



Prognostic effect of preoperative serum albumin to globulin ratio in patients treated with cytoreductive nephrectomy for metastatic renal cell carcinoma

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Background: Accurate identification of ideal candidates for cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma (mRCC) is an unmet need. We 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.

Methods: mRCC patients treated with CN were included. The overall population was therefore divided into two AGR groups using cut-off of 1.43 (low, <1.43 vs. high, ≥1.43). Univariable and multivariable Cox regression analyses tested the association between AGR and OS as well as CSS. The discrimination of the model was evaluated with the Harrel's concordance index (C-index). The clinical value of the AGR was evaluated with decision curve analysis (DCA).

Results: Among 613 mRCC patients, 159 (26%) patients had an AGR <1.43. Median follow-up was 31 (IQR: 16–58) months. On univariable analysis, low preoperative serum AGR was significantly associated with both OS (HR: 1.55, 95% CI: 1.26–1.89, P<0.001) and CSS (HR: 1.55, 95% CI: 1.27–1.90, P<0.001). On multivariable analysis, AGR <1.43 was associated with worse OS (HR: 1.51, 95% CI: 1.23–1.85,

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$P < 0.001$) and CSS (HR: 1.52, 95% CI: 1.24–1.86, $P < 0.001$). The addition of AGR only minimally improved the discrimination of a base model that included established clinicopathologic features (C-index=0.640 *vs.* C-index=0.629). On DCA, the inclusion of AGR marginally improved the net benefit of the prognostic model. Low AGR remained independently associated with OS and CSS in the IMDC intermediate risk group (HR: 1.52, 95% CI: 1.16–1.99, $P = 0.002$).

Conclusions: In our study, low AGR before CN was associated with worse OS and CSS, particularly in intermediate risk patients.

Keywords: Metastatic renal cell carcinoma (mRCC); cytoreductive nephrectomy (CN); overall survival (OS); cancer-specific survival (CSS); albumin to globulin ratio (AGR)

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Introduction

Approximately 25% of patients with newly diagnosed renal cell carcinoma (RCC) present with metastatic disease (mRCC) in industrialized countries (1). Therapeutic strategies for mRCC are based on the International metastatic renal cell carcinoma Database Consortium (IMDC) risk stratification (2). For IMDC favorable and intermediate risk patients cytoreductive nephrectomy (CN) remains a valuable treatment option (3). Ideally, preoperative biomarkers could help identify the right therapy for the right patient. However, preoperative biomarkers able to predict either treatment response or other oncological outcomes in mRCC patients are still lacking. Inflammation and the immune response play a major role in tumor development, proliferation and metastatic spreading (4). Several markers of systemic inflammatory response have been already investigated in RCC (5-9). However, none of them have been yet implemented in the clinical decision making (3).

Albumin and globulins are two major serum proteins that play a pivotal role in the inflammatory process (10). Instead of the absolute concentration of albumin and globulin, albumin to globulin ratio (AGR) is a ratio that combines the two indexes. Previously, AGR was mainly used for the diagnosis of liver function and immunological diseases (11). Recently, AGR, which reflects the systemic inflammatory response and the systemic nutritional status, has shown prognostic ability in predicting oncological outcomes in various malignancies (12-15).

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.

This study tested the association between preoperative serum AGR and oncological outcomes in mRCC patients treated with CN, after accounting for IMDC risk stratification. We present the following article in accordance with the STROBE reporting checklist (available at: <http://dx.doi.org/10.21037/tau-20-1101>).

Methods

Study design

We retrospectively reviewed our established international multicenter database to identify mRCC patients treated with CN at tertiary centers in the United States and Europe. We excluded patients with other malignant primaries tumors mRCC. However, concomitant hematologic, liver diseases, chronic inflammatory disease including autoimmune disorder and infection within the last 12 months were not excluded.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the University of Texas Southwestern (Dallas, Texas, USA) Institutional Review Board (UT SW IRB File 0698 26900). Because of the retrospective nature of the research, the requirement for informed consent was waived.

Management and follow-up

Dedicated uro-pathologists assigned pathologic stage according to the 2010 American Joint Committee on Cancer (AJCC) tumor, node and metastasis (TNM) staging system. All pathology reports from prior to 2010 were reviewed according to 2010 criteria. According to the IMDC patients were stratified into favorable *vs.* intermediate *vs.* poor risk groups (2).

All laboratory tests were done within one month prior to CN. Serum AGR value has been calculated as baseline serum albumin to baseline total protein-baseline serum albumin ratio. To define the optimal pretreatment AGR cut-off value, we carried out a time-dependent receiver operating characteristic curve analysis for 3-year OS as the end-point, considering the median OS time (12 months). The median value of AGR was calculated as 1.59 (IQR: 1.39–1.78). The cut-off of 1.43 was determined as having the maximum Youden index value. The overall population was therefore divided into two AGR groups using this cut-off (lower <1.43 *vs.* higher \geq 1.43). OS time was calculated from the date of CN to death or last follow-up. CSS time was calculated from the date of CN to death from disease or last follow-up.

Statistical analysis

Associations between AGR status and categorical variables were assessed using χ^2 or Fisher's exact tests. Differences in continuous variables were analyzed with the Mann-Whitney U test. Univariable and multivariable Cox regression analyses tested the association of AGR with OS and CSS. The risk of survival was expressed as hazard ratios (HR) and 95% CIs. Kaplan-Meier survival curves were used to graphically depict the association between AGR and survival. The log-rank test was used to determine the statistical difference between the AGR <1.43 and AGR \geq 1.43 groups with respect to death. The discrimination of the model was evaluated using the Harrel's concordance index (C-index). The clinical value of the AGR was evaluated with decision curve analysis (DCA) (19,20). Statistical significance was set at $P < 0.05$. All tests were 2-sided. Analyses were performed using R version 3.6.2. (2009–2020 RStudio, Inc.).

Results

Overall, 613 patients were included in the analyses. Among

them, 159 (26%) patients had low AGR status (AGR <1.43). Patient characteristics are shown in *Table 1*. The number of patients with liver metastasis was significantly higher in patients with low preoperative AGR in contrast to those with high AGR (10.7% *vs.* 5.3%, $P = 0.03$).

At median follow-up of 31 (IQR 16–58) months, a total of 472 (77%) patients died and 99% of deaths were due to mRCC. Kaplan-Meier analyses showed a significant reduction in OS (log-rank test $P < 0.001$) and CSS (log-rank test $P < 0.001$) in patients with a preoperative low AGR (*Figure 1*). Median OS was 12 months (95% CI: 10–15 months) and 22 months (95% CI: 19–25 months) in patients with low and high AGR, respectively.

On univariable analysis, low preoperative serum AGR was associated with lower OS (HR: 1.55, 95% CI: 1.26–1.89, $P < 0.001$) and lower CSS (HR: 1.55, 95% CI: 1.27–1.90, $P < 0.001$) (*Table 2*). These results were confirmed in multivariable analyses, which adjusted for the effect of established clinicopathologic features. Low AGR levels remained significantly associated with worse OS (HR: 1.51, 95% CI: 1.23–1.85, $P < 0.001$) and worse CSS (HR: 1.52, 95% CI: 1.24–1.86, $P < 0.001$). The addition of AGR improved the discrimination of a base model that included established clinicopathologic features (C-index = 0.640 *vs.* C-index = 0.629). In DCA, the model including IMDC risk groups, type of systemic therapy, BMI and sarcomatoid features led to superior outcomes for any decision associated with a threshold probability above 25%. The inclusion of the AGR marginally improved the net benefit of the base model by a clinically non-significant margin (*Figure 2*).

In subgroup analyses of intermediate IMDC risk patients, preoperative serum AGR <1.43 was associated with significantly lower OS and CSS rates (HR: 1.52, 95% CI: 1.17–1.98, $P = 0.002$). Similarly, in poor risk patients, low preoperative serum AGR was associated with worse OS and CSS rates (HR: 1.70, 95% CI: 1.00–2.89, $P = 0.04$) (*Figure 3*). After adjusting for possible confounders on multivariable analyses, low AGR remained independently associated with worse OS and CSS in the intermediate risk group (both: HR: 1.52, 95% CI: 1.16–1.99, $P = 0.002$) (*Table 3*) but not in the high risk group (all $P > 0.05$). No statistically significant association was recorded in favorable risk patients (all $P > 0.05$).

In the subgroup of 111 patients with sarcomatoid features, low preoperative AGR was associated with both OS and CSS (both: HR: 1.79, 95% CI: 1.16–2.76, $P = 0.01$) in univariable analysis (*Figure 4*). After adjusting for possible

Table 1 Clinicopathologic features of 613 patients treated with cytoreductive nephrectomy for metastatic renal cell carcinoma, stratified according to preoperative serum albumin to globulin ratio (AGR)

Parameters	All (n=613)	AGR <1.43 (n=159)	AGR ≥1.43 (n=454)	P value
Age, median (IQR)	57 (50–64)	58 (51–65)	57 (49–64)	0.37
BMI groups, n (%)				0.79
BMI ≥25	435 (71.0)	111 (69.8)	324 (71.4)	
BMI <25	178 (29.0)	48 (30.2)	130 (28.6)	
BMI, median (IQR)	27.5 (24.5–30.0)	28.0 (24.2–30.3)	27.5 (24.6–30.0)	0.93
Sex, n (%)				0.13
Male	428 (69.8)	103 (64.8)	325 (71.6)	
Female	185 (30.2)	56 (35.2)	129 (28.4)	
ECOG before nephrectomy, n (%)				0.93
0	410 (66.9)	105 (66.1)	305 (67.2)	
1	186 (30.3)	49 (30.8)	137 (30.2)	
2	17 (2.8)	5 (3.1)	12 (2.6)	
Prognostic groups according to IMDC criteria, n (%)				0.16
Favorable	186 (30.3)	40 (25.2)	146 (32.2)	
Intermediate	343 (56.0)	92 (57.8)	251 (55.3)	
Poor	84 (13.7)	27 (17.0)	57 (12.5)	
Karnofsky Performance status				0.96
≥80%	596 (97.2)	154 (96.9)	442 (97.4)	
<80%	17 (2.8)	5 (3.1)	12 (2.6)	
Hemoglobin g/dL, median (IQR)	11.9 (10.5–13.5)	11.7 (10.1–13.2)	12.0 (10.7–13.6)	0.08
Abnormal hemoglobin, n (%)				0.14
≥ LLN	299 (48.8)	69 (43.4)	230 (50.7)	
< LLN	314 (51.2)	90 (56.6)	224 (49.3)	
Calcium, mg/dL, median (IQR)	9.3 (8.9–9.7)	9.3 (8.9–9.7)	9.3 (8.9–9.7)	0.87
Abnormal calcium, n (%)				0.59
≤ ULN	556 (90.7)	142 (89.3)	414 (91.2)	
> ULN	57 (9.3)	17 (10.7)	40 (8.8)	
Neutrophils, 10 ⁹ /L, median (IQR)	5.5 (4.2–7.0)	5.6 (4.4–7.2)	5.4 (4.2–6.8)	0.35
Abnormal neutrophils, n (%)				0.32
≤ ULN	463 (75.5)	115 (72.3)	348 (76.7)	
> ULN	150 (24.5)	44 (27.7)	106 (23.3)	
Platelet, 10 ⁹ /L, median (IQR)	312 (240–410)	333 (237–445)	305 (240–399)	0.13
Abnormal platelet, n (%)				0.02
≤ ULN	448 (73.1)	104 (65.4)	344 (75.8)	
> ULN	165 (26.9)	55 (34.6)	110 (24.2)	

Table 1 (continued)

Table 1 (continued)

Parameters	All (n=613)	AGR <1.43 (n=159)	AGR ≥1.43 (n=454)	P value
Largest metastasis size, cm, median (IQR)	2.00 (2.00–3.00)	2.00 (2.00– 3.00)	2.00 (2.00–3.00)	1
Number of metastasis sites, n (%)				0.3
Single	370 (60.4)	90 (56.6)	280 (61.7)	
Multiple	243 (39.6)	69 (43.4)	174 (38.3)	
Site of metastases, n (%)				
Adrenal glands	91 (14.8)	27 (17.0)	64 (14.1)	0.45
Bones	181 (29.5)	43 (27.0)	138 (30.4)	0.49
Brain	20 (3.3)	5 (3.1)	15 (3.3)	1
Liver	41 (6.7)	17 (10.7)	24 (5.3)	0.03
Lung	415 (67.7)	112 (70.4)	303 (66.7)	0.45
Lymph nodes	138 (22.5)	42 (26.4)	96 (21.1)	0.21
Other	38 (6.2)	6 (3.8)	32 (7.0)	0.2
Time from diagnosis to nephrectomy				0.2
Less than 12 months	584 (95.3)	148 (93.1)	436 (96.0)	
More than 12 months	29 (4.7)	11 (6.9)	18 (4.0)	
Lymphadenectomy, n (%)				0.14
No	361 (58.9)	102 (64.2)	259 (57.0)	
Yes	252 (41.1)	57 (35.8)	195 (43.0)	
Histology, n (%)				0.47
Clear cell carcinoma	529 (86.3)	134 (84.3)	395 (87.0)	
Other	84 (13.7)	25 (15.7)	59 (13.0)	
Sarcomatoid features, n (%)				0.37
No	502 (81.9)	126 (79.2)	376 (82.8)	
Yes	111 (18.1)	33 (20.8)	78 (17.2)	
Grade, n (%)				0.31
G1/G2	65 (10.6)	13 (8.2)	52 (11.5)	
G3/G4	548 (89.4)	146 (91.8)	402 (88.5)	
Neoadjuvant therapy, n (%)				0.45
No	500 (81.6)	126 (79.2)	374 (82.4)	
Yes	113 (18.4)	33 (20.8)	80 (17.6)	
Adjuvant therapy, n (%)				0.29
No	132 (21.5)	29 (18.2)	103 (22.7)	
Yes	481 (78.5)	130 (81.8)	351 (77.3)	

IQR, interquartile range; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium Risk Model; LLN, lower limit of normal; ULN, upper limit of normal.

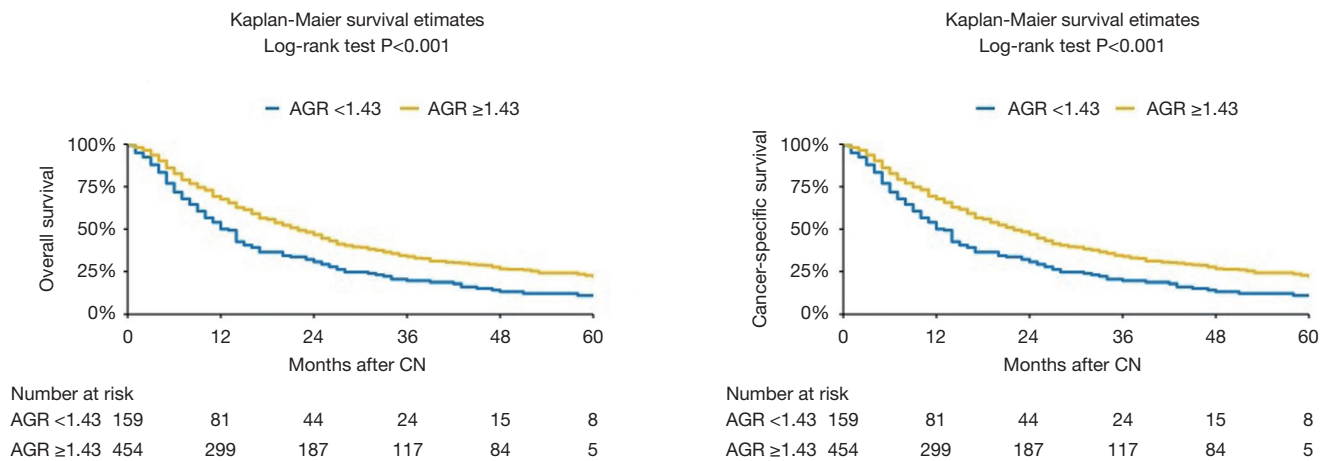


Figure 1 Kaplan-Meier analysis for overall and cancer-specific survival in 613 patients treated with cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma, stratified according to preoperative serum albumin to globulin ratio (AGR) at a cut-off of 1.43.

Table 2 Univariable and multivariable Cox regression analysis predicting OS and CSS in patients treated with cytoreductive nephrectomy for metastatic renal cell carcinoma

Variables	OS				CSS				
	Univariable		Multivariable		Univariable		Multivariable		
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	
Age	1	0.33	1.01	0.01	1	0.38	1.01	0.01	
Sex (female)	1.05	0.61	0.91	0.38	1.04	0.71	0.9	0.3	
BMI ≥25	0.91	0.37	0.88	0.22	0.91	0.34	0.88	0.19	
ECOG ≥1	1.05	0.65	1.07	0.49	1.04	0.68	1.07	0.51	
IMDC criteria									
Favorable	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Intermediate	1.19	0.09	1.05	0.63	1.2	0.08	1.06	0.57	
Poor	1.52	0.01	1.48	0.01	1.51	0.01	1.46	0.02	
AGR <1.43	1.55	<0.001	1.51	<0.001	1.55	<0.001	1.52	<0.001	
Multiple metastatic sites	1.43	<0.001	1.51	<0.001	1.44	<0.001	1.51	<0.001	
Clear cell carcinoma histology	0.55	<0.001	0.54	<0.001	0.55	<0.001	0.54	<0.001	
Sarcomatoid features	1.94	<0.001	1.87	<0.001	1.95	<0.001	1.89	<0.001	
C-index with AGR	0.64				0.642				
C-index without AGR	0.629				0.63				

OS, overall survival; CSS, cancer-specific survival; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium Risk Model; AGR, albumin globulin ratio.

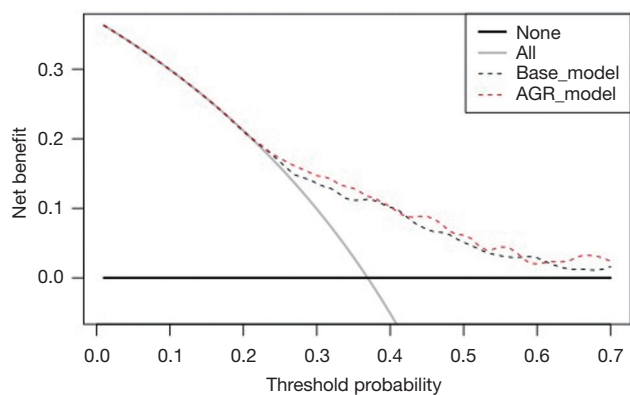


Figure 2 Decision curve analysis assessing the clinical impact of current prognostic models (Base model) with the integration of the albumin to globulin ratio (AGR model) estimating overall mortality at 1 year, in 613 patients treated with cytoreductive nephrectomy for metastatic renal cell carcinoma. The two models are compared with the strategies of treating all or none of the patients with cytoreductive nephrectomy.

confounders on multivariable analyses, AGR was not associated with neither OS nor CSS (all $P > 0.05$). In the subgroup of patients treated with tyrosine kinase inhibitor (TKI) therapy, AGR was neither associated with OS nor CSS (all $P > 0.05$).

Discussion

The exact mechanism underlying the association between low AGR and increased tumor aggressiveness is still unclear. It is hypothesized that this relationship results from a cascade of inflammatory mediators during the systematic inflammation that accompanies tumor progression (4). Both albumins and globulins are related to immunoinflammatory reactions and nutrition status in the human body (10). In presence of inflammation, inflammatory response cytokines, such as interleukin-1, interleukin-6 and TNF (tumor necrosis factor alpha), inhibit the synthesis of albumin (21). Furthermore, chronic inflammation results in vascular endothelial damages and increases vascular permeability (22). As a result, albumin permeates the interstitial space and its serum level decreases (23). This would suggest that low AGR (low albumin-high globulin), results from the inflammatory microenvironment induced by cancer cells, could predict poor oncologic prognosis.

In the present study, we investigated the association of preoperative serum AGR with oncologic outcomes in

patients with mRCC and found an association with both OS and CSS. Moreover, after adjusting for the effects of established clinicopathologic features, AGR retained its statistical significance. These findings are in agreement with a previous retrospective analysis of 592 patients treated with radical or partial nephrectomy for localized or locally advanced RCC, which reported that low AGR level with a cut-off of 1.22 was associated with worse OS (HR: 6.529, 95% CI: 3.036–14.042, $P < 0.001$) and worse CSS (HR: 8.806, 95% CI: 3.891–19.928, $P < 0.001$) (16). The inclusion of AGR in a prognostic model had a better prediction accuracy of 3- and 5-year OS than without the AGR (C-index = 0.884 *vs.* C-index = 0.806). In our study, the addition of AGR only marginally improved the discrimination of a base model (C-index = 0.640 *vs.* C-index = 0.629). Two other studies reported similar results. In 162 patients with localized and locally advanced RCC, OS and DFS were found to be significantly lower in patients with an AGR < 1.40 group ($P = 0.006$ and $P = 0.012$) (18). A study of 895 patients with RCC from all stages, with an AGR cut-off value of 1.47, found an independent association of low AGR with OS (HR: 0.63, 95% CI: 0.43–0.93, $P = 0.022$) (17). However, conventional multivariable analyses are not sufficient to demonstrate that a biomarker has a clinical benefit (19). Indeed, to explore this, in contrast to the above-mentioned studies, we used DCA (24). Our study showed that preoperative serum AGR marginally improved the net benefit of the base model by a clinically non-significant margin. Many explanations for the discrepancy of our results with that of others are possible. First, 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. Second, systemic treatment with TKI was used according to historic recommendations prior to current treatment strategies. 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).

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,

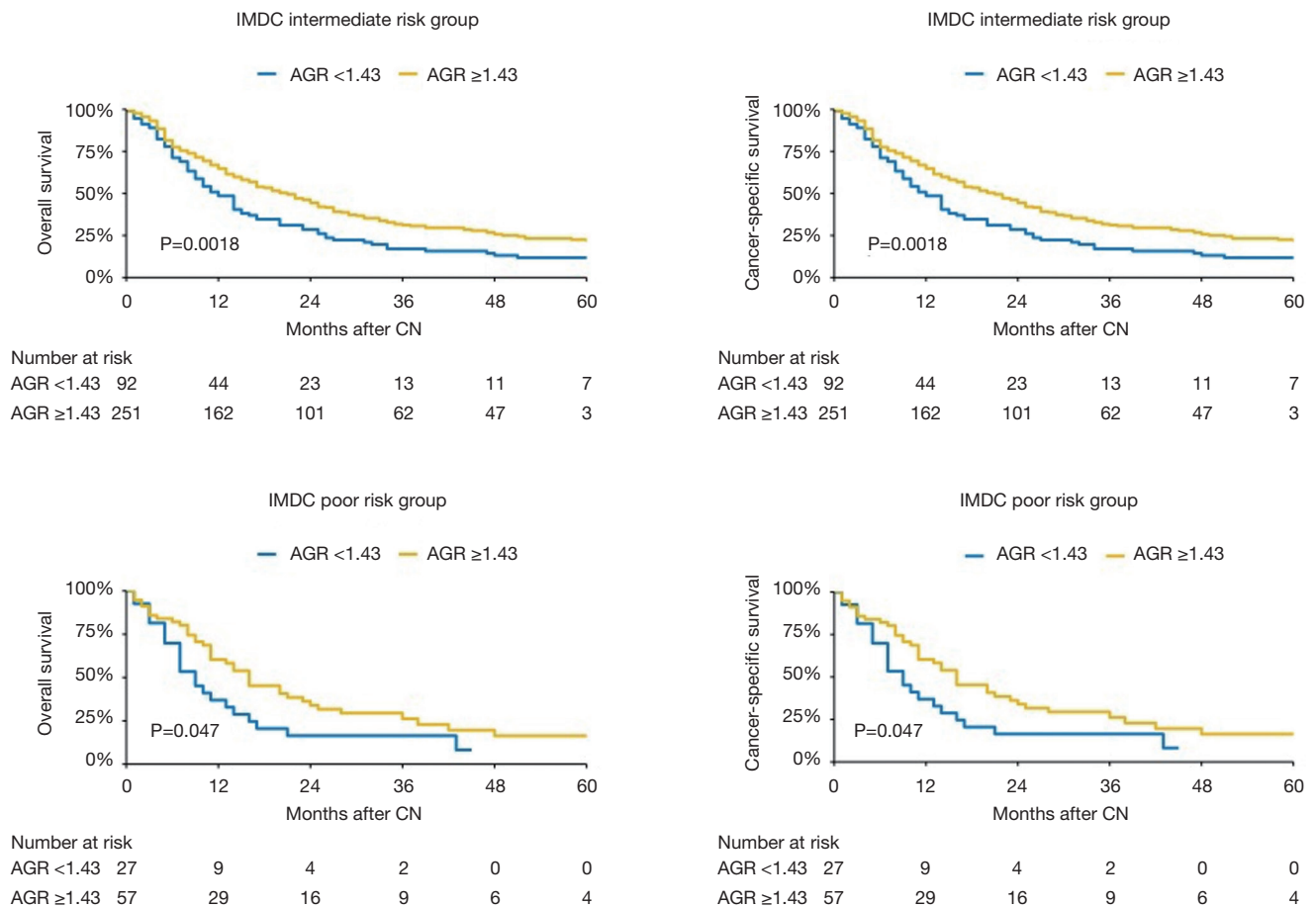


Figure 3 Overall and cancer-specific survival in patients treated with cytoreductive nephrectomy (CN) for intermediate risk metastatic renal cell carcinoma, according to the International Metastatic renal cell carcinoma Database Consortium (IMDC) prognostic model and stratified according to preoperative serum albumin to globulin ratio (AGR) at a cut-off of 1.43.

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). Increased pretreatment platelet to lymphocyte ratio was an independent prognostic marker in patients treated with TKI for mRCC (6). In our study, AGR was not shown to be associated with OS or CSS in mRCC patients treated with TKI therapy. Most of the aforementioned studies were limited by their retrospective designs (29). Moreover, among the weaknesses of these studies, biomarker models were not compared with the well-established IMDC model. Further intensive studies to identify optimal predictive and prognostic biomarkers in a panel of biomarkers for the

heterogenous malignancy that is mRCC are needed.

Our study is not devoid of limitations. 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. The systemic therapy was heterogenous regarding drugs and their mechanisms of actions. 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. 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

Table 3 Multivariable Cox regression analyses predicting OS and CSS in patients treated with cytoreductive nephrectomy for intermediate and poor risk metastatic renal cell carcinoma, according to the IMDC prognostic model

Variables	OS		CSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.01	0.07	1.01	0.07
Sex (female)	0.84	0.20	0.84	0.20
BMI ≥ 25	0.96	0.74	0.96	0.74
ECOG ≥ 1	1.00	0.97	1.00	0.97
AGR < 1.43	1.52	0.002	1.52	0.002
Multiple metastasis sites	1.50	0.001	1.50	0.001
Clear cell carcinoma histology	0.69	0.05	0.69	0.05
Sarcomatoid features	1.73	< 0.001	1.73	< 0.001

OS, overall survival; CSS, cancer-specific survival; IMDC, International Metastatic RCC Database Consortium Risk Model; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; AGR, albumin globulin ratio.

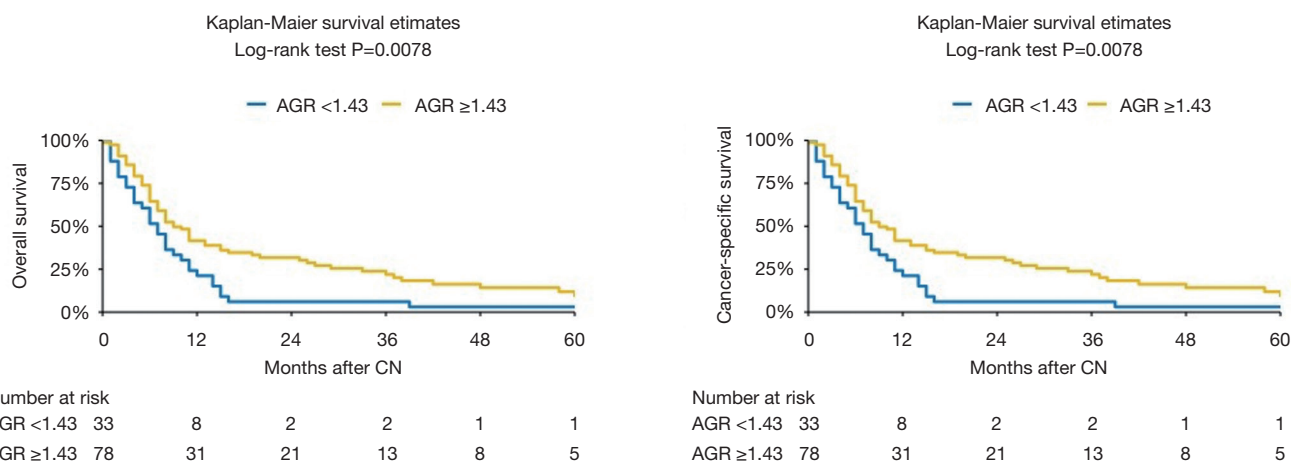


Figure 4 Overall and cancer-specific survival in patients treated with cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma with sarcomatoid features, stratified according to preoperative serum albumin to globulin ratio (AGR) at a cut-off of 1.43.

mRCC patients have not been tested and could be tested in the future studies.

Conclusions

Low AGR before CN was predicted to worse OS and CSS, particularly in patients with intermediate risk mRCC. It did, however, not add prognostically and clinically significant information beyond currently available clinicopathologic characteristics. This study should be the benchmark for future evaluation of AGR as a preoperative blood based

prognostic biomarker in the era of checkpoint inhibitor.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the University of Texas Southwestern (Dallas, Texas, USA) Institutional Review Board (UT SW IRB File 0698 26900). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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