JBUON 2016; 21(4): 925-934
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

The pretreatment albumin to globulin ratio, a validated biomarker, predicts prognosis in hepatocellular carcinoma

Jiahe Zhang, Xinhui Liu, Zike Yang, Yingying Chen, Rongcheng Luo
Cancer Center, Traditional Chinese Medicine-Integrated Hospital, Southern Medical University, Guangzhou, 510315, China

Summary

Purpose: *Although the albumin to globulin ratio (AGR) has been proven to be a prognostic factor in several cancers, no studies have assessed its prognostic significance in hepatocellular carcinoma (HCC). Therefore, this study aimed to investigate the prognostic value of the pretreatment AGR in the survival in HCC patients.*

Methods: *150 patients were enrolled, who were confirmed of HCC from October 2008 to December 2012 in Nanfang Hospital of Southern Medical University. Demographic, clinical and laboratory data were obtained. Univariate and multivariate Cox regression analysis were used to investigate the association of clinicopathological parameters with HCC patients' survival.*

Results: *Patients were divided into 2 groups: AGR<1.18 and AGR ≥1.18. Patients in the high AGR (≥1.18) group had longer overall survival (OS) than those in the low AGR (<1.18) group (60.16 vs 20.48 months, p<0.001). Univariate analysis showed that portal vein tumor thrombosis, grade of differentiation, extrahepatic metastasis, BCLC stage, AFP level and AGR at diagnosis were significantly associated with OS. Multivariate analysis revealed that AGR (p<0.001) and grade of differentiation (p=0.007) were independent prognostic factors for survival of HCC patients. In subgroup analysis based on age and Child-Pugh class, AGR remained a significant prognostic parameter.*

Conclusion: *Low pretreatment AGR was significantly associated with shorter OS in HCC patients. The pretreatment AGR could be a useful and effective prognostic index for identifying patients with poor prognosis, even when patients have well-preserved liver reserve function.*

Key words: *albumin to globulin ratio, hepatocellular carcinoma, inflammation, liver function, nutritional status, prognosis*

Introduction

HCC represents the second leading cause of cancer-related deaths around the world [1]. The incidence of HCC is increasing and more than 700,000 cases are diagnosed yearly, with a mortality rate nearly equal to the incidence rate in most countries [2]. Five-year survival higher than 50% can be achieved as long as cases are diagnosed at early stages and effective treatment is timely administered [3]. Therapeutic measures can be sorted into three types: curative, palliative and systematic. Curative treatment options, such as resection, transplantation and percutaneous ablation, could lead to higher survival rates in early-stage HCC patients [4-6]. Transarterial chemoembolisation (TACE) and administration of sorafenib are the two non-curative treatments with survival benefit for patients at intermediate stage [7,8]. Nevertheless, many HCC patients develop intrahepatic recurrence because of the rapid disease progression, impaired liver function, highly heterogeneic features and the short response to treatment [3,9]. HCC is reported as a malignancy with poor prognosis and insufficient prognostic indicators, so further investigation and evaluation of prognostic factors should be given more attention [10]. Previous studies have reported a few of

Correspondence to: Rongcheng Luo, MD. Traditional Chinese Medicine-Integrated Hospital, Southern Medical University, Guangzhou, 510315, China. Tel: +86 20 62787744, Fax: +86 20 61650054, E-mail: luorcsh@163.com
Received: 30/11/2015; Accepted: 17/12/2015

inflammation-based biomarkers, prognostic for HCC patients, such as the neutrophil-lymphocyte ratio (NLR) [11], the platelet-lymphocyte ratio (PLR) [12] and the prognostic nutritional index (PNI) [13]. However, all of them are not optimal prognostic markers for HCC patients when referring to clinical practice.

Recent studies have shown that nutritional status and cancer-related inflammation may affect the prognosis of patients with malignant tumors [14-16]. Serum albumin and globulins are two major constituents of the total serum protein. The former reflects the nutrition state of patients while the latter plays an important part in inflammation cascades and the immune system [17]. Albumin and globulins have been demonstrated to be associated with various chronic diseases [18,19]. AGR has been reported to be an independent and significant predictor of long-term mortality in several types of cancer including breast cancer [20], colorectal cancer [21], lung adenocarcinoma [22] and nasopharyngeal carcinoma [23]. It is calculated as follows: AGR=albumin/(total protein-albumin). Previous studies have indicated that a high recurrence rate is closely related to abnormally decreased albumin level in HCC patients and albumin itself suppresses the proliferation of hepatoma cell [24,25]. However, there are no studies that have investigated the predictive value of the AGR on survival in HCC patients.

Therefore, this retrospective study aimed to assess the prognostic significance of the pretreatment AGR in HCC. The hypothesis was that AGR, which reflects the degree of liver damage, nutritional state and systemic inflammation, was related to OS in HCC patients.

Methods

Patients

We retrospectively enrolled 150 patients who were diagnosed with HCC between October 2008 and December 2012 in Nanfang Hospital. The HCC diagnosis was confirmed by pathological examination. A multidetector-row computed tomography (MD-CT) scan or a dynamic contrast-enhanced magnetic imaging (DCE-MRI) were employed before the patients were treated. There were 45 patients excluded, due to macroglobulinemia, second primary malignancies, active infection or autoimmune disorders, lost to follow-up and incomplete laboratory data. The remaining 105 patients were included. A wide scope of cutoff points for AGR was obtained with the biostatistical tool Cutoff Finder (59 out of 63 tests, 93.7 %). The optimal cutoff level of AGR for OS in HCC was 1.18. Therefore, all patients were allocated into two groups: AGR<1.18 (N=25) and AGR≥1.18 (N=80). This study was approved by the ethics committee of Southern Medical University. Informed consent was obtained from all individual participants included in the study.

Clinical data collection

Clinicopathological characteristics such as demographics, pathological diagnosis, grade of differentiation, stage, laboratory variables and treatment regimens were obtained from the medical record system. Blood samples were collected before therapeutic intervention to measure serum albumin, total serum proteins, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin levels, prothrombin time, as well as alpha-fetoprotein (AFP) levels. The Child-Pugh score and the Barcelona Clinic Liver Cancer (BCLC) classification [26] were determined, based on liver function and tumor-related variables.

Follow-up

After treatment, serum AFP levels were monitored monthly. In addition, an ultrasound scan or a dynamic CT examination were performed every 3-4 months for the first 3 years. The patients were followed up until death or lost to follow-up until July 2015 (closing date).

Statistics

Continuous variables were expressed as medians and categorized according to medians. The number of patients and percentages were counted to express categorical variables. The associations between AGR and other basic characteristics were evaluated by x^2 test. OS was assessed from the date of diagnosis to the final follow-up or date of death. The OS rates were computed using the Kaplan-Meier method and differences in survival between groups were analyzed by the log-rank test. Variables that had been proven significant in the univariate analysis were included in a multivariate Cox proportional hazard model to assess hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The model comprised AGR, AFP, portal vein tumor thrombosis status, tumor differentiation, extrahepatic metastasis present and BCLC stage. All statistical analyses were performed using SPSS software program version 21.0 (IBM, Armonk, NY, USA). An efficient web application (http://molpath.charite.de/cutoff/) [25] designed by Budczies et al. was used to determine the optimum cutoff value of AGR. A two-sided $p<0.05$ was considered to be statistically significant.

Results

The patient characteristics are shown in Table 1. The patient median age was 49 years (range,

Table 1. Baseline parameters of all patients (N=106) with hepatocellular carcinoma and univariate survival analysis

Characteristics	*Cases*		*p value*
	N	*%*	*(log rank)*
Age (years)			0.063
Mean	50.2		
Median	49		
Range	24 to 72		
Gender			0.245
Female	10	9.5	
Male	95	90.5	
HBsAg			0.211
Positive	94	89.5	
Negative	11	10.5	
Ascites			0.839
Yes	18	17.1	
No	87	82.9	
Portal vein tumor thrombosis			0.013
Yes	15	14.3	
No	90	85.7	
Differentiation grade			<0.001
Well	22	21.0	
Moderate	62	59.0	
Poor	21	20.0	
Extrahepatic metastasis			<0.001
Yes	6	5.7	
No	99	94.3	0.600
Child-Pugh class			
A	88	83.8	
B	17	16.2	
BCLC stage			0.008
0	5	4.8	
A	39	37.1	
B	43	41.0	
C	18	17.1	0.912
ALT			
Normal (≤50 U/L)	66	62.9	
Elevated (>50 U/L)	39	37.1	
AST			0.340
Normal (≤50 U/L)	64	61.0	
Elevated (>50 U/L)	41	39.0	
Total serum bilirubin			0.515
Normal (5-21μmol/L)	77	73.3	
Elevated (>21μmol/L)	28	26.7	
Prothrombin time	0.081		
Normal (10-13s)	52	49.5	
Elevated (>13s)	53	50.5	
Treatment	0.335		
Surgical resection	90	85.7	
Liver transplantation	9	8.6	
Others	6	5.7	
AFP (ug/L)			<0.001
<400	68	64.8	
≥400	37	35.2	
AGR	<0.001		
<1.18	25	23.8	
≥1.18	80	76.2	

HbsAg: hepatitis B surface antigen, BCLC: Barcelona Clinic Liver Cancer classification, AFP: alpha-fetoprotein, ALT: alanine amino-transferase, AST: aspartate aminotransferase, AGR: albumin to globulin ratio

24-72 years). Among 105 patients, there were 95 (90.5%) men and 10 (9.5%) women. Of the patients 94 (89.5%) were hepatitis B surface antigen-positive and 6 (5.7%) developed extrahepatic metastasis confirmed as HCC. The liver function was normal in 88 patients (83.8%) with Child-Pugh A. Thirty-nine (37.1%) were at BCLC stage A, 43 (41%) at stage B and 18 (17.1%) at stage C. Surgical removal of tumors was performed in 90 (85.7%) patients, while liver transplantation was implemented in 9 (8.6%) patients.

A wide scope of cutoff points for AGR was found to be significant (59 out of 63 tests, 93.7 %; Figure 1). All patients were then allocated into two groups: AGR <1.18 (N=25) and AGR ≥1.18 (N=80).

The association between clinicopathological characteristics and AGR of patients with HCC is shown in Table 2. The results showed significant differences in age (p=0.034), Child-Pugh grade (p=0.004), ascites (p=0.012), extrahepatic metastasis (p=0.028) and prothrombin time (p<0.01). Patients were significantly older (in AGR<1.18 vs ≥1.18; 68.0% vs 43.8%, respectively; p=0.034).

The mean OS was 51.25 months. In log-rank test, patients with high AGR (≥1.18) had longer OS compared with patients with low AGR (<1.18) group (60.16 vs 20.48 months, p<0.001; Figure 2). Similarly, low AGR was associated with worse OS irrespective of age (62.05 vs 21.99 months in younger patients, p=0.003; Figure 3A and 53.13 vs 18.12 months in the older group, p<0.001; Figure 3B). Subgroup analysis according to Child-Pugh grade showed the same significant association between AGR and OS in the Child-Pugh A group (58.93 vs 17.69 months, p<0.001; Figure 3C) and the Child-Pugh B group (68.18 vs 24.33 months, p=0.015; Figure 3D). Univariate analysis revealed that portal vein tumor thrombosis (p=0.013), poor differentiation (p<0.001), extrahepatic metastasis (p<0.001), BCLC stage (p=0.008), AFP ≥400 ug/L (p<0.001) and low AGR at diagnosis (p<0.001) were significantly associated with unfavorable OS (Table 1). In multivariate analysis (Table 3), AGR was proven to be an independent prognostic factor in HCC with remarkable statistical significance. Patients with low AGR were associated with more than 5-fold mortality risk compared with those with high AGR group (HR, 5.17; 95% CI, 2.72-9.82; p<0.001). In addition, poor differentiation was significantly related to poor prognosis (HR, 4.76; 95% CI, 1.54-14.74; p=0.007).

Discussion

An increasing number of studies have revealed the relationship of inflammation, malnutrition and cancer [14-16]. As an immune response to disturbed tissue homeostasis, inflammation might be activated by tumor growth, invasion or tumor necrosis [26]. Oncocytes, tumor infiltrating lymphocytes and cancer-associated fibroblasts could promote the generation of inflammatory cytokines, which alter tumor microenvironment and promote further cancer growth, metastasis and resistance to cytotoxic agents [27]. Meanwhile, the chronic systemic inflammatory response with subsequent energy expenditure not only contributes to the progressive nutritional decline that cannot be reversed by simple nutritional supply, but also might result in poor survival of cancer patients [28,29]. Given this theoretical background, there are several systemic inflammation-based scores found to have independent prognostic value in patients with malignant tumors. Among them, the AGR has increasingly drawn the attention for its role in predicting long-term outcome in patients with malignant tumors.

The prognosis of HCC mainly depends on the range of tumor infiltration and liver function [30]. Interestingly, researchers also found that some inflammation-based biomarkers were related to survival of HCC patients, including NLR and PLR [11,12,31], although most of them had nothing to do with the above two. AGR appears to be a clinical index quite different from other markers. It not only reflects the nutritional and inflammatory state of patients but also evaluates the degree of hepatic function impairment.

In this retrospective study, we explored the prognostic value of AGR in patients with HCC. As far as we know, the current study is the first to highlight the prognostic significance of pretreatment AGR in HCC patients.

In this study, the univariate analysis revealed that low AGR was significantly associated with poor OS. After adjusting for AFP level, BCLC stage and other confounders, AGR proved to be an independent prognostic factor. This finding was consistent with previous studies that identified low AGR as a predictor of unfavorable OS in patients with breast cancer, colorectal cancer, lung adenocarcinoma and nasopharyngeal carcinoma [19-22]. Inspired by the studies which associated lower serum albumin and AGR with higher mortality in burn patients [32], Azab et al. revealed that pretreatment AGR was clinically useful in predicting long-term mortality in breast cancer patients [19].

Table 2. Clinicopathological characteristics of all patients stratified by AGR level at diagnosis

Characteristics	*AGR<1.18* *N (%)*	*AGR ≥1.18* *N (%)*	*p value* *(x^2)*
Age (years)			0.034
<49	8 (32.0)	45 (56.2)	
≥49	17 (68.0)	35 (43.8)	
Gender			0.699
Female	3 (12.0)	7 (8.8)	
Male	22 (88.0)	73 (91.2)	
HBsAg			1.000
Positive	23 (92.0)	71 (88.8)	
Negative	2 (8.0)	9 (11.2)	
Portal vein tumor thrombosis			0.343
Yes	5 (20.0)	10 (12.5)	
No	20 (80.0)	70 (87.5)	
Ascites			0.012
Yes	9 (36.0)	9 (11.2)	
No	16 (64.0)	71 (88.8)	
Differentiation grade			0.315
Well	3 (12.0)	19 (23.8)	
Moderate	15 (60.0)	47 (58.8)	
Poor	7 (28.0)	14 (17.4)	
Extrahepatic metastasis			0.028
Yes	4 (16.0)	2 (2.5)	
No	21 (84.0)	78 (97.5)	
Child-Pugh class			0.004
A	16 (64.0)	72 (90.0)	
B	9 (36.0)	8 (10.0)	
BCLC stage			0.097
0	2 (8.0)	3 (3.8)	
A	7 (28.0)	32 (40.0)	
B	8 (32.0)	35 (43.8)	
C	8 (32.0)	10 (12.4)	
AFP (ug/L)			0.293
<400	14 (56.0)	54 (67.5)	
≥400	11 (44.0)	26 (32.5)	
ALT			0.892
Normal (≤50 U/L)	16 (64.0)	50 (62.5)	
Elevated (>50 U/L)	9 (36.0)	30 (37.5)	
AST			0.561
Normal (≤50 U/L)	14 (56.0)	50 (62.5)	
Elevated (>50 U/L)	11 (44.0)	30 (37.5)	
Total serum bilirubin			0.227
Normal (5-21μmol/L)	16 (64.0)	61 (76.3)	
Elevated (>21μmol/L)	9 (36.0)	19 (23.7)	
Prothrombin time			<0.001
Normal (10-13s)	4 (16.0)	48 (60.0)	
Elevated (>13s)	21 (84.0)	32 (40.0)	

For abbreviations see footnote of Table 1

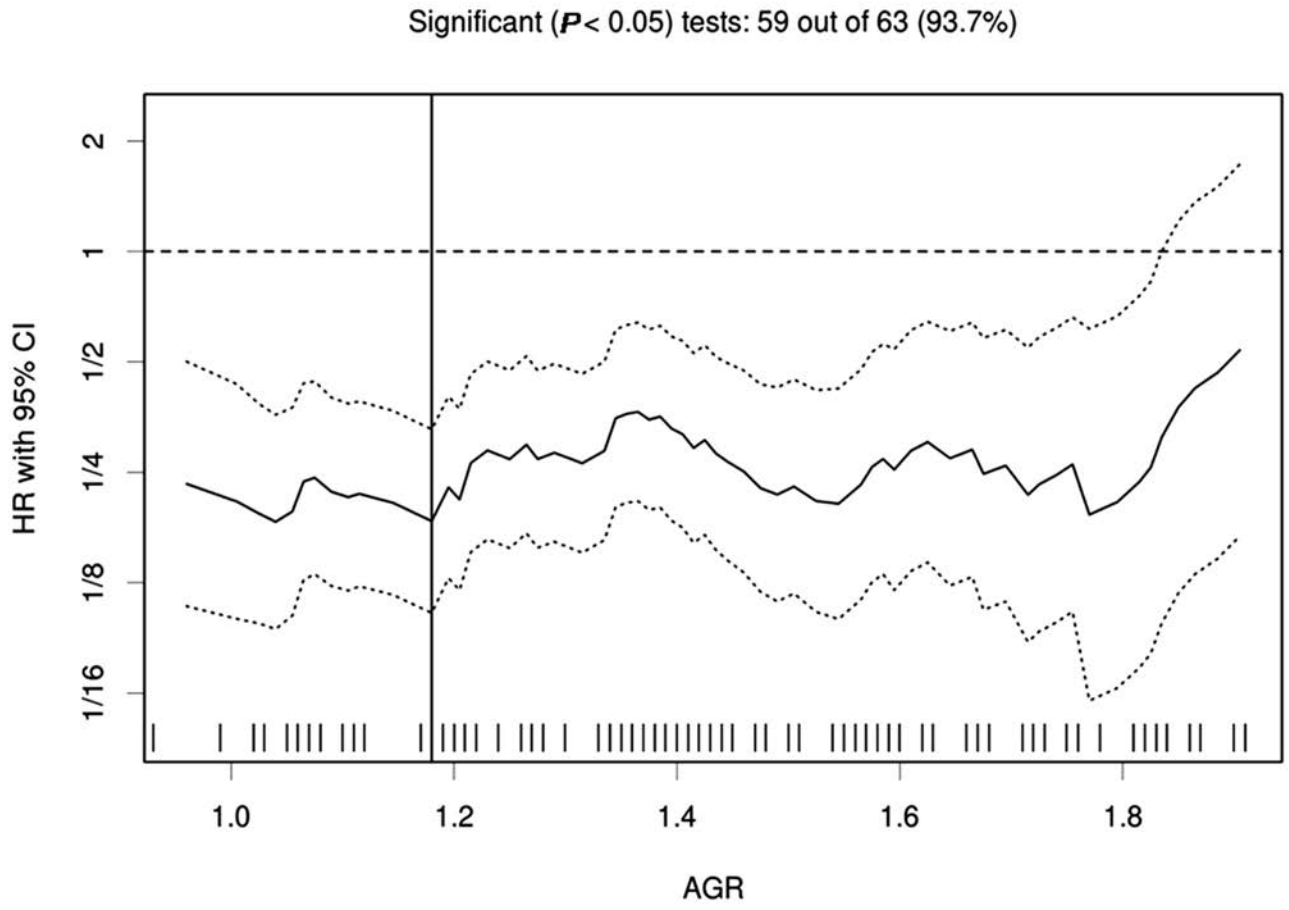

Figure 1. Hazard ratio for overall survival according to cutoff point for albumin globulin ratio (AGR) in hepatocellular carcinoma patients . The perpendicular line represents the most significant split and indicates the optimum cutoff point.

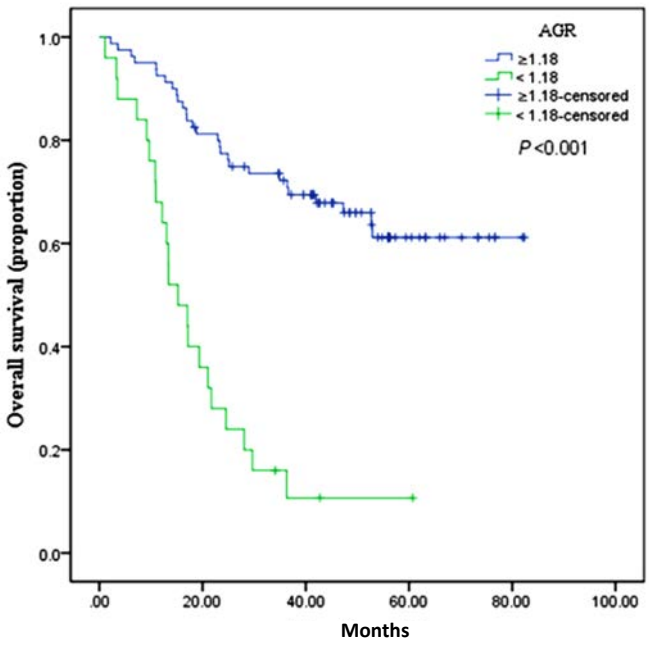

Figure 2. Kaplan Meier survival curves according to albumin globulin ratio (AGR) (log rank, p<0.001)

In addition, Suh et al. demonstrated that low AGR in generally healthy population may increase the risk for cancer development [33].

In this study AGR was computed as serum albumin/(total protein-albumin), since serum albumin and total serum protein are available in common blood tests. A low AGR indicates decreased serum albumin level and/or elevated nonalbumin proteins. Hypoalbuminemia is associated with poor nutritional status, chronic inflammation, severe liver injury and poor survival in cancer patients [18]. Serum albumin can suppress the growth of human HCC through decreasing phosphorylation of Rb and increasing the expression of p21 and p57 [24], while its synthesis can be decreased by malnutrition and inflammation. Apart from globulin, total serum protein includes other inflammatory proteins (eg, C-reactive protein, leukotrienes and ceruloplasmin). Elevated level of globulins, mainly as a result of increased accumulation of immunoglobulins and acute phase proteins, reflects an inflammatory status and a cumulative exposure of different proinflammatory cytokines [34]. In summary, AGR may reveal the

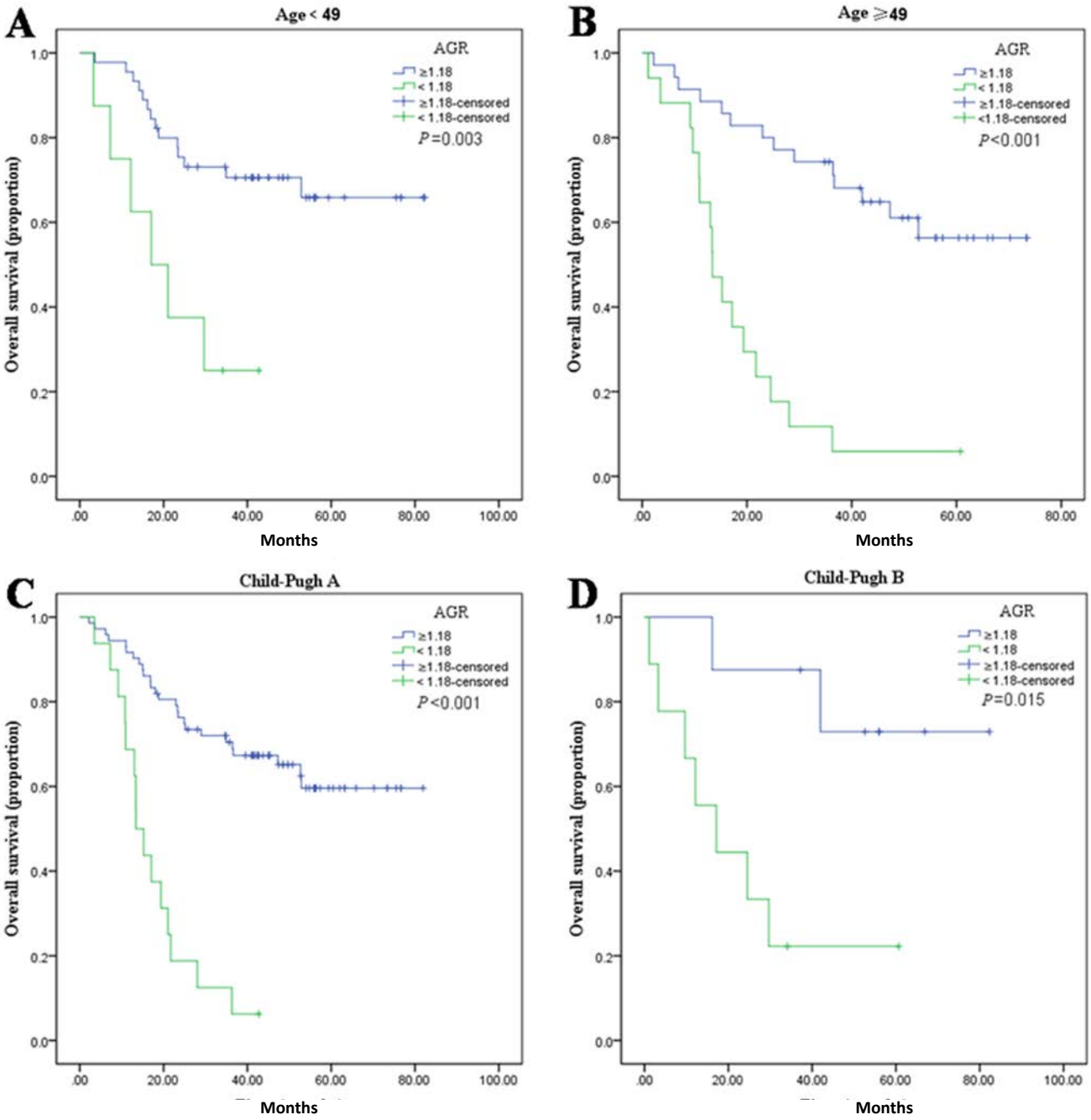

Figure 3. Kaplan-Meier survival curves **A**: Overall survival (OS) stratified by AGR in low age (<49 years) group (p=0.003). **B**: OS stratified by AGR in high age (≥49 years) group (p<0.001). **C**: OS stratified by AGR in Child-Pugh class A group (p<0.001). **D**: OS stratified by AGR in Child-Pugh class B group (p=0.015).

nutritional status, chronic inflammation and liver function of patients, which are associated with prognosis.

Patients in the high AGR group had about 40 months longer OS than those in the low AGR group, with statistically significant difference.

We also explored the association between clinicopathological characteristics and AGR so as to eliminate potential bias. The results showed that low AGR was related to older patients, presence of ascites, extrahepatic metastasis, abnormally extended prothrombin time as well as higher Child-Pugh grade. Elderly patients tend to have a low AGR mainly because they often have comorbidities. In the subgroup analysis according to age, irrespective of age group, patients with high AGR still had longer OS than those in low AGR group. Low AGR was similarly associated with worse OS in Child-Pugh A or B group, which illustrated that AGR remained a significant prognostic factor in HCC patients with well-preserved hepatic reserve function.

Table 3. Multivariate analysis of clinicopathological characteristics for predicting overall survival of patients with hepatocellular carcinoma

Characteristics	*95% CI*	*HR*	*p value (Cox test)*
Portal vein tumor thrombosis			
No		1.0 (ref.)	
Yes	0.35-11.04	1.96	0.444
Differentiation grade			
Well		1.0 (ref.)	
Moderate	1.02-7.64	2.79	0.046
Poor	1.54-14.74	4.76	0.007
Extrahepatic metastasis			
No		1.0 (ref.)	
Yes	0.41-6.65	1.66	0.475
BCLC stage			
0		1.0 (ref.)	
A	0.88-55.92	7.02	0.066
B	0.62-36.59	4.77	0.133
C	0.35-78.06	5.22	0.231
AFP (ug/L)			
<400		1.0 (ref.)	
≥400	0.92-3.48	1.79	0.087
AGR			
≥1.18		1.0 (ref.)	
<1.18	2.72-9.82	5.17	<0.001

For abbreviations see footnote of Table 1

Univariate analysis indicated that low AGR was a powerful prognostic indicator of poor OS among other hepatic biochemical parameters such as ALT, AST, bilirubin and prothrombin time. Although it revealed that high AFP concentration was associated with poor OS, AGR could achieve better stratification with an optimal cutoff since AFP usually doesn't have a defined cutoff. Above all, we propose that AGR is a significantly independent and useful prognosticator of survival in HCC patients.

As noted above, AGR combined individual nutritional state, systematic inflammatory response and liver function to serve as an importan prognostic factor for HCC patients. Additionally, AGR is comprised of two continuous variables, so it is more stable than any of them when facing polytropic physiological conditions. We consider AGR to be a preferable prognostic factor compared to other inflammatory or nutritional parameters. Easily obtained from inexpensive-cost routine blood test, the pretreatment AGR could assist in the stratification of patients into prognostically different groups and provide useful guidance on the management of HCC patients.

Nevertheless, there are several limitations in our study. Firstly, it was a retrospective study conducted with Chinese patients only and most of them were suffering from chronic hepatitis B virus infection. Secondly, subgroup analysis according to different tumor stages was not performed due to the small sample size. Thirdly, AGR was only assessed before treatment, and it is unclear whether the changes of AGR and other biochemical indicators in response to therapy are associated with survival of HCC patients. Therefore, our findings need be validated in a large-scale prospective study for generalization of AGR. The optimal cutoff for AGR also needs further validation.

Conclusion

This study demonstrated that the pretreatment AGR was a significantly independent prognostic factor in HCC patients. It could be conducive to indicating patients with poor prognosis, even when patients have good liver function. Further validation studies are necessary to verify the prognostic value of AGR.

Acknowledgements

This work was funded by National Natural Science Foundation of China (Grant No.81372449).

Conflict of interests

The authors declare no confict of interests.

References

1. Gomaa AI, Waked I. Recent advances in multidisciplinary management of hepatocellular carcinoma. World J Hepatol 2015;7:673-687.
2. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut 2014; 63: 844-855.
3. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245-1255.
4. de Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. J Hepatol 2012;56 (Suppl 1):S75-S87.
5. Mancuso A, Perricone G. Hepatocellular Carcinoma and Liver Transplantation: State of the Art. J Clin Transl Hepatol 2014;2:176-181.
6. Wells SA, Hinshaw JL, Lubner MG, Ziemlewicz TJ, Brace CL, Lee FJ. Liver Ablation: Best Practice. Radiol Clin North Am 2015;53:933-971.
7. Schlachterman A, Craft WJ, Hilgenfeldt E, Mitra A, Cabrera R. Current and future treatments for hepatocellular carcinoma. World J Gastroenterol 2015;21:8478-8491.
8. Gadaleta-Caldarola G, Divella R, Mazzocca A et al. Sorafenib: the gold standard therapy in advanced hepatocellular carcinoma and beyond. Future Oncol 2015;11:2263-2266.
9. Sacco R, Antonucci M, Bargellini I, Marceglia S, Mismas V, Cabibbo G. Transarterial chemoembolization and sorafenib in patients with intermediate-stage hepatocellular carcinoma: time to enter routine clinical practice? Future Oncol 2015:1-3.
10. Maida M, Orlando E, Camma C, Cabibbo G. Staging systems of hepatocellular carcinoma: a review of literature. World J Gastroenterol 2014;20:4141-4150.
11. Xiao GQ, Liu C, Liu DL, Yang JY, Yan LN. Neutrophil-lymphocyte ratio predicts the prognosis of patients with hepatocellular carcinoma after liver transplantation. World J Gastroenterol 2013;19:8398-8407.
12. Li X, Chen ZH, Xing YF et al. Platelet-to-lymphocyte ratio acts as a prognostic factor for patients with advanced hepatocellular carcinoma. Tumour Biol 2015;36:2263-2269.
13. Pinato DJ, North BV, Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). Br J Cancer 2012;106:1439-1445.
14. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 2009;12:223-226.
15. Balkwill F, Mantovani A. Cancer and inflammation: implications for pharmacology and therapeutics. Clin Pharmacol Ther 2010;87:401-406.
16. Alberici PC, Paiva OS, Gonzalez MC. Association between an inflammatory-nutritional index and nutritional status in cancer patients. Nutr Hosp 2013;28:188-193.
17. Loyke HF. Disease states in which blood pressure is lowered. South Med J 1989;82:864-867.
18. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J 2010;9:69.
19. Azab BN, Bhatt VR, Vonfrolio S et al. Value of the pretreatment albumin to globulin ratio in predicting long-term mortality in breast cancer patients. Am J Surgery 2013;206:764-770.
20. Azab B, Kedia S, Shah N et al. The value of the pretreatment albumin/globulin ratio in predicting the long-term survival in colorectal cancer. Int J Colorectal Dis 2013;28:1629-1636.
21. Duran AO, Inanc M, Karaca H et al. Albumin-globulin ratio for prediction of long-term mortality in lung adenocarcinoma patients. Asian Pac J Cancer Prev 2014;15:6449-6453.
22. Du XJ, Tang LL, Mao YP et al. The pretreatment albumin to globulin ratio has predictive value for long-term mortality in nasopharyngeal carcinoma. PLoS One 2014;9:e94473.
23. Nojiri S, Kusakabe A, Shinkai N et al. Factors influencing distant recurrence of hepatocellular carcinoma following combined radiofrequency ablation and transarterial chemoembolization therapy in patients with hepatitis C. Cancer Manage Res 2011;3:267-272.
24. Nojiri S, Joh T. Albumin suppresses human hepatocellular carcinoma proliferation and the cell cycle. Int J Mol Sci 2014;15:5163-5174.
25. Budczies J, Klauschen F, Sinn BV et al. Cutoff Finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization. PLoS One 2012;7:e51862.
26. Balkwill FR, Mantovani A. Cancer-related inflammation: common themes and therapeutic opportunities. Semin Cancer Biol 2012;22:33-40.
27. Lazennec G, Richmond A. Chemokines and chemokine receptors: new insights into cancer-related inflammation. Trends Mol Med 2010;16:133-144.
28. Esper DH, Harb WA. The cancer cachexia syndrome: a review of metabolic and clinical manifestations. Nutr Clin Pract 2005;20:369-376.
29. Laviano A, Koverech A, Mari A. Cachexia: clinical features when inflammation drives malnutrition. Proc Nutr Soc 2015:1-7.
30. Tateishi R, Yoshida H, Shiina S et al. Proposal of a new prognostic model for hepatocellular carcinoma:

an analysis of 403 patients. Gut 2005;54:419-425.

31. Nagaoka S, Yoshida T, Akiyoshi J et al. Serum C-reactive protein levels predict survival in hepatocellular carcinoma. Liver Int 2007;27:1091-1097.
32. Kumar P. Grading of severity of the condition in burn patients by serum protein and albumin/globulin studies. Ann Plast Surg 2010;65:74-79.
33. Suh B, Park S, Shin DW et al. Low albumin-to-globulin ratio associated with cancer incidence and mortality in generally healthy adults. Ann Oncol 2014;25:2260-2266.
34. Gabay C KI. Correction: Acute-Phase Proteins and Other Systemic Responses to Inflammation. N Engl J Med 1999;340:1376.