

Research Paper

Preoperative Albumin to Globulin Ratio (AGR) as Prognostic Factor in Renal Cell Carcinoma

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Abstract

Background: Malnutrition and systemic inflammatory response are frequently associated with prognosis in patients with several types of cancer, including renal cell carcinoma (RCC). The study is aimed to investigate the ability of preoperative serum albumin to globulin ratio (AGR) to predict the long-term mortality of RCC patients.

Methods: The study is a retrospective study of an unselected cohort of 895 RCC patients who underwent a curative radical or partial nephrectomy at the Department of Urology in the Sun Yat-Sen University Cancer Center between January 2000 and December 2012 and had documented preoperative serum total protein and albumin (ALB) levels. The preoperative AGR was calculated as the ratio of ALB to (total protein-ALB) and its association with other clinical indices was assessed using survival analysis.

Results: Low preoperative AGR was associated with older population, lower hemoglobin, higher total protein, lower ALB, lower body mass index and advanced stage. The univariate and multivariate Cox analyses demonstrated that preoperative AGR was an independent prognostic indicator of overall survival (OS) (hazard ratio (HR): 0.63, 95% confidence interval (CI): 0.43 to 0.93, P=0.022). In addition, patients with low preoperative AGR at pT1-2, pT3-4, pN0, pN1, pM0 and pM1 stages had significantly shorter OS than patients with high preoperative AGR.

Conclusion: Preoperative AGR is a proven objective, reproducible, inexpensive survival predictor of RCC patients following surgical resection and should be considered for routine clinical use.

Key words: Renal Cell Carcinoma; Albumin, Total Protein; Albumin to Globulin ratio.

Introduction

Renal cell carcinoma (RCC) is the most common malignant tumor of the kidney, with 66,800 and 62,700 estimated new cases occurring in China each year ¹ and the United State in 2016 ², respectively. Incidental and early stage tumors have been detected more frequently because of increased use of imaging techniques including ultrasound and computed tomography (CT) in recent years ³⁻⁴. Although more

RCC patients are diagnosed at early stage tumors, its mortality is still rising. Approximately 20% to 30% of patients with localized tumors after radical or partial nephrectomy will later develop metastatic disease ⁵. As renal tumors are insensitive to radiotherapy and chemotherapy, majority of metastatic patients die. Although the TNM system proposed by UICC and AJCC ⁶ and Fuhrman's Nuclear Grading system ⁷ are

commonly used for prognosis, they are not entirely reliable⁸. Other well-known prognostic factors are lymphocytic infiltration and histological subtype⁸. Due to the insufficiency of these prognostic factors, new factors including clinical and laboratory indicators are being considered.

Increasing evidence supports the involvement of systemic nutritional status and inflammation in cancer progression⁹⁻¹¹. Albumin (ALB) and globulin (GLB) are the two major components of serum proteins. Hypoalbuminemia in cancer patients not only is an indicator of poor nutritional status but also relates to chronic inflammation¹²⁻¹³. Furthermore, increased level of GLB could serve as a marker of chronic inflammation response and reflect a cumulative exposure of various pro-inflammatory cytokines¹⁴. Recent studies have demonstrated that ALB to GLB ratio (AGR), which is calculated as $AGR = ALB / (total\ protein - ALB)$, is an independent prognostic factor for breast cancer, lung cancer, nasopharyngeal carcinoma, colorectal cancer and so on¹⁵⁻¹⁸. AGR level not only reflects the nutritional status but also represents the systemic inflammation. Thus, discriminating AGR might be a potential independent risk factor for RCC. However, to our best knowledge, the prognostic significance of AGR in RCC has not been reported. The aim of our research was to assess the prognostic significance of preoperative AGR in long-term survival of RCC patients and to evaluate whether it could provide additional prognostic information to well-established clinicopathological parameters.

Material and Methods

Patients

The subjects of the retrospective study were a cohort of 912 consecutive RCC patients who underwent a curative radical or partial nephrectomy at the Department of Urology in Sun Yat-Sen University Cancer Center between January 2000 and December 2012. Among these patients, 17 patients (1.86%) had incomplete laboratory data. Thus, 895 patients were included in the analysis. The study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center and performed in accordance with the ethical standards of the World Medical Association Declaration of Helsinki¹⁹. All included patients provided written informed consent and their information were recorded and registered in our cancer registry system.

Follow-up

Follow-up schedules were established and applied referring to the NCCN Clinical Practice Guidelines. RCC patients at early stage who need to

be closely monitored after partial or radical nephrectomy (pT1a and pT1b) were subjected to follow-up evaluations every six months for the first 2 years and once a year thereafter. RCC patients at advanced stage were subjected to follow-up evaluations every 3-6 months for the first three years and once a year thereafter. The follow-up evaluations included all routine clinical, laboratory and radiological examinations. In addition, all patients were also followed up via telephone interviews. The last follow-up was completed in November 01, 2015. Patients who were still alive at the last follow-up were censored.

Clinical and laboratory parameters

All clinicopathological data including demographic parameters, Fuhrman grade, tumor histology, tumor stage and laboratory data were retrieved from the electronic medical records at our hospital. The AJCC/UICC TNM staging system (the 7th edition) was applied to classify the tumor stage. The laboratory data, including the levels of ALB, total proteins, hemoglobin (HGB), alkaline phosphatase (ALP), serum creatinine (Scr) and uric acid (UA), were measured one day before surgical intervention. Serum ALP >135 U/L, Scr > 130 μ mol/L and UA > 420 μ mol/L were defined as elevated. Preoperative AGR was calculated using the equation: $AGR = ALB / (total\ protein - ALB)$.

Statistical analysis

The end point of the study was overall survival (OS), which was defined as the time interval between the date of surgery and the date of death of individual patient. The optimal cut-off value of preoperative AGR was determined by using the receiver operating curve (ROC) analysis, as previously described²⁰⁻²¹. The threshold that best discriminated the differences between the survived and deceased cases (in terms of sensitivity and specificity) was used, allowing us to treat AGR as a dichotomous variable.

The continuous and categorical variables were presented as means \pm standard deviations (SD) as well as frequencies and percentages, respectively. Continuous data were analyzed using the Mann-Whitney U-test and categorical data were analyzed using the chi-square test. Patients' clinical end points were calculated using the Kaplan-Meier method and compared by the log-rank test. Univariate analysis was performed to determine the significance of variables and Cox regression model was performed for OS. Subsequently, the variables with $P < 0.05$ were further analyzed using multivariate Cox proportion analysis to determine independent prognostic factors. Hazard ratios (HRs) estimated

from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). All Statistical analyses were performed using Empower (R) (www.empowerstats.com, X&Y solutions, Inc., Boston, MA), R (http://www.R-project.org) and Statistical Package for Social Sciences (SPSS) 21.0 software (IBM, Armonk, NY). A two-sided $P < 0.05$ was considered statistically significant.

Table 1. Baseline characteristics of all patients.

Characteristics	Cases (n=895)	Percentage (%)
Age, year (mean±SD)	51.44±13.44	
Hemoglobin, g/L, (mean±SD)	134.21±20.47	
Total protein, g/L (mean±SD)	72.22±6.61	
Serum albumin, g/L (mean±SD)	43.10±4.80	
Body mass index, kg/m ² (mean±SD)	23.41±3.58	
AGR, (mean±SD)	1.54±0.34	
Gender		
Male	600	67.00
Female	295	33.00
Pathological types		
Clear cell carcinoma	696	77.80
Multilocular cystic renal cell carcinoma	64	7.20
Chromophobe renal carcinoma	32	3.60
Others	103	11.50
Fuhrman-grade		
I	205	22.90
II	329	36.80
III	85	9.50
IV	13	1.50
Unknown	263	29.40
pT status		
T1	613	68.50
T2	164	18.30
T3	88	9.80
T4	30	3.40
pN status		
N0	829	92.60
N1	66	7.40
pM status		
M0	852	95.20
M1	43	4.80
pTNM stage		
I	597	66.70
II	143	16.00
III	96	10.70
IV	59	6.60
Alkaline phosphatase, U/L		
Normal	858	95.90
Elevated	37	4.10
Serum creatinine, μmol/L		
Normal	859	96.00
Elevated	36	4.00
Uric acid, μmol/L		
Normal	705	78.80
Elevated	190	21.20
AGR group		
Low AGR group (AGR≤1.47)	371	41.50
High AGR group (AGR>1.47)	524	58.50

Abbreviation: pTNM: pathologic tumor-node-metastasis; AGR: Albumin to Globulin ratio.

Results

Clinicopathological Features

The 895 enrolled patients were 51.44±13.44 years old. Of them, 600 (67.00%) were male and 295 (33.00%) were female. 597, 143, 96 and 59 patients were at stage I, II, III and IV, respectively. The median follow-up time from diagnosis was 69.68 months (95%CI: 65.73–73.63). 171 patients died during the follow-up. Table 1 summarizes patients' characteristics.

Identification of the optimal cut-off value for AGR

Serum ALB and serum total proteins levels were 43.10±4.80 g/L and 72.22±6.61 g/L, respectively. The calculated AGR was 1.54±0.34. ROC curves in **Figure 1** showed that when analyzed as a dichotomous variable, AGR=1.47 as the cut-off value provided the strongest prognostic point for the OS. Therefore, this level was chosen to stratify patients. 371 patients with AGR ≤ 1.47 were classified into low AGR group, whereas 524 with AGR > 1.47 were classified into high AGR group.

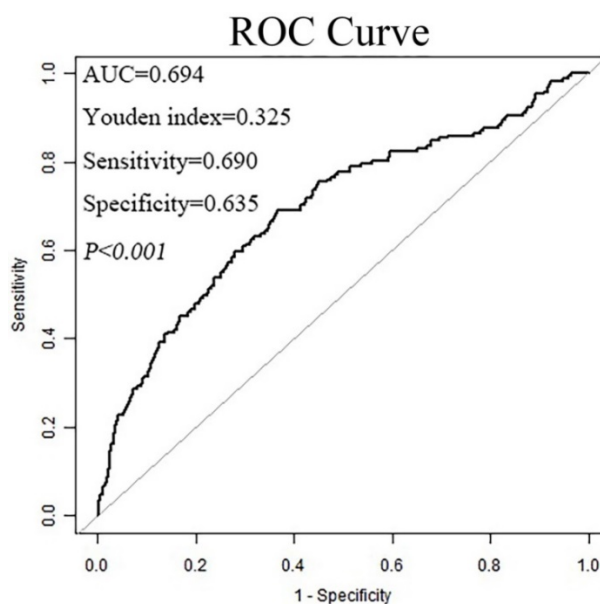


Figure 1. The receiver operating characteristic (ROC) curve for the preoperative albumin to globulin ratio (AGR).

Association of AGR with the clinicopathological features of RCC patients

Patients in different AGR groups showed significant differences in pT-stage ($P < 0.001$), pN-stage ($P < 0.001$), pM-stage ($P < 0.001$), pTNM-stage ($P < 0.001$) and ALP group ($P < 0.001$) (**Table 2**). Additionally, patients in low AGR group were significantly older ($P < 0.001$), and had lower HGB ($P < 0.001$), higher TP

($P < 0.001$), lower ALB ($P < 0.001$) and lower BMI ($P < 0.001$) than patients in high AGR group (Table 2).

Table 2. Characteristics of the 895 patients with RCC.

Characteristics	Low AGR group	High AGR group	P value
Age, year (mean±SD)	55.20 ± 13.33	48.78 ± 12.88	<0.001 ^a
Hemoglobin, g/L, (mean±SD)	126.30 ± 21.40	139.81 ± 17.79	<0.001 ^a
Total protein, g/L (mean±SD)	73.97 ± 6.67	70.98 ± 6.29	<0.001 ^a
Serum albumin, g/L (mean±SD)	40.46 ± 5.14	44.97 ± 3.49	<0.001 ^a
Body mass index, kg/m ² (mean±SD)	22.94 ± 3.48	23.74 ± 3.61	0.001 ^a
Gender			<0.001 ^b
Male	220 (59.30%)	380 (72.50%)	
Female	151 (40.70%)	144 (27.50%)	
Pathological types			0.075 ^b
Clear cell carcinoma	283 (76.30%)	413 (78.80%)	
Multilocular cystic renal cell carcinoma	29 (7.80%)	35 (6.70%)	
Chromophobe renal carcinoma	8 (2.20%)	24 (4.60%)	
Others	51 (13.70%)	52 (9.90%)	
Fuhrman-grade			0.066 ^b
I	80 (21.60%)	125 (23.90%)	
II	125 (33.70%)	204 (38.90%)	
III	46 (12.40%)	39 (7.40%)	
IV	7 (1.90%)	6 (1.10%)	
Unknown	113 (30.50%)	150 (28.60%)	
pT status			<0.001 ^b
T1	203 (54.70%)	410 (78.20%)	
T2	85 (22.90%)	79 (15.10%)	
T3	60 (16.20%)	28 (5.30%)	
T4	23 (6.20%)	7 (1.30%)	
pN status			<0.001 ^b
N0	324 (87.30%)	505 (96.40%)	
N1	47 (12.70%)	19 (3.60%)	
pM status			<0.001 ^b
M0	339 (91.40%)	513 (97.90%)	
M1	32 (8.60%)	11 (2.10%)	
pTNM stage			<0.001 ^b
I	196 (52.80%)	401 (76.50%)	
II	67 (18.10%)	76 (14.50%)	
III	65 (17.50%)	31 (5.90%)	
IV	43 (11.60%)	16 (3.10%)	
Alkaline phosphatase, U/L			<0.001 ^b
Normal	343 (92.50%)	515 (98.30%)	
Elevated	28 (7.50%)	9 (1.70%)	
Serum creatinine, μmol/L			0.159 ^b
Normal	352 (94.90%)	507 (96.80%)	
Elevated	19 (5.10%)	17 (3.20%)	
Uric acid, μmol/L			0.339 ^b
Normal	298 (80.30%)	407 (77.70%)	
Elevated	73 (19.70%)	117 (22.30%)	

Abbreviation: pTNM: pathologic tumor-node-metastasis; AGR: Albumin to Globulin ratio.

^a Mann-Whitney U-test.

^b Chi-square test.

Association of preoperative AGR with OS

Kaplan-Meier survival analysis showed that patients in low AGR group had significantly poorer OS than patients in high AGR group (mean OS: low AGR vs high AGR, 114.01 vs 151.51 months, log-rank

$P < 0.001$; Figure 2). The univariate analysis revealed that preoperative high AGR was associated with decreased risk of death (HR: 0.29, 95% CI: 0.21-0.40, $P < 0.001$, Table 3). Therefore, a multivariate analysis using Cox proportional hazards model for OS was performed to determine various prognostic indicators including age, HGB, BMI, pathology, Fuhrman grade, pT-stage, pN-stage, pM-stage, ALP and AGR. The results showed that preoperative AGR was an independent prognostic indicator of OS (HR: 0.63, 95%CI: 0.43-0.93, $P = 0.022$, Table 3). In addition, serum ALB, pT-stage, pN-stage and pM-stage were also identified as independent prognostic indicators for OS.

Association of preoperative AGR with subgroups

The prognostic influence of preoperative AGR in subgroups of pT-stage, pN-stage and pM-stage were further investigated. Patients with low AGR level had a significantly shorter OS than patients with high AGR level in pT1-2 subgroup (mean OS: low AGR vs high AGR, 127.67 vs 162.92 months, log-rank $P < 0.001$; Figure 3A), pT3-4 subgroup (mean OS: low AGR vs high AGR, 67.29 vs 101.12 months, log-rank $P = 0.010$; Figure 3B), pN0 subgroup (mean OS: low AGR vs high AGR, 125.45 vs 153.87 months, log-rank $P < 0.001$; Figure 3C), pN1 subgroup (mean OS: low AGR vs high AGR, 38.80 vs 74.23 months, log-rank $P = 0.007$; Figure 3D), pM0 subgroup (mean OS: low AGR vs high AGR, 123.11 vs 152.67 months, log-rank $P < 0.001$; Figure 3E) and pM1 subgroup (mean OS: low AGR vs high AGR, 29.25 vs 52.02 months, log-rank $P = 0.033$; Figure 3F).

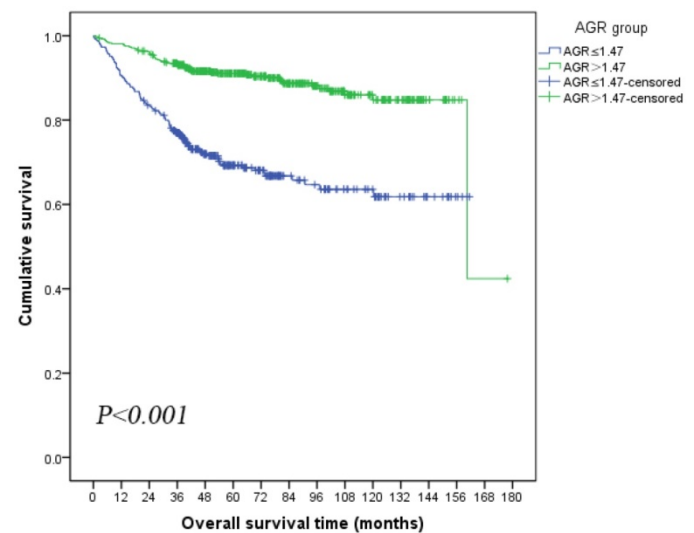


Figure 2. Kaplan-Meier curves depicting overall survival (OS) according to the preoperative optimal value of albumin to globulin ratio (AGR) in patients with renal cell carcinoma.

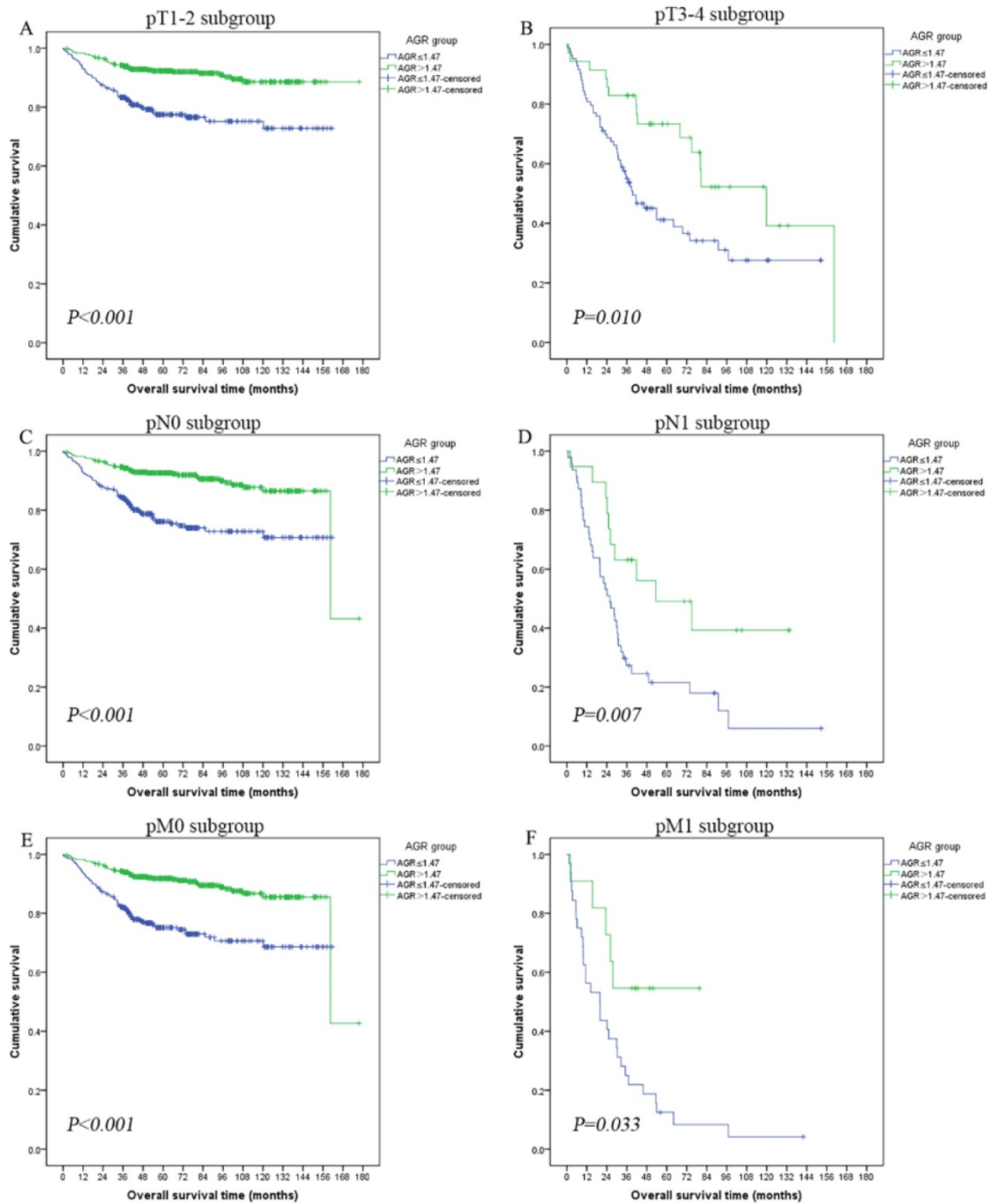


Figure 3. Kaplan-Meier curves showing overall survival (OS) according to the preoperative optimal value of albumin to globulin ratio (AGR) in all patients with renal cell carcinoma. Patients were stratified according to the pT-status, pN-status, and pM-status. (A) Kaplan-Meier analysis of OS in pT1-2 subgroup. (B) Kaplan-Meier analysis of OS in pT3-4 subgroup. (C) Kaplan-Meier analysis of OS in pN0 subgroup. (D) Kaplan-Meier analysis of OS in pN1 subgroup. (E) Kaplan-Meier analysis of OS in pM0 subgroup. (F) Kaplan-Meier analysis of OS in pM1 subgroup.

Table 3. Correlation of basic characteristics in all patients to the overall survival (OS) by Cox regression analyses.

Predictors	univariate analyses			multivariate analyses		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.02	1.01 to 1.03	0.003 ^a	1.00	0.99 to 1.02	0.138 ^b
Hemoglobin	0.98	0.98 to 0.99	<0.001 ^a	0.99	0.98 to 1.00	0.063 ^b
Total protein	1.00	0.98 to 1.02	0.854 ^a			
Serum albumin	0.92	0.90 to 0.94	<0.001 ^a	0.95	0.92 to 0.99	0.015 ^b
Body mass index	0.89	0.85 to 0.93	<0.001 ^a	0.95	0.90 to 1.00	0.054 ^b
Gender						
Male	1.00 (ref.)					

Predictors	univariate analyses			multivariate analyses		
	HR	95% CI	P value	HR	95% CI	P value
Female	0.90	0.65 to 1.25	0.529 ^a			
Pathological types						
Clear cell carcinoma	1.00 (ref.)			1.00 (ref.)		
Multilocular cystic renal cell carcinoma	2.48	1.58 to 3.87	<0.001 ^a	1.58	0.93 to 2.69	0.089 ^b
Chromophobe renal carcinoma	0.19	0.03 to 1.40	0.103 ^a	0.22	0.03 to 1.67	0.146 ^b
Others	1.63	1.08 to 2.46	0.020 ^a	0.97	0.61 to 1.54	0.918 ^b
Fuhrman-grade						
I	1.00 (ref.)			1.00 (ref.)		
II	1.16	0.73 to 1.86	0.525 ^a	1.16	0.72 to 1.88	0.529 ^b
III	2.76	1.61 to 4.73	<0.001 ^a	1.66	0.94 to 2.93	0.079 ^b
IV	4.75	1.96 to 11.48	<0.001 ^a	2.23	0.87 to 5.70	0.092 ^b
Unknown	1.94	1.25 to 3.00	0.003 ^a	1.60	1.00 to 2.56	0.047 ^b
pT status						
T1	1.00 (ref.)			1.00 (ref.)		
T2	2.33	1.57 to 3.46	<0.001 ^a	1.52	0.99 to 2.33	0.053 ^b
T3	5.39	3.66 to 7.93	<0.001 ^a	2.34	1.51 to 3.62	<0.001 ^b
T4	11.60	7.20 to 18.67	<0.001 ^a	1.75	0.91 to 3.36	0.091 ^b
pN status						
N0	1.00 (ref.)			1.00 (ref.)		
N1	8.21	5.87 to 11.50	<0.001 ^a	3.05	1.97 to 4.74	<0.001 ^b
pM status						
M0	1.00 (ref.)			1.00 (ref.)		
M1	9.84	6.74 to 14.36	<0.001 ^a	3.49	2.19 to 5.57	<0.001 ^b
pTNM stage						
I	1.00 (ref.)					
II	1.91	1.19 to 3.07	0.007 ^a			
III	6.25	4.21 to 9.26	<0.001 ^a			
IV	15.62	10.46 to 23.31	<0.001 ^a			
Alkaline phosphatase						
Normal	1.00 (ref.)			1.00 (ref.)		
Elevated	2.33	1.36 to 3.97	0.001 ^a	0.54	0.29 to 1.00	0.050 ^b
Serum creatinine						
Normal	1.00 (ref.)					
Elevated	1.66	0.92 to 2.99	0.092 ^a			
Uric acid						
Normal	1.00 (ref.)					
Elevated	1.15	0.80 to 1.65	0.455 ^a			
AGR group						
Low AGR group	1.00 (ref.)			1.00 (ref.)		
High AGR group	0.29	0.21 to 0.40	<0.001 ^a	0.63	0.43 to 0.93	0.022 ^b

Abbreviation: HR, hazard ratio; CI, confidence interval; pTNM: pathologic tumor-node-metastasis; AGR: Albumin to Globulin ratio.

^a univariate cox regression analyses;

^b multivariate cox regression analyses.

Discussion

In our study, we demonstrated that preoperative AGR could be used as a prognostic factor of OS for RCC patients. Although several studies have shown a relationship between AGR and prognosis of patients with various types of cancers^{15-18, 21}, to our best knowledge, this is the first study to assess the value of preoperative AGR as a prognostic maker for predicting OS of patients with RCC.

Serum ALB and GLB are two main constituents of serum total protein and can be easily and cost-effectively measured, thus providing a simple means of estimating visceral protein function. Serum ALB is a hepatic protein with a half-life of 14-20 days. It functions as a carrier molecule for various minerals, hormones and fatty acids and also helps to maintain oncotic pressure in capillaries²². In addition, Serum

ALB is characterized as a negative acute-phase protein, and its pool is affected by a number of inflammatory conditions²³. Besides, a previous research revealed that serum ALB inhibited the proliferation of human breast cancer cell lines by modulating the activities of autocrine growth regulatory factors in vitro²⁴. Moreover, albumin synthesis might be suppressed by malnutrition and systematic inflammation, resulting in hypoalbuminemia, which could weaken human immune defense mechanisms. Recent studies have revealed that hypoalbuminemia was more attributed to systemic inflammation than malnutrition in the dialysis patients²⁵. As part of cancer-related systemic inflammation, activation of proinflammatory cytokines such as IL-6 and tumor necrotic factor- α could lead to low serum ALB concentration²⁶. In addition, elevated accumulation of acute phase

proteins, immunoglobulins as well as other serum proteins may increase serum GLB level. These changes were reflective of an inflammatory state. Some researchers have demonstrated that serum GLB is associated with the prognosis of cancer patients²⁷⁻²⁸.

Taken together, we hypothesized the AGR is a more accurate prognostic indicator than serum ALB or GLB alone. A large retrospective cohort study demonstrated that low AGR level was associated with an increased risk for cancer incidence and mortality in both short- and long-term follow-up in generally healthy population²⁹. Although cancer types are implicated, low AGR level is widely accepted to be linked to tumor progression³⁰. Based on observations that cancer often rises at the site of chronic inflammation and inflammatory cells are present in tumor sites³¹, this phenomenon may be caused by chronic inflammation. We believe that nutritional status and systemic inflammatory response play major roles in the progression of RCC and preoperative AGR could be a prognostic indicator for RCC patients.

In this large retrospective cohort study, a cut-off preoperative AGR value of 1.47 was used for predicting the OS of RCC patients. The results showed that preoperative AGR ≤ 1.47 was associated with older age population, low HGB, low BMI, low ALB and advanced RCC stage. The reason is that low preoperative AGR was associated with malnutrition and inflammatory response, which was consistent with that weight loss and ongoing inflammation-like response contribute to the subsequent death of RCC patients, especially in advanced stages. According to the Kaplan-Meier curves and log-rank test, patients with low preoperative AGR level had significantly shorter OS than patients with high AGR level. Furthermore, the univariate and multivariate Cox regression models revealed that AGR was a significant independent predictor for OS of RCC patients subjected to surgery. Besides, subgroup analysis of patients at pT1-2, pT3-4, pN0, pN1, pM0 and pM1 stages showed that patients with low preoperative AGR had significantly shorter OS than patients with high preoperative AGR. For these reasons, we believe that preoperative AGR is an independent prognostic factor for RCC patients.

The study has several limitations. Firstly, some specific inflammatory markers such as C-reactive protein and cytokine levels, which were also important factors of inflammation, were not measured because they were not routinely measured at our hospital prior to 2006. Secondly, preoperative AGR was only assessed at a single time point before surgery and in a single center. Further large-scale population-based prospective studies are needed to

fully consolidate the results.

Despite the aforementioned limitations, our study had some clinical implications. First of all, we are the first to show that low preoperative AGR may be a clinical indicator associated with shorter OS of RCC patients. Secondly, AGR is routinely measured at low cost in clinical practice, thus it has potential as a simple, convenient predictive and stratification factor to assist with clinical decision-making for RCC patients. Thirdly, at least in theory, AGR is a predictive factor superior to other nutritional or inflammatory indicators. Nutritional assessment and support as well as anti-inflammatory therapy may be suitable treatment choices for patients with AGR ≤ 1.47 . Although Algra et al. have demonstrated the ability of anti-inflammatory therapy (e.g., aspirin and other non-steroidal anti-inflammatory drugs) to prevent and/or treat some cancers³², the value of anti-inflammatory therapy for RCC patients needs to be further studied. At least, AGR can provide a useful tool for future clinical trials and patient management.

In conclusion, preoperative AGR is a proven objective, reproducible and inexpensive predictor of survival of RCC patients subjected to surgical resection and consideration should be given for its routine clinical use.

Implications for Practice

The serum albumin to globulin ratio (AGR) not only reflects patients' nutritional status but also represents their systemic inflammation. This prospective cohort study of 895 patients with renal cell carcinoma (RCC) showed that preoperative AGR was an independent prognostic indicator of overall survival (OS) of RCC patients.

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Author Contributions

Conception and Design: YK, HXB, GSJ.

Provision of Study Material or Patients: YK, HXB, GSJ, CD, HH.

Collection and Assembly of Data: YK, HXB, GSJ, CD, CX, ZYJ, HQM, XYF,

Data Analysis and Interpretation: YK, HXB,

GSJ, YGW, QZK, LZW, ZM, LRW, ZFJ.

Manuscript Writing: YK, HXB, GSJ, CD, LRW, ZFJ, HH.

Final Approval of Manuscript: All the authors.

Conflicts of interest

All the authors state they have no conflicts of interest.

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