


# Clinical impact of pretreatment albumin–globulin ratio in patients with colorectal cancer

## A meta-analysis

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### Abstract

**Background:** Accumulating evidence have revealed that pretreatment albumin to globulin ratio (AGR) may be a predictor of prognosis among patients with colorectal cancer (CRC). However, these findings are inconsistent. The aim of the present study was to investigate the prognostic value of pretreatment AGR in CRC.

**Methods:** A systematic meta-analysis was conducted by searching MEDLINE, EMBASE, and Cochrane Library databases.

**Results:** A total of 9 studies with 7939 patients were finally included. Low pretreatment AGR was associated with worse overall survival (pooled hazard ratio [HR]: 2.07, 95% CI: 1.60–2.67,  $P < .001$ ) and disease-free survival/progress-free survival (pooled hazard ratio [HR]: 2.10, 95% confidence interval [CI]: 1.34–3.31,  $P = .001$ ). Subgroup analyses revealed that the pooled correlation did not alter these results. Moreover, low pretreatment AGR were associated with elderly patients, tumor diameter ( $\geq 50$  mm), tumor node metastasis stage (III–IV), depth of tumor (T3–4), and CA19-9 ( $>37$  U/mL).

**Conclusion:** The present meta-analysis suggests that low pretreatment AGR was associated with advanced clinicopathological features and worse prognosis, suggesting AGR is a useful prognostic biomarker for CRC patients.

**Abbreviations:** AGR = albumin to globulin ratio, CEA = carcinoembryonic antigen, CRC = colorectal cancer, DFS = disease-free survival, NOS = Newcastle-Ottawa quality assessment scale, OS = overall survival, PFS = progress-free survival, TNM = tumor node metastasis.

**Keywords:** albumin to globulin ratio, colorectal cancer, meta-analysis, prognosis

## 1. Introduction

Colorectal cancer (CRC) ranks third and fourth among malignancies in terms of prevalence and lethality, with steadily rising morbidity and mortality in underdeveloped nations, and stable or declining trend in industrialized nations that currently show highest CRC burden around the globe.<sup>[1]</sup> Despite progress in early detection and treatment strategies, the overall prognosis of CRC remains poor and a major cause of mortality due to the high recurrence rates and distant metastases.<sup>[2–4]</sup> Therefore, it is critically urgent to identify new clinical biomarkers to predict the poor prognosis of high-risk CRC patients.

Tumor-associated inflammation has been reported to be a key determinant of disease progression and survival in cancer patients.<sup>[5]</sup> Tumor-associated inflammatory response consists of inflammatory cells and a series of inflammatory mediators.<sup>[6]</sup> Some inflammation-based factors have been reported to predict prognosis in many cancer types: Glasgow Prognostic Score,<sup>[7]</sup> C-reactive protein to albumin ratio (CRP/Alb),<sup>[8]</sup> the neutrophil to lymphocyte ratio,<sup>[9]</sup> the platelet to lymphocyte ratio,<sup>[10]</sup> and the lymphocyte to monocyte.<sup>[11]</sup> These factors, combined with findings of complete blood count and serum chemistry, which are routine tests at the initial visit, help to easily and accurately evaluate the severity of the systemic inflammation in patients

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JYM, GL, and LZP contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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with cancer. As a novel inflammation-based score, a combination of albumin and globulin has been reported to be correlated with the prognosis of CRC patients.<sup>[12–14]</sup> However, these results are inconclusive or even contradictory and there is no meta-analysis performed to evaluate the prognostic value of albumin to globulin ratio (AGR) in CRC.<sup>[15,16]</sup> Therefore, the present meta-analysis aimed to evaluate the correlation between pretreatment AGR, the clinicopathological feature, and prognosis of CRC patients.

## 2. Materials and methods

### 2.1. Search strategy

A comprehensive literature search was carried out on the databases of Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from the inception dates to July 2019. The key words used included: (“albumin/globulin ratio” or “albumin to globulin ratio” or “albumin-to-globulin ratio” or “albumin globulin ratio”) and (“colorectal cancer” or “colon cancer” or “rectal cancer” or “colorectal tumor” or “colorectal carcinoma” or “colorectal neoplasms” or “CRC”). Moreover, the reference lists of the identified studies were manually searched to avoid missing potential studies. Detailed search strategies can be found in Supporting Information. This study was approved by The Institutional Review Board of the Huangshi Central Hospital of Edong Healthcare Group, Hubei Polytechnic University.

### 2.2. Inclusion and exclusion criteria

The included studies should meet the following criteria: studies reporting the correlation between pretreatment AGR, clinical traits, and prognosis of CRC patients; hazard ratio (HR) and 95% CIs can be extracted directly from the study or sufficient data are provided to calculate these values; and study reported the cut-off value of AGR as a categorical variable. Studies were excluded under the following criteria: duplicate data, with insufficient data such that the statistics of clinical traits or survival could not be calculated, and conference abstracts, case series, reviews, and letters to editors.

### 2.3. Data extraction and quality assessment

The data of interest were extracted independently by 2 authors, including the following information: study characteristics: basic characteristics (first author, publication year, ethnicity, sample size, cut-off value, analysis method, and Newcastle-Ottawa quality assessment scale [NOS] score; clinicopathological outcomes, including patient age and gender, ethnicity, performance status, tumor location, size, differentiation, tumor, node, metastasis [TNM] stage, depth of tumor, and lymph node metastasis, and venous invasion), and clinicopathological traits (treatment, AGR cut-off values, carbohydrate antigen 19-9 [CA19-9], and carcinoembryonic antigen [CEA] level, patient’s survival outcome, and duration of the follow-up period). Performance status is an important factor in determining the quality of life, the choice of treatment, and prognostic tool in patients.<sup>[17]</sup>

The NOS was used to assess the methodological quality of each included study.<sup>[18]</sup> There are 3 quality parameters in the NOS tool, which are selection, comparability, and outcome assessment. Studies with NOS values >6 are considered high-quality studies.

### 2.4. Statistical analysis

To evaluate the correlations between AGR and the survival of CRC patients, we combined HRs with their corresponding 95% CIs from each eligible study to estimate the pooled impact of AGR on overall survival (OS) and disease-free survival (DFS)/progress-free survival (PFS). ORs and the corresponding 95% CIs were calculated to assess the correlation between AGR and clinicopathological outcomes. An OR >1 indicated a positive correlation between AGR and clinicopathological outcomes. The HRs and 95% CIs were directly extracted, otherwise, they were calculated according to Tierney method.<sup>[19,20]</sup> Statistical heterogeneity was tested with  $I^2$ . In case with significant heterogeneity ( $I^2 > 50%$ ) random-effect model would be employed, while fixed-effect model would be selected when presenting with excellent homogeneity. A subgroup meta-analysis was conducted to identify or confirm the underlying heterogeneity of a given variate. Moreover, sensitivity analysis was conducted to assess the underlying heterogeneity of a single study included in the meta-analysis.<sup>[21]</sup> If the number of included studies is >11, the publication bias was estimated by visual inspection of Begg funnel plot and Egger linear regression test and defined significantly at a  $P$  value <.05.<sup>[22,23]</sup>

## 3. Results

### 3.1. Study retrieving and selection

A total of 38 studies were identified initially in a comprehensive search in Cochrane Library, EMBASE, and Medline databases. The titles and abstracts of 27 articles were reviewed after duplicates removed. After title and abstract screening, 12 studies were omitted due to irrelevance. For further eligibility evaluation, full-text reading was conducted, and 6 studies were removed because of conference abstract ( $n=1$ ) and AGR as a continuous variable ( $n=1$ ). Nine articles involving 7939 patients were finally included.<sup>[12–16,24–27]</sup> The flow diagram of the study selection process is shown in Fig. 1.

### 3.2. Study characteristics

The patients were from China ( $n=4$ ), Japan ( $n=4$ ), and the USA ( $n=1$ ). The sample size ranged from 66 to 5336, with a median of 882. Five studies for CRC, 3 for rectum, and 1 for the colon. Most studies were reported at mixed disease, and 2 studies were reported in metastatic disease. Eight studies assessed the association of AGR with OS, and 6 studies assessed the association of AGR with DFS/PFS. The quality of each included study included was assessed based on the NOS tool, and all of the studies were of high quality with scores ranging from 6 to 9 stars. The summarized study characteristics and quality assessment are shown in Table 1.

### 3.3. Impact of AGR on OS

Eight studies involving 7868 patients were enrolled in the analysis of the relationship between AGR and OS of CRC patients. A random-effects model was used to conduct the meta-analysis because of the heterogeneity ( $I^2 = 50.4%$ ), the OS was indicated to be obviously different between the high AGR and low AGR group (pooled HR: 2.07, 95% CI: 1.60–2.67,  $P < 0.001$ ; Fig. 2). Furthermore, to further investigate the underlying heterogeneity, we performed subgroup analyses according to ethnicity, sample size, treatment, tumor stage, and cut-off value

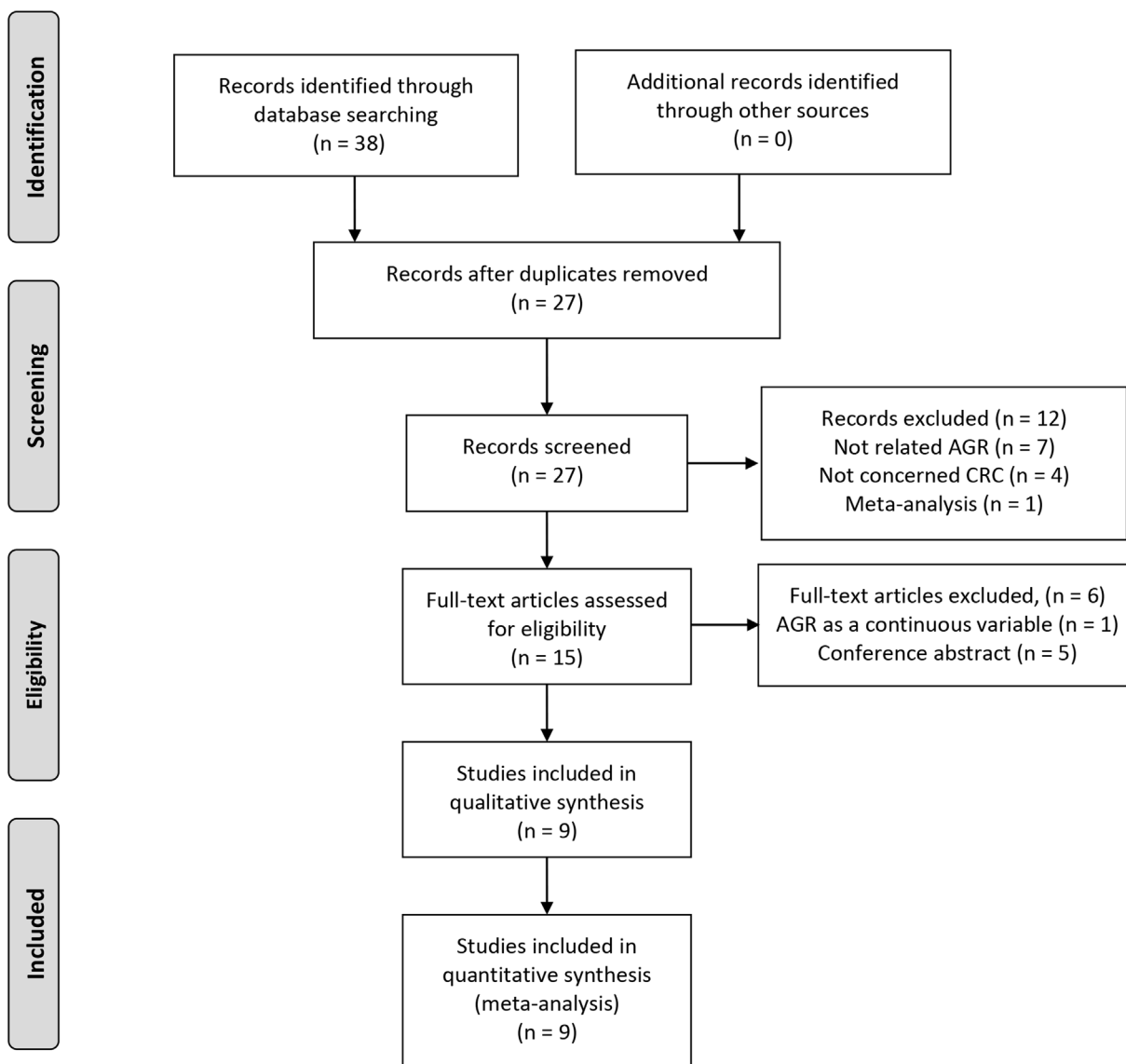


Figure 1. Flow diagram of the selection process.

Table 1

Characteristics of the studies included in the meta-analysis.

Author	Year	Country	Ethnicity	Sample size	Location	Treatment	Stage	Cut-off value	Outcome	Analysis	NOS score
Azab	2013	USA	Caucasian	651	CRC	Mixed	Mixed	1.03	OS	MV	8
Fujikawa	2017	Japan	Asian	248	Colon	Surgery	Mixed	1.32	OS/DFS	MV	6
Hachiya	2018	Japan	Asian	941	CRC	Mixed	Mixed	1.20	OS	MV	7
Li	2015	China	Asian	293	Rectum	Mixed	Mixed	1.20	OS	MV	6
Li	2016	China	Asian	5336	CRC	Mixed	Mixed	1.50	OS/DFS	MV	8
Zhang	2019	China	Asian	71	CRC	Chemotherapy	Metastatic	1.40	PFS	UV	7
Shibutani	2015	Japan	Asian	66	CRC	Chemotherapy	Metastatic	1.25	OS/PFS	MV	6
Toiyama	2018	Japan	Asian	114	Rectum	Mixed	Mixed	1.18	OS/DFS	MV	6
Xu	2019	China	Asian	219	Rectum	Surgery	Mixed	1.43	OS/DFS	MV	8

CRC=colorectal cancer, DFS=disease-free survival, MV=multivariate, NA=not available, OS=overall survival, PFS=progression-free survival, UV=univariate.

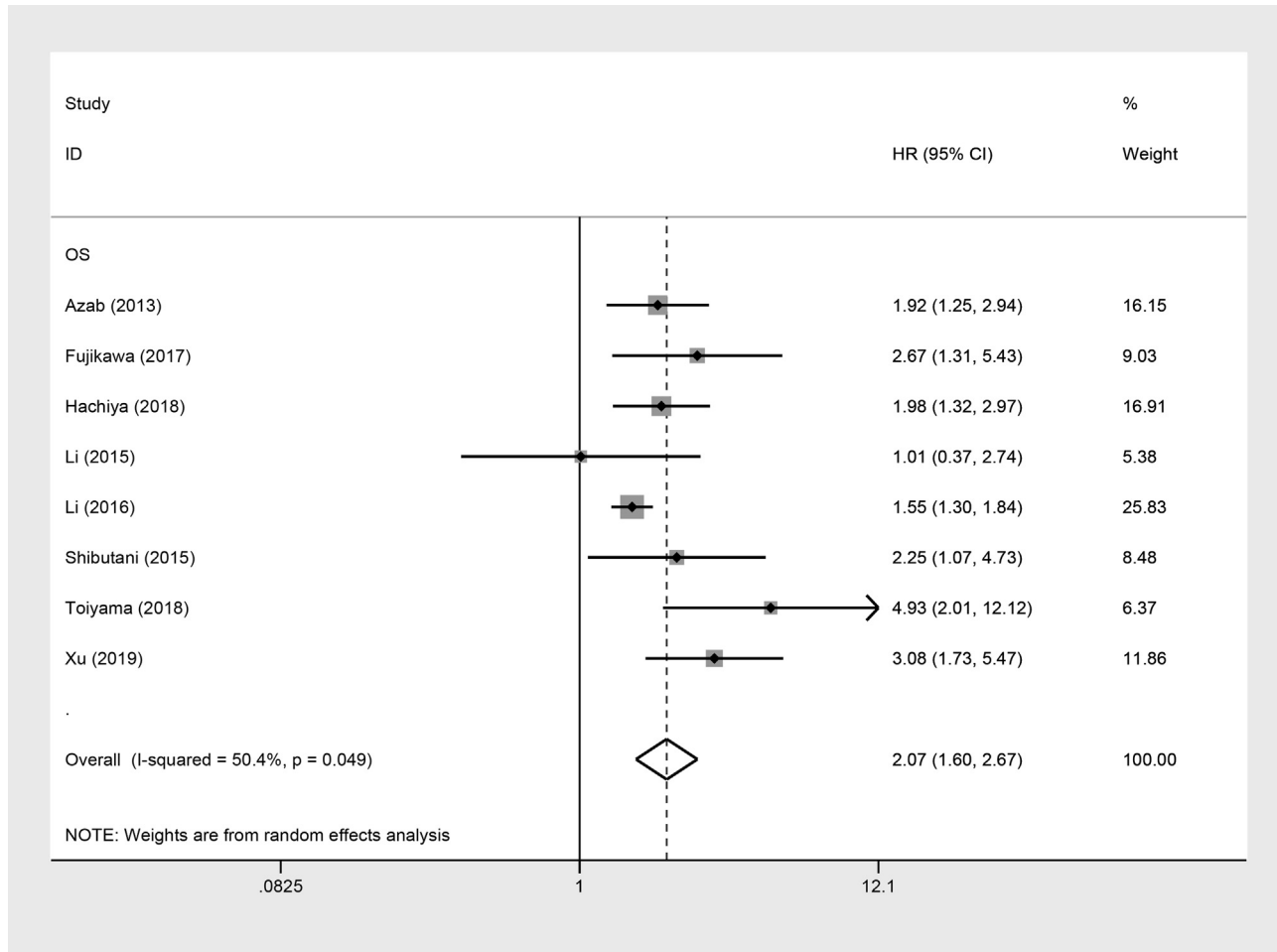


Figure 2. Forest plots of the correlation between AGR and OS in CRC patients. AGR=albumin to globulin ratio, CRC=colorectal cancer, OS=overall survival.

**Table 2**  
**Pooled hazard ratios (HRs) for OS according to subgroup analyses.**

Subgroup	No. of studies	No. of patients	HR (95% CI)	P value	Heterogeneity	
					I <sup>2</sup> (%)	Ph
Overall	8	7868	2.07 (1.60–2.67)	<.001	50.4	0.049
Ethnicity						
Asian	7	7217	2.14 (1.57–2.92)	<.001	57.1	0.030
Caucasian	1	658	1.92 (1.25–2.94)	.003	–	–
Sample size						
≥300	2	6928	1.63 (1.34–1.98)	<.001	15.5	0.277
<300	6	940	2.39 (1.71–3.32)	<.001	30.5	0.206
Treatment						
Surgery	2	467	2.91 (1.86–4.55)	<.001	0	0.759
Mixed	5	7335	1.85 (1.38–2.47)	<.001	52.0	0.080
Chemotherapy	1	66	2.25 (1.07–4.72)	.032	–	–
Stage						
Mixed	7	7802	2.07 (1.56–2.74)	<.001	56.3	0.033
Metastatic	1	66	2.25 (1.07–4.72)	.032	–	–
Cut-off for AGR						
<1.20	2	870	2.82 (1.14–7.00)	.025	71.0	0.063
≥1.20	6	6998	1.94 (1.48–2.54)	<.001	43.6	0.115

AGR=albumin to globulin ratio, OS=overall survival.

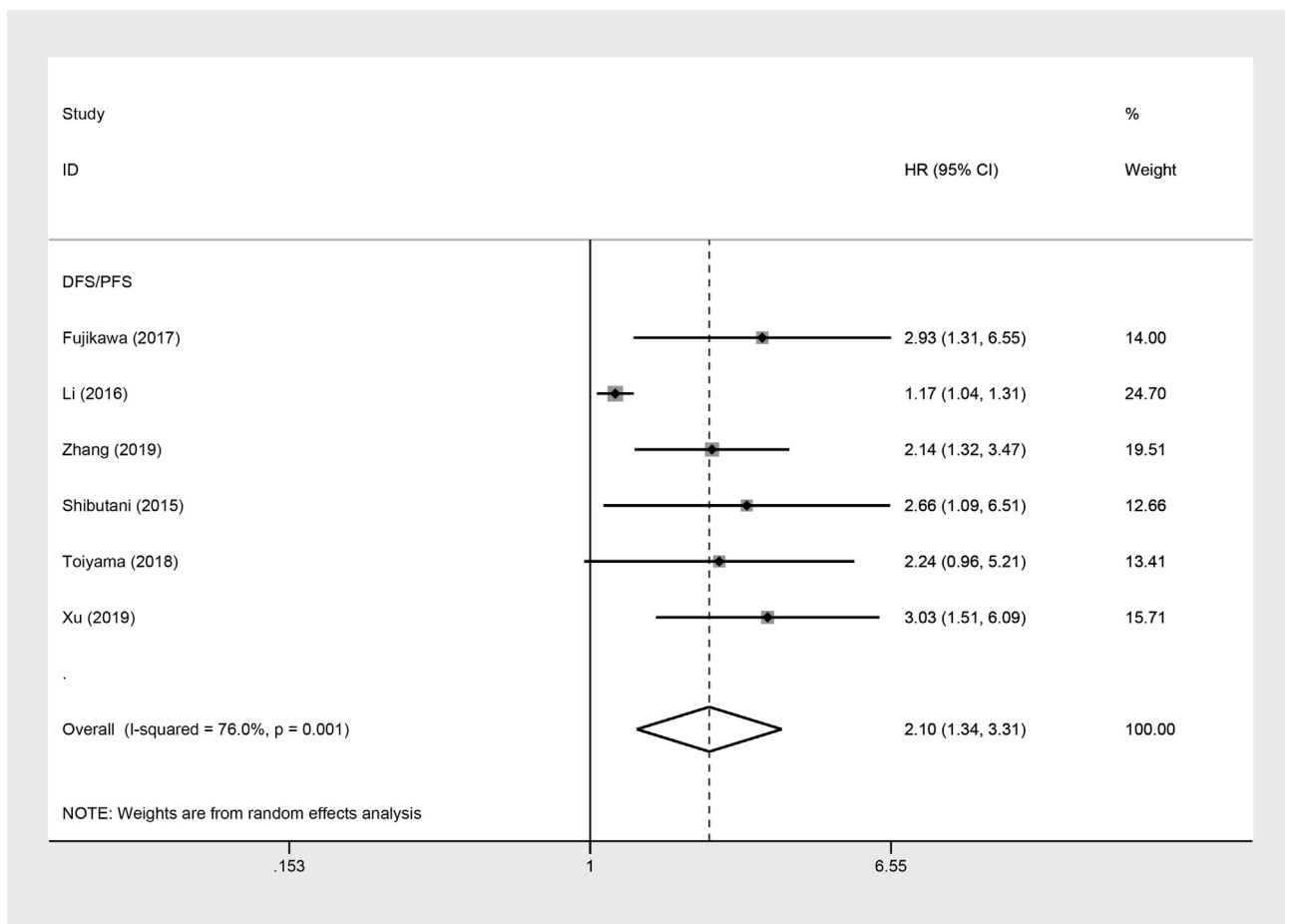
for AGR (Table 2). The results revealed that neither the pooled heterogeneity nor the correlation between AGR and OS of CRC patients in each subgroup analysis was altered. As tumor stage was of great importance in the prognosis of CRC patients, a subgroup meta-analysis was conducted based on stage (mixed/metastatic). Patients with metastatic stage (pooled HR: 2.25; 95% CI=1.07–4.72;  $P=.032$ ) and mixed stage (pooled HR: 2.07; 95% CI=1.56–2.74;  $P<.001$ ) were all obviously correlated with poor OS. For the analysis stratified by cut-off for AGR, significant worse OS was observed in patients with CAR <1.20 (pooled HR: 2.82; 95% CI=1.14–7.00;  $P=.025$ ) and CAR  $\geq$ 1.20 (pooled HR: 1.94; 95% CI=1.48–2.54;  $P<.001$ ). Furthermore, the ethnicity, sample size, and treatment also did not affect the significant prognostic role of AGR in patients with CRC.

**3.4. Impact of AGR on DFS/PFS**

For studies evaluating DFS/PFS, a random-effects model was used to conduct the meta-analysis because of an obvious heterogeneity ( $I^2=76.0\%$ ,  $P=.001$ ). According to the final pooled HR of 2.10 (95% CI=1.34–3.31,  $P=.001$ ), it revealed that low AGR was correlated with decreased DFS/PFS (Fig. 3).

**3.5. AGR and clinicopathological features**

A comprehensive meta-analysis of 12 studies was conducted to evaluate the correlation between AGR and patient age, gender, performance status, tumor site, tumor size, depth of tumor, differentiation, TNM stage, CA19-9 level, CEA level, lymph node metastasis, and venous invasion. The results (Table 3) indicated that low AGR was positively correlated with age (>median vs <median; OR=1.72, 95% CI: 1.56–1.90,  $P<.001$ ), tumor size ( $\geq$ 50mm vs <50mm; OR=2.33, 95% CI: 1.59–3.42,  $P<.001$ ), TNM stage (III–IV vs I–II; OR=1.48, 95% CI: 1.21–1.80,  $P<.001$ ), depth of tumor (T3–4 vs T1–2; OR=1.81, 95% CI: 1.38–2.38,  $P<.001$ ), CA19-9 (>37U/mL vs <37U/mL; OR=2.95, 95% CI: 1.46–5.94,  $P=.002$ ). Nevertheless, AGR was not correlated with gender (male vs female; OR=0.9, 95% CI: 0.51–1.58,  $P=.72$ ), performance status ( $\geq$ 1 vs 0; OR=5.59, 95% CI: 0.73–42.80,  $P=.10$ ), tumor site (colon vs rectum; OR=1.38, 95% CI: 0.98–1.94,  $P=.07$ ), tumor differentiation (low vs moderate/high; OR=1.29, 95% CI: 0.87–1.90,  $P=.20$ ), CEA (>5 ng/mL vs <5 ng/mL; OR=1.09, 95% CI: 0.68–1.74,  $P=.73$ ), lymph node metastasis (yes vs no; OR=1.09, 95% CI: 0.99–1.20,  $P=.88$ ), and venous invasion (yes vs no; OR=1.22, 95% CI: 0.87–1.72,  $P=.24$ ).

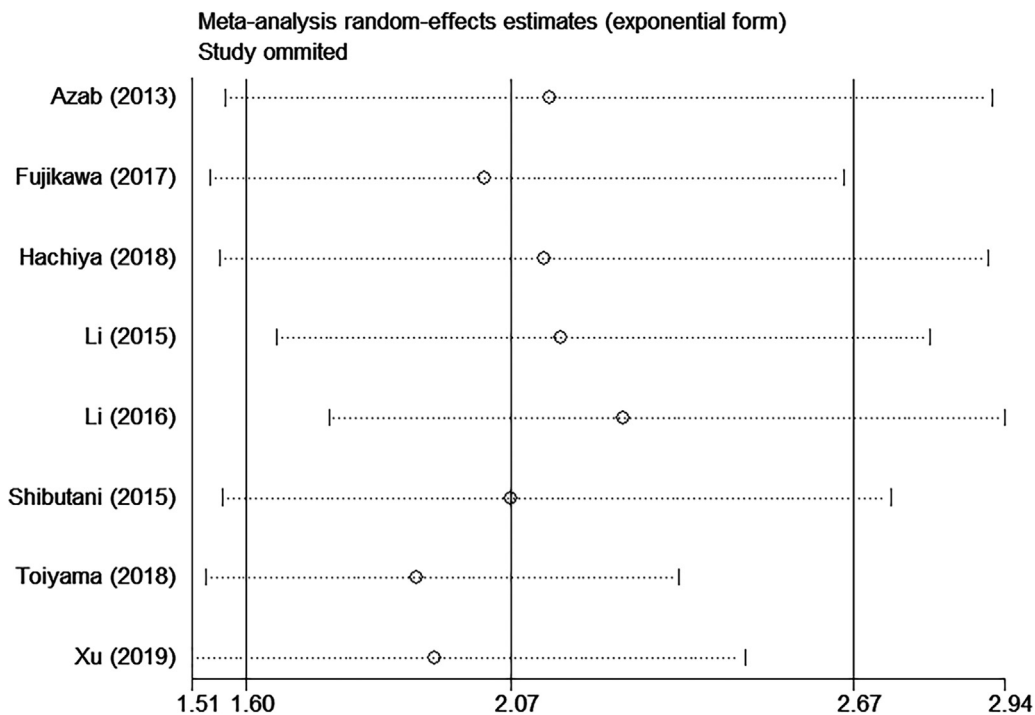


**Figure 3.** Forest plots of the correlation between AGR and DFS/PFS in CRC patients. AGR=albumin to globulin ratio, CRC=colorectal cancer, DFS=disease-free survival, PFS=progress-free survival.

**Table 3**  
**Meta-analysis of the association between AGR and clinicopathological features of CRC.**

Characteristics	No. of studies	No. of patients	OR (95% CI)	P	Heterogeneity	
					I <sup>2</sup> (%)	Ph
Age (>median vs <median)	4	6568	1.72 (1.56–1.90)	<.001	0	0.82
Gender (male vs female)	3	6496	0.9 (0.51–1.58)	.72	92	<0.001
Performance status (≥1 vs 0)	3	1076	5.59 (0.73–42.80)	.10	92	<0.001
Tumor site (colon vs rectum)	3	6343	1.38 (0.98–1.94)	.07	74	0.02
Tumor diameter (≥50 mm vs <50)	3	6413	2.33 (1.59–3.42)	<.001	80	0.007
Differentiation (low vs moderate/high)	6	7161	1.29 (0.87–1.90)	.20	70	0.005
TNM Stage (III–IV vs I–II)	3	1634	1.48 (1.21–1.80)	<.001	0	0.56
Depth of tumor (T3–4 vs T1–2)	3	6134	1.81 (1.38–2.38)	<.001	55	0.11
CEA (>5 ng/mL vs <5 ng/mL)	3	356	1.09 (0.68–1.74)	.73	32	0.23
CA19-9 (>37 U/mL vs <37 U/mL)	2	137	2.95 (1.46–5.94)	.002	40	0.20
Lymph node metastasis (yes vs no)	3	6417	1.09 (0.99–1.20)	.08	0	0.86
Venous invasion (yes vs no)	2	5848	1.22 (0.87–1.72)	.24	76	0.04

CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen.



**Figure 4.** Sensitivity analysis of AGR on OS in CRC patients. AGR=albumin to globulin ratio, CRC=colorectal cancer, OS=overall survival.

**3.6. Sensitivity analysis**

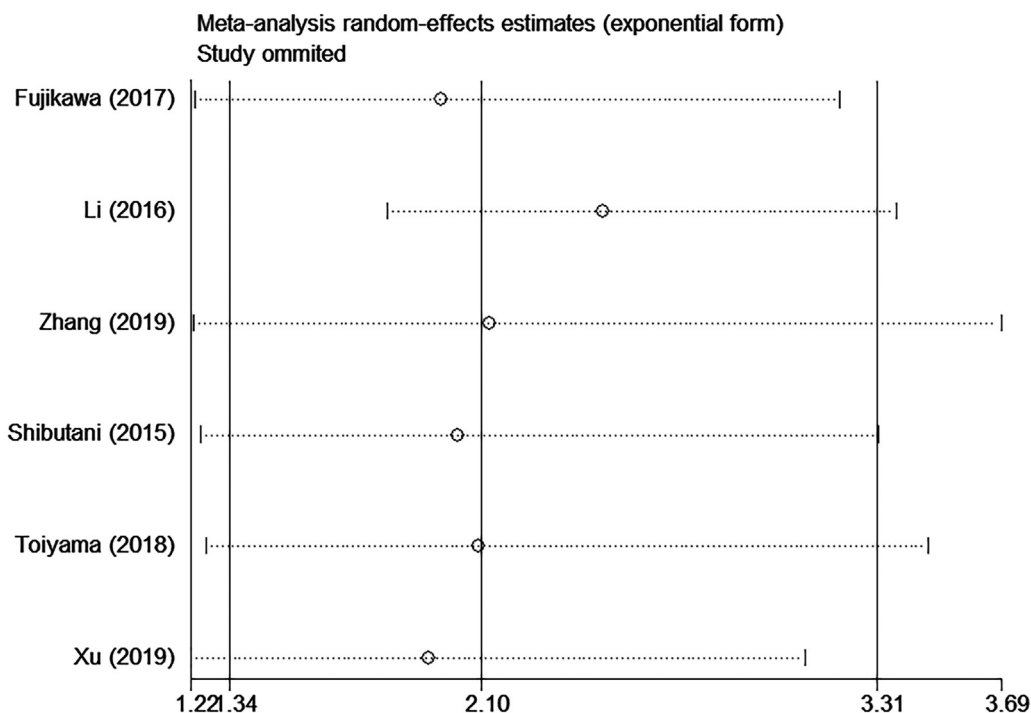
We conducted sequential leave-one-out sensitivity analysis to assess the stability and reliability of the results. As shown in (Figs. 4 and 5), no substantial changes were observed in the pooled results after removing each study, which indicated the robustness of the results.

**4. Discussion**

Strength of this study is that a large cohort of CRC was used for the first time to systematically to explore the prognostic role of

pretreatment AGR in CRC. Our study gives robust evidence of an association between low pretreatment AGR and worse prognosis based upon 9 studies including 7939 CRC patients. The prognostic value of AGR remained regardless of ethnicity, sample size, treatment, tumor stage, and cut-off value for AGR. Furthermore, low pretreatment AGR was linked to advanced clinical traits, such as elderly patients, large tumor size, advanced tumor stage and depth of tumor, and high CA19-9 level. Therefore, AGR might be a potential and valuable prognosticator for CRC patients.

It is well recognized that inflammatory cells are known to be powerful tumor promoters.<sup>[28,29]</sup> However, the precise mechanisms between the inflammatory response and tumor progres-



**Figure 5.** Sensitivity analysis of AGR on DFS/RFS in CRC patients. AGR=albumin to globulin ratio, CRC=colorectal cancer, DFS=disease-free survival, PFS=progress-free survival.

sion are not entirely elucidated. Accumulating evidence indicates that these inflammatory factors are associated with malnutrition, poor immune response, up-regulation of growth factors, and angiogenesis, thereby leading to carcinogenesis.<sup>[30,31]</sup> Several inflammatory/immune cells have been identified in the tumor microenvironment, such as tumor-associated macrophages and tumor-infiltrating lymphocytes.<sup>[32,33]</sup> Due to this inflammatory tumor microenvironment, inflammation-based factors are increasingly being investigated for their ability to predict cancer-specific outcomes. AGR, as an inflammatory marker, has been confirmed as a prognostic factor in various cancers, including CRC.<sup>[34]</sup>

AGR has been confirmed as a prognostic factor in many solid organ malignant tumors.<sup>[35-37]</sup> A previous meta-analysis revealed that high preoperative AGR was correlated with poor OS, DFS, and PFS across various types of cancer.<sup>[34]</sup> Moreover, the prognostic value of preoperative AGR remained constant regardless of AGR cut-off values and cancer type, although AGR cut-off values were heterogeneous, ranging from 0.9 to 1.93 for some cancers. In present study, the AGR cut-off values were relatively uniform, ranging from 1.01 to 1.50. The prognostic role of AGR in patients with CRC may be explained by several possible mechanisms involved in patients' inflammatory and nutritional status. The AGR was calculated from the serum albumin and globulin levels. Serum albumin, accounting for approximately 60% of the total protein,<sup>[38]</sup> is typically used to reflect nutritional status.<sup>[39]</sup> It is produced by the liver and is the major protein in the blood that helps maintain intravascular osmotic pressure and acts as a free radical scavenger.<sup>[40]</sup> It is one of the most commonly used markers for evaluating patients' nutritional status. More than half of CRC patients are diagnosed with malnutrition at presentation, possibly due to the progression of masticatory dysfunction, dysphagia, and cachexia, which

are associated with adverse survival outcomes. Malnutrition may impair a number of human defense mechanisms, such as anatomic barriers, humoral and cellular immunity, and phagocytic function,<sup>[41]</sup> which can be accurately detected based on serum albumin levels.<sup>[42]</sup> Therefore, patients may not be sufficiently fit to receive treatment, resulting in poorer survival than patients who have normal serum albumin.

In addition to being a nutritional marker, albumin has also been considered a marker of inflammatory responses.<sup>[26]</sup> Decreased albumin levels are associated with increased inflammatory responses to tumors, poor nutritional status, and increased cytokine release. Albumin acts as an antioxidant against carcinogens by organizing cell growth and DNA stabilization.<sup>[43]</sup> Several studies have shown that hypoproteinaemia is associated with cancer.<sup>[44]</sup> Hypoalbuminemia may be caused by the decreased production of ALB by hepatocytes because of cytokines released by the tumor, such as interleukin (IL)-1, IL-6, and tumor necrotic factor  $\alpha$ , which blocks hepatocyte albumin production.<sup>[45,46]</sup> Increased TNF- $\alpha$  and cytokine levels may be a surrogate for more aggressive disease.<sup>[47]</sup> Hypoproteinaemia may also be due to the intense systemic inflammatory response that accompanies the tumor, which may be a surrogate for more aggressive malignancies.<sup>[48]</sup> Due to possible gastrointestinal obstruction and malabsorption, gastrointestinal tumor patients have a higher risk of hypoproteinaemia than other cancer patients.<sup>[49]</sup>

Globulin is the main protein produced by immune organs, which reflects the body's inflammation and immune status.<sup>[50]</sup> According to its electropherogram, globulin includes  $\alpha$ 1,  $\alpha$ 2,  $\beta$ , and  $\gamma$  globulin. The  $\gamma$  globulin, also known as immunoglobulins or antibodies, play an important role in immunity and inflammation.<sup>[51]</sup> In chronic inflammation, the level of globulin gradually increases due to the activity of inflammatory

cytokines.<sup>[52]</sup> High levels of globulin resulting from immunoglobulin and acute phase protein aggregation may indicate inflammation and host immune responses in the malignancy microenvironment. As a biomarker of systemic inflammation, an increased preoperative C-reactive protein (CRP) level predicts poor survival in CRC.<sup>[53]</sup> Furthermore, elevated complement 3 and IgA levels have been considered as a prognostic factors in patients with CRC.<sup>[54]</sup> Because albumin and globulin are affected by many factors such as stress, liver failure, and dehydration, they also show measurement variability. However, because the AGR represents albumin/globulin ratio and is therefore less affected by measurement variability, making it a more appropriate indicator than serum albumin or globulin alone. We believe that nutritional status and the systemic inflammatory response have important effects on the oncological outcomes of patients with CRC. The AGR is a combination of these 2 predictors of adverse outcome, which may enhance its predictive value. Taken together, AGR may represent a balance between the nutritional status and inflammation, may serve as a predictor of prognosis in CRC patients.

The present meta-analysis has several limitations. First, most of the studies included were from Asia countries. Hence, our findings need to validate in populations of other ethnicities. Second, there existed a moderate between-study heterogeneity, which might have originated from different definitions of cut-off value. Random-effects model, subgroup analysis, and sensitivity analysis were performed to adjust this shortcoming. Finally, all included studies were retrospective studies. It would give rise to select bias when getting past information. In addition, they are more prone to selection bias due to the retrospective nature of the study design.

## 5. Conclusions

The present meta-analysis suggests that low pretreatment AGR was associated with advanced clinicopathological features and worse prognosis, suggesting AGR is a useful prognostic biomarker for CRC patients.

## Author contributions

Jian-Ying Ma and Zhong-Zhong Zhu designed the study. Gang Liu, Liang-Zhi Pan, and Zhong-Zhong Zhu contributed to the collection of clinical information and data analysis. Jian-Ying Ma, Gang Liu, Liang-Zhi Pan, and Min Hu analyzed and interpreted the data. Jian-Ying Ma and Gang Liu wrote and revised the manuscript. Zhong-Zhong Zhu supervised the study.

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