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Review

# Pretreatment albumin to globulin ratio can serve as a prognostic marker in human cancers: a meta-analysis

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ABSTRACT

*Purpose:* Our meta-analysis aims to investigate the prognostic role of pretreatment albumin to globulin ratio (AGR) in human cancers.

*Methods:* Available databases were searched up to Sept 25th, 2017. Pooled hazard ratios (HRs) and risk ratio (RRs) with their corresponding 95% confidence intervals (CIs) were used to assess the prognostic impact of AGR on overall survival (OS)/disease-free survival (DFS)/progression-free survival (PFS) and 5-year mortality respectively.

*Results:* Totally, 28 studies with 15 356 cancer patients were included. Our results demonstrated that low pretreatment AGR is associated with poor OS (HR = 2.08, 95%CI:1.78–2.44, univariate results; HR = 1.75, 95%CI:1.56–1.97, multivariate results), poor DFS (HR = 1.96, 95%CI:1.48–2.59, univariate results; HR = 1.64, 95%CI:1.26–2.14, multivariate results) and poor PFS (HR = 1.89, 95%CI:1.61–2.22, univariate results; HR = 1.66, 95%CI:1.32–2.0, multivariate results). Meanwhile, low pretreatment AGR is also associated with increased 5-year mortality (RR = 2.12, 95%CI:1.48–3.03). Moreover, this significant correlation was not altered by stratified analysis according to publication times, sample sizes, patient origins, AGR cutoff values, cancer systems, treatment methods or HR sources.

*Conclusion:* Low pretreatment AGR is associated with poor prognosis in human cancers, and AGR should be used as a prognostic marker during cancer therapy.

## 1. Introduction

The number of cancer survivors continues to increase because of advances in early detection and treatment, as well as the aging and growth of population [1]. However, cancer is still a major public health problem worldwide, and it is the second leading cause of death in the United States [2]. It is estimated that 1,688,780 new cancer cases and 600,920 cancer deaths would occur in the United States in 2017 [2]. Till now, the prognostic markers for human cancers are numerous, but most of whose tests are either expensive or unavailable before treatments. Therefore, identifying new prognostic marker may be helpful in relieving this human burden.

The albumin and globulin are abundant protein in human serum. As a major serum component, albumin is usually used to reflect nutritional status and systemic inflammatory response in cancer patients [3]. Meanwhile, hypoalbumin has also been used as a prognostic marker in human cancers, including lung cancer [4], breast cancer [5], gastrointestinal cancer [6,7], lymphoma [8], endometrial cancer [9], and renal cancer [10]. The other major component of serum protein, globulin, is the primary cortisol binding protein, playing an important role in immunity and inflammation [11,12]. Recently, the albumin to globulin ratio (AGR), calculated as AGR = albumin/globulin, is widely used as prognostic indicator in diverse human cancers.

However, the prognostic role of AGR on human cancers has not been clarified yet. Thus, we performed this meta-analysis to investigate the role of AGR as a prognostic marker in human cancers.

## 2. Materials and methods

### 2.1. Search strategy

Comprehensive literature search was conducted in the following databases, including PubMed, Web of Science, Wanfang and Cochrane library (Up to Sept 25th 2017). In each database, ('albumin globulin ratio' or 'albumin:globulin ratio' or 'albumin/globulin ratio' or 'albumin to globulin ratio') and ('overall survival' or 'disease-free survival' or 'recurrence' or 'mortality', 'prognosis' or 'prognostic') were used as key words. The search strategy used in PubMed was '((((((overall survival

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[Title/Abstract]) OR disease-free survival[Title/Abstract]) OR recurrence [Title/Abstract]) OR prognosis[Title/Abstract]) OR prognostic [Title/Abstract])) AND ((((albumin globulin ratio[Title/Abstract]) OR albumin:globulin ratio[Title/Abstract]) OR albumin/globulin ratio [Title/Abstract]) OR albumin to globulin ratio[Title/Abstract])', and searching strategy was adjusted accordingly in other databases. Meanwhile, reference lists of retrieved articles were examined manually to further identify potentially relevant publications. If analysis was based on the same patients origin, only the latest research was considered.

### 2.2. Inclusion criteria

Studies would be included if they met the following criteria: (1) the prognostic impact of AGR on human cancers was investigated; (2) survival results were provided in the article, including overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), mortality or recurrence rate; (3) the impact of AGR on survival outcomes should be provided in form of hazard ratio (HR) with 95% confidence interval (CI), Kaplan-Meier curve, or provided data for calculating HR with its corresponding 95% CI. Otherwise, studies such as reviews and duplicates would be excluded.

### 2.3. Data extraction

Data was extracted from each included study, including study ID (first author plus publication year), country, study sample size, cancer location, cancer stage, cutoff value for AGR, treatment method, survival outcome, analysis model for survival outcomes, HR source and follow-up period. When only survival data rather than HR was provided, we calculated HR by Tierney et al.'s method [13]. If only Kaplan-Meier curves were available, survival plots were read by the Engauge Digitizer version 4.1 (http://sourceforge.net), then estimated HR was also calculated by Tierney et al.'s method [13]. We extracted as many survival results as possible from both univariate and multivariate analysis. During this process, two investigators extracted the data independently and eliminated disagreements through discussion.

### 2.4. Statistical analysis

In this research, we used STATA 10 to perform meta-analysis. HRs and corresponding 95%CIs were combined to assess the prognostic impact of AGR on OS/DFS/PFS, and risk ratios (RRs) and 95%CIs were combined to assess the prognostic impact of AGR on 5-year mortality. A final HR/RR > 1 indicates a negative effect on prognosis, otherwise it indicates a positive effect. Heterogeneity between studies was measured by Cochran's Q test and Higgin's $I^2$ statistic [14]. Fixed-effect model was used when no heterogeneity was found ($I^2$ < 50%, $P$ > 0.1), otherwise random-effect model would be used. Publication bias was evaluated by both Begg's test and Egger's test [15,16]. During the analysis, a $P$-value < 0.05 was believed to be significant.

## 3. Results

### 3.1. Procedures of searching included studies

169 articles were identified according to the defined keywords in available databases. Subsequently, 139 articles were excluded because they did not meet the eligibility criteria, including letters, reviews, duplicates, and papers without survival outcomes. By reading full-text of remained 30 studies, we excluded one of 2 studies because they were based on the same patients origin [17]. During data extraction, one study was found to assess the prognostic role of AGR on healthy adults rather than cancer patients [18]. As a result, we discarded 2 studies and kept the other 28 studies in our meta-analysis (Fig. 1).

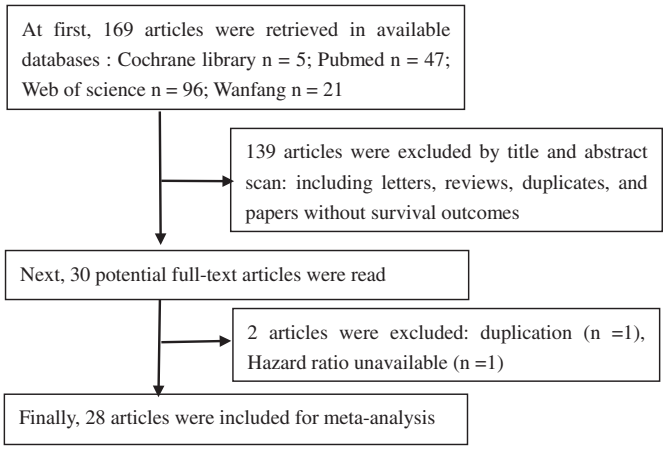


**Fig. 1.** Flowchart of searching studies in this meta-analysis.

### 3.2. Characteristics of included studies

The main characteristics of included studies are shown in Table 1. Totally, 28 studies with 15 356 cancer patients were included in our research [19–46]. Among them, there is one special study based on two cohorts [26]. The publication dated from 2013 to 2017, and the study sample size ranged from 66 to 5336, with the middle size 316. The cutoff value for AGR ranged from 0.9 to 1.93, with 1.379 as the middle number. In terms of survival outcomes, all of 28 included studies provided overall survival (OS) results, 9 studies provided disease-free survival (DFS) results, 4 studies provided progression-free survival (PFS) results, and 6 studies provided 5-year survival rate. The other informations, patients origin, cancer location/stage, and treatment method, could also be seen in Table 1.

### 3.3. Meta-analysis on OS

In this research, the prognostic impact of AGR on OS was assessed by both univariate analysis results and multivariate analysis results. On one hand, 25 studies with 14 109 patients were conducted on the prognostic value of AGR on human cancers according to univariate analysis. Since heterogeneity was found between included studies ($I^2$ = 87.4%, $P$ = 0.000), random-effect model was used. Pooled meta-analysis results demonstrated that low pretreatment AGR was associated with poor OS (HR = 2.08, 95%CI: 1.78–2.44, $P$ = 0.000) (Fig. 2A). On the other hand, 25 studies with 13 591 patients performed on the prognostic value of AGR on human cancers from multivariate analysis results. Pooled meta-analysis results from random-effect model ($I^2$ = 57.2%, $P$ = 0.000) proved the same result (HR = 1.75, 95%CI: 1.56–1.97, $P$ = 0.000) (Fig. 2B). These results suggested that cancer patients with low pretreatment AGR would suffer from decreased survival rate.

### 3.4. Meta-analysis on DFS/PFS

13 studies with 9 310 patients and 10 studies with 7 848 patients assessed the prognostic role of AGR on DFS/PFS from univariate analysis results and multivariate analysis results respectively. Pooled meta-analysis results from univariate analysis ($I^2$ = 80.3%, $P$ = 0.000; random-effect model) demonstrated that low pretreatment AGR was correlated with poor DFS/PFS (HR = 1.93, 95%CI: 1.57–2.37, $P$ = 0.000) (Fig. 3A). Pooled meta-analysis results from multivariate analysis ($I^2$ = 57.9%, $P$ = 0.011; random-effect model) proved the same result.(HR = 1.64, 95%CI: 1.35–2.01, $P$ = 0.000) (Fig. 3B). These results suggested that cancer patients with low pretreatment AGR would suffer from high cancer recurrence/progression rate.