Peer Review File

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Review Comments

The manuscript entitled 'Prognostic effect of preoperative serum albumin to globulin ratio in patients treated with cytoreductive nephrectomy for metastatic renal cell carcinoma' tested the association between preoperative value of systemic albumin to globulin ratio (AGR) and overall survival (OS) as well as cancer-specific survival (CSS) in mRCC patients treated with CN, indicating that low AGR before CN was associated with worse OS and CSS, particularly in intermediate risk patients. However, before this paper is accepted for publication, there are still some problems that need to be addressed by the authors.

Comment 1: How to avoid the influence of selective bias on the results of retrospective study?

Reply 1: We thank the reviewer for a thorough analysis of our work and extensive comment on it. The reviewer has stressed an important and challenging point. In a retrospective cohort study, selection bias occurs if the selection of exposed and non-exposed subjects is somehow related to the outcome. However, in our study, we did not select patients (an exposed person) if they have the outcome of interest. We analysed all available patient's data from the multicenter database. Moreover, patients did not differ between two groups (AGR<1.4 and AGR>1.4) regarding the most of clinic-pathological features.

Nevertheless, we took into account this comment and added following sentence in the limitation section (Page 10, line 195-197).

Changes in the text: ***The main limitation of the study was its retrospective and multicenter design, which may result in selective bias, lack of standardized laboratory, pathological, surgical and treatment approaches that could confound the results.***

Comment 2: Agr may be affected by other diseases; does it affect the research results?

Reply 2: We thank the reviewer for this meaningful comment. Indeed, the presence of an undetected liver, hematologic or immunologic diseases or a drug interaction may affect blood protein levels of albumin and globulins. Consequently, it might affect the AGR level. In our study, data on the presence of these diseases was not available due to the retrospective design of our study. However, despite the lack of selection according to these specific factors our study might better represent a clinical external validity as population has not been over screened.

We mentioned the drawback of the heterogeneous patient population in the limitation section (Page 10, line 199-201).

Changes in the text: ***Another limitation of our study is the fact that AGR might have been biased by the presence of an undetected liver, hematologic or immunologic diseases or a drug interaction that may have affected a blood protein levels of albumin and globulins.***

Comment 3: It is speculated that the dynamic change of agr over time is related to the

treatment response and tumor prognosis of MRCC patients?

Reply 3: We thank the reviewer for this comment. We believe that monitoring of blood-based biomarker levels at various time points may provide enhanced diagnostics. Biological heterogeneity is present both among cells within the tumor at a given time and in cells during the development of the tumor from earlier to later points in time. This fact can affect the biomarker level over time. Additionally, biomarker might have a relationship with therapy. Thus, AGR variability over time might change in response to therapy and show its relationship to the oncological prognosis of mRCC patients. However, in our study, AGR was assessed preoperatively at a single time point, and it was impossible to perform additional AGR level measurements due to the retrospective design of our study. The changes in blood over time and in response to treatment and their relationships to the prognosis should be investigated in future prospective studies and we emphasis this point in the future perspectives part. We mentioned this point in the limitation section (Page 10, line 201-204).

Changes in the text: ***Additionally, AGR was assessed preoperatively at a single time point. AGR variability over time, in response to therapy and its relationship to the oncological prognosis of mRCC patients have not been tested and could be tested in the future studies.***

Comment 4: It was pointed out that the study population only included patients with metastatic diseases, which were quite different from local and locally advanced diseases in terms of immune regulation and systemic inflammation. What is the relationship between AGR and OS in local tumors? Our population included only patients with metastatic disease, which is very different from locally and locally advanced diseases in terms of immunomodulation and systemic inflammation.

Reply 4: We thank the reviewer for this meaningful comment. According to available literature, it was shown that low AGR level was associated with worse OS in patients with localized or locally advanced RCC (1-3). At the same time, the value of AGR as a predictor of oncological outcomes in patients with metastatic RCC remains uninvestigated. This fact stresses the importance of our study, which investigated the association in mRCC patients for the first time. Thanks to the valuable comment from the reviewer, we mentioned and clarify the rational for the relation between AGR and OS in the Background section.

Changes in the text: ***Previous studies have already suggested that AGR could be a potential biomarker to predict overall survival (OS), disease-free survival (DFS) and cancer-specific survival (CSS) in patients with localized or locally advanced RCC (16–18). Specifically, low preoperative AGR was associated with worse survival. However, the value of AGR as a predictor of oncological outcomes in patients treated with CN remains uninvestigated.***

1. Chen Z, Shao Y, Yao H, et al. Preoperative albumin to globulin ratio predicts survival in clear cell renal cell carcinoma patients. Oncotarget. 2017;
2. He X, Guo S, Chen D, et al. Preoperative Albumin to Globulin Ratio (AGR) as prognostic factor in renal cell carcinoma. J Cancer. 2017;
3. Koparal MY, Polat F, Çetin S, et. al. Prognostic role of preoperative albumin to globulin ratio in predicting survival of clear cell renal cell carcinoma. Int Braz J Urol. 2018;

Comment 5. Besides low agr, what are the biomarkers of OS and CSS deterioration in

mRCC patients? Can these biomarkers be combined with agr to improve the accuracy of prediction?

Reply 5: The reviewer has stressed an important point. Indeed, several other prognostic blood-based biomarkers have been investigated in mRCC patients. Previous studies have suggested explanations for the systemic immune-inflammation index ability to predict oncological outcomes in patients with mRCC (1-5). Fukuda et al. showed that the neutrophil-to-lymphocyte ratio was the most useful inflammation-based prognostic score for predicting OS in patients with mRCC (5). C-reactive protein,lymphocyte to monocyte ratio, and systemic inflammation response index were also associated with OS in mRCC (6,7).

We believe that combining AGR with other biomarkers may improve the accuracy of prognosis models. Thanks to the valuable comment from the reviewer, we mentioned and clarify the rational for the relation between other biomarkers and OS and/or CSS in mRCC patients in the Discussion section (Page 10, line 182-187).

Changes in the text: ***It is also important to consider that combining AGR with other biomarkers may improve the accuracy of prognosis models. Several other prognostic serum-based biomarkers have been investigated in RCC patients (7,27). For instance, neutrophil to lymphocyte ratio and C-reactive protein were associated with OS in mRCC (9). Other markers of systemic inflammation, lymphocyte to monocyte ratio and systemic inflammation response index, were associated with OS and pathological parameters in mRCC patients (28).***

1. C. Lolli et al., "Systemic immune-inflammation index predicts the clinical outcome in patients with metastatic renal cell cancer treated with sunitinib," Oncotarget, 2016, doi: 10.18632/oncotarget.10515.

2. P. Chrom, J. Zolnierek, L. Bodnar, R. Stec, and C. Szczylik, "External validation of the systemic immune-inflammation index as a prognostic factor in metastatic renal cell carcinoma and its implementation within the international metastatic renal cell carcinoma database consortium model," Int. J. Clin. Oncol., 2019, doi: 10.1007/s10147-018-01390-x.

3. U. De Giorgi et al., "Association of systemic inflammation index and body mass index with survival in patients with renal cell cancer treated with nivolumab," Clin. Cancer Res., 2019, doi: 10.1158/1078-0432.CCR-18-3661.

4. S. K. Barua et al., "Predictors of Progression-Free Survival and Overall Survival in Metastatic Non-Clear Cell Renal Cell Carcinoma: A Single-Center Experience," World J. Oncol., 2019, doi: 10.4021/wjon.v10i2.1188.

5. H. Fukuda, T. Takagi, T. Kondo, S. Shimizu, and K. Tanabe, "Predictive value of inflammation-based prognostic scores in patients with metastatic renal cell carcinoma treated with cytoreductive nephrectomy," Oncotarget, 2018, doi: 10.18632/oncotarget.24507

6. Boissier R, Campagna J, Branger N, et. al. The prognostic value of the neutrophil-lymphocyte ratio in renal oncology: A review. Urologic Oncology: Seminars and Original Investigations. 2017

7. Gu L, Ma X, Wang L, et al. Prognostic value of a systemic inflammatory response index in metastatic renal cell carcinoma and construction of a predictive model. Oncotarget. 2017

Comment 6. Due to its strong association with immune inflammatory reactions, Agr may

represent a valuable predictive and predictive marker for MRCC patients treated with immune checkpoint inhibitors as it has been already already shown in non-small cell lung cancer?

Reply 6: The reviewer has stressed an important and challenging point. Indeed, AGR has been already shown as prognostic and predictive marker for patients treated with immune checkpoint inhibitors for non-small cell lung cancer (1). We believe that in the era of immunotherapy, the predictive value of AGR should be assessed in mRCC patients treated with immune checkpoint inhibitors in further studies. This point was discussed in Discussion section (Page 10, line 177-181).

Changes in the text: ***Ideally, contemporary predictive value of AGR should be assessed in the era of immune checkpoint inhibitors (25). Due to its strong association with immuno-inflammatory reactions, AGR might represent a valuable prognostic and predictive marker for mRCC patients treated with immune checkpoint inhibitors as it has been already shown in non-small cell lung cancer (26).***

1.Nakanishi Y, Masuda T, Yamaguchi K, et al. Albumin–globulin ratio is a predictive biomarker of antitumor effect of anti-PD-1 antibody in patients with non-small cell lung cancer. Int J Clin Oncol. 2020