EUROPEAN UROLOGY OPEN SCIENCE 70 (2024) 109–115

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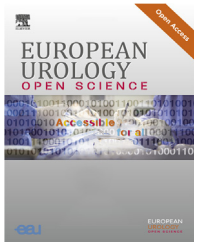

European Association of Urology

Kidney Cancer

Dynamic Changes in Serum Immunoglobulin G Predict Clinical Response and Prognosis in Metastatic Clear-cell Renal Cell Carcinoma

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Article info

Article history:
Accepted October 3, 2024

Associate Editor:
Silvia Proietti

Keywords:
Immunoglobulin G
Metastatic clear-cell renal cell carcinoma
Prognosis
Tyrosine kinase inhibitor
Immunotherapy
Combination therapy

Abstract

Background and objective: Systemic treatments involving immunotherapy-tyrosine kinase inhibitor (IO-TKI) combinations and TKI monotherapy have significantly improved outcomes for patients with metastatic clear-cell renal cell carcinoma (mccRCC). However, there are no biomarkers for predicting the efficacy of these treatments. Our aim was to investigate the prognostic and therapeutic significance of serum immunoglobulin G (IgG) in patients with mccRCC patients receiving systemic therapy.

Methods: We included 318 patients with mccRCC who received TKI or IO-TKI therapy. Patients were classified into groups according to whether they had an increase or decrease in serum IgG after systemic treatment. The association between baseline serum IgG and the objective response rate (ORR) was compared between the groups using a *t* test. The association of the change in serum IgG with progression-free survival (PFS) and overall survival (OS) was evaluated via Cox proportional-hazards regression, and survival curves were generated using the Kaplan-Meier method.

Key findings and limitations: Baseline serum IgG was not significantly associated with ORR (p = 0.055). After 3-mo systemic therapy, 133 patients (42%) exhibited an increase in serum IgG. The group with an IgG increase had significantly poorer median PFS (5.6 vs 16.2 mo; hazard ratio [HR] 3.36, 95% confidence interval [CI] 2.58–4.36; p < 0.001) and OS (26.0 vs 52.2 mo; HR 2.26, 95% CI 1.66–3.08;

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https://doi.org/10.1016/j.euros.2024.10.004

$p < 0.001$) than the group with an IgG decrease. Multivariable analysis revealed that an increase in serum IgG after 3-mo systemic therapy was an independent risk factor for both PFS (HR 3.28, 95% CI 2.51–4.30; $p < 0.001$) and OS (HR 1.94, 95% CI 1.41–2.68; $p < 0.001$). An increase in serum IgG after 1-mo treatment ($n = 160$) was also significantly associated with poorer median PFS (7.9 vs 13.7 mo; HR 1.62, 95% CI 1.13–2.32; $p = 0.008$) and OS (32.6 vs 50.5 mo; HR 1.68, 95% CI 1.09–2.59; $p = 0.017$).

Conclusions and clinical implications: The change in serum IgG after 3-mo systemic therapy can predict the therapeutic effect and prognosis for patients with mccRCC. This predictive value was observed as early as 1 mo after treatment initiation. Our findings highlight the potential of serum IgG as a predictive biomarker in this setting. Further validation is required in large prospective studies.

Patient summary: We found that for patients with metastatic kidney cancer, changes in the level of an antibody called immunoglobulin G (IgG) in blood during systemic treatment can predict their overall response. Early measurement of IgG could help doctors in personalizing treatment plans and might possibly improve the effectiveness of treatment for these patients.

1. Introduction

Clear-cell renal cell carcinoma (ccRCC) is the most common RCC subtype and accounts for the majority of kidney cancer deaths [1]. Clinically, 20–30% of all patients with ccRCC are diagnosed with metastatic ccRCC (mccRCC) and nearly 40% of the patients who undergo surgical excision of a localized tumor will have distant metastases [2].

Currently, a tyrosine kinase inhibitor (TKI) targeting VEGF combined with an immune checkpoint inhibitor (ICI) is the first-line systemic treatment recommended for patients with mccRCC [3,4]. TKIs were previously the primary systemic treatment recommended, and some patients still chose targeted therapy [5,6]. The International mRCC Database Consortium (IMDC) model has been widely used for risk stratification and helps in predicting prognosis and guiding drug selection for patients with mRCC [7]. In the IO-TKI era, the IMDC model still plays a crucial prognostic role. Given the dependence of the IMDC model on hematological parameters, investigation of these parameters for potential markers that can predict prognosis and treatment efficacy may provide valuable clinical perspectives.

Immunoglobulin G (IgG) is the most abundant antibody in human serum, accounting for 75% of the immunoglobulins and 10–20% of all circulating plasma proteins [8]. Traditionally, it was thought that IgG is only secreted by B lymphocytes and plasma cells. However, mounting evidence indicates that IgG is also expressed or secreted by many types of cancer cells, which is termed cancer-derived IgG [9,10]. Studies have shown that IgG within tumor tissue promotes the progression of cancer cells [8,11,12]. Specifically, the presence of IgG in ccRCC tissue is associated with positive responses to ICI treatment [13]. In a recent study, we found that high expression of cancer-derived IgG in mccRCC tissues was linked to poorer survival outcomes, underscoring its prognostic significance [14]. However, studies to date have primarily focused on IgG in tumor tissues, and IgG in blood has not been investigated. It remains unknown whether cancer-derived IgG can be secreted into the bloodstream. Moreover, the functions of B-cell–derived IgG and cancer-derived IgG are still largely unexplored.

Our aim in the current study was to analyze the prognostic and therapeutic significance of baseline levels of serum IgG and dynamic changes after treatment to provide insights into the predictive value of serum IgG for mccRCC treatment outcomes.

2. Patients and methods

2.1. Patient selection

This retrospective, single-center study included 318 patients with mccRCC who were treated at the National Cancer Center/Chinese Academy of Medical Sciences and Peking Union Medical College Cancer Hospital from January 2006 to December 2022. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The key inclusion criteria were: (1) age $\geq$18 yr; (2) newly diagnosed with primary ccRCC and metastatic sites; (3) receipt of TKI or IO-TKI therapy; and (4) initiation of first-line systemic therapy on or after January 1, 2006. The exclusion criteria were: (1) paired IgG information before and after IO-TKI or TKI therapy unavailable ($n = 435$); (2) history of other malignant tumors or systemic therapy ($n = 403$); and (3) and dates missing for clinicopathological and follow-up information ($n = 107$). The study was approved by the ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (approval number 20/245-2441).

2.2. Data collection and definition of variables

Fresh peripheral blood samples were collected from patients before treatment, and at 1 mo and 3 mo after

initiation of therapy. These samples were promptly sent to the clinical laboratory and serum IgG levels were measured via a turbidimetric inhibition immunoassay. IgG concentrations were determined by measuring the turbidity caused by the formation of antigen-antibody complexes and were quantified via comparison to a standard curve. Patients were classified into groups according to whether their IgG decreased or increased from baseline after systemic treatment. Variables for inclusion in multivariate models were selected on the basis of clinical relevance, including age at systemic therapy initiation, sex, TNM stage according to the 8th edition of American Joint Commission on Cancer system, IMDC risk group, number of metastatic sites, and presence of metastases in the bone, brain, or liver. The primary endpoint was progression-free survival (PFS), defined as the time from initiation of treatment to the first documentation of disease progression. The secondary endpoint was overall survival (OS), defined as the time from initiation of treatment to death from any cause or last follow-up. Median follow-up was determined for patients who were still alive (patients who did not have an event). The objective response rate (ORR) was determined according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.

2.3. Statistical analysis

Statistical analyses were conducted using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and associated packages. Results for continuous variables are reported as the median and interquartile range (IQR), and results for categorical variables as the frequency and percentage. Restricted cubic splines with four knots at the 5th, 35th, 65th, and 95th percentiles were used for flexible modeling of the association between the change in serum IgG and both PFS and OS. A likelihood ratio test was applied to assess the presence of any nonlinearity in the relationships (*rms*, *survival*, and *ggplot2* packages). The *t* test was used to compare baseline serum IgG levels between groups with a complete response (CR)/partial response (PR) or stable disease (SD)/progressive disease (PD) using the *ggplot2* and *ggpubr* packages for R. For survival analysis, Kaplan-Meier curves were plotted and the hazard ratio (HR) and associated 95% confidence interval (CI) were estimated using a Cox proportional-hazard models (*survival* and *survminer* packages). Follow-up was truncated in Kaplan-Meier survival curves when the number at risk in any group fell below five [15]. To analyze the impact of IgG levels on PFS and OS, Cox proportional-hazards model were constructed with adjustment for age, sex, T stage, N stage, number of metastatic sites, presence of metastasis in bone, brain, or liver, and IMDC risk group.

3. Results

3.1. Demographic and clinical characteristics of the patients

Overall, 318 patients with mccRCC with complete information on IgG at baseline and after 3-mo treatment were included (Supplementary Fig. 1). In this cohort, the median age at initiation of systemic therapy was 55 yr (IQR 49–63). Some 20% of the patients were female, 43% presented with advanced T stage (T3 or T4), and 20% had N1 lymph node involvement. According to the IMDC risk factors, approximately half of the patients had intermediate risk. The systemic therapy used was TKI in the majority of cases and the ORR was 42% in the overall cohort. After 3-mo systemic treatment, 42% of the patients exhibited an increase in serum IgG. Table 1 summarizes the clinicopathologic characteristics of the cohort.

3.2. Association of serum IgG with response to systemic therapy and prognosis

The median follow-up for surviving patients treated with systemic therapy was 43.4 mo. Figure 1 shows the percentage distribution of serum IgG changes. Restricted cubic splines were used to illustrate the relationship between the change in serum IgG and the HR for PFS (Fig. 1A) and for OS (Fig. 1B) for patients with mccRCC. The curves indicate that as serum IgG levels increased, the risks of disease progression and mortality significantly increased with, particularly for IgG levels exceeded the reference value (−0.45 g/l). This relationship was statistically significant and exhibited a nonlinear pattern (p values for nonlinearity were <0.001 for PFS and 0.008 for OS).

Notably, we did not find evidence of an association between baseline serum IgG and ORR in the overall cohort (p = 0.055; Supplementary Fig. 2A). Supplementary Figure 2B shows the distribution of serum IgG levels at baseline and 3 mo after therapy for the CR/PR group (n = 135); the mean change in serum IgG was −1.83 g/l (95% CI −2.26 to −1.41). For the SD/PD group (n = 183) the mean change in serum IgG was +0.85 g/l (95% CI 0.48–1.25; Supplementary Fig. 2C).

We also found that the change in IgG after 3-mo systemic treatment had a significant impact on PFS and OS: median PFS was 5.6 mo in the group with an increase in IgG versus 16.2 mo in the group with a decrease in IgG (HR 3.36, 95% CI 2.58–4.36; p < 0.001; Fig. 2A). Median OS was 26.0 mo in the group with an increase in IgG versus 52.2 mo in the group with a decrease in IgG (HR 2.26, 95% CI 1.66–3.08; p < 0.001; Fig. 2B). Multivariable Cox regression analysis adjusted for the effects of the change in serum IgG after 3 mo of treatment, age, sex, T stage, N stage, number of metastatic sites, metastasis in bone, brain, or liver, and IMDC risk group revealed an increase in serum IgG as an independent risk factor associated with worse PFS (HR 3.28, 95% CI 2.51–4.30; p < 0.001) and OS (HR 1.94, 95% CI 1.41–2.68; p < 0.001; Supplementary Table 1).

3.3. Serum IgG has potential for early prognostic value

We investigated whether early changes in serum IgG could serve as an early indicator of prognosis in mccRCC. Of the 318 patients, 158 did not have 1-mo serum IgG data available for various reasons, including loss to follow-up and incomplete records; 160 had serum IgG data available after 1-mo treatment with either IO-TKI or TKI. The results for these 160 patients demonstrate prognostic value of the change in serum IgG level after 1-mo treatment. Median PFS was 7.9 mo in the group with an increase in IgG at

Table 1 – Demographic and clinical characteristics of the 318 patients with metastatic clear-cell renal cell carcinoma

Parameter	Result
Median age at STx initiation, yr (IQR)	55 (49–63)
Female, *n* (%)	63 (20)
T stage, *n* (%)	
T1	100 (31)
T2	83 (26)
T3	110 (35)
T4	25 (8)
N stage, *n* (%)	
N0	255 (80)
N1	63 (20)
Two or more metastatic sites, *n* (%)	147 (46)
Bone, brain, or liver metastases, *n* (%)	104 (33)
IMDC risk group, *n* (%)	
Favorable	94 (30)
Intermediate	154 (48)
Poor	70 (22)
STx, *n* (%)	
TKI	220 (69)
IO-TKI combination	98 (31)
Best overall response, *n* (%)	
Complete/partial response	135 (42)
Stable/progressive disease	183 (58)
Change in IgG after 3-mo treatment, *n* (%)	
Decrease	185 (58)
Increase	133 (42)

STx = systemic therapy; TKI = tyrosine kinase inhibitor; IO = immunotherapy; IQR = interquartile range; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IgG = immunoglobulin G.

1 mo versus 13.7 mo in the group with a decrease in IgG at 1 mo (HR 1.62, 95% CI 1.13–2.32; $p = 0.008$; Fig. 3A). Median OS was 32.6 mo in the group with an increase in IgG at 1 mo versus 50.5 mo in the group with a decrease in IgG at 1 mo (HR 1.68, 95% CI 1.09–2.59; $p = 0.017$; Fig. 3B).

4. Discussion

This is the first study to demonstrate the prognostic and therapeutic significance of the change in serum IgG after systemic treatment in patients with mccRCC. Notably, the group with a decrease in IgG after treatment had superior PFS and OS, suggesting that monitoring of serum IgG could represent a valuable noninvasive biomarker for predicting treatment responses. The prognostic value of the change in serum IgG as early as 1 mo after treatment initiation stands out as a pivotal discovery, and this parameter might potentially predict patient treatment responses earlier than imaging techniques. This finding provides a new biomarker for clinical decision-making that could help physicians in optimizing treatment decisions on the basis of the change in serum IgG after treatment initiation.

Despite the emerging novel targeted and immune-based treatments, the proportion of patients benefiting from systemic therapy remains comparatively limited, posing challenges for prediction of drug responses [16,17]. While PD-L1 shows promise as a biomarker of response to ICIs in several solid tumors, its predictive ability in mccRCC has not been demonstrated [18]. Moreover, the predictive and prognostic value of a multitude of biomarkers, including gene signature profiles, the tumor mutational burden, circulating tumor DNA, and other molecules, remain contentious, and these markers have not been used for mccRCC in clinical practice [19,20]. The IMDC model is recognized as a prognostic tool for patient stratification into risk groups to assess the prognosis and responses to treatment in mccRCC [18]. The IMDC model includes several hematological indicators and changes in serum IgG also hold significant prognostic value. This suggests that studying specific blood biomarkers may offer critical insights for predicting prognosis and assessing treatment efficacy.

Monitoring of serum IgG levels represents a noninvasive biomarker for real-time assessment of response to therapy in patients with mRCC receiving IO-TKI or TKI treatment. We found that a significant decrease in IgG after 3-mo treatment was associated with better prognosis, indicating that these patients may benefit from deintensified therapy. In

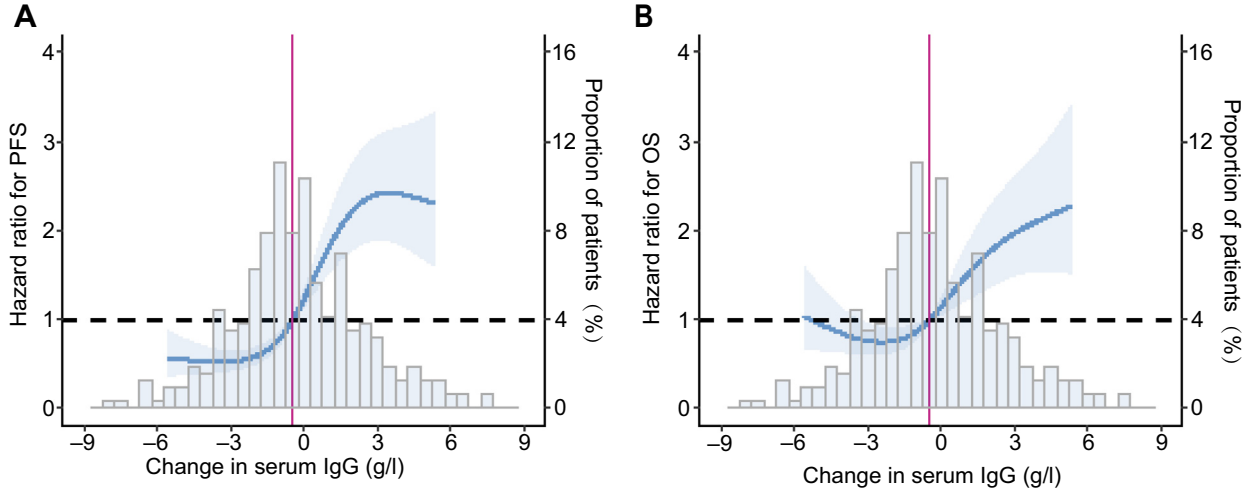

Fig. 1 – Relationship between the change in serum immunoglobulin G (IgG) and the hazard ratio for (A) PFS and (B) OS. The histograms show the percentage distribution of serum IgG changes, represented on the secondary *y*-axis. Hazard ratios are indicated by solid lines and 95% confidence intervals by shaded areas. The reference point is -0.45 g/l, for which the hazard ratio is equal to 1, with knots at the 5th, 35th, 65th, and 95th percentiles for the change in serum IgG after 3-mo therapy. The *p* values for nonlinearity were <0.001 for PFS and 0.008 for OS according to a likelihood ratio test. PFS = progression-free survival; OS = overall survival.

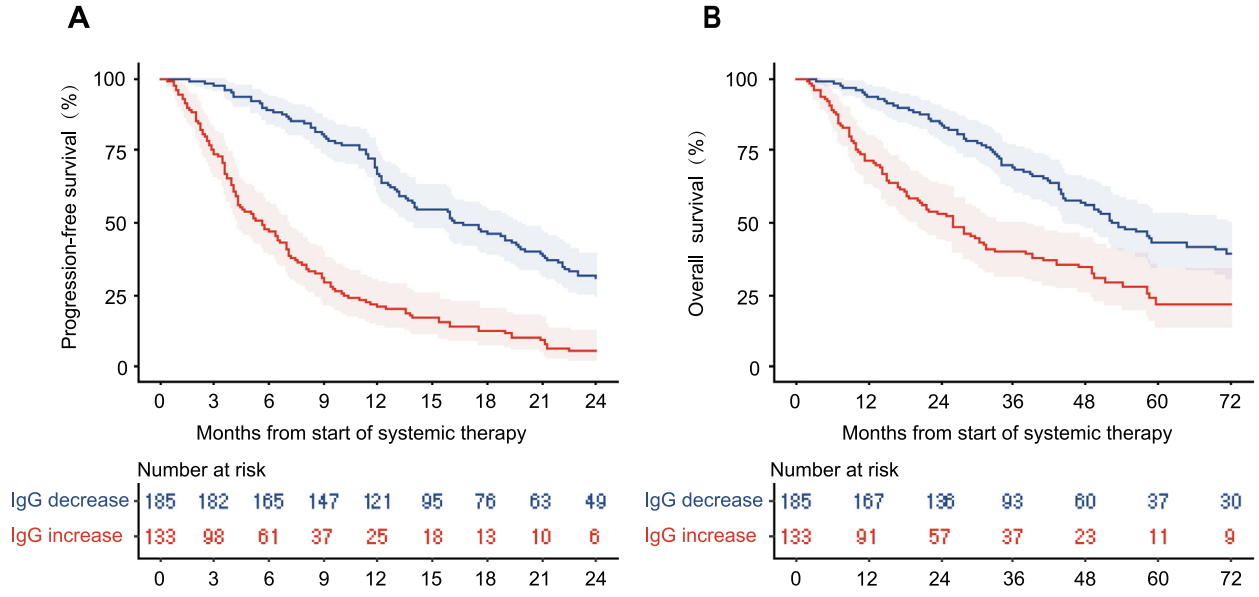

Fig. 2 – Kaplan-Meier curves and risk tables for (A) progression-free survival and (B) overall survival for the groups with a decrease (blue line) or increase (red line) in serum immunoglobulin G (IgG) after 3-mo treatment (*n* = 318) with 95% confidence intervals.

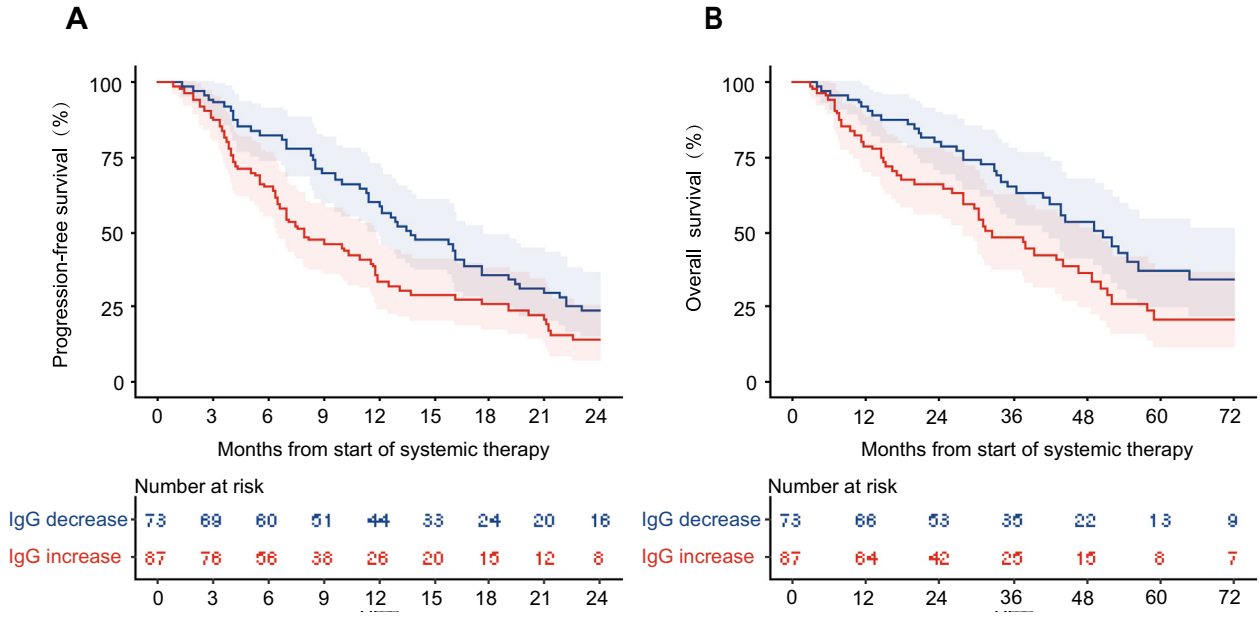

Fig. 3 – Kaplan-Meier curves and risk tables for (A) progression-free survival and (B) overall survival for the groups with a decrease (blue line) or increase (red line) in serum immunoglobulin G (IgG) after 1-mo treatment (*n* = 160), with 95% confidence intervals.

addition, IgG monitoring could serve as an early indicator of treatment efficacy, potentially allowing for earlier modification of therapeutic strategies. This could be particularly valuable in identifying nonresponders sooner and switching them to alternative therapies.

RCC is an immunogenic and immune-responsive tumor, containing abundant B cells and IgG, which has long been overlooked for its functions in tumor immunity [21]. Research on IgG in kidney cancer has been limited. A recent study revealed the presence of intratumoral tertiary lymphoid structures in RCC with a high frequency of IgG-producing plasma cells, and IgG expression in tumor tissue was significantly associated with ICI responses [13]. Qiu et al [22] were the first to detect IgG in cancer tissues and demonstrated it was expressed by cancer cells themselves. We recently investigated the presence of cancer-derived IgG in mccRCC tissues and found that high expression of cancer-derived IgG was linked to poorer survival outcomes [14]. However, all of the findings mentioned above relate to IgG expression in tumor tissue, with no evidence regarding

serum IgG. The underlying cause of a decrease in serum IgG after treatment—such as changes in B cells or an unidentified tumor source—remains to be elucidated. Indeed, there is no single origin for serum IgG: tumor-infiltrating and circulating B cells and plasma cells, as well as the tumor itself, are important sources of serum IgG [23,24]. Evidence indicates that cancer-derived IgG accounted for a substantial proportion of IgG deposited in the tumor microenvironment [25]. To date, the precise source of IgG in serum is still not fully understood, and exploration of the origin of IgG in serum is a pivotal aspect of our future research.

Our study has several limitations. First, the study has a retrospective design over a considerable time span, during which systemic treatments for mRCC underwent significant evolution, and the cohort comprises patients who received IO-TKI or TKI therapy, potentially limiting the applicability of our findings to contemporary clinical practice. Second, some patients lacked IgG measurement data at 1 mo after treatment initiation and were therefore excluded from this analysis, which limited the cohort size. Reasons for missing 1-mo IgG data were varied, including loss to follow-up and incomplete records. We assumed that the missing data were completely random and would not substantially impact the study conclusions. Finally, we did not explore whether the serum IgG source involved release from tumor tissues.

5. Conclusions

The change in serum IgG after 3-mo systemic therapy can predict prognosis and the overall therapeutic effect in patients with mccRCC; this predictive value was observed as early as 1 mo after treatment initiation. These findings underscore the potential of serum IgG as a predictive biomarker. The study spans a large timeframe and includes patients from the targeted therapy era, which may limit the applicability of the findings to current clinical practice. Further validation of these findings will require large prospective studies.

Author contributions: Jianzhong Shou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shou, Zhou.
Acquisition of data: Cui, Wu, Hu, Bai.
Analysis and interpretation of data: Cui, Wu.
Drafting of the manuscript: Shou, Cui, Wu.
Critical revision of the manuscript for important intellectual content: Hu, Dong, Qu, Shang, Du, Xie, Guan, Shi, Bi.
Statistical analysis: Shou, Cui, Wu.
Obtaining funding: Shou.
Administrative, technical, or material support: Li, Ma.
Supervision: Shou, Zhou.
Other: None.

Financial disclosures: Jianzhong Shou certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This work was financially supported by the National Natural Science Foundation of China (grant number 82072837).

Acknowledgments: We thank Xiaoyan Qiu and Weiyan Xu from the Department of Immunology, School of Basic Medical Sciences, Peking University, Beijing, for their support. We also thank Xuesi Dong and Hongmei Zeng from the Office of Cancer Screening at the National Cancer Center for their guidance with the statistical analysis.

Ethics considerations: This study was approved by the ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (approval number 20/245-2441).

Data sharing statement: The data supporting the findings of this study are available within the article and its supplementary material.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.10.004.

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