

# Promising Biomarkers in Renal Cell Carcinoma

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## Abstract

Renal cell carcinoma (RCC) incidence has been increasing in recent years, and it now represents the sixth most common cancer diagnosis in men and the tenth in women. Although this is partly due to increased detection of incidental small renal masses on unrelated imaging, advanced RCC continues to be diagnosed in a significant portion of patients, with more than 15% presenting with distant metastases. Biomarkers can be a cost-effective tool to identify high-risk patients and institute appropriate individualised therapies. While the literature in this field is nascent, this paper focuses on several biomarkers that have been extensively investigated in the diagnosis and prognosis of RCC, as well as in predicting its response to treatments, particularly the newer immuno-oncology drugs.

## Introduction

Renal cell carcinoma (RCC) is a heterogeneous disease with a relatively unpredictable natural history. There are few reliable markers to distinguish between indolent and aggressive lesions at the time of diagnosis, predict relapse, and guide treatment decisions in the management of RCC.

Biomarkers have long been anticipated to deliver on the promise of precision medicine, and thus lead to better patient care and lower health care costs[1]. They are defined as “objectively measurable indicators of normal biological processes, pathogenic processes or pharmacologic responses to therapeutic intervention”[2]. Diagnostic biomarkers can allow for an early detection and classification of cancer. Prognostic biomarkers can inform clinicians about the natural course of an individual cancer and guide their decision of whom to treat, and how aggressively to treat. Predictive biomarkers assess the probability of a patient benefiting from a particular treatment.

Despite significant advances in our knowledge of RCC at a molecular level, there are no validated biomarkers for this disease. An array of serum, urine, and tissue-based biomarkers have been described, but each has its own practical limitations. Profiling complex fluids, such as serum and urine, requires awareness of the effect of other circulating proteases and nucleases on marker signals, as well as pre-fractionation strategies, given the vast difference in orders of magnitude in protein concentrations[3]. On the other hand, tumour heterogeneity may limit the utility of tissue-based markers[4].

This paper summarises the current status of the most widely studied molecular and genetic biomarkers in RCC. It is only a broad overview, and detailed description of individual markers should be sought in the referenced literature. While the recent advances in proteomics and metabolomics are likely to provide a more nuanced understanding of this disease in the future, their discussion is outside the scope of this paper.

### Key Words

Biomarkers, kidney cancer, diagnosis, prognosis

### Competing Interests

None declared.

### Article Information

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## Abbreviations

CAIX	carbonic anhydrase IX
CRP	C-reactive protein
RCC	renal cell carcinoma
VEGF	vascular endothelial growth factor

## Diagnostic Biomarkers

Improved characterisation of small renal masses is required to avoid surgical intervention in those with benign or indolent lesions and treat those with high metastatic potential in a timely manner. Given the high level of discordance in pathological subtyping as seen in non-clear cell RCC cases[5,6] or biopsy specimens[7], a diagnostic biomarker would be particularly useful.

### Carbonic anhydrase IX (CAIX)

CAIX is a downstream effector of HIF-1 $\alpha$  and is thought to play a role in regulating intracellular and extracellular pH in tumour cells. It is highly expressed in 95% of clear cell RCC (ccRCC), compared with minimal expression in oncocytomas, chromophobe, and papillary RCC[8–10]. CAIX is also expressed in other tumours, including carcinomas of lung, breast, uterus, oesophagus, and brain, as well as in normal gastric mucosa[11]. While this somewhat limits the use of CAIX as a diagnostic marker for metastatic disease, there is ongoing enthusiasm for its utility in characterisation of the small renal mass. Several clinical trials have demonstrated the possibility of improving the performance of positron emission tomography/ computed tomography (PET/CT) by using radio-labelled girentuximab, a chimeric monoclonal antibody against CAIX. REDECT, a phase III open-label multi-centre trial, assessed the diagnostic accuracy of 124I-girentuximab PET/CT in 195 patients undergoing nephrectomy and reported a sensitivity of 86.2% and specificity of 85.9% in non-invasively identifying ccRCC. Sensitivity was higher in tumours >2cm, and the overall positive predictive value was 94.4%, obviating the need for an invasive biopsy in these cases[12].

### Gene expression profiling

Gene expression arrays have been created to differentiate between RCC subtypes and identify the aggressiveness and metastatic potential of tumours. Multiple studies have correlated the genetic expression profile of different types and grades of RCC with their morphological classification[13–15]. Analysis of these signatures from early stage ccRCC have also informed us of additional pathways in tumourigenesis, including the down-regulation of transcription factors required for normal renal development, such as GATA3, TFCP2L1, TFAP2B,

and DMRT2. Other studies have identified a panel of up to 34 genes that is predictive of tumour aggression, and may function as a biomarker in the future[16].

### Urinary biomarkers

Urine is an easily accessed source for biomarkers. Profiling studies have identified 2 promising proteins originating from the proximal tubule, aquaporin 1 and adipophilin, that may be shed in urine and have diagnostic potential. Initial results indicate that both proteins are significantly elevated in urine from patients with RCC compared with healthy controls, declining to control levels following nephrectomy[17,18]. Nuclear matrix protein 22 (NMP22), an accepted urothelial cancer marker, was found to also be significantly elevated in urine samples from patients with RCC in a few studies conducted more than 15 years ago; however, there have been no further reports since[19–21]. Other markers, eg, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and matrix metalloproteinases (MMPs) have been inadequate in differentiating renal malignancy[22,23].

### Tissue biomarkers

There is a wide panel of antibodies that are currently used for diagnostic purposes, including CK7, CD10, Pax 2, Pax 8, vimentin, and alpha-methylacyl-CoA (AMACR)[24]. Because of the particular difficulty in differentiating between benign and malignant eosinophilic tumours, a number of additional biomarkers have been studied to better characterise chromophobe RCC and oncocytoma such as Hale's colloidal iron, several cadherins, and BCA2[25]. Additional analysis of distinct chromosomal aberrations, such as TFE3 and TFEB, is now established for translocation-associated RCCs.

### Composite biomarkers

The optimal future biomarker will likely be a panel of biomarkers utilising the strengths of those mentioned above. One such biomarker is the composite 3-marker panel of nicotinamide N-methyltransferase (NNMT), L-plastin (LCP1), and non-metastatic cell 1 protein (NM23A) that was evaluated in a cohort study of 189 patients, and further validated in 100 patients. Plasma levels of NNMT, LCP1, and NM23A were significantly elevated in patients with kidney cancer. This composite assay had a positive predictive value of 87.2%, and a negative predictive value of 97% for diagnosis of renal cell carcinoma[26]. A recent validation of this assay was conducted in 9 centres with 1042 individuals, resulting in similar findings: the diagnostic sensitivity and specificity were 0.871 and 0.894, respectively, and the resulting area under curve of receiver operating characteristic was 0.917[27].

## Prognostic Biomarkers

Accurate prognostic markers are the cornerstone of cancer management, and are indispensable in patient counselling, determining need for adjuvant therapies, and developing appropriate surveillance strategies. Currently, at least 8 prognostic nomograms are frequently utilised for predicting the risk of relapse and survival in RCC[28–32]. However, recent prospective validation of these models, using data from the ASSURE trial, showed a more substantial decrease in each of their prognostic abilities than previously reported in retrospective external validation studies[33]. Most models only marginally outperformed standard staging, and all had a C-index below 0.7[34]. The search for more precise prognostic markers therefore continues.

### Routine blood markers

Serum LDH, calcium, and haemoglobin have been widely reported to have independent prognostic significance in metastatic disease and are included in several nomograms[35,36].

Several studies have reported that C-reactive protein (CRP) is a strong predictor of metastasis and overall mortality after nephrectomy for localised RCC[37–41]. Immunohistochemical studies have also demonstrated significant intratumoural production of CRP which can be correlated with survival outcomes[42,43]. Interestingly, after adjusting for tumour staining, preoperative serum CRP was not a significant predictor of overall survival (OS) ( $P = 0.741$ ) in one of these studies[43].

Thrombocytosis, another marker of the inflammatory milieu, is also an adverse prognostic factor in many cancers, including RCC [44–46]. However, in a predictive model comprising TNM stage, age, Fuhrman grade, histological subtype, and preoperative haemoglobin, thrombocytosis did not add any meaningful value, with a predictive accuracy gain of 0.3% only[47].

Increased peripheral blood or intratumoural neutrophils is also associated with poor survival[48–52]. Furthermore, a number of studies have demonstrated that a higher blood neutrophil/lymphocyte ratio (NLR) portends a poorer prognosis[53–55]. NLR is emerging as a prognostic factor in several other cancers, and is thought to represent an impaired cell-mediated immune response due to systemic inflammation[56].

Changes in coagulation pathways are also well-recognised in malignancy. Cohort studies have reported significantly higher concentrations of plasma fibrinogen and D-dimer in patients with metastatic disease, and identified independent association with reduced cancer-specific survival (CSS) and OS[57–59].

## The VHL, HIF, and VEGF axis

Mutation of the VHL gene has been associated with a longer progression-free survival (PFS) and CSS in ccRCC in some studies[60,61]; however, this was not reproduced in other analyses[62–64]. Similarly, analyses of elevated HIF-1 $\alpha$  levels and survival have varied, with some studies demonstrating favourable prognosis, and others associating it with worse outcomes[65,66].

Increased vascular endothelial growth factor (VEGF) concentration has consistently been associated with worse tumour stage and grade, necrosis, microvessel invasion, and CSS[67,68]. However, given that VEGF is contained within platelets and released on clotting, falsely elevated results due to contamination of plasma with platelets or coagulation due to delays in processing the sample can occur, compromising its clinical applicability[69].

CAIX is one of the HIF target genes, and is associated with tumour growth, aggressive phenotype, and poor prognosis in most cancers[70–72]. In contrast, high CAIX expression is associated with a better prognosis in RCC in several studies[73–76]. In a larger study, however, CAIX expression was not an independent prognostic factor, after adjusting for the effect of nuclear grade, sarcomatoid differentiation, and tumour necrosis[11]. These findings were further validated at the 5-year follow-up of this study[77].

### Immunologic markers

The B7 family of immune regulatory ligands produce co-stimulatory or co-inhibitory T-cell signals, and therefore have been identified as promising prognostic biomarkers. B7-H1 functions as a negative regulator of immunity, and its over-expression is independently associated with significantly increased progression to metastatic disease (RR 3.46;  $P < 0.001$ ) and cancer-specific mortality (RR 3.92;  $P < 0.001$ )[78, 79]. B7-H4 and, less strongly, B7-H3 have also been implicated as adverse prognostic factors[80, 81]. Non-invasive immunoassays for the soluble forms of the B7 family are being developed with promising early results[82].

Given the immunogenic nature of RCC, pathologic specimens harbour a high number of tumour-infiltrating lymphocytes (TILs). Their prognostic significance is not established because of inconsistent findings on various multivariate analyses to date[83–85].

### Markers of cell proliferation and apoptosis

Various nuclear proteins that regulate cell growth, proliferation, and apoptosis are established as prognostic markers in other cancers. Some of these are also very promising in RCC, as summarised in Table 1[86–99].

**TABLE 1.**

Markers of cell proliferation and apoptosis as prognostic biomarkers

Prognostic biomarker	Role	Supporting literature	Reference
Insulin-like growth factor II mRNA-binding protein 3 (IMP3)	Oncofoetal RNA-binding protein; cell proliferation and invasion	Expression associated with significantly worse outcomes, >1400 patients total in 3 major studies	86
		• 5-year OS 27% vs 82%, $P < 0.0001$	87
		• OS HR 1.42, $P = 0.024$ ; risk of distant metastases HR 4.71, $P < 0.001$	88
		• Risk of metastases specifically in chromophobe or papillary RCC - HR 13.45, $P < 0.001$	89
Ki-67	Cell proliferation marker	Poor prognosis in many cancers, including RCC	90
		HR 2.18 and 2.50 for CSS in 741 tumours with and without necrosis respectively	91
		Expression correlates with increasing stage and grade	92
		Only independent predictor of RCC recurrence, in a study of several markers (CAIX, CRP, HIF) in 216 patients; HR 3.73	93
Survivin	Member of the inhibitor of apoptosis protein (IAP) family	Overexpressed in almost all human cancers, including RCC	95–98
		Worse CSS, HR 2.4, $P < 0.001$ ; and PFS, HR 1.9, $P = 0.02$ Confirmed in several retrospective studies	
p53	Induces apoptosis when DNA damaged	Over-expression is noted in 70% of papillary, 27% of chromophobe and 12% of clear cell tumours. Prognostic significance not yet established.	99

The cell cycle progression (CCP) score is an RNA expression assay that measures the activity of 31 genes involved in cellular proliferation, which has been widely validated for use in prostate cancer. Most recently, its prognostic utility has also been demonstrated in predicting recurrence and mortality in a cohort of 565 RCC patients undergoing nephrectomy[100]. In another study from the same authors, a higher CCP score on renal mass biopsy was correlated with adverse pathology on surgery, suggesting its clinical value in risk-stratifying patients being considered for active surveillance of small renal masses[101].

### Utility of biomarkers in prognostic models

Incorporation of molecular markers into existing prognostic models, as well as combining markers to create molecular signatures of the disease, will certainly be of greater utility than any single marker. A prognostic model using p53, CAIX, gelsolin, and vimentin, combined with metastatic status, T-stage and ECOG (Eastern Cooperative Oncology Group) performance status was 79% accurate in a cohort of 318 patients[102]. In another study of 634 patients, the integration of BioScore, which is based on expression of Ki-67, survivin and B7-H1, with the UISS and SSIGN models improved the prognostic accuracy of the models by 4.5% and 1.6% respectively. Furthermore, patients with high BioScores

were noted to be 5 times more likely to die from RCC (HR 5.03;  $P < 0.001$ )[103].

Lastly, the prognostic value of multi-gene assays, such as ClearCode-34 and 16-gene signature, has been reported to be greater than the established predictive models, and has now been validated in at least one prospective cohort. There are certainly caveats around tumour heterogeneity and misclassification due to sample bias; however, the results so far have been encouraging[104–107].

### Predictive Biomarkers

The therapeutic landscape in metastatic RCC has transformed in the past decade with the introduction of targeted and immuno-oncology treatments. Identifying markers that can reliably predict the response to specific treatments is essential to optimise patient management. This section focuses on predictive markers for these contemporary treatments.

#### Immune checkpoint inhibitors

Immunohistochemical expression of PD-L1 is the most studied marker in this realm. Studies to date have not established its independent predictive value. In all prospective trials, PD-L1 expression has been associated with worse prognosis, but not with response to checkpoint inhibitors[108–110]. Biological and

logistical challenges in using PD-L1 as a biomarker have been well described, including intratumoural heterogeneity, discordant expression in primary and secondary sites, dynamic expression, and variation in immunohistochemical assays[111].

Biomarker analysis from trial JAVELIN-101 was recently published, and included a 26-gene expression signature and mutations and polymorphisms based on whole exome sequencing, in addition to PD-L1 expression[112]. PD-L1 expression was not predictive of response to avelumab. As in previous studies, tumour mutational burden did not demonstrate any significant predictive value[113]. Several genetic mutations and the 26-gene signature were implicated in predicting treatment response; however, these findings need to be further validated.

Likewise, the phase II IMmotion-150 trial demonstrated the utility of gene expression signatures, reflecting angiogenesis and effector T-cell response, in predicting response to atezolizumab. A high angiogenic signature was associated with improved response rate and PFS in patients treated with sunitinib, and patients with high effector T-cell signature had better responses to ICB. These findings were subsequently confirmed by the phase III IMmotion-151 trial[114].

Other predictive markers under investigation include tumour-infiltrating lymphocytes, mutation signatures and microsatellite instability, HLA classification, TGF- $\beta$  expression, PD-L2, CTLA-4, mutational or neoantigen burden, and commensal gut microbiome[115,116].

### VEGF-related therapies

VHL mutation status failed to show any predictive value in various studies[117,118]. However, downstream effectors of angiogenesis have shown some promise. High IL-6 concentration is associated with improved

PFS benefit from pazopanib compared with placebo, as well as improved OS benefit from bevacizumab plus IFN- $\alpha$  compared with IFN- $\alpha$  alone[119,120]. The results for baseline levels of VEGF-A, VEGF receptor 2 and 3, HIF-1 $\alpha$  and 2 $\alpha$  and CAIX have been variable and inconsistent. Similar limitations were seen in analysis of other markers such as osteopontin, MMP, tissue inhibitor of metalloproteinase I (TIMP-I), TNF-related apoptosis-inducing ligand (TRAIL), and NLR[121,122].

The role of PD-L1 status was evaluated in 2 recent trials comparing the efficacy of cabozantinib to everolimus (METEOR), and sunitinib (CABOSUN). Although PD-L1 expression was associated with shorter PFS and OS in both studies, it was not predictive for response to either treatment[123,124].

### Limitations

A major barrier to translating research findings to clinically applicable tools has been a lack of standardisation in study methodologies and small sample sizes lacking statistical power to demonstrate any meaningful correlation. A shift to collaborative efforts of large research networks involving industry and scientific experts in prospective trials, instead of the traditional model of small laboratory-based retrospective studies, is hoped to yield higher quality data and provide us with an exciting and unprecedented opportunity for the discovery and large-scale validation of reliable, precise and cost-effective RCC biomarkers.

### Conclusion

Volumes of literature have been published on numerous promising diagnostic, prognostic and predictive RCC biomarkers. None of these have yet been established for routine clinical use in management of this heterogeneous disease.

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