decreased over sequential lines of therapy, with 42% receiving only one line, 58% progressing to second-line, and <25% receiving third-line therapy. This reflects expected attrition seen in real-world datasets.

The survival outcomes of patients with metastatic renal cell carcinoma (mRCC) varied significantly according to IMDC risk classification and prior nephrectomy status. Stratification by IMDC risk groups revealed a clear gradient in overall survival (OS): patients in the favourable-risk group exhibited a markedly prolonged median OS of 87 months, followed by intermediate-risk patients with a median OS of 36 months, and poor-risk patients with a substantially shorter median OS of 9 months. The differences across these groups were statistically significant (Log-Rank test, $p < 0.001$), underscoring the strong prognostic value of IMDC risk classification (Table 2, Figures 1 and 2).

Prior nephrectomy was more frequent in patients with favourable IMDC risk scores. Among favourable-risk patients, 26 of 27 (96%) had undergone prior nephrectomy, compared with 21 of 61 (34%) intermediate-risk patients and 7 of 24 (29%) poor-risk patients. Thus, the group with the best prognosis was also the group with the highest proportion of prior nephrectomy (Table 3, Figure 3).

Table 2. Mean and median overall survival by IMDC risk category in metastatic RCC.

Risk Group	Mean (Months)	Std Error	CI Lower	CI Upper	Median (Months)	Std Error	CI Lower	CI Upper
Favourable	86.947	10.438	66.488	107.406	87.0	17.115	53.454	120.546
Intermediate	41.612	5.382	31.064	52.16	36.0	3.936	29.286	43.714
Unfavourable	17.0	2.866	11.382	22.618	9.0	4.082	0.998	17.002
Overall	49.03	4.836	39.552	58.508	36.0	4.7	26.787	45.213

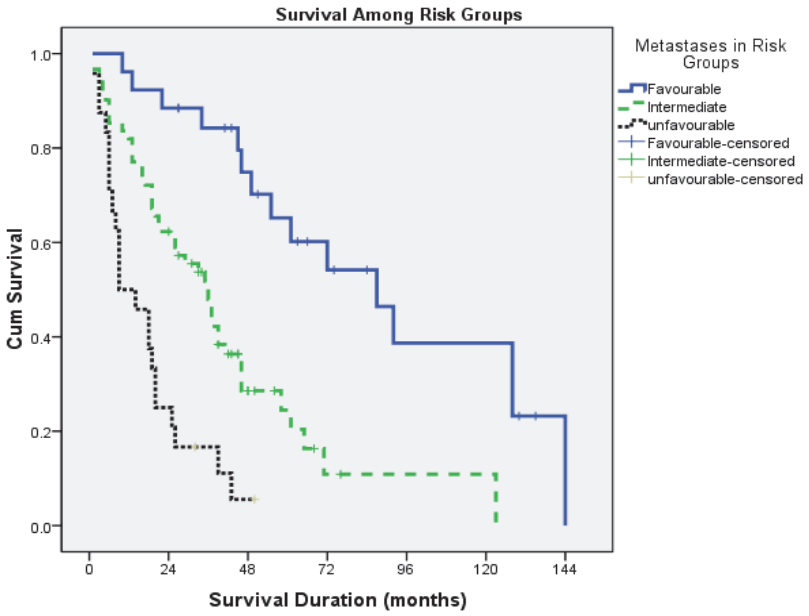

Figure 1. Kaplan–Meier overall survival curves by IMDC risk groups in mRCC patients.

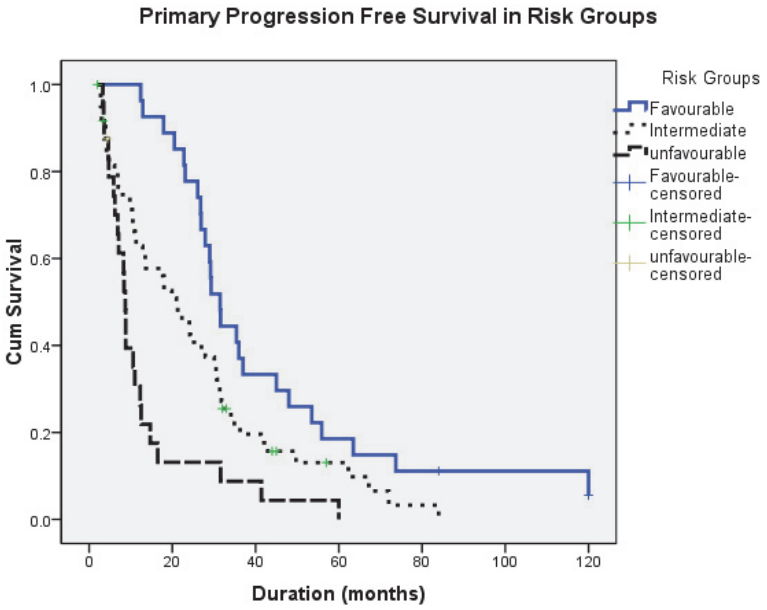

Figure 2. Kaplan–Meier curves of progression-free survival by IMDC risk groups in mRCC patients.

In a multivariable logistic regression model including prior nephrectomy and IMDC risk group, prior nephrectomy was associated with a non-significant trend towards reduced odds of death at last follow-up (adjusted OR 0.52, 95% CI 0.18–1.53; $p = 0.24$). Compared with patients in the favourable IMDC group, those in the poor-risk group demonstrated a numerically higher risk of death (adjusted OR 4.48, 95% CI 0.73–27.44; $p = 0.10$), while

outcomes for the intermediate-risk group were similar to those of the favourable group (adjusted OR 1.19, 95% CI 0.35–3.99; $p = 0.78$). These findings suggest that the apparent survival benefit of prior nephrectomy observed in the unadjusted analysis may be partly explained by its strong association with favourable IMDC risk, although a clinically relevant independent effect cannot be excluded due to the wide confidence intervals (Table 4).

Table 3. Survival outcomes by nephrectomy status with IMDC stratification.

Group	n	Median OS (Months)	Median PFS (Months)
Nephrectomy-YES	**54**	**~55**	**29**
Favourable IMDC	26	66.5	31.5
Intermediate IMDC	21	44.7	21
Poor IMDC	7	32.2	8.7
Nephrectomy-NO	**58**	**~21**	**10.9**
Favourable IMDC	1	-*	Not reliable (n = 1)
Intermediate IMDC	40	44.1	11.1
Poor IMDC	17	27.4	8.3

* Not calculable median.

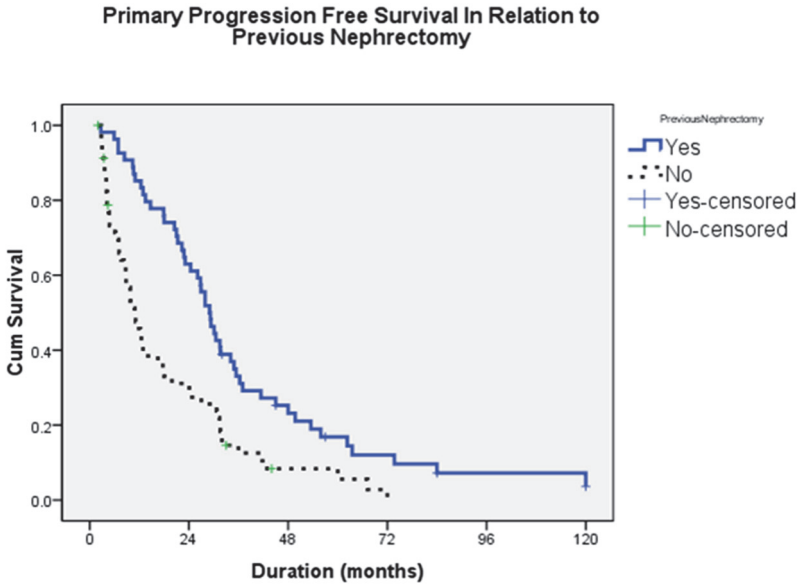

Figure 3. Kaplan–Meier progression-free survival curves by nephrectomy status in mRCC patients.

Table 4. Multivariable logistic regression for overall survival status at last follow-up.

Variable	Category/ Comparison	Adjusted OR	95% CI	*p* Value
Prior nephrectomy	Yes vs. No	0.52	0.18–1.53	0.24
IMDC risk group	Intermediate vs. Favourable	1.19	0.35–3.99	0.78
	Poor vs. Favourable	4.48	0.73–27.44	0.10

There was a trend toward improved PFS in patients who underwent nephrectomy (29 vs. 10.9 months), although this did not reach statistical significance.

We also noted that favourable-risk patients who underwent prior nephrectomy had the longest survival and conversely, poor-risk patients without nephrectomy had the shortest survival.

4. Discussion

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk model based on simple clinical and laboratory parameters (Time from diagnosis to treatment, Haemoglobin, corrected calcium, performance status, neutrophil, and platelet count) has been widely used in the prognostication and clinical management of mRCC. These prognostic variables used in IMDC risk classification reflect underlying tumour biology or host response to disease [15] and can be easily applied in a variety of clinic settings without the need for complex molecular tests. Our study also demonstrated clear prognostic separation between the three IMDC risk groups and would be consistent with the established literature, reinforcing that IMDC remains a robust, reproducible tool in predicting long-term outcomes.

Importantly, the prognostic power of IMDC risk classification remains valid across modern therapeutic settings, including the use of immune checkpoint inhibitor (IO) combinations and VEGF TKI regimens. This suggests that despite advances in therapy, underlying patient and disease characteristics captured by the IMDC model still influence response to treatment and overall prognosis. In clinical practice, IMDC risk stratification aids in treatment selection, clinical trial design, and patient counselling, offering a standardised approach to risk-adjusted care. It also plays a pivotal role in shared decision-making, particularly when balancing aggressive therapy against expected benefit [7].

The role of nephrectomy continues to be a key factor in determining prognosis for patients with metastatic renal cell carcinoma (mRCC), even in the era of immunotherapy and targeted therapies. Historically, cytoreductive nephrectomy (CN) provided a survival advantage in the interferon era, but its relevance in the setting of modern systemic treatments remains an area of active investigation [8–11].

In our cohort, the proportion of patients undergoing prior nephrectomy varied substantially across IMDC risk groups, with almost all favourable-risk patients (96%) having had nephrectomy compared with only approximately one-third of intermediate- and poor-risk patients. This strong imbalance raises the possibility that baseline prognostic factors captured by the IMDC score could confound the apparent association between nephrectomy and survival.

To address this, we performed a multivariable analysis adjusting for IMDC risk group and performance status. In this model, prior nephrectomy was no longer statistically significantly associated with overall survival, although the effect estimate was consistent with a potential survival benefit (adjusted OR 0.52, 95% CI 0.18–1.53). These findings suggest that at least part of the observed survival advantage in the nephrectomy group may reflect the more favourable baseline characteristics of these patients, particularly their over-representation in the IMDC favourable-risk category. However, given the limited sample size and wide confidence intervals, a clinically meaningful independent effect of nephrectomy cannot be excluded, and larger datasets are needed to confirm these observations.

5. Conclusions

This study reaffirms that IMDC risk stratification remains a valid tool in determining prognosis of mRCC patients, even in the era of combination immunotherapy and VEGF-targeted treatments. Our data also indicate that the apparent survival advantage associated with prior nephrectomy is attenuated and no longer statistically significant after adjusting for IMDC risk group and performance status, suggesting potential confounding by baseline prognostic factors. Nevertheless, the direction of effect remains consistent with a possible benefit, and nephrectomy should continue to be considered on an individualised basis in carefully selected patients with favourable- or intermediate-risk disease.

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Abbreviations

The following abbreviations are used in this manuscript:

IMDC	International mRCC Database Consortium
VEGF	Vascular Endothelial Growth Factor
TKI	Tyrosine Kinase Inhibitor
IO	Immunotherapy
PFS	Progression Free Survival
OS	Overall Survival

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