Prognostic Biomarkers in Patients with Renal Cell Carcinoma: Where are We Going from Here?

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Abstract
Treatment algorithm in metastatic renal cell carcinoma (RCC) patients has rapidly evolved during the last decade, and determining the prognosis of these patients has become a priority step for correctly planning the treatment. In the present article, we firstly address the most currently used prognostic models and how they have changed the treatment algorithm in routine clinical care; then we assess whether patient selection may be improved in the first-line treatment and the usefulness of a prognostic model following first-line failure; ultimately we culminate in new clinical and molecular prognostic factors under investigation. For this last issue, biomarkers for immunotherapy and angiogenesis inhibitors, as well as biomarkers for liquid analysis and for clinical obesity are presented.

Keywords
Metastatic renal cell carcinoma; Patients; Risk factors; Prognostic models; Clinical biomarkers; Molecular biomarkers

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1. BACKGROUND

Recent data have pointed out that the incidence of renal cell carcinoma (RCC) will increase in the future decades [1]. Over the last years, there has been a growing development of new molecules and treatment combinations in RCC patients. Until now, in metastatic RCC (mRCC) patients the most used prognostic classifications have been published respectively by the Memorial Sloan Kettering Cancer Center (MSKCC) [2-4], and by the International Metastatic Database Consortium (IMDC) [5,6], and referred to as the Motzer and Heng model, respectively. Both models have considered pretreatment clinical features and biochemical parameters. Specifically, in 1999 a group headed by Motzer [2] carried out a retrospective analysis on 670 mRCC patients treated with cytokines (interferon-alpha (IFN-alpha) or interleukin-2 (IL-2)), chemotherapy, and hormone therapy at the MSKCC. The authors identified 5 pretreatment factors, such as low Karnofsky performance status (KPS) < 80%, low serum hemoglobin level < the lower limit of normal, high serum lactate dehydrogenase (LDH) >1.5 the upper limit of normal (ULN), high corrected serum calcium > 10 mg/dl, and absence of prior nephrectomy, that were independent risk factors of survival at a multivariate analysis. Each patient was included in one of three risk groups, and in particular no risk factor identified a favorable risk group, one or two risk factors an intermediate risk group, and patients with three or more risk factors identified a poor risk group. As for the survival outcomes, patients with 0 risk factors (25% of the total patient population) had 20 months of median overall survival (OS) and 3-year OS in 31% of them; patients with 1-2 risk factors (53% of the total patient population) had 10 months of median OS and 3-year OS in 7% of them; patients with > 3 risk factors (22% of the total patient population) had 4 months of median OS, no patient had a 3-year OS [2]. Three years later, to further establish prognostic criteria, Motzer and colleagues focused on 463 mRCC patients enrolled in clinical trials who received exclusively interferon-alpha as initial systemic therapy. The authors identified nine variables encompassing clinical and laboratory parameters, five of which represented by LDH, hemoglobin, calcium, KPS, and the interval from diagnosis to treatment of less than 1 year, resulted significant risk factors for survival at the multivariate analysis. Of interest, bootstrap validation analysis revealed that percent inclusion for the parameter “time from diagnosis to treatment” was 85% versus 29% for the “absence of prior nephrectomy”. These five variables are entered in and currently characterize the MSKCC prognostic factor model [3]. An independent group headed by Mekhail at the Cleveland Clinic further validated the MSKCC prognostic criteria for survival in untreated mRCC patients [4].

IMDC or Heng’s model [5] was in turn based on a retrospective analysis of 645 mRCC patients treated with tyrosine kinase inhibitors (TKI)/monoclonal antibody combination (sunitinib, sorafenib, bevacizumab plus IFN-alpha), in which 6 clinical parameters of short survival were identified. Four of the 5 risk factors by Motzer criteria were confirmed as adverse survival parameters, in detail, KPS, hemoglobin and calcium level, and the interval from diagnosis to treatment start less than 1 year. In addition, neutrophil and platelet count > ULN were validated as independent adverse prognostic factors. Based on these 6 prognostic factors, patients were stratified into 3 prognostic categories: 0 risk factors identified a favorable risk category (23% of the total patient population), in such case a 2-year OS was 75%; 1-2 risk factors identified an intermediate risk category (51% of the total patient population), in which 27 months of median OS and 53% of 2-year OS were associated; 3-6 risk factors identified a poor risk class (26% of the total patient population), with a median OS of 8.8 months and 2-year OS of 7% [5]. Heng and coworkers further validated the accuracy of the model in an external population of mRCC patients treated with front-line vascular endothelial growth factor (VEGF)-targeted treatment. A total of 1028 patients collected at 13 cancer centers and who had not participated to the initial creation of the model were included in the study. The findings successfully demonstrated that the six Heng risk factors were independent predictors of poor OS in the external validation set [6].

Taking all this into consideration and while noting the progressive development of novel molecules and treatment combinations -mainly encompassing immune checkpoint inhibitors (ICI)- in mRCC patients,
unfortunately daily clinical practice remained devoid of new updated and validated prognostic systems. As a consequence, elaborating prognostic models has become a priority to properly plan pharmacological treatments in these patients.

The present article aims to perform an overview of biomarkers in mRCC patients, in an attempt to propose new putative prognostic factors to optimize patient management in daily routine practice.

2. ARTICLE SELECTION

We performed a PubMed search focusing on the keywords “metastatic renal cell carcinoma”, “patients”, “risk factors”, “prognostic models”, “clinical biomarkers”, and “molecular biomarkers”. The authors reviewed the most relevant articles published in English in conjunction with their references, and accordingly a selection was made for the present article. For article selection, priority was mainly given to scientific articles published within the last 5 years. We arbitrarily selected clinical studies addressing certain biomarkers/prognostic tools most likely, in our opinion, to be translated into routine clinical care in the near future. Therefore, two fields of biomarkers were distinguished, clinical biomarkers and molecular biomarkers, respectively [Table].

<table>
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<th>Table. Selected putative prognostic biomarkers in RCC patients</th>
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<td><strong>Clinical biomarkers</strong></td>
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| **Molecular biomarkers**                                     | **Disease setting** | **Therapy line** | **Type of therapy** | **Survival Impact** | **Comment**          |
| PD-L1                                                       | mRCC               | 1st              | ICI-based therapy  | OS (controversial findings) | Needs insights   |
| NLR                                                         | mRCC               | 1st              | ICI                | Longer OS/PFS      | Needs validation    |
| STAT-3                                                      | Any stage          | also 1st         | TKI                | Increased CSS      | Needs validation    |
| VHL                                                         | mRCC               | 1st, 2nd         | TKI                | No survival correlation | Controversial role |
| VEGF (serum/tumor)                                          | mRCC               | 1st              | ICI-based therapy  | Poor CSS/PFS       | Needs validation    |
| PBMR1                                                       | mRCC               | 1st              | TKI/ICI            | Longer PFS         | Needs validation    |
| BAP1                                                        | mRCC               | 1st              | mTORi              | Shorter PFS        | Needs validation    |
| SETD2                                                       | Early stage        | NA               | NA                 | Worse OS and CSS   | Needs validation    |
| ANGPTL1/2                                                   | mRCC               | 1st              | ICI-based therapy  | Longer PFS         | Needs validation    |
| c-Met                                                       | Any stage          | also 1st         | TKI                | Worse OS and CSS   | Needs validation    |
| CTCs                                                        | Early stage        | also 1st         | NA                 | Poor OS            | Needs insights      |

Abbreviations: mRCC, metastatic renal cell carcinoma; TKI, tyrosine kinase inhibitors; OS, overall survival; mTORi, mechanistic target of rapamycin inhibitor; ACL, albumin, c-reactive protein, lactate dehydrogenase; ICI, immune checkpoint inhibitors; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; STAT-3, signal transducer and activator of transcription; CSS, cancer specific survival; VHL, von Hippel-Lindau; VEGF, vascular endothelial growth factor; PBMR1, Polybromo-1; BAP1, BRCA1-associated protein-1; SETD2, Set domain-containing 2; NA, not applicable; ANGPTL1/2, angiopoietin-like protein 1/2; c-Met, mesenchymal-epithelial transition factor; CTCs, circulating tumor cells.
2.1. Defining the prognosis, why is it crucial?

Discussing the concept of prognosis in mRCC patients involves addressing many issues. Why is prognosis important in mRCC patients? What are the most used prognostic models in clinical practice? How has the treatment algorithm changed over the last years? Can patient selection be improved in the front-line treatment? Is a prognostic model useful after the front-line failure? Are there any new clinical and molecular prognostic factors to date?

Determining the prognosis is a fundamental step for correctly planning the treatment of patients with mRCC. In this article, we use and we agree with the definition of prognostic biomarker proposed by Clark et al., according to which a prognostic marker identifies a measurement correlated with some clinical outcomes, such as OS, irrespective of the therapy rendered [7]. The usefulness of a prognostic marker is, for example, to select a group of patients who will have a more aggressive natural history of the disease. A predictive factor instead is an estimation correlated with the outcome to a specific therapy [7].

There are several reasons for determining the prognosis, as follows: (i) doing a patient stratification according to cancer-related risk of death; elaborate some data about disease course; induce a data comparison among clinical trials; making a homogeneous patient stratification to avoid selection bias; optimally identify certain responding patients; support data interpretation and patient management. According to these points derives the importance to elaborate prognostic scoring systems to define risk groups of RCC patients by prognostic factors for survival.

Motzer and Heng criteria have been used in clinical trials for risk stratification of patients among different treatment arms, but never used to customize treatment in clinical practice. This paradigm changed in 2017 with the results of CABOSUN [8] followed by CheckMate214 in 2018 [9], in which intermediate and poor prognosis risk group patients benefitted respectively by cabozantinib as single agent and by nivolumab plus ipilimumab combination, both treatments matched versus the comparator sunitinib. From this, patient selection for treatment decision is now a daily routine step in mRCC patients.

3. CLINICAL BIOMARKERS

3.1. New prognostic toll in intermediate/poor prognosis risk class

Recently, a new prognostic tool according to the IMDC prognostic factors has been elaborated by a cooperative italian group in mRCC patients [10]. The authors retrospectively evaluated sunitinib first-line treatment in 634 patients, 457 of whom in intermediate / poor prognosis risk class were included in the study. Three categories were identified and divided as follows: favorable-intermediate risk group whether 1 prognostic factor was present, real-intermediate risk group whether 2 prognostic factors were present, and poor risk group with > 2 prognostic factors. The results demonstrated a median OS benefit when comparing the favorable-intermediate risk group against the real-intermediate risk group, 32 months versus 20 months, respectively (p <.001), and when matching the real-intermediate risk group against the poor-risk group, 20 months versus 10 months, respectively (p <.001). Of interest, the main prognostic factor in the real-intermediate group was the time between diagnosis and the start of therapy [10].

3.2. Heng criteria beyond first-line treatment

In 2015, a population study on 1021 patients treated in second-line with targeted therapy (sunitinib, sorafenib and mechanistic target of rapamycin (mTOR) inhibitor) was published by Ko and co-workers [11]. A total of 60% of patients was in intermediate risk class, 30% in poor risk class, and 10% in favorable risk class. Five out of 6 Heng risk factors (except hypercalcemia) were independent prognostic factors of poor OS on a multivariate analysis, with significantly
separated survival curves among the three classes, 35 months, 16 and 5, respectively for the favorable class, intermediate class, and poor class. The only previous model in a second-line setting was that of the MSKCC by Motzer et al. \[12\] in which 50% of the patients received cytokines in the first-line: in the second-line, KPS, calcium and hemoglobin were the prognostic factors associated with survival. Ko and colleagues compared the Heng model with the 3 factors of the MSKCC model demonstrating a better predictive accuracy. The authors of this study concluded by stating that Heng criteria can be applied in the second-line treatment with a prognostic role\[13\].

Along this line, in the following years, Heng criteria were also used in the third-line\[13\] and fourth-line metastatic setting\[14\]. In a retrospective multicenter study on 1020 consecutive mRCC patients treated with third-line targeted therapy, the authors observed that favorable- (7%) and intermediate-risk (65%) patients experienced the highest OS benefit, 29 months and 15 months, respectively, versus poor-risk (27%) patients who had only 5 months of improvement in OS\[13\]. In another large retrospective analysis, a total of 594 mRCC patients were treated with a fourth-line targeted therapy. The findings revealed that patients with favorable-, intermediate-, and poor-risk class benefited of 23, 13, and 7 months of OS, respectively\[14\].

3.3. The ACL model
A novel prognostic model using systemic inflammatory markers (e.g. albumin and c-reactive protein) has been recently published in a second-line setting with targeted therapy\[15\]. A total of 78 candidates have been retrospectively evaluated, 60% of whom treated with Axitinib. In the multivariate analysis that also included the 6 Heng criteria, only albumin < 3.5 g/dl, c-reactive protein > 0.5 mg/dl and LDH > 1.5 x ULN were independent prognostic factors associated with poor OS. From this, the ACL model was created. It consisted of 3 patient groups: the favorable prognosis group (without risk factors) characterized by a median OS of 50 months, the intermediate prognosis group (1 risk factor) by a median OS of 25 months, and the poor prognosis group ( > 1 risk factor) by a median OS of 8 months. The ability of the ACL model to predict OS was also compared with the MSKCC and IMDC model through the Harrell concordance index: at any time-point (in months) from the start of the second-line treatment the ACL model was associated with greater accuracy than the two other models\[15\].

3.4. Clinical obesity biomarkers
Retrospective clinical evidences showed advantageous survival outcomes in mRCC patients with a body mass index (BMI) exceeding 30 kg/m2 -a condition known as obesity- and treated with targeted therapies and/ or ICI\[16\]. In particular, obesity patient receiving TKI as well as ICI had a longer OS. On the other hand, the role of two obesity biomarkers such as visceral fat area (VFA) and subcutaneous fat area (SFA) appeared more uncertain in terms of PFS/OS, being associated with contradictory results. Along this line, in a phase III study with avelumab plus axitinib, no significant survival correlation was noted with BMI modifications, and in a large series of patients under nivolumab a BMI < 25 (not obesity index) correlated with shorter OS\[16\]. Therefore, obesity may likely influence the course of mRCC patients although the interplay between clinical obesity biomarkers and RCC would require a prospective confirmation through a large patient population.

3.5. Tumor flare
Tumor flare (TF) has been considered to be a continuous phenomenon that begins with the cessation of antiangiogenic therapy\[17\]. In a retrospective study in 63 consecutive mRCC patients treated with sunitinib or pazopanib as front-line treatment, the authors aimed to assess the prognostic role of the TF, termed as the difference between the tumor growth rate following treatment discontinuation and that immediately before. The findings demonstrated a stronger prognostic correlation of TF as a poor survival variable in progressing patients (p value = 0.006) or in those who discontinued treatment for toxicity reasons (p value = 0.01)\[17\].
4. MOLECULAR BIOMARKERS

4.1. Biomarkers for immunotherapy

As far concerns biomarkers for immunotherapy, it is known that ICI target some immunomodulators, in particular co-inhibitory molecules, such as programmed cell death protein (PD)-1 (nivolumab, pembrolizumab), programmed death-ligand 1 (PD-L1) (avelumab, atezolizumab), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) (ipilimumab). A meta-analysis of six studies on PD-L1 in RCC patients demonstrated that higher level of PD-L1 was a prognostic factor significantly associated with worse OS \[18\]. On the contrary, a meta-analysis of six randomized trials in mRCC patients focusing on PD-L1 showed no significant correlation between PD-L1 and OS \[19\]. Some data suggest that PD-1/PD-L1 expression is discordant across matched primary and metastatic tumors, higher expression in primary tumors seems to occur. Higher PD-1 expression was associated with metastases occurrence and lower cancer-specific survival (CSS) \[20\]. In two phase III trials matching a combination therapy as pembrolizumab plus axitinib and nivolumab plus ipilimumab, respectively, versus the standard sunitinib, the OS benefit by the combination treatment resulted independent of PD-L1 expression \[21,9\].

Of further interest, together with the previous systemic inflammatory markers over mentioned, the neutrophil-to-lymphocyte ratio (NLR) has been investigated in mRCC patients under treatment with PD-1/PD-L1 ICI. In 142 mRCC, Lalani et al. retrospectively demonstrated that a pre-treatment NLR < 3 and a decrease in NLR by > 25% at 6 weeks after the initiation therapy was significantly associated with longer PFS and OS \[22\].

Before this evidence, in 151 mRCC patients under a front-line targeted therapy, the pre-treatment NLR was focused as a prognosticator for late relapsing beyond 5 years. The authors retrospectively displayed that patients with a NLR < 3 had significantly longer OS and PFS than those with NLR > 3. These survival outcomes were confirmed at a multivariate analysis, indicating NLR as an independent prognostic factor for late relapsing mRCC patients \[23\].

Signal transducer and activator of transcription (STAT) proteins are crucial in regulating the immune response over cancer progression, and STAT-3 is a transcription factor of this STAT protein family. Recently, 166 RCC patients undergoing primary surgery were interrogated for the immunohistochemical analysis of STAT-3 expression in an attempt to find any correlation with CSS. Of interest, in high-risk patients according to UICC (28%) as well as in mRCC patients (7%) under antiangiogenic agents, STAT-3 expression < 110 significantly correlated with increased CSS \[24\].

4.2. Biomarkers for angiogenesis inhibitors

Biomarkers for angiogenesis inhibitors have been intensively evaluated in RCC patients as well \[25\]. Data have demonstrated that the von Hippel-Lindau (VHL) gene alterations did not correlate both with OS than PFS under anti-VEGF therapy, so defining VHL as a biomarker of controversial prognostic significance. Serum VEGF level significantly correlated with CSS and longer PFS in patients treated with pembrolizumab plus axitinib combination; in turn, tumor VEGF expression was associated with worse OS, and high VEGF-A mRNA levels correlated with sunitinib resistance. Polybromo-1 (PBMR1) is a chromatin regulating gene. PBMR1 gene loss resulted significantly associated with an advanced disease stage, tumor aggressiveness, and worst patient outcome; PBRM1 mutation resulted to correlate with longer PFS over sunitinib and ICI treatment. BRCA1-associated protein-1 (BAP1) in turn is a tumor suppressor gene, loss of BAP1 gene correlated with advanced disease stage and poor survival. Set domain-containing 2 (SETD2) is another chromatin regulating gene demonstrated to correlate with worse survival, both OS and CSS, and higher stage of disease. As far the angioptoinet-like protein 1/2 (ANGPTL 1/2), decreased levels resulted associated with longer PFS under pembrolizumab plus axitinib combination. Lastly, the TK receptor for hepatocyte growth factor, so-called mesenchymal-epithelial transition factor (c-Met), is notoriously involved in cancer cell proliferation, angiogenesis VEGF-driven, and tumor metastasization. Evidences
correlate in a negative way a higher c-Met expression with many crucial survival endpoints, such as OS, recurrence-free survival, and CSS [25].

4.3. Liquid biomarkers

Over the years, circulating tumor cells (CTCs) have been investigated across various human cancers, setting themselves up as promising biomarkers for prognosis, treatment response and monitoring. Recent data on blood samples collected from mRCC patients have documented epithelial CTCs were found in 28%, non-epithelial CTCs in 62%, and both CTC types in 71% [26]. A proof-of-concept study on 60 RCC patients underwent laparoscopic/open radical/partial nephrectomy has demonstrated a significant higher frequency of postoperative CTCs in open than in laparoscopic radical nephrectomy [27]. As regards the role of CTCs in RCC patients, an observational evidence in 154 RCC patients showed that the detection of CTCs in peripheral blood significantly correlated with poor OS as well as with the occurrence of lymph node metastases and synchronous metastases [28]. Overall, the available evidence does not allow firm conclusions to be drawn as far the usefulness of CTCs in RCC patients, and accordingly clinical applicability of CTCs still seems far away.

5. CLOSING REMARKS

In mRCC patients, the development of prognostic models does not seem to grow in a parallel way with the evolution of systemic pharmacological treatments. From the first immunotherapy with two cytokine therapies such as high-dose IL-2 and IFN-alpha introduced before the 2000s, up to the following era with VEGFR-targeted agents (over a time period longer than a decade), the way of stratifying patients has continued to be based solely on clinical and laboratory parameters. And surprisingly, this attitude has also been maintained and translated into the development of current combination therapies with new immunotherapies.

Currently, HENG model guides formally the initial treatment choice of mRCC patients with intermediate/poor risk class. Nevertheless, we strongly believe that clinical judgment cannot be underestimated during daily activity and ultimately it significantly contributes to defining the treatment choice regardless of the risk class.

Intermediate modified risk class in first-line sunitinib treatment [10] would seem to be a promising prognostic tool, shedding light on the different survival outcome between one or two risk factors. Unfortunately, clinical data with this prognostic tool in patients under ICI combinations are lacking.

Although the National Comprehensive Cancer Network (NCCN), the European Association of Urology, and the Italian Association of Medical Oncology guidelines do not mention HENG risk reclassification over the disease course, developing prognostic models in mRCC patients after the first-line treatment deserves attention. With this in mind, it is remarkable in our opinion the ACL model encompassing three clinical criteria (albumin, c-reactive protein, and LDH), easy to determine and inexpensive, that was successfully compared both with the MSKCC and IMDC model. Of interest, very recently an ACL-modified model, so-called ACN (albumin ≤ 3.5 g/dl, C-reactive protein > 0.5 mg/dl and NLR > 3), was published in mRCC patients treated with first-line targeted agents [29]. From a total of 325 mRCC patients, the authors identified 3 patient groups according to the 3 risk factors. Patients with 0 risk factors had a median OS of 63 months (32%, favorable risk group), with 1 risk factor a median OS equal to 37 months (27%, intermediate risk group), and with > 1 risk factor median OS resulted of 11 months (40%, poor risk group). The authors further demonstrated that this new prognostic model resulted to be superior to the MSKCC and the IMDC models [29].

Several studies have shown a certain correlation between PD-L1 expression on tumor cells and poor prognosis as well as high grade/advanced disease stage of RCC patients [30].
According to the available data, however, the prognostic role of PD-L1 is not well-clarified yet, and firm survival implications cannot be drawn. In fact, NCCN guidelines do not require any PD-L1 determination. Overall, the scenario of molecular biomarkers in RCC patients still appears far from being used in clinical practice.

6. PERSPECTIVES

RCC is notoriously considered to be a metabolic disease, highly dependent on dysregulated expression of several metabolic pathways involved in oxygen, energy, and nutrients control. In short, VHL/HIF oxygen-sensing pathway triggers the up-regulation of HIF-responsive genes (VEGF, EGF, PDGF) and glucose transporters (GLUT1 and GLUT4) which motivate the aerobic glycolysis attitude of RCC tumors; energy-sensing pathway in turn induces succinate dehydrogenase- and fumarate hydratase-deficient RCC tumors, finally determining HIF accumulation in cell cytoplasm; nutrient sensing cascade is characterized by the deregulation of PI3K-Akt-mTOR pathway\(^{[30]}\). Improving the knowledge of this complex scenario can indisputably help to identify prognostic factors in RCC patients and thus to optimize patient care.

Along with this line of research, study proposals of immediate practical utility could take into consideration large-scale prospective assessment of BMI in mRCC patients under TKI as well as ICI-combinations. A prospective evaluation of the NLR in mRCC patients treated with ICI regimens would be necessary to confirm the promising retrospective data that pointed out survival implications. Further, a prospective validation of the prognostic ACL model following the first-line treatment as well as regarding the ACN model in initial molecular-targeted therapy in mRCC patients could be useful.

EXPERT OPINION

In daily clinical practice, there are still no validated biomarkers as a prognostic tool in RCC patients. In our opinion, in the wake of HENG clinical model, it would be appropriate to develop clinical-laboratory tools that are feasible in any Hospital worldwide. Overall, taking into account the above mentioned data, we believe that in this era of nanomedicine against cancer, there will still be one certainty: we can reasonably continue to be Doctors!

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