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Prognostic Factors and Predictive Models in Renal Cell Carcinoma: A Contemporary Review

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Abstract

Context: The natural history of renal cell carcinoma (RCC) is highly unpredictable. Small renal masses may be accompanied by metastatic disease. Conversely, patients with locally advanced disease may enjoy long-term disease-free survival.
Objective: To review the status of prognostic factors in RCC.
Evidence acquisition: A literature review was performed using the PubMed, MEDLINE, and Cochrane databases for articles published as of February 15, 2010. Electronic articles published ahead of print were also considered. Search was limited to the English language. Search was conducted using the following keywords: *renal cell carcinoma, molecular, tissue, markers, blood, urine, progression, prognosis, risk factor,* and *survival.* Studies were selected according to the relevance of the study, the number of patients included, originality, actuality, and clinical applicability of the results.
Evidence synthesis: Four areas of prediction were examined: (1) new RCC diagnostics, (2) RCC grade and stage at diagnosis, (3) disease progression, and (4) disease-specific mortality. All identified reports represented either case series or controlled studies. Although a large number of markers were identified, only a few were validated. Several prognostic factors were integrated in predictive or prognostic models.
Conclusions: Several prognostic factors can help discriminate between favourable and unfavourable RCC phenotypes. Of those, several clinical, pathologic, and biologic markers have been tested and validated, and they are used in predictive and prognostic models. Nonetheless, the search continues, especially for informative markers predicting the response to targeted therapies.

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1. Introduction

The natural history of renal cell carcinoma (RCC) may be unpredictable. For example, between 4.2% and 7.1% of patients with tumours ≤4 cm that are usually indolent harbour metastatic disease at presentation and are at an elevated risk of disease-specific mortality [1]. Conversely, as many as 40% of patients with lymph node metastases

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diagnosed at nephrectomy are alive 5 yr after surgery [2]. Several approaches have been proposed to help predict the natural history of treated RCC and to distinguish between poor and favourable risk patients. In this paper, we briefly address the history of prognostics. We review the existing prognostic factors, as well as factors predicting response to targeted therapy, and complete the review with established prognostic models.

2. Evidence acquisition

A literature review was performed using the PubMed, Medline, and Cochrane databases for articles published as of February 15, 2010. Electronic articles published ahead of print were also considered. Search was limited to the English language. Search was conducted using the following keywords: *renal cell carcinoma, molecular, tissue, markers, blood, urine, progression, prognosis, risk factor,* and *survival.* Studies were selected according to the relevance of the study, the number of patients included, originality, actuality, and clinical applicability of the results.

3. Evidence synthesis

3.1. History of prognostics in renal cell carcinoma

In 1988, Elson et al. pioneered the approach to multivariable modelling in the prediction of cancer-specific mortality (Table 1) [3]. In 1999, Motzer et al. (n = 670) identified five predictors (Karnofsky performance status [KPS], lactate

Table 1 – Prediction of overall survival and/or progression-free survival in metastatic renal cell carcinoma

Model	Sample size	Target population	Predictors	C-index
Elson et al. [3]	610	mRCC	- ECOG-PS - Time from initial diagnosis - Number of metastatic sites - Prior cytoxic chemotherapy - Weight loss	n.r.
Motzer et al. [4]	670	mRCC treated with NT	- Lactate dehydrogenase >ULN - Haemoglobin >ULN - KPS - Corrected serum calcium >ULN - Absence of NT	n.r.
Motzer et al. [5]	463	mRCC treated with NT/IFN	- KPS - Lactate dehydrogenase <ULN - Haemoglobin >ULN - Corrected serum calcium >ULN - Time from diagnosis to IFN	n.r.
Motzer et al. [6]	251	mRCC treated with NT/IFN	- KPS - Haemoglobin >ULN - Corrected serum calcium >ULN	n.r.
Négrier et al. [134]	782	mRCC treated with cytokine	- Presence of biologic signs of inflammation - Short time interval from renal tumour to mRCC - Elevated neutrophil count - Liver metastases - Bone metastases - Performance status - Number of metastatic sites - Alkaline phosphatase - Haemoglobin	n.r. (OS)
Négrier et al. [134]	782	mRCC treated with cytokine	- Presence of hepatic metastases - Short interval from renal tumour to metastases - ≥1 metastatic site - Elevated neutrophil count	n.r. (PFS)
Leibovich et al. [137]	173	mRCC treated with NT/IL-2	- N classification - Constitutional symptoms - Location of metastatic sites - Histologic subtype - Sarcomatoid features - Thyroid-stimulating hormone levels	n.r.
Leibovich et al. [112]	727	Metastatic clear cell RCC treated with NT	- Age - Gender - Symptoms at NT - Time from NT to mRCC - Location/surgical treatment of metastases - Presence/level of tumour thrombus - Histologic subtype - TNM (2002) - Tumour size - Perinephritic fat invasion - Lymph node invasion - Nuclear grade	67%

Table 1 (*Continued*)

Model	Sample size	Target population	Predictors	C-index
			- Tumour necrosis - Sarcomatoid differentiation	
Negrier et al. [9]	782	mRCC patients treated with cytokine	- ≥1 metastatic site - Having received combination of therapies	n.r. (efficacy)
Mekhail et al. [7]	353	mRCC	- Multifocality - Time from diagnosis to study entry - Lactate dehydrogenase >ULN - Corrected serum calcium >ULN - Previous radiotherapy - Presence of Hepatic/pulmonary/ retroperitoneal/lymph node metastases	n.r.
Donskov et al. [174]	120	mRCC patients treated with IL-2	- Lactate dehydrogenase - Lymph node metastases - Haemoglobin - KPS - Bone metastases - High blood neutrophil count - Presence of intratumoural neutrophils - Low intratumoural $CD57^+$ natural killer cell count	n.r.
Choueiri et al. [13]	120	mRCC patients treated with VEGF agents	- Corrected serum calcium >ULN - Neutrophil count >ULN - Platelet count >ULN - ECOG-PS - Time from diagnosis to study start	n.r.
Escudier et al. [8]	300	mRCC patients who failed immunotherapy	- Alkaline phosphatase >ULN - Corrected serum calcium >ULN - Lactate dehydrogenase >ULN - Number of metastatic sites - Time from diagnosis to metastatic diagnosis	n.r.
Motzer et al. [12]	375	mRCC patients treated with sunitinib	- Corrected serum calcium - Number of metastatic sites - Haemoglobin >ULN - Prior NT - Lung metastases - Liver metastases - ECOG-PS - Thrombocytosis - Time from diagnosis to treatment - Alkaline phosphatase - Lactate dehydrogenase	63%
Heng et al. [10]	645	mRCC patients treated with VEGF agents	- KPS - Time from diagnosis to treatment - Haemoglobin >ULN - Corrected serum calcium >ULN - Neutrophil >ULN - Platelet >ULN	73%
Karakiewicz et al. [11]	628	mRCC patients treated with bevacizumab plus IFN or IFN alone	- KPS - Time from primary diagnosis to treatment - Baseline albumin - Baseline alkaline phosphatase	73%, 75%, 73%, and 71% at 6, 12, 18, and 24 mo (PFS)

mRCC = metastatic renal cell carcinoma; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; n.r. = not reported; NT = nephrectomy; ULN = upper limit normal; KPS = Karnofsky performance status; IFN = interferon; OS = overall survival; PFS = progression-free survival; IL-2 = interleukin-2; VEGF = vascular endothelial growth factor.

dehydrogenase [LDH], haemoglobin, corrected calcium, and presence/absence of nephrectomy) of metastatic RCC (mRCC) mortality [4]. The developed Motzer score stratified patients as favourable (0 risk factors), intermediate (one to two risk factors), and poor risk (three or more risk factors) [4]. In 2002, an update of the Motzer score ($n = 463$) replaced nephrectomy status with time from diagnosis to start of interferon [5]. In 2004, a second update ($n = 251$) reduced the score to three predictors (KPS, haemoglobin, and corrected calcium) [6].

In 2005, Mekhail et al. suggested several modifications to the 2002 Motzer score variables (KPS, LDH, haemoglobin, corrected calcium, and time from diagnosis to start of interferon) [5] such as the addition of previous exposure to radiotherapy and variables indicating the presence of nodal, hepatic, and/or lung metastases ($n = 353$; Table 1) [7]. In 2007, Escudier et al. also suggested the replacement of KPS with the number of metastatic sites [8]. Unfortunately, none of the original Motzer models were formally externally validated. Thus their accuracy, performance characteristics, and impact on clinical decision making remain unknown.

A report from the Groupe Français d'Immunothérapie suggested a different prognostic model, which identified four variables that were statistically significantly associated

with progression in patients receiving immunotherapy (Table 1). These consisted of time from RCC diagnosis to metastases, number of metastatic sites, presence of hepatic metastases, and the neutrophil count [9]. Recently, Heng et al. [10] devised and internally validated a model that replicates the Motzer methodology and relies on four of the five Motzer criteria (haemoglobin, corrected calcium, KPS, and time from diagnosis to treatment), in addition to neutrophil and platelet counts. Of all the models, the Heng et al. [10] model was the only one subjected to internal validation, which showed 73% accuracy in the prediction of mortality after therapy with vascular endothelial growth factor (VEGF). It awaits its external validation. Nonetheless, the Motzer criteria rely on factors that were developed in the immunotherapy era. The identification of factors that can be used in the era of targeted therapy is essential. To date, only a few such models exist [11–13].

The Motzer, Mikhail, Groupe Français d'Immunothérapie, and Heng models apply exclusively to patients with mRCC. Other models have been developed for patients with all stages or non-mRCC. For example, investigators from the University of California, Los Angeles (UCLA) devised an integrated staging system (UISS) for the prediction of survival in patients with all stages of RCC (Table 2) [14,15]. This model relies on the TNM stage, Fuhrman grade, and Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and it has been widely tested and validated (concordance indices [c-indices]: 58–86%) [16–22]. A multi-institutional collaborative group of European and North American investigators developed two prognostic models that address cancer-specific mortality based on variables that can be obtained either before (Table 3) or after nephrectomy (Table 4). These two models can predict the natural history of RCC after nephrectomy. However, they are not designed to account for the effect of targeted therapies in patients with mRCC [23,24]. The discrimination of the prenephrectomy model for prediction of cancer-specific mortality at 5 yr is 86.7% versus 86.8% for the postnephrectomy model (Table 2). Similar models were developed by other investigators and allow estimation of recurrence-free survival [25,26] or metastatic progression after nephrectomy [27], with discrimination between 65%

Table 2 – Postoperative assessment of cancer-specific mortality

Model	Sample size	Target population	Predictors	C-index
Zisman et al. [14]	661	RCC of all stages	- AJCC - Fuhrman grade - ECOG-PS	82–86%
Zisman et al. [15]	814	RCC of all stages	- TNM (1997) plus ECOG-PS	73% 79–86%
Frank et al. [30]	1801	Localized clear cell RCC	- TNM (1997) - Tumour size - Nuclear grade - Tumour necrosis	85% (int.) 81–82% (val.)
Kim et al. [86]	318	RCC of all stages	- M stage - Metastatic CAIX - p53 - Vimentin - Gelsolin	79%
Kim et al. [187]	150	Metastatic clear cell RCC	- T stage - ECOG-PS - CAIX - Vimentin - p53 - PTEN	68%
Thompson et al. [116]	1560	Localized clear cell RCC	- TNM (1997) - Tumour size - Nuclear grade - Tumour necrosis	n.r.
Karakiewicz et al. [23]	2530 (dev.) 1422 (val.)	Clear cell, papillary, chromophobe RCC	- pT stage - pN stage - M stage - Tumour size - Fuhrman grade - Symptoms classification	88–89% (val.)
Karakiewicz et al. [189]	2530 (dev.) 3560 (val.)	RCC of all stages	- pT stage - pN stage - M stage - Tumour size - Fuhrman grade - Symptoms classification	87–91% (val.)
Parker et al. [29]	818	Clear cell RCC	- B7-H1 - Survivin - Ki-67	73%

RCC = renal cell carcinoma; AJCC = American Joint Committee on Cancer; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; int. = internal; val. = validation; CAIX = carbonic anhydrase IX; PHEN = phosphatase and tensin homolog; dev. = development.

Table 3 – Preoperative assessment of prognosis

Model	Sample size	Outcome	C-index
Yaycioglu et al. [26]	296	Recurrence after nephrectomy	65.1%
Cindolo et al. [25]	660	Recurrence after nephrectomy	67.2%
Raj et al. [27]	290 (dev.) 94 (val.)	Clear cell RCC	82% (dev.) 76% (val.)
Lane et al. [190]	851	Benign vs malignant Indolent vs aggressive	64.4% 55.7%
Hollingsworth et al. [191]	26618	CSM and OS	n.r.
Hutterer et al. [192]	2522 (dev.) 2136 (val.)	Lymph node metastases at nephrectomy	78.4%
Raj et al. [27]	2517	Metastatic recurrence after nephrectomy	80.0%
Karakiewicz et al. [24]	2474 (dev.) 1972 (val.)	CSM	84-88%
Hutterer et al. [193]	2660 (dev.) 2716 (val.)	Distant metastases at nephrectomy	85.0%
Kutikov et al. [194]	30 801	CSM, OCM, NCM	n.r.

dev. = development; val. = validation; RCC = renal cell carcinoma. CSM = cancer-specific mortality; OS = overall survival; n.r. = not reported; OCM = other-cancer mortality; NCM = non-cancer-related mortality.

Table 4 – Postoperative assessment of recurrence

Model	Sample size	Target population	Predictors	C-index
Kattan et al. [28]	601	Localized RCC	- Symptom classification - Histologic subtype - Tumour size - pT stage	74.0% (overall rec.)
Frank et al. [195]	1864	Localized clear cell RCC	- Age - Gender - Symptom classification - TNM (1997) - Nuclear grade - Tumour necrosis - Sarcomatoid feature - Cystic architecture - Multifocality - Surgical margin status - Nephrectomy type	80.5% (abdominal rec.) 82.6% (thoracic rec.) 80.0% (bone rec.)
Sorbellini et al. [196]	701	Localized clear cell RCC	- Symptom classification - Tumour size - pT stage - Fuhrman grade - Tumour necrosis - Vascular invasion	82.0% (overall rec.)
Lam et al. [197]	559	Localized/locally advanced RCC	- TNM (1997) - Nuclear grade - ECOG-PS	n.r. (solitary rec., chest rec., abdominal rec., bone rec., brain rec.)

RCC = renal cell carcinoma; rec. = recurrence; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; n.r. = not reported.

and 80%. Multivariable models such as the UISS [14], the Kattan postoperative nomogram [28], BioScore [29], and SSIGN score (tumour stage, size, grade, necrosis) [30] have better prognostic ability than anatomic staging alone (Table 4). Despite their adequate prognostic ability, none of these models is 100% accurate. In consequence, the search for more accurate markers continues. Molecular events that can unveil the biologic heterogeneity underlying the varied clinical behaviour of RCC may help improve individualised prognostication and risk-stratified clinical decision making. The hope and interest lies in the identification of accurate markers that will predict the responses to the existing effective but toxic systemic therapies [31–35].

Over the past two decades, the molecular dissection of cancer has increased our understanding of the pathways that are altered in neoplastic cells. Although some biomarkers were shown to be associated with other established clinical and/or pathologic characteristics of RCC (Table 5), others demonstrated a meaningful effect with progression-free survival, overall survival, cancer-specific mortality, prognosis, and even added value when incorporated with existing prognostic models (Table 6). The following paragraphs outline the existing biomarkers that have demonstrated a potential for improving the predictive and/or prognostic ability of clinical and pathologic variables.

3.2. *Renal cell carcinoma biomarkers*

3.2.1. *Tissue-based biomarkers*

3.2.1.1. Von Hippel-Lindau gene. The Von Hippel-Lindau (VHL) gene was originally described, isolated, and identified as a tumour suppressor gene on chromosome 3p resulting in deficient protein isoforms pVHL19 and pVHL30 (Fig. 1). Its absence in the VHL familial tumour syndrome predisposes to retinal angiomas, central nervous system hemangioblastomas, pancreatic tumours, pheochromocytomas, and multiple

Table 5 – Molecular marker and its association with other established clinical and/or pathological characteristics of renal cell carcinoma (RCC)

Marker	Histology	Tumor stage	Tumor size	Tumor necrosis	Tumor grade	Metastatic disease/progression	Other
Neutrophil							
C-reactive protein						+	
VHL						+	
HIF-α	+ (clear cell)						
Tissue-based							
VEGF	+/ns (papillary)	+	+	+	+		Predictor of microvessel invasion
CAIX				ns	ns	+	
mTOR							
pS6						+	
PTEN		+					
pAkt					+		+
Other							
Caveolin-1	+ (clear cell)						
p53	+ (papillary)					+	
Ki-67							
Survivin	+ (all HS)				+		Predictor of aggressive disease
B7-H1						+	
Vimentin	+ (clear cell/papillary)						
Fascin	+ (sarcomatoid)	+	+			+	
MMP	+ (non clear cell)				+		Predictor of aggressive disease
IMP3	+ (sarcomatoid)	+		+		+	Predictor of lymph node involvement
Blood-based							
VEGF							
CAIX	+ (clear cell)	+/ns	+		ns		
NGAL							
SAA						+	
IGF-I							
NMP-22							Predictor of RCC diagnosis

+: associated with; ns: not significant.

bilateral clear cell RCC lesions. VHL is inactivated in almost all patients with VHL syndrome and approximately 70% of sporadic clear cell RCC [36]. Alteration in the VHL proteins results in impaired degradation of hypoxia inducible factor (HIF) 1-α, which accumulates even under normal (non-hypoxic) conditions. Other VHL gene effects include regulation of the cell-cycle arrest via p53 and deposition of extracellular matrix.

The presence of VHL alterations (mutation or hypermethylation) predicts longer progression-free survival and lower mortality for stage I–III clear cell RCC ($p = 0.024$ and 0.023, respectively) [36]. However, the survival rate of patients with VHL mutations was not different from patients without VHL mutations in other analyses [37]. The investigators postulated that regulation of angiogenesis and proliferation of RCC is not directly influenced by VHL mutations but that "loss-of-function" VHL mutations directly influence the progression of RCC.

Rini et al. showed that 60% of mRCC patients had VHL mutations and that 48% of those patients achieved an objective response to targeted therapy versus 35% for patients with no VHL mutation or methylation [38]. The independent prognostic effect of VHL mutation was also reported even after adjusting for ECOG-PS, haemoglobin, corrected calcium, LDH, radiation exposure, previous therapy, and number of metastatic sites [39]. In pazopanib-treated patients, a 76% clinical benefit rate (partial response plus stable disease) was achieved in patients with VHL gene variation versus 63% in those without [40]. Similar findings were recorded where loss-of-function VHL mutation conferred a 52% response rate (partial response plus complete response) to targeted therapies versus 31% for wild-type VHL ($p = 0.04$) [41]. Additional studies are clearly needed to better elucidate the role of VHL mutations in sporadic RCC, especially in the context of targeted therapies. However, added data quantifying the added benefit and externally validated accuracy results of models that integrate VHL are not yet available.

3.2.1.2. Hypoxia inducible factor. HIF-α accumulates either in hypoxic cell conditions or when the pVHL gene is deficient (Fig. 1). Increased expression of HIF-α was recorded in 75% (24 of 32) of clear cell RCC and only 38% (3 of 8) of non–clear cell RCC cases [42]. None of the HIF-1α–negative clear cell RCC patients showed a mutation of the VHL gene. The level of HIF-α appeared to correlate with the presence of VHL mutation. Lidgren et al. showed that the clear cell RCC variant had significantly higher HIF-1α expression compared with papillary or chromophobe RCC variants [43]. The prognostic significance of HIF-α levels was recorded only in patients with clear cell RCC ($p = 0.02$) but not in patients with papillary RCC ($p = 0.2$) [43].

The same authors reported no survival difference between patients with high and low HIF-1α expression in

Table 6 – Molecular marker and its association with progression-free survival (PFS), overall survival (OS), cancer-specific mortality (CSM), prognosis, treatment efficacy and its added value in established risk stratification for renal cell carcinoma (RCC)

Marker	Prognosis	PFS	OS	CSM	Treatment efficacy	Added value in prognostic models
Neutrophil		+	+ (in IL-2 patients)	+	ns (low response rate in IL-2 patients)	+ (Leibovich)
C-reactive protein			+			+
VHL		+/ns	+/ns	+	+ (predicts response to targeted therapy)	+
HIF-α			+		+ (predicts response to sunitinib)	
Tissue-based						
VEGF		+		+		
CAIX	+					+
mTOR						
pS6			+		+ (predicts response to temsirolimus)	
PTEN			+		+ (predicts response to mTOR inhibitors)/ns (low response in temsirolimus)	
pAkt	+ (for localized and metastatic RCC)			+	+ (predicts response to temsirolimus)	
Other						
Caveolin-1			+/ns (coexpression with Akt/mTOR)			
p53			ns			
Ki-67		+	+	+ (coexpression with CAIX)		
Survivin		+	+			
B7-H1			+	+		
Vimentin	+					
Fascin						
MMP			+			
IMP3		+		+		+ (SSIGN)
Blood-based						
VEGF		+/ns	+/ns (in metastatic RCC)/+ (in sorafenib patients)		+ (predicts response rate in sunitinib)/ns (does not predict response rate in sorafenib)	
CAIX		+		+		
NGAL		+				
SAA			+			
IGF-I			+			
NMP-22						

+: association; ns: not significant.

either clear cell or papillary RCC variants (all $p \geq 0.1$) [44]. Conversely, Klatte et al. showed worse survival (13.5 vs 24.4 mo; $p = 0.005$) with elevated HIF-1α tumour tissue levels. Methodological and analytical differences may account for the different findings [45].

In patients exposed to sunitinib, high levels of HIF-1α ($p = 0.003$) or of HIF-2α ($p = 0.001$) confer more favourable response to therapy (defined as complete or partial response) [46]. Clearly, standardised methodology and more studies are needed to better understand the prognostic and predictive role of HIF-α. Added value and external validity data are awaited.

3.2.1.3. Vascular endothelial growth factor. VEGF, a dimeric glycoprotein and a member of the platelet-derived growth factor, affects tumour angiogenesis in both normal and pathologic conditions (Fig. 1). In tumours, angiogenesis is induced by VEGF. In clear cell RCC, the upregulation of VEGF mRNA is expected due to the dysregulation of HIF-1α as a result of the loss of VHL protein in addition to the hypoxic environment. Larger tumours have inadequate blood supply and exacerbate hypoxia causing further upregulation of VEGF expression. Enhanced VEGF concentration correlates with VHL gene inactivation [47,48]. Increased VEGF production occurs in RCC patients with VHL gene alterations ($p < 0.001$) and advanced grade ($p < 0.001$) [49]. Elevated VEGF expression was reported in 29% of patients with clear cell RCC and unexpectedly in 67% of patients with papillary RCC ($p = 0.02$) [50] but could not be confirmed in other studies [51]. In clear cell RCC, VEGF expression correlates with tumour size ($p = 0.05$) [50], Fuhrman grade ($p = 0.002$), tumour necrosis ($p = 0.001$), tumour stage ($p = 0.006$) [52], microvessel invasion ($p = 0.01$) [53], RCC progression rate ($p = 0.01$) [52], and RCC-specific survival [50–52]. Further confirmatory studies are needed to assess VEGF pathway with downstream molecules such as phospho-extracellular signal-regulated kinase (pERK) possibly serving as a biomarker for therapy response. Despite its promising characteristics, VEGF awaits confirmation of its added value and external validity.

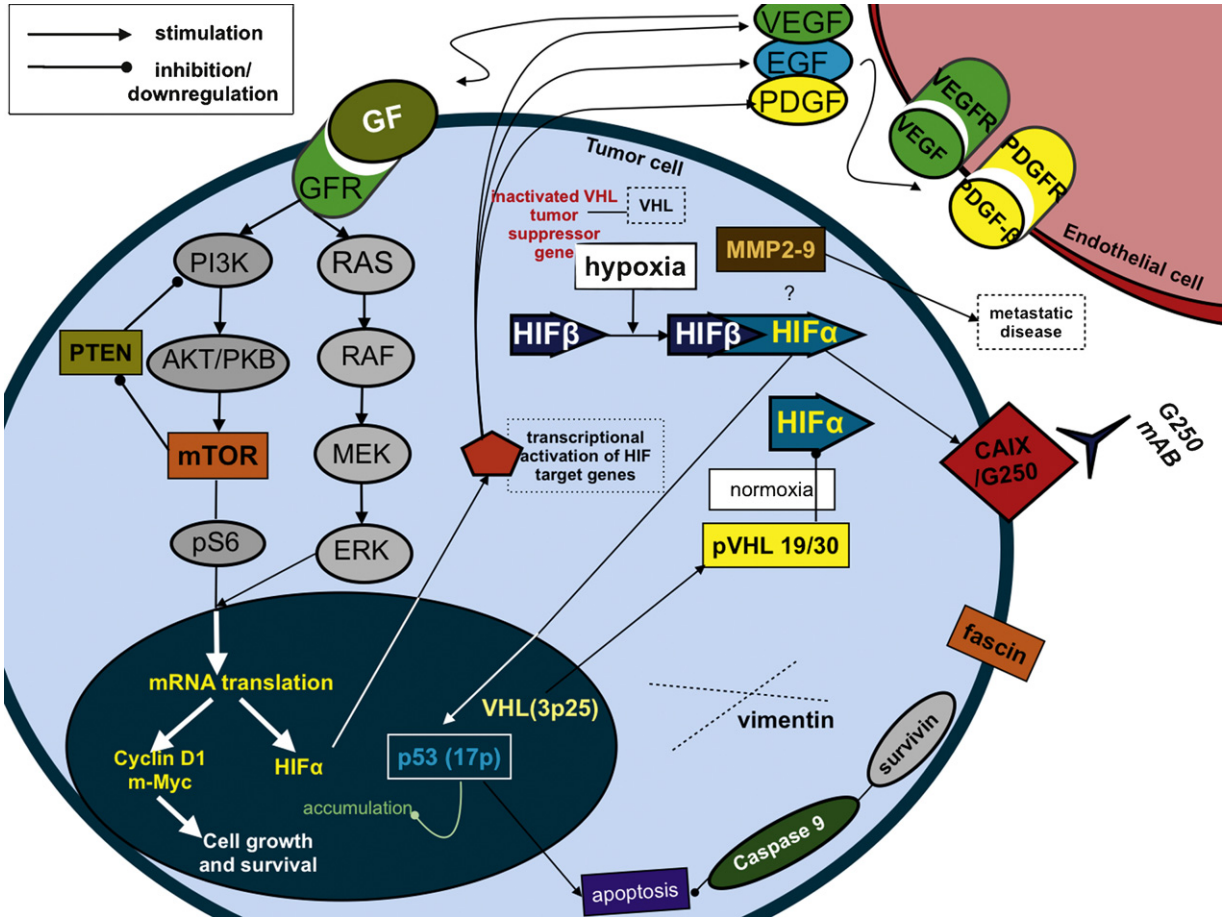

Fig. 1 – Biologic pathways and markers in renal cell carcinoma.
AKT/PKB = akt/protein kinase B (gene); CAIX = carbonic anhydrase IX; EGF = endothelial growth factor; ERK = extracellular signal-regulated kinase; GF = growth factor; GFR = growth factor receptor; HIF = hypoxia-induced factor; MEK = methyl ethyl ketone; MMP = matrix metalloproteinase; mTOR = mammalian target of rapamycin; PDGF = platelet-derived growth factor; PDGFR = platelet-derived growth factor receptor; PTEN = phosphatase and tensin homolog; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; VHL = Von Hippel-Lindau.

3.2.1.4. Carbonic anhydrase IX. Carbonic anhydrase IX (CAIX) is a HIF-1α-regulated transmembrane protein associated with neoplastic growth, aggressive tumour phenotype, and poor prognosis in a large spectrum of human tumours (Fig. 1) [54–57]. CAIX is thought to assist in regulating intracellular and extracellular pH levels in response to tumoural hypoxia and subsequent anaerobic metabolism. In RCC, especially clear cell RCC, CAIX can establish the diagnosis as it is expressed in >80% of RCC samples and 90% of clear cell RCC specimens. Interestingly, high CAIX expression is associated with a better prognosis in localised RCC and mRCC [58–61].

For example, CAIX staining levels have been shown to be inversely related to metastatic spread ($p = 0.036$), and high CAIX expression predicted better survival, even after adjusting for the effects of T stage, Fuhrman grade, nodal status, and performance status (all $p \leq 0.005$) [59]. Low CAIX staining (≤85%) predicted a worse outcome in patients with mRCC (hazard ratio [HR]: 3.10; $p < 0.001$) [59] and even after adjustment for the effects of clinical and pathologic characteristics (HR: 4.76; $p < 0.001$) [58]. Similar findings were reported in patients who received interleukin-2 therapy ($p = 0.04$) [61]. However, low CAIX expression was not associated with RCC death after adjusting for the effect of tumour grade ($p = 0.3$) or coagulative tumour necrosis ($p = 0.1$) [62]. It is hoped that data from ongoing trials will provide better insight into this highly promising marker [63,64]. Besides prognostic value, the tumour-specific and high prevalence of CAIX in RCC makes it a great target for imaging and therapy using monoclonal antibodies such as G250.

3.2.2. Mammalian target of rapamycin

The mammalian target of rapamycin (mTOR) pathway regulates cell growth, and its upregulation in tumours contributes to many critical cellular functions such as protein degradation and angiogenesis (Fig. 1) [65]. The prognostic role of mTOR as a biomarker is sparse and inconclusive. However, mTOR inhibitors (temsirolimus [34], everolimus [35]) have come to represent agents of choice for mRCC. The prognostic and predictive relevance of mTOR and its upstream (ie, phosphatase and tensin homolog [PTEN]) and downstream (ie, phosphorylated S6 ribosomal protein) molecules are being critically evaluated to identify responders to these agents.

3.2.2.1. Ribosomal protein S6. Ribosomal protein S6 (pS6), a downstream mTOR target, has S6 kinase activity [66], and the phosphorylated S6 (pS6) protein affects its downstream targets, altering mRNA translation (Fig. 1) [67]. pS6 is differentially overexpressed in clear cell mRCC and appears to be associated with activation of the mTOR pathway [68]. pS6 is a predictor of survival in both localised (HR: 3.14, $p = 0.002$) and mRCC (HR: 1.55; $p = 0.04$) [68]. Indeed, high expression of S6 kinase ($p = 0.02$) predicted response to temsirolimus in 20 patients [69] and may prove to be useful in predicting optimal biologic doses of mTOR inhibitors (ie, everolimus) [70].

3.2.2.2. Protein kinase B. pAkt, also called protein kinase B, regulates both growth and survival mechanisms by phosphorylating a wide spectrum of substrates in the cytoplasm and the nucleus (Fig. 1) [71]. In univariable, but not multivariable, analyses, elevated pAkt immunostaining was associated with higher grade ($p = 0.04$), higher rate of metastatic disease ($p = 0.004$), and poorer RCC-specific survival ($p = 0.01$) [72]. Others reported a favourable prognosis in localised RCC with high pAkt expression (HR: 0.66; $p = 0.3$) [68]. Conversely, poor prognosis was reported with high cytoplasmic pAkt expression in mRCC (HR: 1.31; $p = 0.2$) [68]. It is noteworthy that nuclear pAkt expression was higher in localised RCC tissue than in mRCC tissue [68]. As such, the localisation of pAkt may be relevant for determination of its effect on tumour behaviour and resulting prognostic value.

Tumour samples from a subset of patients ($n = 19$) within a randomised phase 2 trial of temsirolimus in mRCC were studied [69]. High pAkt expression may predict response to temsirolimus-treated patients with advanced RCC ($p = 0.07$). Objective tumour response was observed only in patients with high expression of pAkt. Confirmation of these findings is necessary before conclusions can be made.

3.2.2.3. Phosphatase and tensin homolog. PTEN is a tumour suppressor protein encoded by the tumour suppressor gene *PTEN* (Fig. 1). Upstream to mTOR, the phosphatase PTEN regulates the mTOR pathway by inhibiting Akt phosphorylation through PI3K [73]. Although PTEN mutation may be a rare event, *PTEN* loss occurs during carcinogenesis and is associated with adverse prognosis in RCC [73]. PTEN expression is higher in tumours with lower T stage, non–clear cell RCC, and localised stage. High PTEN expression improves survival (HR: 0.74; $p = 0.3$) [68]. mTOR inhibitors may be most beneficial in patients with low PTEN expression. However, recently no correlation between baseline PTEN and temsirolimus efficacy was found in poor-risk mRCC patients [74].

3.2.3. Alternative biomarkers

3.2.3.1. Survivin. Deregulation of apoptosis is a hallmark in human carcinogenesis, facilitating the acquisition of deleterious cancer traits, including loss of tumour suppressor genes, angiogenic changes, and immortalisation (Fig. 1). Survivin is a member of the inhibitor of apoptosis gene family that has been found to control mitotic progression and induce changes in gene expression that are associated with tumour cell invasiveness. Survivin mRNA is selectively expressed during embryonic and foetal development, becomes undetectable or expressed at low levels in most differentiated normal adult tissues, and is overexpressed in humans cancers [75–78] including RCC [79]. Survivin is expressed in all RCC variants [80]. High survivin expression is associated with poor differentiation, more aggressive behaviour (all $p < 0.05$) [80], and lower survival in clear cell RCC (even after adjusting for the effects of ECOG-PS, TNM, and grade [HR: 2.4; $p < 0.001$]) [81]. In localised RCC, high survivin expression predicted disease progression (HR: 1.9; $p = 0.02$) [81].

3.2.3.2. p53. The p53 protein is a DNA binding molecule involved in the regulation of transcription (Fig. 1) [82]. p53 has an important role in regulating cell growth and proliferation by stopping cell cycle and inducting apoptosis when DNA damage occurs [83]. p53 mutations allow detection through immunohistochemical staining due to their extended half-life [84]. p53 overexpression in papillary, chromophobe, and clear cell RCC was recorded in 70%, 27%, and 12% of tumours, respectively [85]. p53 overexpression was an independent predictor of metastasis-free survival in patients with localised clear cell RCC ($p = 0.01$) [85]. The prognostic role of p53 in RCC remains controversial with studies failing to show any independent prognostic value for survival (HR: 1.75; $p = 0.07$) [86]. In other studies, its prognostic significance was limited to patients with localised disease only ($p = 0.002$) [87].

3.2.3.3. Matrix metalloproteinases. The matrix metalloproteinase (MMP) family of enzymes is composed of critically important extracellular matrix remodelling proteases whose activity has been implicated in a number of key normal and pathologic processes (Fig. 1). The latter include tumour growth, progression, and metastasis as well as the dysregulated angiogenesis associated with these events. As a result, these proteases have come to represent important therapeutic and diagnostic targets for the treatment and detection of human cancers. In RCC, MMP-2 and MMP-9 were found to be overexpressed in 67–76% and 43% of tumours, respectively [88–90]. In addition, overexpression of MMP-2 and MMP-9 was more common in non–clear cell RCC tumours. MMP-2 and MMP-9 overexpression was associated with aggressive behaviour, tumour grade, and survival [88–90]. These associations are important because there are several synthetic (ie, batimastat, marimastat) and natural (ie, bryostatins) MMP inhibitors that could help prevent and/or treat MMP-overexpressing cancers [91].

3.2.3.4. Insulin-like growth factor II mRNA-binding protein 3. IMP3 is an oncofoetal RNA-binding protein that regulates transcription of insulin-like growth factor II mRNA. IMP3 is expressed in developing epithelium, muscle, and placenta during early stages of human and mouse embryogenesis, but it is expressed at low or undetectable levels in adult tissues. IMP3 expression has been associated with cell proliferation and invasion in various cancers.

In RCC, IMP3 is associated with higher RCC stage, grade, sarcomatoid differentiation, and cancer-specific mortality. In a cohort of 371 patients with localised clear cell, papillary, chromophobe, and unclassified RCC, Jiang et al. reported that tumour cell IMP3 expression was significantly associated with progression to distant metastases and death, even after multivariate adjustment for the effects of patient age, sex, tumour size, stage, grade, and histologic variant [92]. The prognostic value of IMP3 was externally validated in 716 clear cell RCC tumours showing that IMP3 expression was significantly associated with advanced T stage and grade, increased regional lymph node involvement, and distant metastases, as well as an increased likelihood for coexistent coagulative tumour necrosis and sarcomatoid differentiation [93]. In addition, even after multivariable adjustment for prognostic features comprising the SSIGN score, positive IMP3 expression was independently associated with an increased risk of death from RCC.

In a 2008 paper, Jiang et al. showed that addition of IMP3 expression to tumour stage improves its prediction of metastasis [94]. IMP3 expression is a predictor of metastatic progression and death from RCC, and assessment of IMP3 expression may prove useful to identify at-risk patients who might benefit from aggressive adjunctive therapy after primary tumour resection. Ultimately, IMP3 and the IGF pathway may provide useful targets to improve clear cell RCC therapy; however, further studies are warranted before any definitive conclusions can be made.

3.2.3.5. Ki-67. Ki-67 is a cell proliferation marker [95] associated with an aggressive phenotype in clear cell RCC [96–98]. High Ki-67 expression predicts higher recurrence rates (HR: 1.05; $p = 0.02$) [99] and worse survival (HR: 1.95; $p < 0.001$) [29,100–102]. Interestingly, the combination of Ki-67 and CAIX (HR: 1.76; $p < 0.001$) surpassed the prognostic ability of nuclear grade in cancer-specific mortality analyses [98].

3.2.3.6. Caveolin-1. Caveolin-1 is a structural component of caveolae. These are plasma membrane microdomains involved in the intracellular signalling pathways that regulate cell adhesion, growth, and survival [103]. Increased caveolin-1 expression has been associated with a poor clinical outcome in several cancers such as prostate, lung, and oesophageal malignancies [104–109]. Membranous caveolin-1 is expressed in 86% of clear cell RCC and <5% of chromophobe or papillary RCC. Caveolin-1 coexpression with Akt/mTOR pathway components portended worse survival (HR: 2.13; $p < 0.001$) [110]. Others, however, could not confirm these findings (HR: 1.35; $p = 0.9$) [111].

3.2.3.7. Tumour necrosis. Controversy exists regarding the importance of tumour necrosis in RCC prognostics. Tumour necrosis represents one of the components of the scoring algorithm of Leibovich et al. [112]. Previous evaluation of tumour necrosis as a potential marker for RCC mortality and recurrence revealed that it confers no added value when standard clinical and/or pathologic tumour characteristics were considered [96,113–116]. Tumour necrosis improved prediction of survival in patients with localised RCC ($p = 0.03$) but not in patients with mRCC ($p = 0.4$) [96]. To improve its prognostic ability, Klatte et al. suggested quantifying the extent of tumour necrosis, instead of dichotomising between its presence versus its absence [115]. Added value and external accuracy remain to be proven.

3.2.3.8. C-reactive protein. Several investigators have examined the prognostic significance of C-reactive protein. For example, C-reactive protein was a strong predictor of metastasis ($p < 0.001$) and overall mortality ($p < 0.001$) after nephrectomy for localised RCC in 130 patients [117]. C-reactive protein increased the predictive accuracy of several established clinical and pathologic predictors by 3.7% ($p < 0.001$) [118]. A gain of 10% (76.6% vs 86.5%) was reported by Iimura et al. in a different cohort ($n = 539$) within an external validation [119]. Thus this inexpensive and widely available biomarker is highly promising. Its capability to predict response to targeted therapy as a predictive markers remains to be proven.

3.2.3.9. Vimentin. A cytoplasmic intermediate filament, vimentin is not usually expressed in epithelial cells (Fig. 1). Vimentin expression is common in clear cell (26–51%) and papillary RCC (61%) [120–124]. Others found low frequency of vimentin staining in clear cell RCC [125]. Vimentin overexpression (30–53%) predicted poor prognosis ($p < 0.007$), independent of the effect of T stage and grade [124].

3.2.3.10. Fascin. Fascin is a globular actin cross-linking protein involved in cell adhesion and motility (Fig. 1). High fascin expression ($p < 0.001$) correlated with sarcomatoid transformation, high tumour stage ($p = 0.008$), high tumour grade ($p = 0.002$), and larger tumour size ($p < 0.001$) [126]. Moreover, fascin expression predicted metastatic progression (HR: 7.2; $p < 0.001$). Other investigators confirmed these findings [127].

3.3. Blood-based biomarkers

3.3.1. Thrombocytosis

The prognostic potential of thrombocytosis was reported in five studies [128–132]. However, the question of whether a biomarker can improve the ability of established predictors of cancer outcome requires more than the conventional univariable and multivariable analyses, with associated HRs and p values. For a biomarker to be clinically useful, it must add unique predictive information, thus improving the performance of a predictive model constructed without the new biomarker by a significant margin. Thrombocytosis did not add any meaningful value (+0.3%) to a model that comprised TNM stage, age, tumour size, Fuhrman grade, histologic subtype, and preoperative haemoglobin ($n = 1828$) [128]. Nonetheless, it achieved independent predictor status (HR: 1.49; $p = 0.01$) in predicting overall survival in patients with mRCC treated with VEGF-targeted agents ($n = 645$) [10].

3.3.2. Neutrophils

Several investigators have demonstrated independent predictor status for peripheral blood and intratumoural

neutrophils when mortality was considered as an end point [133–135]. In a phase 2 study, Donskov et al. evaluated 63 mRCC patients treated with interleukin-2 or interleukin-2 plus histamine [135]. High peripheral blood neutrophil counts predicted very poor survival and lack of response to interleukin-2 alone or interleukin-2 plus histamine. Serum neutrophils were also included among six most informative predictors in the Heng et al. [10] survival model. In addition, the presence of intratumoural neutrophils also independently predicted shorter recurrence-free survival (HR: 3.0; $p < 0.001$), higher RCC mortality (HR: 3.5; $p < 0.001$), and poor overall survival (HR: 3.1; $p < 0.001$) in 121 patients with localised RCC [136]. Finally, intratumoural neutrophil counts improved the predictive accuracy of the Leibovich et al. scoring algorithm from 74% to 80% [137]. Despite those promising results, the added value of intratumoural neutrophils was not confirmed. This variable awaits its external validation.

3.3.3. *Vascular endothelial growth factor*

Plasma VEGF levels correlate strongly with tissue VEGF expression ($p = 0.01$) [52]. Similarly, serum levels of VEGF correlate with clinical stage and tumour grade of RCC [52,138,139], vascular invasion ($p = 0.03$), tumour size ($p = 0.01$) [139], and survival [138–140]. For example, in 302 mRCC patients, baseline serum VEGF levels predicted progression-free survival (HR: 1.19; $p < 0.001$) and overall survival (HR: 1.39; $p < 0.001$) after treatment [140]. However, serum VEGF failed to achieve independent predictor status in other studies [138–141]. This may be due to analytical problems in some of the studies. It has been previously found that VEGF levels are higher when measured in serum than when measured in plasma [142].

Because VEGF is present in platelet granules and released upon platelet activation, the higher levels of VEGF in serum were likely due, at least in part, to release from damaged platelets, making the quantification of non–platelet-derived VEGF less accurate. After sunitinib exposure, lower VEGF plasma levels predicted response to therapy ($p < 0.05$) [143] and decreased risk of disease progression (HR: 1.96; 95% confidence interval, 1.47–2.45) [144]. Low baseline soluble VEGF levels also predicted response to sunitinib after bevacizumab failure [145]. Conversely, VEGF levels failed to predict response to sorafenib according to the Response Evaluation Criteria in Solid Tumors criteria ($p = 0.6$) but were associated with overall survival in these patients ($p = 0.01$) [146]. The validation of VEGF levels as a prognostic factor in targeted therapies is currently being evaluated in two separate trials (NCT00538772 and NCT00930345).

3.3.4. *Serum amyloid A*

Human serum amyloid A (SAA) is a high-density lipoprotein known to play a major role as a modulator of inflammation and in the metabolism and transport of cholesterol. SAA is a potentially useful biomarker to monitor patients harbouring human tumours such as gastric, nasopharyngeal, and lung cancer. In RCC, SAA concentrations were higher in metastatic patients and SAA levels were an independent predictor of all-cause survival [147]. A protein pattern, including SAA identified by surface-enhanced laser desorption ionisation time-of-flight mass spectrometry analysis of serum samples of 50 clear cell RCC patients and 50 volunteers, was able to discriminate the two groups with a sensitivity of 70–78% and a specificity of 82–92%, respectively [148]. One major problem with the use of SAA, an acute phase reactant, as a potential serum marker in human cancer patients is the fact that its elevation in the serum of patients is suggested to be of liver origin rather than a tumour cell product. Indeed, SAA level in the blood may elevate up to 1000-fold in response of the body to various injuries including trauma and various inflammations in addition to neoplasia.

3.3.5. *CAIX*

An assay for detecting low levels of CAIX in blood has been developed [149]. Higher serum CAIX levels correlated with clear cell RCC variant (86%; $p = 0.001$) but not with tumour stage or grade [150]. Others found a correlation of higher serum CAIX levels with tumour size and disease stage ($p = 0.004$) [151,152], as well as disease recurrence ($p = 0.001$) [152] and mortality ($p = 0.048$) [153]. An ongoing trial will determine the prognostic value of serum CAIX as a valid biologic marker of treatment response to immunotherapy and/or targeted therapy in patients with mRCC (NCT00942058).

3.3.6. *Neutrophil gelatinase-associated lipocalin*

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein upregulated in "distressed" cells, such as the case when in the presence of a tumour [154]. It demonstrated high correlation with MMP-9, a protein involved in the degradation of the extracellular matrix, which relates to tumour invasion and metastases [155]. NGAL has a protective effect against acute ischemic injury [156] and is high in several human cancers [157]. Above-threshold level of NGAL resulted in decreased progression-free survival relative to those with below-threshold level of NGAL in patients treated with sunitinib (3.4 vs 8.2 mo; $p = 0.03$) [158].

3.3.7. *Insulin-like growth factor-1*

Whereas there are many varied roles of insulin-like growth factor (IGF)-1, and it exists in different biocompartments, there is abundant scientific evidence demonstrating that IGF-1 is an important metabolic biomarker associated with a variety of health- and exercise-related outcomes. In most cases (muscle, bone, tendon, body composition, and cognitive function), elevated IGF-1 concentrations are considered beneficial; however, cancer remains a notable exception. In a series of 256 RCC patients, serum IGF-1 levels were associated with all-cause survival after adjusting for the effects of tumour stage [159]. Although interesting, the prognostic role of the IGF axis in RCC is only in its infancy.

3.4. *Urine markers*

The urinary nuclear matrix protein (NMP)-22 is a biomarker approved by the US Food and Drug Administration for bladder cancer screening and monitoring [160–162]. It has also been examined as a diagnostic marker for RCC. Three

studies showed that urinary NMP-22 levels were higher in RCC patients compared with those in control subjects (all $p \leq 0.005$) [163–165]. Well-done large-scale studies are needed to establish the utility of NMP-22 in RCC diagnosis and potentially prognosis.

3.5. Immunologic markers

3.5.1. Tumour-infiltrating lymphocytes

RCC is considered an immunogenic cancer, with pathologic specimens harbouring a high number of tumour-infiltrating lymphocytes (TILs) [166,167]. TILs are considered manifestations of host immune reactions against cancers. Previous authors demonstrated that increased TILs were positively correlated with higher stage and grade [168–170]. However, these findings could not be confirmed in another study [171]. Among surgically managed patients, those with prominent TILs ($CD8^+$) were more likely to recur and to succumb to mortality in univariable analyses [172]. However, none of the examined TILs (intratumoural $CD8^+$ cells, peritumoural $CD8^+$ T cells, peritumoural $CD4^+$ T cells, and peritumoural TILs) remained significantly associated statistically with worse prognosis in multivariable analyses, after adjusting for stage, grade, and histologic subtype.

3.5.2. Natural killer cells

Cózar et al. [173] found a high number of natural killer (NK) cells in TILs relative to peripheral blood lymphocytes (25 vs 14%; $p = 0.03$), which are not normally found in great numbers in advanced human cancers. In another study, authors examined potential immunologic prognostic factors in mRCC patients treated with interleukin-2 ($n = 120$) [174]. They showed that low intratumoural NK cells ($CD57^+$) were associated with worse survival (HR: 2.1; $p = 0.01$). Conversely, intratumoural macrophages ($CD4^+$, $CD8^+$, $CD20^+$, $CD56^+$) were not. NK cells kill tumour cells that have reduced major histocompatibility complex (MHC) class I expression [175]. Consequently, previous investigators sought to evaluate the expression of MHC class I molecules in RCC, and they observed that MHC class I was downregulated in 38% of clear cell non-mRCC and remained independently associated with a worse prognosis (HR: 4.76; $p = 0.03$) [175].

3.5.3. Regulatory T cells

Among TILs, regulatory T cells (Treg), which maintain the activation of other T cells, hold a crucial role in impeding immune surveillance against cancer and hampering the development of effective antitumour immunity [176]. A previous report showed that Treg increases both in the peripheral blood and tumour microenvironment in RCC, and can suppress proliferation of autologous T cells in vitro [177]. From the same authors, increased presence of Tregs (>10%) in intratumoural areas of RCC ($CD4^+CD25^+Foxp3^-$) was associated with higher stage (TNM IV: 22 vs 11%; $p = 0.01$), increasing tumour size ($\geq$10 cm: 36 vs 20%; $p = 0.02$), and the presence of coagulative tumour necrosis (14 vs 6%; $p = 0.03$). Its presence was also significantly associated with cancer-specific mortality (HR: 1.03; $p = 0.007$). In another study, authors showed that high Tregs in the peritumuoral areas ($Foxp3^+$) portended to worse survival. In contrast, intratumoural Tregs (cyclooxygenase-2) were not associated with prognosis in patients with RCC [178].

3.5.4. B7-H1

B7-H1 is a cell-surface glycoprotein within the B7 family of T-cell costimulatory molecules [179]. B7-H1 expression inhibits tumour-specific T-cell-mediated immunity through induction of T-cell apoptosis, impairs cytokine production, and diminishes the cytotoxicity of activated T cells [172,180–182]. High B7-H1 expression was associated with higher RCC-specific mortality (HR: 3.92; $p < 0.001$) and all-cause mortality (HR: 2.37; $p < 0.001$) in 306 patients treated with nephrectomy for clear cell RCC [183–185]. In localised disease, tumours with high B7-H1 expression were more likely to metastasize (HR: 4.13; $p < 0.001$) even after adjusting for the effects of T stage, grade, and performance status (HR: 1.78; $p = 0.04$) [183]. In localised clear cell RCC (HR: 3.32; $p = 0.002$), as well as in all RCC stages (HR: 3.25; $p < 0.001$), high B7-H1 expression in combination with Survivin expression predicted higher mortality after adjusting for the effects of TNM stage, tumour grade, and ECOG-PS ($n = 298$) [186].

3.6. Use of biomarkers in prognostic models

A prognostic model for prediction of survival in RCC using primarily molecular markers as predictors (p53, CAIX, gelsolin, vimentin, and metastatic status) was 79% accurate ($n = 318$; Table 2) [86]. Subsequently, the same group of authors evaluated a slightly different model of molecular markers (CAIX, PTEN, vimentin, p53) and was 64% accurate ($n = 150$). Adding ECOG-PS and tumour stage increased predictive accuracy by 4%. Predictive accuracy relying on clinical and molecular markers (68%) was statistically significantly higher ($p = 0.003$) than that of the UISS system alone (62%) [187]. The integration of the BioScore [29] (tumour expression levels of B7-H1, Survivin, Ki-67) in clear cell RCC patients ($n = 634$) to the UISS and the SSIGN models gained 4.5% and 1.6% accuracy, respectively (Table 4).

Others evaluated the prognostic value of biomarkers with clinical and/or pathologic characteristics in patients with advanced RCC treated with VEGF- or mTOR-targeted therapies or immunotherapy [8,11–13,133,174]. Recently, factors associated with longer overall survival within sunitinib-treated patients included time from diagnosis to treatment of more than a year, ECOG-PS, corrected calcium, absence of bone metastases, low LDH, and high haemoglobin [188]. Factors associated with longer overall survival within patients treated with interferon-α patients included male gender, absence of bone or lymph node metastases, lower LDH, higher haemoglobin, corrected calcium, higher neutrophil count, and interval from diagnosis to treatment > 1 yr [188].

In anti-VEGF therapy-naive mRCC, haemoglobin ($p < 0.001$), corrected calcium ($p < 0.001$), KPS ($p < 0.001$), time from diagnosis to treatment ($p = 0.01$), neutrophils ($p <$

0.001), and platelets ($p = 0.01$) were adverse prognostic factors for overall survival (accuracy: 73%; $n = 645$) [10].

4. Conclusions

The search for predictive and prognostic markers stems from the unpredictable nature of RCC in its localised, locally advanced, and metastatic stages. A number of such markers emerged. Of those, many show promise by virtue of stratifying the survival curves or discriminating between stage distributions (eg, CAIX, VEGF). Other markers achieved independent predictor status (eg, Ki-67, serum CAIX) when their contribution to the prediction of the end point of interest was examined. Finally, the most valuable ones (C-reactive protein, BioScore [Survivin, B7-H1, Ki-67]) demonstrated an added value when combined accuracy was quantified with and without their contribution. Independent confirmation of their value, within external validation studies and using standardised measurements, represents an unconditional requirement before their integration into routine clinical practice. Validation of informative markers of response to targeted agents represents a priority consideration.

The value of novel markers is required within the framework of existing markers and models. For example, a recent model that relies on clinical and radiologic information can predict the probability of mortality from 1 to 10 yr after nephrectomy [24]. It relies on clinical and radiologic variables and results in 84–88% accuracy. A similar model that integrated pathologic characteristics resulted in 88–89% accuracy for predictions of mortality from 1 to 10 yr after nephrectomy [23]. Neither of the models relied on biomarker data. The highly accurate nature of these models raises the bar for novel biomarkers because it is relatively difficult to improve accuracy beyond the 90% mark. Conversely, the dearth of models capable of accurately predicting the probability of response to targeted therapies represents an important unmet need in the field of RCC prognostics.

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Study concept and design: Sun, Shariat, Karakiewicz.
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