International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 07, Issue 12, December 2022,
https://doi.org/10.23958/ijirms/vol07-i12/1578

Original article

Prognostic Factors in First-line Metastatic Renal Cell Carcinoma: How to Improve the Prognostic Ability of the IMDC and MSKCC Score?

Andreea Parosanu [*1], Miruna Stanciu [1], Cristina Parlog [1], Cristina Orlov [1], Mihaela Olaru [1], Ana Maria Popa [1], Horia Cotan [1], Radu Vrabie [1], Cristian Iaciu [1], Oana Moldoveanu [2], Catalin Baston [2], Cornelia Nitipir [1]

[1]Oncology, University Emergency Elias Hospital Bucharest,11461, Romania.
[2]Urology, Fundeni Clinical Institute Bucharest, 22328, Romania.

*Corresponding author: Andreea Parosanu; *aparosanu@yahoo.com*

Received 20 November 2022; Accepted 15 December 2022; Published 18 December 2022

Abstract

Background: The incidence of metastatic renal cell carcinoma has steadily increased. Therefore, it is essential to identify precise biomarkers to predict survival and improve clinical care. ***Objectives:*** This study aimed to evaluate potential prognostic factors among patients with mRCC. ***Methods:*** We retrospectively analyzed 74 patients with metastatic RCC treated between January 2020 and October 2022. We analyzed which risk factors from the MSKCC and IMDC models more accurate correlated with survival in advanced kidney cancer. ***Results:*** We identified that poor performance status, late treatment initiation, anemia, and high LDH are statistically significant prognostic factors for predicting overall survival (OS). ***Conclusion:*** Our study raised the possibility of actualization of the classical prognostic factors in metastatic RCC patients.

Keywords: ***MSKCC, IMDC, Metastatic, Renal cell carcinoma***

Introduction

Up to 25% of patients are diagnosed with advanced or metastatic disease, with poor overall survival at five years [1].

The current management of metastatic RCC has changed with the introduction of targeted therapy and immunotherapy. Although the prognosis for advanced-stage patients has historically been poor, survival depends on clinical, laboratory, and pathologic variables [2]. In addition, all these patient and tumor-related prognostic factors also significantly impact choosing the proper treatment.

The Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) are two predictive models developed to predict survival by the presence or absence of easy-to-use and affordable clinical and laboratory factors [3,4].

The current study aimed to evaluate which risk factors from the MSKCC and IMDC models more accurate correlated with survival in advanced kidney cancer.

Materials and Methods

We conducted a retrospective analysis of patients treated at our Medical Center between January 2020 and September 2022. Inclusion criteria were age over 18 years, advanced or metastatic disease, and clear cell renal cell carcinoma histology. Exclusion criteria were no histologic confirmation, non-clear cell histologies, and metastatic renal cancer from a different primary tumor.

All patients received first-line therapy with tyrosine kinase inhibitors (sorafenib, pazopanib, or sunitinib) and immunotherapy (nivolumab and ipilimumab) until progression or toxicities.The parameters analyzed were: performance status defined by a Karnofsky score, time of treatment, hemoglobin, platelets, neutrophils, calcium, or LHD values.

Results

The clinical and pathological characteristics of patients with mRCC are detailed in table 1.

Table 1: The clinical and pathological characteristics of patients

Corrected calcium	
$> upper\ limit\ of\ normal$	58(78.4%)
$< upper\ limit\ of\ normal$	16(21.6%)
Hemoglobin	
$> lower\ limit\ of\ norm$	33(44.6%)
$< lower\ limit\ of\ normal$	41(55.4%)
LDH	
$< 1.5x\ upper\ limit\ of\ normal$	62(83.8%)
$> 1.5x\ upper\ limit\ of\ normal$	12(16.2%)
Platlets	
$< upper\ limit\ of\ normal$	50(67.6%)
$> upper\ limit\ of\ normal$	24(32.4%)
Neutrophil	
$< upper\ limit\ of\ normal$	62(83.8%)
$> upper\ limit\ of\ normal$	11(14.9%)
NA	1(1.4%)
Diagnosis to treatment time	
$> 12\ months$	22(29.7%)
$< 12\ months$	52(70.3%)

Karnofsky score	
> 80	57(77.0%)
< 80	17(23%)

The median follow-up was 14.3 months (range 4.3-22.6). Most of the patients were considered intermediate and poor risk using the IMDC model (51.4%, 41.9%) and MSKCC model (66.2%), 23.0%), respectively.

The univariate analysis indicated that poor survival was associated only with 4 variables: poor performance status defined by a Karnofsky score <80% (HR 11.60, 95%; p < 0.001), late treatment initiation (over 12 months) (HR 1.04 95% CI p = 0.01), hemoglobin <lower limit of normal (HR 5.52, CI 95% p = 0.002), LHD over 1.5x upper limit of normal, (HR 3.31, 95% CI p = 0.002). The platelet and neutrophil counts were not statistically associated with survival.

Discussion

Our data bring relevant information about potential prognostic factors in metastatic RCC. This study showed that four variables that distinguish itself from previous IMDC and MSKCC (Karnofsky performance status <80, time from RCC diagnosis to first-line therapy <1 year, hemoglobin < lower limit of normal, and high lactate dehydrogenase >1.5 times upper limit of normal) were associated with worse survival.

A longer time interval from diagnosis to treatment initiation may be in many ways detrimental: high risk of relapse, low survival rate, and more significant disease-related complications [7]. In our research, we showed that patients who started first-line treatment early than a year from diagnosis had better survival than those who delayed the treatment (13 months vs. 9.5 months, p=0,001). The results were similar to what was found in previous studies, showing that the risk of death significantly increases with a more significant time interval from diagnosis to treatment [8,9].

Several reports have examined the prognostic role of clinical and biological characteristics of metastatic renal cell carcinoma [10-15]. For example, Xu Y et al. showed that a poor performance status in metastatic RCC was significantly associated with inferior overall survival (pooled HR: 2.08, 95% CI: 1.78-2.45) and progression-free survival (pooled HR: 1.51, 95% CI: 1.20-1.91) [11]. In addition, a meta-analysis including 19 studies identified performance status as the most decisive independent prognostic factor for survival in a multivariate analysis of 6780 patients with metastatic RCC [13].

Anemia is a biological feature reported to predict adverse prognosis in patients with advanced renal cell carcinoma. Low hemoglobin value is described in over 30% of patients diagnosed with renal cell carcinoma [14]. The underlying mechanisms of cancer-related anemia include the disturbance in the iron hemostasis due to the tumor cells, which remove iron from the circulation and depose it as hemosiderin, the consequences of chronic inflammation associated with advanced neoplasia, and a possible chronic renal disease [15]. Xia L et al. completed a meta-analysis on 8,673 patients with metastatic RCC and showed that low hemoglobin level was associated with renal cell carcinoma-specific mortality and recurrence [16]. Our data also suggested that anemia at the time of first-line treatment initiation predicted poorer survival overall (6 months vs. 12 months, p=0.04)

Aerobic glycolysis is the most prominent characteristic of a cancer cells, and a large amount of lactate is produced during this process [17]. In recent years, many studies have demonstrated that serum LDH levels are linked to the prognosis of RCC [18-20]. Shen J et al. showed that serum LDH might be a cheap and non-invasive tool for predicting the prognosis of RCC. They concluded that patients with all stages of RCC who maintained elevated serum lactate dehydrogenase (LDH) levels experienced worse overall survival and progression-free survival (OS, HR = 2.41, 95% CI = 1.09-5.33) [20]. Notably in our study high lactate dehydrogenase (>1.5 times upper limit of normal) was also associated with worse survival (5.5 months vs.11 months, p=0,003).

Conclusions

Our study confirmed the data in the literature about the classical prognostic factors in metastatic RCC patients. We identified that poor performance status, late treatment initiation, anemia, and high LDH are statistically significant prognostic factors for predicting overall survival (OS). Our study raised the possibility of actualization of the classical prognostic factors in metastatic RCC patients. However, a more extensive prospective study is needed to validate these results.

Ethics approval and consent to participate

The study is approved by the Ethics Committee, of Elias University Emergency Hospital

List of abbreviations

MSKCC = Memorial Sloan Kettering Cancer Center
IMDC= the International Metastatic Renal Cell Carcinoma Database Consortium
RCC= renal cell carcinoma
mRCC= metastatic renal cell carcinoma
LDH= lactate dehydrogenase

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Statement

No funding and no financial support

Authors' contributions

All authors contributed equally. All authors read and approved the final manuscript.

References

[1] https://gco.iarc.fr/today/data/factsheets/cancers/29-Kidney-fact-sheet.pdf, Accessed on 11 November 2022
[2] Dutcher JP, Flippot R, Fallah J, et al. “On the Shoulders of Giants: The Evolution of Renal Cell Carcinoma Treatment-Cytokines, Targeted Therapy, and Immunotherapy”. Am Soc Clin Oncol Educ Book. 2020 Mar; 40:1-18. doi: 10.1200/EDBK_280817. PMID: 32243201.
[3] Kim JK, Kim SH, Song MK, et al. “Application of the International Metastatic Renal Cell Carcinoma Database Consortium and Memorial Sloan Kettering Cancer Center Risk Models in Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma: A Multi-Institutional Retrospective Study Using the Korean Metastatic Renal Cell Carcinoma Registry”. Cancer Res Treat. 2019 Apr;51(2):758-768. doi: 10.4143/crt.2018.421. Epub 2018 Sep 7. PMID: 30189720; PMCID: PMC6473260.
[4] Tenold M, Ravi P, Kumar M, et al. “Current Approaches to the Treatment of Advanced or Metastatic Renal Cell

Carcinoma". Am Soc Clin Oncol Educ Book. 2020 Mar; 40:1-10. doi: 10.1200/EDBK_279881. PMID: 32239988.

[5] Padala SA, Barsouk A, Thandra KC, et al. "Epidemiology of Renal Cell Carcinoma".World J Oncol. 2020 Jun;11(3):79-87. doi: 10.14740/wjon1279. Epub 2020 May 14. PMID: 32494314; PMCID: PMC7239575.

[6] Yuen JS. "Molecular targeted therapy in advanced renal cell carcinoma: A review of its recent past and a glimpse into the near future". Indian J Urol. 2009 Oct-Dec;25(4):427-36. doi: 10.4103/0970-1591.57899. PMID: 19955664; PMCID: PMC2808643.

[7] Cone EB, Marchese M, Paciotti M, et al. "Assessment of Time-to-Treatment Initiation and Survival in a Cohort of Patients with Common Cancers". JAMA Netw Open. 2020 Dec 1;3(12):e2030072. doi: 10.1001/jamanetworkopen.2020.30072. PMID: 33315115; PMCID: PMC7737088.

[8] Iacovelli R, Galli L, De Giorgi U, et al. "The effect of a treatment delay on outcome in metastatic renal cell carcinoma". Urol Oncol. 2019 Aug;37(8): 529.e1-529.e7. doi: 10.1016/j.urolonc.2019.03.005. Epub 2019 Mar 29

[9] Sagie S, Sarfaty M, Levartovsky M, et al. "RCC Real-World Data: Prognostic Factors and Risk Stratification in the Immunotherapy Era". Cancers (Basel). 2022 Jun 26;14(13):3127. doi: 10.3390/cancers14133127. PMID: 35804899; PMCID: PMC9265130.

[10] Brown LC, Desai K, Wei W, et al. "Clinical outcomes in patients with metastatic renal cell carcinoma and brain metastasis treated with ipilimumab and nivolumab". J Immunother Cancer. 2021 Sep;9(9): e003281. doi: 10.1136/jitc-2021-003281. PMID: 34518292; PMCID: PMC8438842.

[11] van Laar SA, Gombert-Handoko KB, Groenwold RHH, et al. "Real-World Metastatic Renal Cell Carcinoma Treatment Patterns and Clinical Outcomes in The Netherlands". Front Pharmacol. 2022 Mar 23; 13:803935. doi: 10.3389/fphar.2022.803935. PMID: 35401238; PMCID: PMC8983834.

[12] Xu Y, Zhang Y, Wang X, et al. "Prognostic value of performance status in metastatic renal cell carcinoma patients receiving tyrosine kinase inhibitors: a systematic review and meta-analysis". BMC Cancer. 2019 Feb 22;19(1):168. doi: 10.1186/s12885-019-5375-0. PMID: 30795756; PMCID: PMC6385458.

[13] Motzer RJ, Mazumdar M, Bacik J, et al. "Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma". J Clin Oncol. 1999;17(8):2530-40.

[14] Grzegorz Prokopowicz, Marcin Życzkowski, Krzysztof Nowakowski, et al. "Basic Parameters of Blood Count as Prognostic Factors for Renal Cell Carcinoma", BioMed Research International, vol. 2016, Article ID 8687575, 7 pages, 2016. https://doi.org/10.1155/2016/8687575

[15] Madeddu C, Gramignano G, Astara G, et al. "Pathogenesis and Treatment Options of Cancer Related Anemia: Perspective for a Targeted Mechanism-Based Approach". Front Physiol. 2018 Sep 20; 9:1294. doi: 10.3389/fphys.2018.01294. PMID: 30294279; PMCID: PMC6159745.

[16] Xia L, Hu G, Guzzo TJ. "Prognostic significance of preoperative anemia in patients undergoing surgery for renal cell carcinoma: a meta-analysis". Anticancer Res. 2017;37(6):3175-8

[17] Jiang B. "Aerobic glycolysis and high level of lactate in cancer metabolism and microenvironment. Genes Dis. 2017 Feb 14;4(1):25-27. doi: 10.1016/j.gendis.2017.02.003. PMID: 30258905; PMCID: PMC6136593.

[18] Wang Y, Li G, Wan F, et al. "Prognostic value of D-lactate dehydrogenase in patients with clear cell renal cell carcinoma". Oncol Lett. 2018 Jul;16(1):866-874. doi: 10.3892/ol.2018.8782. Epub 2018 May 22. PMID: 29963157; PMCID: PMC6019897.

[19] Girgis H, Masui O, White NM, et al. "Lactate dehydrogenase A is a potential prognostic marker in clear cell renal cell carcinoma". Mol Cancer. 2014 May 5; 13:101. doi: 10.1186/1476-4598-13-101. PMID: 24885701; PMCID: PMC4022787.

[20] Shen J, Chen Z, Zhuang Q, Fet al. "Prognostic Value of Serum Lactate Dehydrogenase in Renal Cell Carcinoma: A Systematic Review and Meta-Analysis". PLoS One. 2016 Nov 18;11(11): e0166482. doi: 10.1371/journal.pone.0166482. PMID: 27861542; PMCID: PMC5115746.