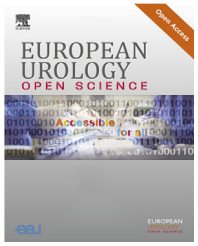
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Research Letter: Open Science

High Expression of Cancer-derived Immunoglobulin G is Associated with Poor Survival in Metastatic Clear Cell Renal Cell Carcinoma

The treatment landscape for metastatic clear cell renal cell carcinoma (mccRCC) has evolved over the past two decades from cytokine regimens to targeted therapy, and now immunotherapy-based drug combinations [1]. However, there is a lack of confirmed prognosis biomarkers for patients with mccRCC [2]. Immunoglobulin G (IgG), an immune molecule secreted by B cells, has recently been detected in various types of cancer cells and has been termed cancer-derived IgG. Notably, it has been demonstrated that IgG derived from epithelial cancer cells has a unique N-glycosylation pattern that is highly sialylated [3]. In this study, we explored the expression of sialylated cancer-derived IgG (SIgG) in mccRCC tissues using the monoclonal antibody RP215, and evaluated the prognostic value of SIgG in patients with mccRCC.

A total of 179 patients with mccRCC with complete clinicopathological information and survival data from January 2006 to June 2022 were included in the study. Tumor tissue from the primary tumor was collected during surgery and fixed in 10% buffered formalin and then embedded in paraffin. Tissue microarray slides were then constructed for immunohistochemistry (IHC). SIgG expression was evaluated semiquantitatively on the basis of the IHC signal density and the proportion of positively stained cells.

The cohort characteristics and clinical data are shown in Supplementary Table 1. Among the patients, 146 received first-line tyrosine kinase inhibitor (TKI) monotherapy, 15 received first-line immune-oncology (IO)-TKI therapy, and 18 received second-line IO-TKI therapy. The primary endpoint was overall survival (OS), defined as the time from initiation of systemic treatment to death or last follow-up.

IHC results show that SIgG was mainly expressed in the cell membrane and cytoplasm (Fig. 1A) and high SIgG expression was significantly correlated with poor OS in this mccRCC cohort (hazard ratio [HR] 2.281; $p < 0.001$; Fig. 1C). Moreover, multivariable Cox regression analysis revealed that high SIgG expression was an independent prognostic factor for OS in mccRCC (HR 2.110; $p < 0.001$), as well as poor International Metastatic RCC Database Consortium (IMDC) risk group (HR 2.123; $p = 0.018$; Supplementary Table 2). Time-dependent ROC curve also suggested the promising prognostic value of SIgG, with a 5-year AUC of 0.679 for SIgG alone and 0.742 for SIgG combined with IMDC risk model (Fig. 1D). According to subgroup analyses, the prognostic value of SIgG was more marked for the groups with intermediate (HR 2.191; $p = 0.019$) and poor (HR 2.111; $p = 0.058$) IMDC risk, and lung metastasis (HR = 1.970, P = 0.009). Notably, the prognostic value of SIgG was significant in both synchronous and metachronous metastasis patients (Fig. 1E).

In 2023, Huang et al first reported that cancer cells of epithelial origin could produce IgG and that blockade of cancer-derived IgG could inhibit the growth of cancer cells [3]. It has subsequently been demonstrated that the expression of cancer-derived IgG is correlated with survival in several malignancies, including metastatic lung adenocarcinoma and pancreatic ductal adenocarcinoma [4,5]. In contrast to B cell–derived IgG, cancer-derived IgG is involved in tumor progression and drug resistance. The potential mechanisms include inhibition of programmed cell death, mediation of tumor immune escape, and induction of inflammation and platelet aggregation [3].

ccRCC is a highly heterogeneous disease, especially mccRCC, and prediction of mccRCC prognosis remains challenging [2]. In our study, SIgG was a reliable predictor for OS for patients with mccRCC, and SIgG combined with the IMDC risk model was a more effective prognostic model than the IMDC risk group alone. The IMDC risk model was first introduced in 2009 for patients treated with TKI and then prospectively validated in CheckMate-214 [2]. The model contains six clinical parameters but lacks a tumor-related factor. SIgG could be a promising supplement to the IMDC risk model.

Some limitations of our study must be noted. First, this was a single-center retrospective study with a relatively small patient cohort. Second, the proportion of patients who received first-line IO-TKI was small. Further multicenter prospective studies are required for validation of the results and investigation of the mechanism underlying the association between SIgG and OS before widespread adoption of SIgG as a biomarker.

Conflicts of interest: The authors have nothing to disclose.

https://doi.org/10.1016/j.euros.2024.01.001

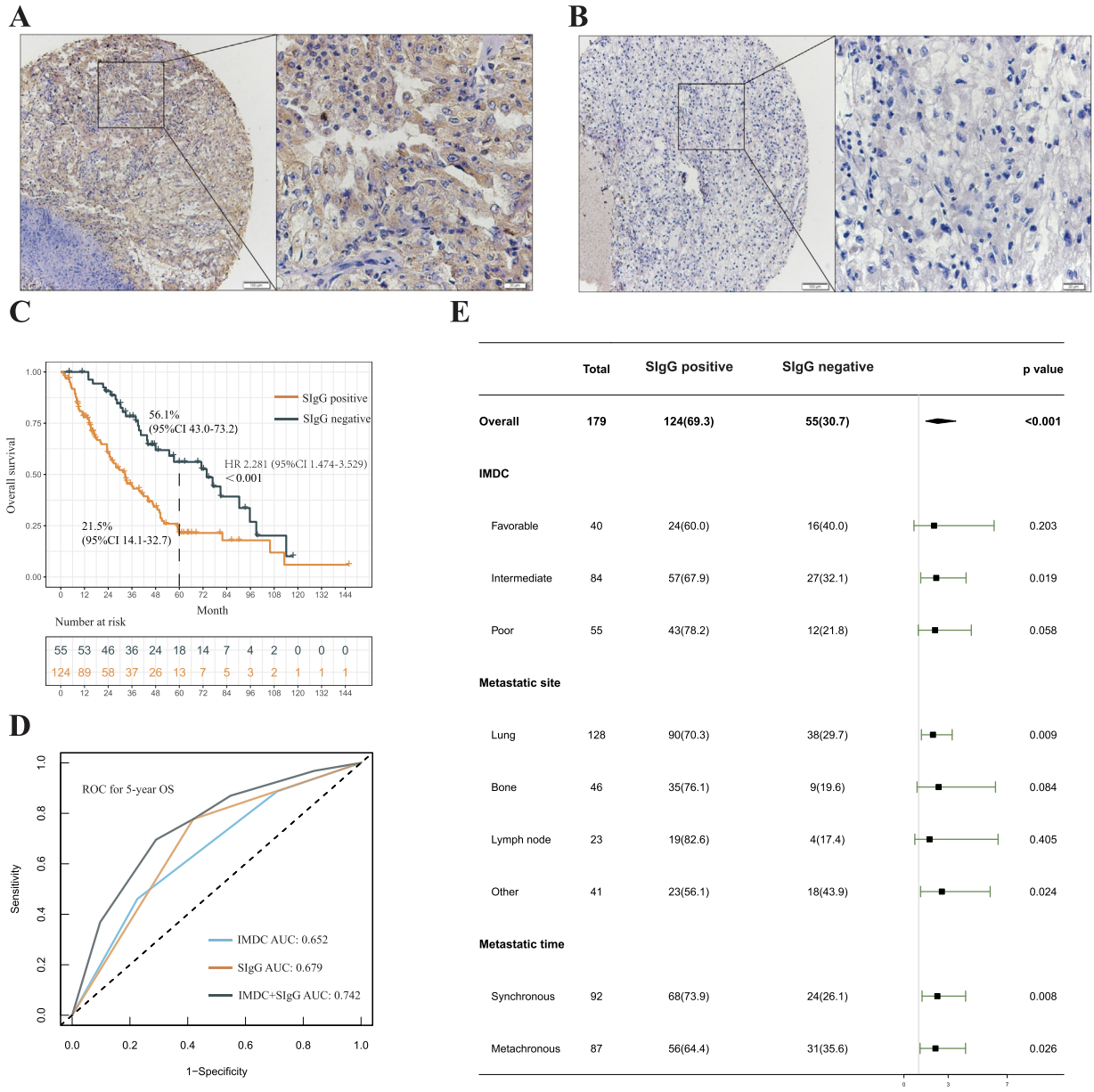


Fig. 1 – (A) Positive and (B) negative SIgG expression in mccRCC tissues. (C) Kaplan-Meier curves of OS for mccRCC patients stratified by SIgG expression level. (D) Time-dependent ROC curve for the predictive value of SIgG and IMDC risk group for 5-yr OS for patients with mccRCC. (E) Forest plot summarizing the HRs for OS for patients with mccRCC, stratified by SIgG expression level. AUC = area under the ROC curve; HR = hazard ratio; IMDC = International Metastatic RCC Database Consortium; mccRCC = metastatic clear cell renal cell carcinoma; OS = overall survival; ROC = receiver operating characteristic curve; SIgG = sialylated cancer-derived IgG.

Ethics considerations: This study was approved by the institutional ethics committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Informed consent was obtained from all patients.

Data sharing statement: The original data used in the study are included in the article and Supplementary material; further inquiries can be directed to the corresponding authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.01.001.

References

[1] Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology guidelines on renal cell carcinoma: the 2022 update. Eur Urol 2022;82:399–410.
[2] Dudani S, Savard MF, Heng DYC. An update on predictive biomarkers in metastatic renal cell carcinoma. Eur Urol Focus 2020;6:34–6.
[3] Huang X, Zhang S, Tang J, et al. A self-propagating c-Met-SOX2 axis drives cancer-derived IgG signaling that promotes lung cancer cell stemness. Cancer Res 2023;83:1866–82.
[4] Liu Y, Liu D, Wang C, et al. Binding of the monoclonal antibody RP215 to immunoglobulin G in metastatic lung adenocarcinomas is correlated with poor prognosis. Histopathology 2015;67:645–53.
[5] Cui M, You L, Zheng B, et al. High expression of cancer-derived glycosylated immunoglobulin G Predicts poor prognosis in pancreatic ductal adenocarcinoma. J Cancer 2020;11:2213–21.

Hong-lei Cui [a,†]
Jie Wu [a,†]
Rui-Yang Xie [a]
Wei-Yan Xu [b]
Hong-Zhe Shi [a]
Ai-Ping Zhou [c]
Xiao-Yan Qiu [b,*]
Jian-Zhong Shou [a,*]

[a] *Department of Urology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[b] *Department of Immunology, School of Basic Medical Sciences, Peking University, Beijing, China*
[c] *Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

* Corresponding authors. Department of Urology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China (J.-Z. Shou). Peking University Health Science Center, Beijing 100191, China (X.-Y. Qiu).
E-mail addresses: qiuxy@bjmu.edu.cn (X.-Y. Qiu) shoujianzhong@cicams.ac.cn (J.-Z. Shou).

† These authors contributed equally to this work.

January 2, 2024