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Original Article

Impact of albumin to globulin ratio on survival outcomes of patients with metastatic renal cell carcinoma

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ABSTRACT

Objective: The albumin to globulin ratio (AGR) has been demonstrated to be associated with survival outcomes in various tumor types. However, the prognostic value of AGR in patients with metastatic renal carcinoma (mRCC) remains unclear. Therefore, this study aimed to investigate the impact of AGR values in predicting overall survival (OS) of patients with mRCC treated with targeted therapy.

Material and methods: A total of 163 patients with mRCC treated with targeted therapy between 2008 and 2019 were enrolled. The AGR value was measured as AGR: albumin/(total protein–albumin). The Kaplan-Meier method with long-rank testing and Cox proportional hazard models were used to estimate the correlation of AGR with OS.

Results: The receiver operating characteristic curve analysis showed that the optimal cut-off value of AGR in predicting OS was 1.11 with a sensitivity of 37.25% and specificity of 85.25% (area under curve, 0.62; 95% confidence interval [CI], 0.54-0.69; p=0.005). OS was significantly higher in patients with AGR>1.11 than in those with AGR≤1.11 (36.2 vs. 12.4 months; p<0.001). After adjustment for the number of covariates, multivariate Cox regression analysis identified a high AGR as an independent indicator of better OS (hazard ratio, 0.476; 95% CI, 0.304-0.745; p=0.001).

Conclusion: Our results suggested that AGR value, which is an easily obtainable and cost-effective marker in routine biochemistry testing, could function as an independent predictor of OS in patients with mRCC treated with targeted therapy.

Keywords: Albumin to globulin ratio; metastatic renal cell carcinoma; targeted therapy.

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Introduction

Renal cell carcinoma (RCC) is the 9th most commonly diagnosed cancer type in the United States and has a dismal prognosis with a 5-year survival rate of 12%.[1] Patients with distant metastases constitute approximately 30% of the RCC cases at the time of diagnosis.[2] Immune checkpoint inhibitors and targeted therapies have been used in combination or separately for the treatment of metastatic RCC (mRCC) according to risk groups in prognostic scoring systems.[3,4] The International mRCC Database Consortium (IMDC) scoring system incorporates 6 laboratory and clinical parameters to stratify patients into favorable, intermediate, and poor-risk groups.[5] However, a novel prognostic scoring model remains an urgent need to provide a better individualized treatment design.

The determinants of systemic inflammatory response, such as neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are linked to poor survival outcomes in a variety of malignant neoplasms, including RCC.[6,7] In addition, the albumin to globulin ratio (AGR) has been evaluated as an emergent prognostic marker in predicting the overall survival of various tumors because of its well-known association with the degree of systemic inflammation.[8-10] Albumin levels are associated with the nutritional status and chronic inflammation in patients with cancer.[11] A systematic review including 59 papers which analyzed the prognostic value of albumin in predicting survival of patients with gastroin-

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testinal, lung, and gynecological cancers demonstrated that a low albumin level was an indicator of poor survival.[12] The globulin component of serum is composed of alpha, beta, and gamma globulins, however, the functional roles in the immune system are mainly accomplished by the gamma subtype, which is produced as an antibody by B cells. In addition to its role in chronic inflammation, an increased level of gamma globulins has been shown as a prognostic factor in numerous cancer types, remarkably in hematological cancers.[13] However, recent studies that investigated the prognostic value of albumin and globulin in cancer were mostly conducted with AGR, which is measured as albumin/(total protein–globulin), instead of separate values because AGR is the ratio of 2 independent prognostic factors. AGR has been determined as a prognostic determinant for survival in various types of cancer, including gastric cancer, colorectal cancer, hepatocellular cancer, breast cancer, and prostate cancer.[9,10,14-16] To date, the effect of AGR on the survival of patients with RCC has been analyzed with a preoperative AGR level by a few studies in the literature. However, the association between AGR and survival outcomes of mRCC has not been investigated. Thus, in this study, we analyzed for the first time the prognostic impact of baseline AGR value at treatment initiation on progression-free survival (PFS) and overall survival (OS) of patients with mRCC who were treated with targeted therapy, sunitinib, and pazopanib.

Material and methods

Patients

This retrospective observational study included 163 consecutive patients with mRCC who were treated with targeted therapy, sunitinib or pazopanib between 2008 and 2019 at Hacettepe University Cancer Institute (Ankara, Turkey). The baseline clinicopathologic characteristics and the parameters of IMDC prognostic scoring system in patients with mRCC were recorded.[5] All the patients had a pathologically proven RCC diagnosis. Patients who were lost to follow-up and those with acute or chronic inflammatory diseases (especially liver diseases, infections, and chronic kidney disease) and other concurrent or previous cancer history were excluded. The baseline albumin and globulin levels were retrieved from the routine biochemistry reports. The albumin and total protein levels were measured after the separation of serum by centrifugation at 2,000 gravity. The globulin levels were calculated by subtracting the albumin from the total protein. The measurement methodology remained the same during the study period. All procedures in this study were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by Hacettepe University ethics committee (02 July 2019-Decision No: GO 19/697) and all the participants or their relatives gave written informed consent.

Main Points:

- To the best of our knowledge, this study, for the first time, analyzed the prognostic value of albumin to globulin ratio (AGR) in the survival outcomes of patients with metastatic renal carcinoma (mRCC) who were treated with targeted agents.
- The AGR value>1.11 was determined as an independent indicator for better OS.
- AGR could be integrated into the current prognostic systems if our findings are supported by future studies.

Statistical analysis

Descriptive statistics were presented using the median and interquartile range, and categorical variables were presented using frequency and percent. AGR was calculated as follows:

$$AGR = {Albumin}/{(total\ protein - albumin)}$$

Comparisons between independent groups were performed with the Mann-Whitney U test and chi-squared test, respectively. The cut-off value for AGR was determined with the receiver operating characteristic (ROC) analysis using Youden's J index. OS was calculated as the time frame from the initiation of the 1st line treatment to the last follow-up and/or death, and the progression-free survival was calculated as the duration from the initiation to the end of the 1st line treatment and/or death. The survival analyses were done using the Kaplan-Meier method, and the comparisons between prognostic sub-groups were done with the log-rank test. The multivariate analyses of survival were done using Cox regression method. All analyses were significant at the $p<0.05$ level, and Statistical Package for Social Sciences, version 25, (IBM SPSS Corp., Armonk, NY, USA) software was used for the statistical analyses in the study.

Results

Baseline patient characteristics

The study cohort consisted of 163 patients with mRCC treated with targeted therapy (men/women:120/43) after the exclusion of patients with chronic kidney disease or acute infectious or inflammatory conditions that could affect the AGR values (n=17) and patients lost to follow-up (n=20). Demographic and clinicopathologic characteristics of the study population stratified according to the AGR values are presented in Table 1. The most common histopathologically detected RCC was the clear cell subtype with grade III and IV. The ROC analysis showed that AGR value of 1.11 was determined as the optimal cut-off point for OS prediction with the sensitivity of 37.25% and specificity of 85.25% (area under curve [AUC], 0.62; 95% confidence interval [CI], 0.54-0.69; p=0.005) (Figure 1). Furthermore, the optimal cut-off point of AGR for PFS prediction was 1.30 (AUC, 0.58; sensitivity, 63%; specificity, 58%). A total of 104 mRCC-related deaths were recorded dur-

Table 1. Baseline clinicopathologic characteristics of the patients stratified according to AGR cut-off

Characteristics	All patients (n=163)	Low AGR (≤1.11; n=47)	High AGR (>1.11; n=116)	p
Age (years)	60 (53-65)	61 (52-66)	60 (53-65)	0.229
Sex				
Women	27.3	19.1	22.7	
Men	72.7	80.9	77.3	0.133
Histology				
Clear cell	78	73.3	73.7	
Non-clear cell	22	26.7	26.3	0.044
AGR	1.48 (1.16-2.03)	0.90 (0.80-1.03)	1.33 (1.24-1.54)	
Lung metastasis				
Yes	75.2	76.6	75.3	
No	24.8	23.4	24.7	0.942
Liver metastasis				
Yes	23	34	27.8	
No	77	66	72.2	0.058
Bone metastasis				
Yes	25.5	36.2	30.9	
No	74.5	63.8	69.1	0.039
Brain metastasis				
Yes	4.2	-	4.1	
No	95.8	100	95.9	1
Tumor grade				
Grade I-II	29.7	23.7	23.6	
Grade III-IV	70.3	76.3	76.4	0.034
IMDC risk group				
Favorable	14.6	12.8	9.3	
İntermediate	59.8	38.3	57.7	
Poor	25.6	48.9	33	0.011
Treatment group				
Pazopanib	68.1	36.2	30.2	
Sunitinib	31.9	63.8	69.8	0.457
PFS (months)	11.5	8.7	16.5	0.001
OS (months)	25.6	12.4	36.2	0.000

Continuous variables are represented as median with interquartile range; dichotomous variables as percentages. AGR: albumin to globulin ratio; BMI: body mass index; MCV: mean corpuscular volume; HCT: hematocrit; RBC: red blood cell; WBC: white blood cell; PFS: progression free survival; OS: overall survival; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

ing the median follow-up time of 19.05 months (minimum-maximum: 1.31-102.60 months). When we compared the AGR values among favorable, intermediate, and poor-risk groups stratified on the basis of the IMDC scoring system, patients in the poor-risk group had significantly higher AGR values than those in the favorable and intermediate-risk groups (p=0.001) (Figure 2). However, patients in the favorable and intermediate-risk groups had similar AGR values.

Impact of albumin to globulin ratio on survival outcomes

The median PFS and OS of the study population were 11.2 (95% CI, 8.8-13.6) months and 24.7 (95% CI, 20-29.4) months, re-

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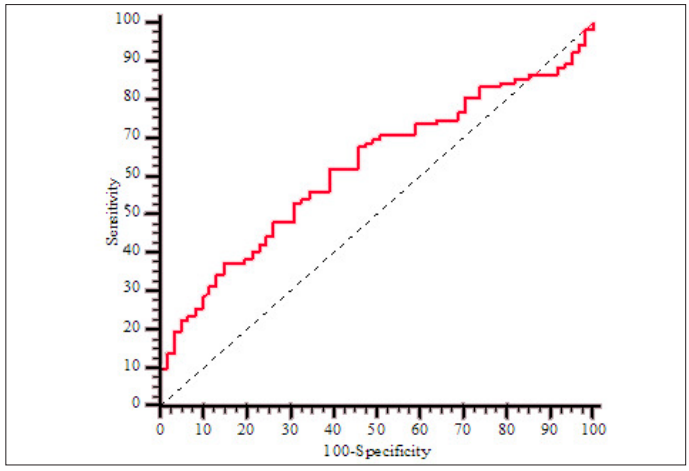

Figure 1. Receiver operating characteristic analysis revealing that albumin to globulin ratio of 1.11 is the optimal cut-off point for overall survival prediction (area under curve, 0.620; Youden index, 0.225; sensitivity, 37.2%; specificity, 85.2%; p=0.005)

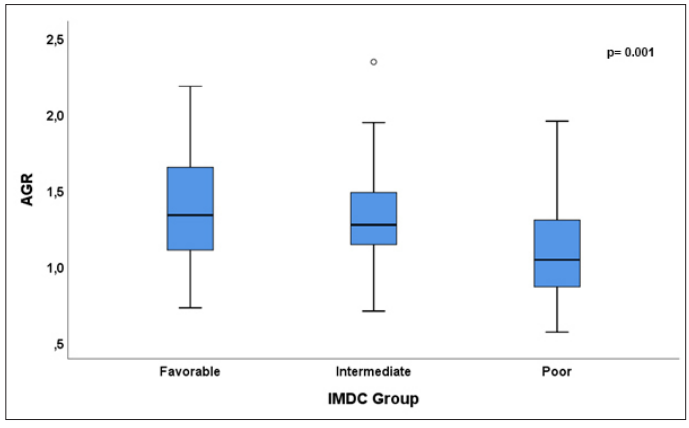

Figure 2. Demonstration of albumin to globulin ratio among the International Metastatic Renal Cell Carcinoma Database Consortium risk groups

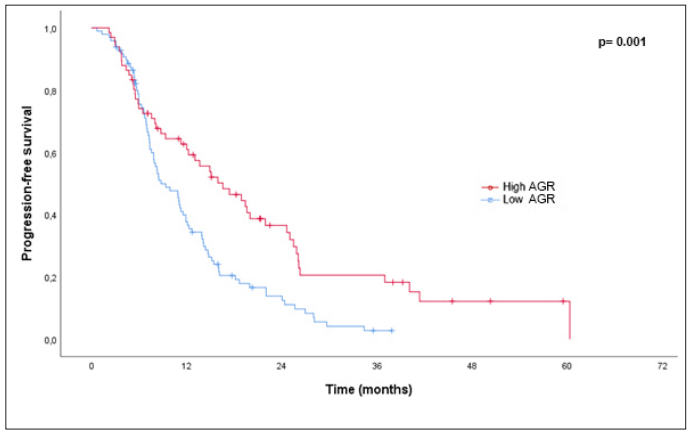

Figure 3. Demonstration of the Kaplan-Meier curve stratified according to albumin to globulin ratio for progression-free survival

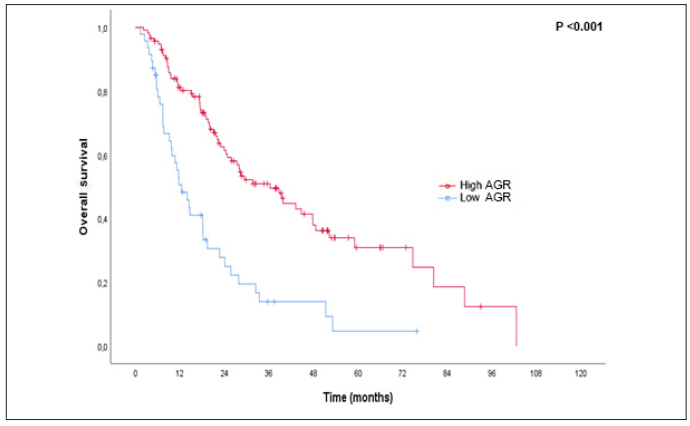

Figure 4. Demonstration of the Kaplan-Meier curve stratified according to albumin to globulin ratio for overall survival

spectively. Considering the IMDC risk groups, the median PFS times were 25 months (favorable-risk group; 95% CI, 20-29.9), 12.2 months (intermediate-risk group; 95% CI, 10-14.5), and 5.9 months (poor-risk group; 95% CI, 4.5-7.3). The median OS was not reached in the favorable-risk group; and on continued follow-up, the median OS times of patients in the intermediate and poor-risk groups were 31.6 months (95% CI, 22.1-41) and 10.6 months (95% CI, 8.1-13.2), respectively. We found that patients with higher AGR had superior PFS and OS times than those with lower AGR using the Kaplan-Meier survival analysis (PFS 16.5 months vs. 8.7 months, p=0.001; OS 36.2 months vs. 12.4 months, p<0.001, respectively) (Figures 3 and 4). As presented in Table 2, the identified prognostic determinants in predicting OS by univariate Cox regression analyses status were AGR (hazard ratio [HR], 0.364; 95% CI, 0.241-0.549; p<0.001); bone metastasis status (HR, 1.710; 95% CI, 1.128-2.593; p=0.012), and IMDC scoring system (p<0.001). We also demonstrated that high AGR was associated with better PFS in univariate analysis (HR, 0.544; 95% CI, 0.377-0.784; p=0.001). As presented in Table 3, multivariate Cox analysis revealed that AGR at treatment initiation was determined as an independent prognostic parameter in predicting OS (HR, 0.476; 95% CI, 0.304-0.745; p=0.001) (Table 3). In addition to AGR, the IMDC risk group and the presence of bone and brain metastases were determined as independent predictors of OS.

Discussion

This study was performed to elucidate the potential role of AGR in patients with mRCC who were treated with targeted therapy. Although AGR has been proved as a predictive determinant in diversified types of cancers, to the best of our knowledge, this is the first study that analyzed the impact of AGR level just before treatment initiation of targeted therapy on survival outcomes of patients with mRCC. Our results revealed that higher AGR values were independently associated with better survival in mRCC treated with targeted therapy, sunitinib, and pazopanib.

Table 2. Univariate Cox regression analysis of the associations between clinicopathological factors and PFS and OS

	PFS		OS	
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age (years)	1.007 (0.990-1.024)	0.412	1.017 (0.997-1.037)	0.094
Lung metastasis				
No	Reference			
Yes	0.912 (0.616-1.352)	0.647	1.215 (0.764-1.932)	0.412
Liver metastasis				
No	Reference			
Yes	1.287 (0.860-1.926)	0.220	1.164 (0.735-1.843)	0.518
Bone metastasis				
No	Reference			
Yes	1.364 (0.938-1.982)	0.104	1.710 (1.128-2.593)	0.012
Brain Metastasis				
No	Reference			
Yes	1.803 (0.838-3.880)	0.132	2.034 (0.883-4.688)	0.095
Tumor grade				
I	Reference			
II	1.143 (0.401-3.260)	0.802	1.217 (0.362-4.090)	0.751
III	1.359 (0.487-3.791)	0.557	1.276 (0.385-4.230)	0.690
IV	1.396 (0.500-3.901)	0.524	1.750 (0.530-5.777)	0.358
Histology				
Clear cell	Reference			
Non-clear cell	0.719 (0.463-1.118)	0.143	0.984 (0.607-1.596)	0.948
IMDC risk group				
Favorable	Reference			
Intermediate	1.050 (1.177-3.569)	0.011	1.783 (0.847-3.754)	0.128
Poor	8.371 (4.406-15.902)	0.000	7.029 (3.234-15.276)	0.000

PFS: progression free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

Albumin prevents sex hormone-related malignancy formation by balancing DNA replication, cell proliferation, and sex hormone homeostasis.[17] It was shown that albumin had a negative effect on the growth of a human estrogen responsive breast cell line, MCF-7, by regulating the effects of growth factors with autocrine functions.[18] However, malnutrition and systemic inflammation may cause decreased albumin synthesis, resulting in debilitated phagocytosis, humoral, and cellular immunity functions of immune mechanisms. Malnutrition is related to poor survival outcomes and a deterioration in the quality of life in cancers via decreased tumor responsiveness to anticancer therapy and increased chemotherapy associated adverse effects.[19] There are several laboratory markers for determining the nutritional status of patients with cancer, including the measurement of prealbumin, albumin, and transferrin in serum.[20] Albumin constitutes a major part of serum proteins, and its production takes place in the liver. Albumin level is linked to cancer associated systemic inflammation because of the inhibitory effect of activated pro-inflammatory markers, including tumor necrosis factor α and interleukin-1 and interleukin-6.[21] The non-albumin part of serum total protein includes C-reactive protein (CRP), serum immunoglobulins, and complement system proteins, which have a pro-inflammatory role in immune response. Saito et al.[22] have found that patients with elevated preoperative CRP had worse cancer specific and recurrence-free survival than those with non-elevated CRP. Moreover, pre and postoperative IgA and postoperative C3 levels above upper limit of normal were associated with poor prognosis in patients with

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Table 3. Multivariate Cox regression analysis for estimating the independent factors for OS prediction

		95% CI for HR		
Overall survival	**HR**	**Lower**	**Upper**	**p**
Age (years)	1.012	0.992	1.032	0.253
Bone metastasis				
No	Reference			
Yes	1.617	1.045	2.501	0.031
Brain metastasis				
No	Reference			
Yes	3.997	1.658	9.638	0.002
AGR				
≤1.11	Reference			
>1.11	0.476	0.304	0.745	0.001
IMDC risk group				
Favorable	Reference			
Intermediate	1.836	0.829	4.065	0.134
Poor	6.748	2.909	15.652	0.000

OS: overall survival; HR: hazard ratio; CI: confidence interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

colorectal carcinoma operated with radical intent.[23] However, AGR is evaluated as a more effective marker for estimating prognosis in cancer than separate albumin and globulin levels in serum because the volume changes of body fluids, dehydration, or fluid retention can affect the serum albumin concentration.[15] Furthermore, Azab et al.[14] have shown that AGR was an independent determinant for cancer specific mortality in all their patients with colorectal cancer and in the subset of patients with normal serum albumin. Chen et al.[24] have investigated the impact of baseline AGR before nephrectomy on survival outcomes of patients with clear cell RCC and demonstrated that low AGR was associated with poor cancer specific survival (HR, 8.806; 95% CI, 3.891-19.928; p<0.001) and OS (HR, 6.799; 95% CI, 3.215-14.377; p<0.001). Similarly, He et al.[25] have determined an AGR value of 1.47 as the optimal cut-off in the prediction of OS and have shown that high preoperative AGR value was an independent prognostic determinant of OS in patients with RCC (HR, 0.63; 95% CI, 0.43-0.93; p=0.022). However, these studies investigated the prognostic value of preoperative AGR on the survival outcomes of patients with RCC. Our study analyzed the impact of AGR on PFS and OS in patients with mRCC who were treated with targeted therapy. AGR values of 1.11 and 1.30 were determined as the optimal cut-offs in the prediction of PFS and OS, respectively. Our results showed that high baseline AGR before initiation of targeted therapy was found as an independent indicator of better OS. Considering the patients' IMDC status, we also showed that patients in the poor-risk group had significantly higher AGR values than those in the favorable and intermediate-risk groups.

For the first time, we demonstrated the impact of AGR on survival outcomes of patients with mRCC treated with targeted therapy. However, our study had some limitations. This was a retrospective study conducted in a single institution. We also could not evaluate the prognostic value of pro-inflammatory cytokines, immunoglobulins, complement proteins, and CRP on survival outcomes because the measurement of these markers is not a part of routine clinical practice. Thus, we had no chance of analyzing the association between AGR and these specific inflammation markers. Finally, our study population consisted mostly of patients with intermediate-risk (59.8%); therefore, the predictive value of AGR should be analyzed in a more homogeneous study group.

In summary, we demonstrated for the first time the predictive role of AGR in patients with mRCC treated with targeted therapy. High AGR was independently associated with better OS in patients with mRCC in addition to the risk groups according to IMDC scores. We believe that once our results are confirmed in the prospective studies, the AGR value will be an easily available and practical marker for the prediction of survival outcomes in patients with mRCC in clinical practice.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hacettepe University (02 July 2019-Decision No: GO 19/697).

Informed Consent: Written informed consent was obtained from all the participants or their relatives who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept – O.H.A., G.G., M.E.; Design – O.H.A., G.G., D.C.G., M.E.; Supervision – O.H.A., D.Y., M.E.; Resources – D.C.G.; Materials – H.Ç.Y., D.C.G.; Data Collection and/or Processing – T.K.Ş., F.S.A., H.T.; Analysis and/or Interpretation – O.H.A., D.Y., H.H.Y., M.E.; Literature Search – O.H.A., H.C.Y., G.G.; Writing Manuscript – O.H.A., M.E.; Critical Review – D.C.G., G.G., H.H.Y.

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