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ORIGINAL RESEARCH

Preoperative albumin-to-globulin ratio as a significant prognostic indicator in urologic cancers: a meta-analysis

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Yi Zhang[1]
Lijuan Wang[2]
Shibu Lin[3]
Rong Wang[1]

[1]Department of General Surgery, The First People's Hospital of Neijiang, Neijiang 641000, Sichuan Province, China; [2]Department of Nephrology, Shangrao People's Hospital, Shangrao 334000, Jiangxi Province, China; [3]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Hainan Medical College, Haikou 570102, Hainan Province, China

Background: Emerging studies reported that preoperative albumin-to-globulin ratio (AGR) correlated with tumor progression and prognosis in several types of cancer. The aim of this study was to systematically explore the association between preoperative AGR and clinical outcomes in cancers of the urinary system.

Methods: Relevant articles were searched in PubMed, Embase and Web of Science by two independent investigators from inception to June 1, 2018. Eligible studies were selected based on predetermined selection criteria. Summarized HRs or ORs and 95% CIs were calculated for prognosis and clinicopathologic features with the fixed-effects or random-effects models.

Results: Eight cohort studies comprising 2,668 patients were included for analysis. The pooled results showed that a low AGR significantly correlated with poor OS (HR: 0.38, 95% CI: 0.27–0.48, $P<0.001$), worse cancer-specific survival (CSS) (HR: 0.36, 95% CI: 0.22–0.50, $P<0.001$) and inferior event-free survival (EFS) (HR: 0.36, 95% CI: 0.25–0.48, $P<0.001$) in urologic cancers. In addition, patients in low and high AGR groups showed significant differences in lymphovascular invasion ($P<0.001$), pT status ($P<0.001$) and pN status ($P<0.001$).

Conclusion: Preoperative AGR might be a valuable, cheap and reproducible prognostic biomarker in urologic cancers following surgical resection.

Keywords: albumin-to-globulin ratio, urologic cancer, prognosis, clinical features

Introduction

Albumin (ALB) and globulin (GLB) are two major abundant proteins in human serum. Increasing evidence has shown that albumin levels reflect nutritional status and also correlate with systemic inflammatory response.[1–3] Furthermore, albumin could be used as a useful prognostic marker in cancers, such as ovarian cancer, gastric cancer, lung cancer and colorectal cancer.[4–7] On the other hand, globulin, another major component of serum protein, has been reported to be involved in a series of immune and chronic inflammation responses,[8–11] and might serve as a predictor of tumor progression and survival.[12–15]

However, the levels of albumin and globulin in serum could be easily influenced by other confounding factors, and this could affect the efficiency and accuracy in prognosis detection. To overcome the deficiency, a novel prognostic index, the albumin-to-globulin ratio (AGR), was identified and reported.[16,17] AGR is a combination of serum albumin and globulin. It has been suggested that the AGR might be a more stable and reliable indicator than serum albumin or globulin alone in prognostication.[18,19] It has been demonstrated to be a valuable and promising prognostic tumor marker in various types of cancers.[18–22]

Correspondence: Rong Wang
Department of General Surgery, The First People's Hospital of Neijiang, Jiaotong Road, Neijiang 641000, Sichuan Province, China
Email 460532929@qq.com

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Recently, several studies have reported the relationship between AGR and prognosis in urologic cancers, such as bladder cancer, renal cell carcinoma and upper tract urothelial carcinoma.[23–26] However, reports on the prognostic effect of AGR in urologic cancers are inconsistent and debatable, and most studies published to date also have been restricted with small samples. Therefore, in order to provide clear evidence in favor of the prognostic significance of the AGR, it is necessary to conduct a meta-analysis to synthetically investigate the association between the AGR and clinical outcomes in patients with urinary system cancer.

Methods

Literature retrieval and study selection

A systematic literature search was performed in PubMed, Embase and Web of Science for eligible studies assessing the prognostic significances of the AGR in cancers of the urinary system until June 1, 2018. The search strategy combined the following terms: "albumin/globulin," "albumin to globulin," "albumin and globulin," "albumin to globulin ratio," or "AGR," and "bladder," "kidney," "prostate," "testicular," "renal," or "urothelial," and "cancer," "carcinoma," "adenocarcinoma," "tumor," or "malignancy."

Inclusion and exclusion criteria

Studies were identified eligible and included if they met the following inclusion criteria:

1. All patients enrolled were histologically confirmed to be primary urologic cancers;
2. The study reported the association between the preoperative albumin-to-globulin ratio (AGR) and OS/CSS/DFS/PFS/RFS;
3. Cases were divided into two groups according to the cutoff value of AGR;
4. Full-text studies were published in English.

The exclusion criteria were as follows:

1. Nonoriginal studies, such as letters, reviews, meta-analysis, poster session or abstracts;
2. Studies on cancers that not derived from urinary system;
3. Insufficient data for calculating the HR and 95% CI.

Data extraction and quality assessment

The following data were extracted by two independent researchers: the surname of the first author, publication year, country of research, cancer type, included period, number of cases, study type, number of male and female, age distribution, survival type, cutoff value of AGR, cutoff selection, treatment method, follow-up time, overall survival (OS), CSS, disease-free survival (DFS), progression-free survival (PFS) and recurrence-free survival (RFS). The HRs and the 95% CI for cancer survival were extracted from the multivariate analysis, since they balanced many confounding factors. Additionally, the number of the patients for the clinicopathologic characteristics (tumor grade, lymphovascular invasion, pT status, pN status, pM status and pTNM stage) was extracted from the eligible studies. The Newcastle–Ottawa Scale (NOS) was utilized to assess the quality of the included studies.[27,28] The scores according to NOS varied from 0 to 9. A score of 6 or more was identified as high quality.

Statistical analysis

Pooled HRs or ORs and their 95% CIs for cancer prognosis and clinical relevance were evaluated by Stata version 12.0 (Stata Corporation, College Station, TX, USA). DFS/PFS/RFS values were merged into one survival outcome described as EFS.[29,30] The heterogeneity among studies was tested by Cochran's Q and Higgins I^2 statistics; in the presence of significant heterogeneity (P_{het} <0.1 and/or I^2 >50%), the random-effect model was employed; otherwise, the fixed-effect model was applied. Publication bias was evaluated by Begg's test and funnel plot analysis. The sensitivity analysis was carried out by sequentially omitting individual studies to assess the robustness of the pooled results. A two-sided P<0.05 was considered statistically significant.

Results

The detailed process of study selection is shown in Figure 1. According to the inclusion and exclusion criteria, eight full-texts were considered eligible and included in the meta-analysis, with a total of 2,668 cases.[23–26,31–34] In these eight articles, three different kinds of urinary system cancers were included as follows: renal cell carcinoma (RCC, two articles), upper urinary tract urothelial carcinoma (UTUC, two articles) and bladder cancer (BC, four articles). All the included studies were prospective cohort trials. These studies were all published in English and released in the year of 2015 (one study), 2016 (one study), 2017 (two studies) and 2018 (four studies). These studies were carried out in three countries, namely, Turkey (one study), Japan (one study), P. R. China (six studies). All cases in the eligible studies were classified into two groups (low and high AGR groups), and the clinicopathologic characteristics of the patient data are shown in Table S1. Among these studies, six studies reported

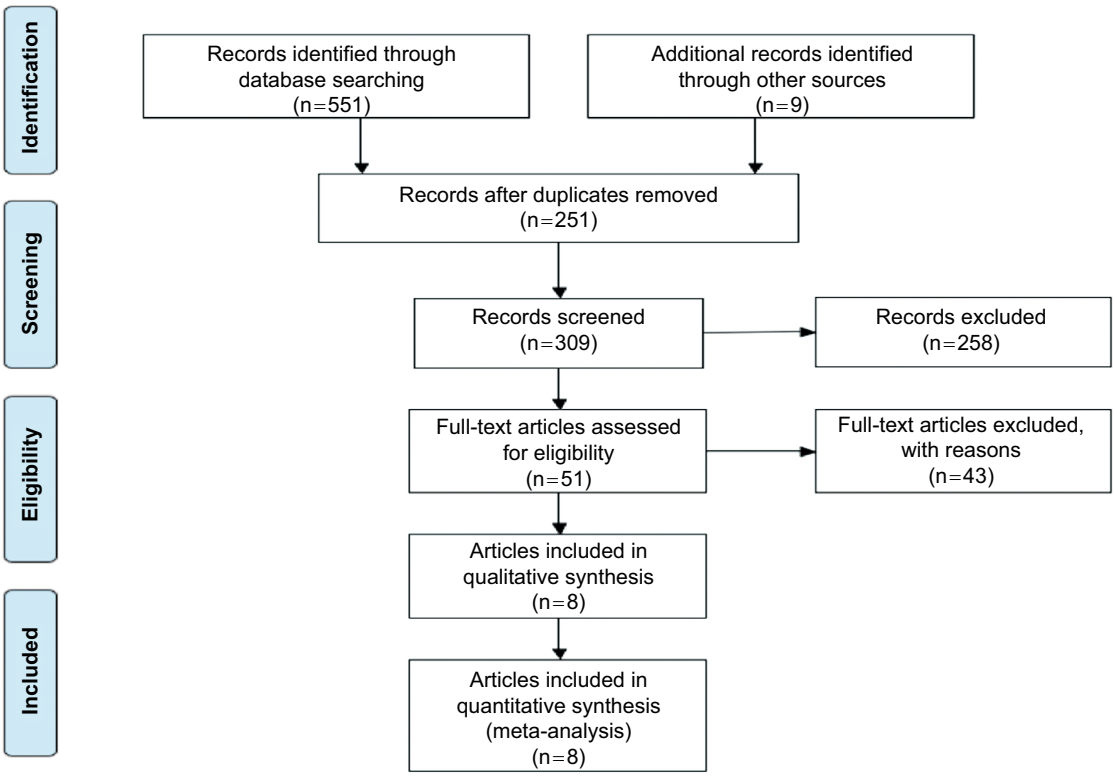

Figure 1 Flow diagram of the meta-analysis.

the association between AGR and OS, four studies reported the relationship between AGR and cancer-specific survival (CSS), and two studies for PFS, RFS, DFS, respectively. The main characteristics of all included studies are presented in Table 1.

AGR and prognosis

Overall survival

A total of six studies involving 2008 patients reported the effect of AGR on OS in urologic cancer. The pooled results showed that low AGR was significantly related with poor OS (HR: 0.38, 95% CI: 0.27–0.48, $P<0.001$) with no significant heterogeneity ($I^2=41.2\%$, $P_{het}=0.132$; Figure 2).

As shown in Table 2, when stratified by the cancer type, low AGR had significantly worse OS in UTCC (HR: 0.37, 95% CI: 0.18–0.56, $P<0.001$), RCC (HR: 0.63, 95% CI: 0.38–0.88, $P<0.001$) and BC (HR: 0.30, 95% CI: 0.16–0.44, $P<0.001$). In addition, the significant differences were also consistently observed in subgroup meta-analysis stratified by the sample size and cutoff value (Table 2).

Cancer-specific survival

Four studies with 1,142 cases reported data on the relationship between AGR and CSS in urologic cancer. The meta-analysis suggested that low AGR significantly correlated with worse CSS (HR: 0.36, 95% CI: 0.22–0.50, $P<0.001$), with no significant heterogeneity across studies ($I^2=10.0\%$, $P_{het}=0.343$; Figure 3). Notably, the negative effect of high AGR on CSS was also observed in patients with bladder carcinoma (HR: 0.33, 95% CI: 0.18–0.49, $P<0.001$).

Event-free survival

Six studies reported the association between AGR and EFS in urologic cancer; there were two studies focusing on PFS, DFS and RFS. As shown in Figure 4, the pooled results indicated that the patients with low AGR had an inferior EFS in urologic cancer (HR: 0.36, 95% CI: 0.25–0.48, $P<0.001$) with no obvious heterogeneity among studies ($I^2=0.0\%$, $P_{het}=0.577$). And significant associations were also found between AGR and RFS (HR: 0.47, 95% CI: 0.30–0.64, $P<0.001$), PFS (HR: 0.27, 95% CI: 0.11–0.43, $P<0.001$) and DFS (HR: 0.35, 95% CI: 0.06–0.75, $P<0.001$).

AGR and clinicopathologic characteristics

Tumor grade

A total of six studies with 2,009 patients reported the relationship between AGR and tumor grade. As an obvious

Table 1 Main characteristics of eligible studies in the meta-analysis

Study, year	Disease type	Country	Study type	Included period	No. of cases	Male/ female	Age (years)	Survival type	Cutoff value	Cutoff selection	Follow-up	MVA	NOS score
Zhang et al 2015[24]	UTCC	China	R	2006–2008	187	85/102	median: 70	OS, CSS	1.45	ROC	≥5 years	yes	7
Liu et al 2016[25]	BC	China	R	2000–2013	296	250/46	mean: 61.71	CSS, RFS	1.6	ROC	≥5 years	yes	7
He et al 2017[33]	RCC	China	R	2000–2012	895	600/295	mean: 51.44	OS	1.47	ROC	≥5 years	yes	8
Liu et al 2017[26]	BC	China	R	2009–2013	189	165/24	NA	OS, PFS, CSS	1.55	ROC	≥5 years	yes	7
Koparal et al 2018[23]	RCC	Turkey	R	2010–2016	162	102/60	mean:56.5	OS, DFS	1.4	ROC	≥5 years	yes	6
Niwa et al 2018[32]	BC	China	R	2000–2015	364	294/70	median: 71	RFS, PFS	1.6	NA	≥5 years	yes	8
Shang et al 2018[34]	BC	China	R	2004–2011	470	354/188	median: 70	OS, CSS	1.68	ROC	≥5 years	yes	8
Fukushima et al 2018[31]	UTCC	Japan	R	2003–2016	105	74/31	median: 74	OS, DFS	1.24	ROC	≥5 years	yes	6

Abbreviations: BC, bladder carcinoma; CSS, cancer-specific survival; DFS, disease-free survival; MVA, multivariate analysis; NA, not available; NOS, Newcastle–Ottawa Scale; OS, overall survival; PFS, progression-free survival; R, retrospectively; RCC, renal cell carcinoma; RFS, recurrence-free survival; ROC, receiver operating characteristic curve; UTCC, upper tract urothelial carcinoma.

heterogeneity existed among studies (I^2=84.5%, P_{het}=0.000), the random-effect model was used. The pooled results indicated that there was no significant association between AGR and tumor grade (OR: 1.12, 95% CI: 0.64–1.95, P=0.69; Figure 5)

Lymphovascular invasion (LVI)

Only three studies with 481 patients explored the correlation between AGR and lymphovascular invasion. As shown in Figure 6, no significant heterogeneity was observed (I^2=44.0%, P_{het}=0.168), and the patients with low AGR were more likely to have lymphovascular invasion (OR: 2.20, 95% CI: 1.43–3.39, P<0.001)

pT status

Six articles with 1,834 cases coved the effect of low AGR on pT status. The random-effects model was employed (I^2=68.2%, P_{het}=0.008); the combined results indicated that low AGR was significantly associated with deeper depth of tumor invasion (OR: 2.68, 95% CI: 1.70–4.22, P<0.001; Figure 7).

pN status

Five studies, consisting of 1,672 patients, explored the association between AGR and pN status. Analysis revealed the pooled OR of 3.42 with 95 % CI: 2.39–4.89 (P<0.001) (Figure 8) with no obvious heterogeneity (I^2=0.0%, P_{het} =0.650). The pooled results showed that patients with low AGR were at significantly greater risk of lymph node metastasis.

pM status and pTNM stage

Only one study by He et al[32] reported the associations of AGR with clinicopathologic features of the pM status and pTNM stage in RCC patients. Patients in low and high AGR groups showed significant differences in pM-stage (P<0.001) and pTNM stage (P<0.001).

Publication bias

Funnel plot and Begg's test were utilized to assess the publication bias. The result of Begg's test confirmed that there was no evidence of significant publication bias among studies (P_{OS}=0.707; P_{CSS}=0.308; P_{EFS}=1.000; $P_{tumor\ grade}$ = 1.000; P_{LVI}=1.000; P_{pT} = 1.000; P_{pN} = 0.462; Figure 9A–G).

Sensitivity analysis

Sensitivity analysis was performed to determine whether the pooled data would be affected by any individual cohorts, and the answers were negative (Figure 10A–G).

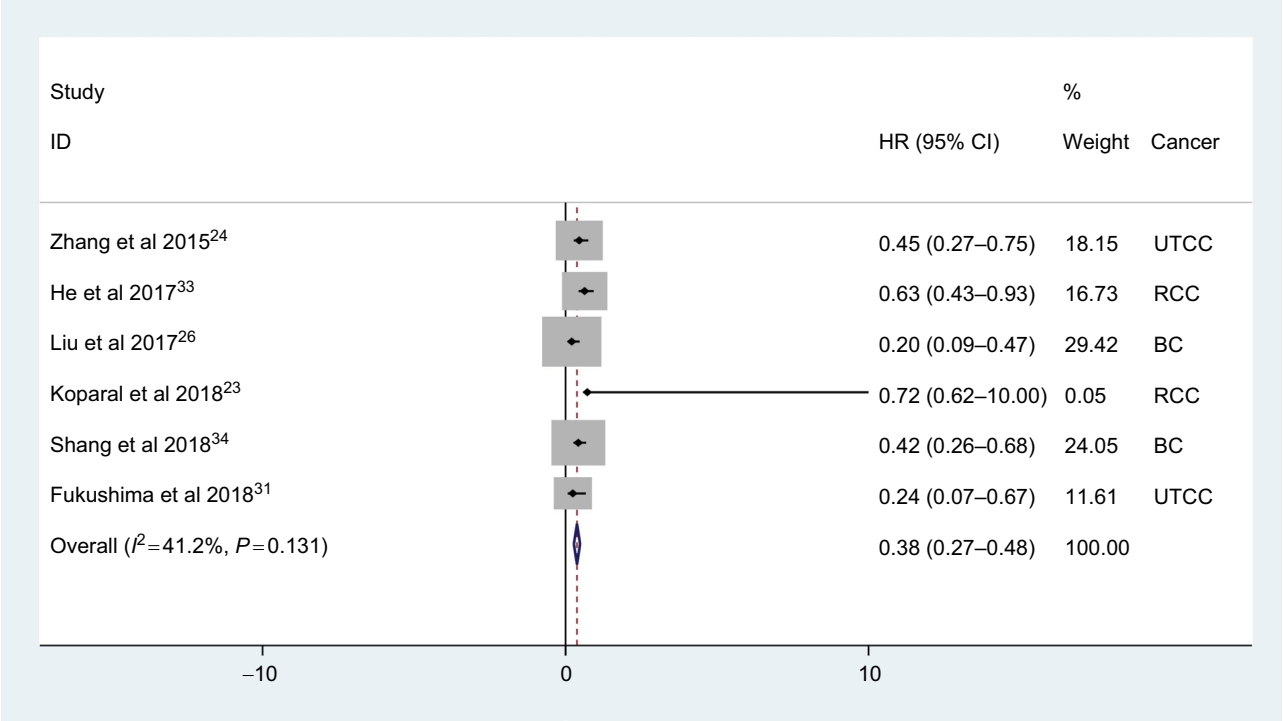

Figure 2 Meta-analysis of the relationship between AGR and OS.
Abbreviations: AGR, albumin-to-globulin ratio; BC, bladder carcinoma; OS, overall survival; RCC, renal cell carcinoma; UTCC, upper tract urothelial carcinoma.

Table 2 Subgroup analysis of the association between AGR and OS

Subgroup factor	Divided standard	No. of studies	Pooled HR (95% CI)	*P*-value	Heterogeneity	
					I^2 (%)	P_{het}
Cancer type	UTCC[24,31]	2	0.37 (0.18–0.56)	<0.001	14.5	0.279
	RCC[23,33]	2	0.63 (0.38–0.88)	<0.001	0.0	0.970
	BC[26,34]	2	0.30 (0.16–0.44)	<0.001	55.9	0.132
Sample size	≥300[33,34]	2	0.51 (0.35–0.67)	<0.001	36.8	0.208
	<300[23,24,26,31]	4	0.29 (0.16–0.42)	<0.001	0.0	0.445
Cutoff value	≥1.47[26,33,34]	3	0.38 (0.26–0.50)	<0.001	72.6	0.026
	<1.47[23,24,31]	3	0.37 (0.18–0.56)	<0.001	0.0	0.551

Abbreviations: BC, bladder carcinoma; RCC, renal cell carcinoma; UTCC, upper tract urothelial carcinoma.

Discussion

Recently, a series of scores/ratios based on hematological parameters have been reported, such as modified Glasgow prognostic score (mGPS) and C-reactive protein (CRP) and albumin ratio; they were found to be potential prognostic markers in various human cancers.[35–38] Additionally, some other important systemic inflammatory (SIR) markers, including neutrophil-to-lymphocyte ratio (NLR), neutrophil-platelet score and lymphocyte-to-monocyte ratio were reported; their prognostic values have also been widely evaluated in multiple malignancies, including gastric cancer, Ewing sarcoma and urologic tumors.[39–41]

To the best of our knowledge, as yet, no meta-analyses have been performed to assess the prognostic and clinicopathologic relevance of the AGR in cancers of the urinary system. In this meta-analysis, a total of eight studies comprising 2,668 patients were included to explore the association between AGR and the prognosis of patients with urologic cancers. The pooled results indicated that a low pretreatment AGR was significantly associated with worse clinical outcomes in urologic cancers.

Albumin accounts for the largest proportion of serum albumin in the human body. It is synthesized by hepatocytes and could be used as one of the evaluation indexes of liver

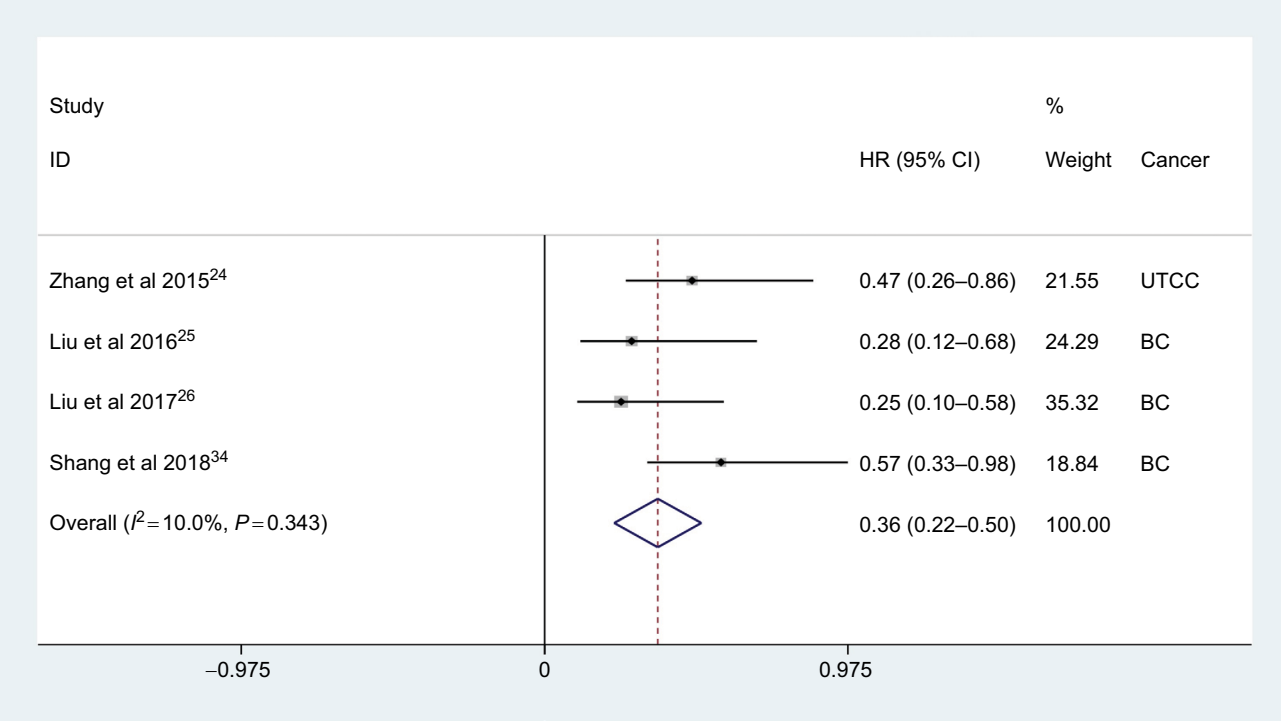

Figure 3 Meta-analysis of the relationship between AGR and CSS.
Abbreviations: AGR, albumin-to-globulin ratio; BC, bladder carcinoma; CSS, cancer-specific survival; UTCC, upper tract urothelial carcinoma.

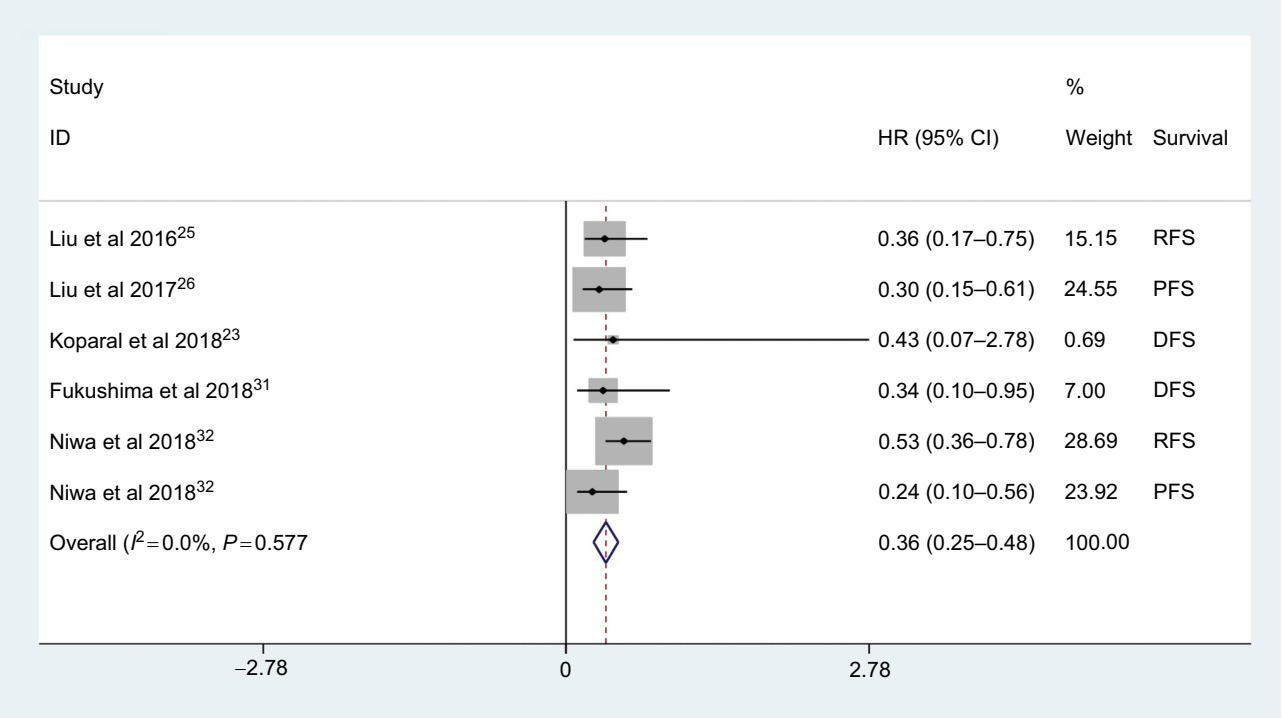

Figure 4 Meta-analysis of the relationship between AGR and EFS.
Abbreviations: AGR, albumin-to-globulin ratio; DFS, disease-free survival; EFS, event-free survival; PFS, progression-free survival; RFS, recurrence-free survival.

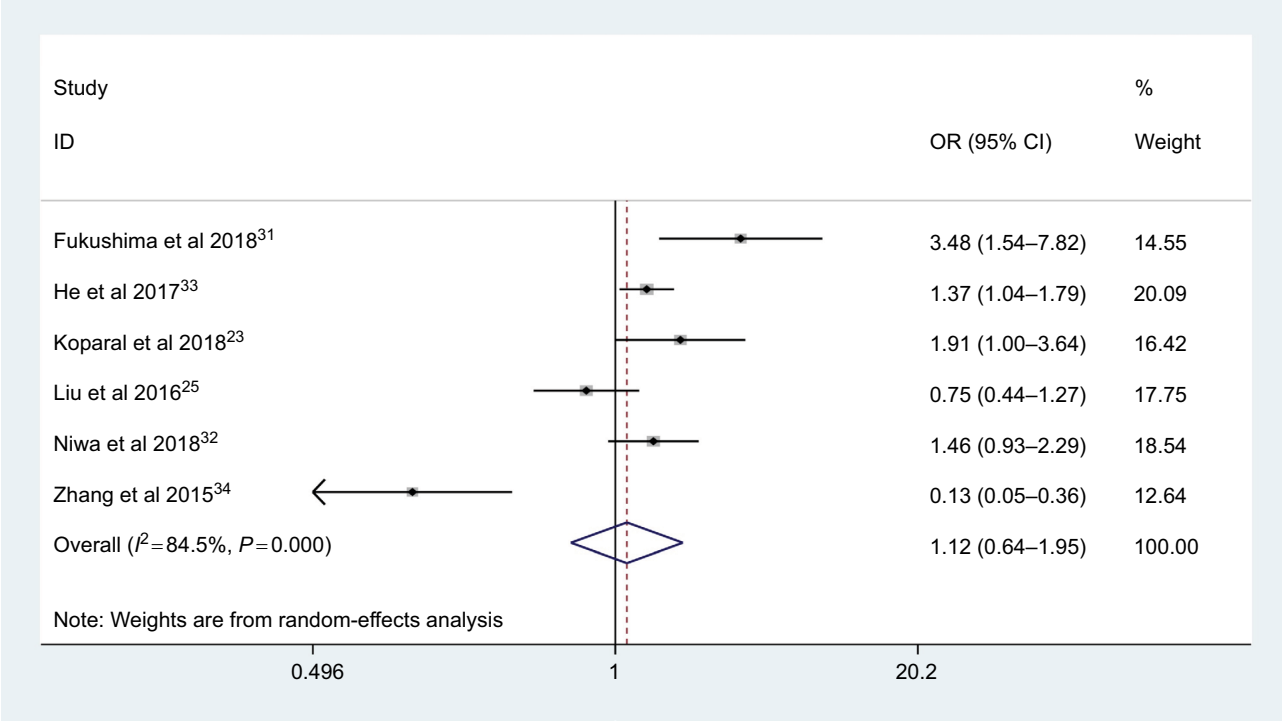

Figure 5 Meta-analysis of the association between AGR and tumor grade.
Abbreviation: AGR, albumin-to-globulin ratio.

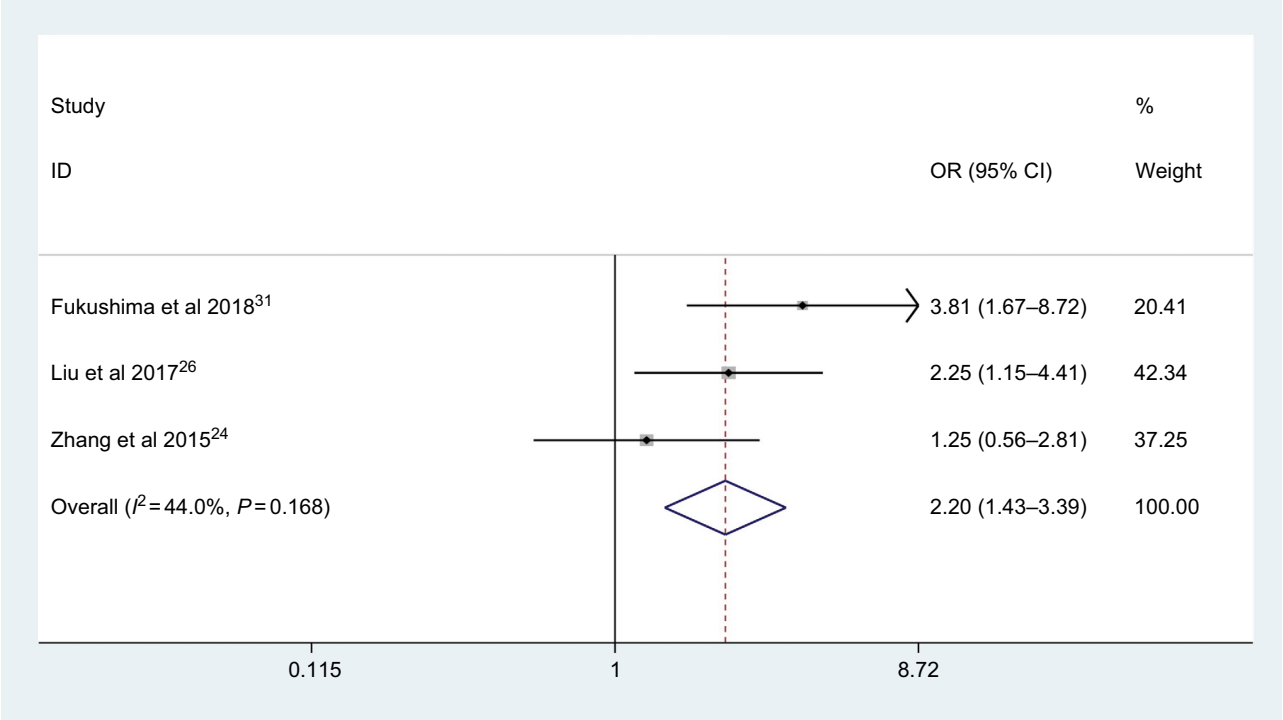

Figure 6 Meta-analysis of the association between AGR and lymphovascular invasion.
Abbreviation: AGR, albumin-to-globulin ratio.

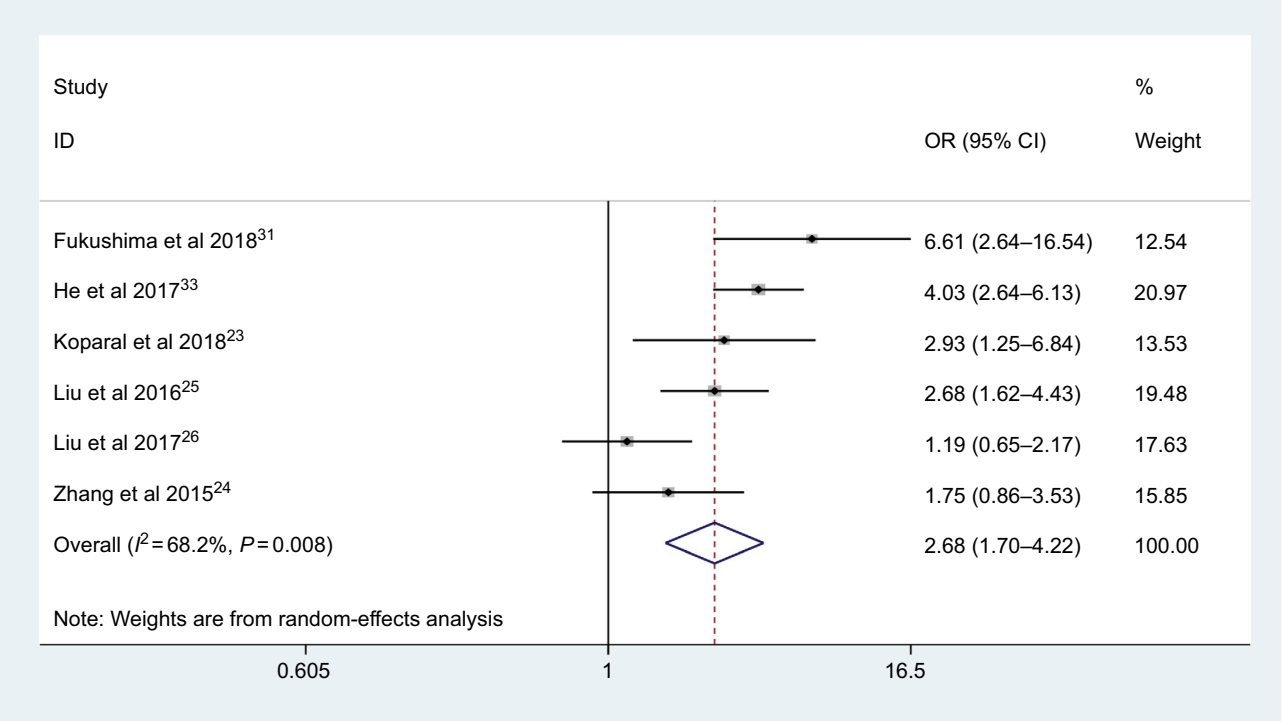

Figure 7 Meta-analysis of the association between AGR and pT status.
Abbreviation: AGR, albumin-to-globulin ratio.

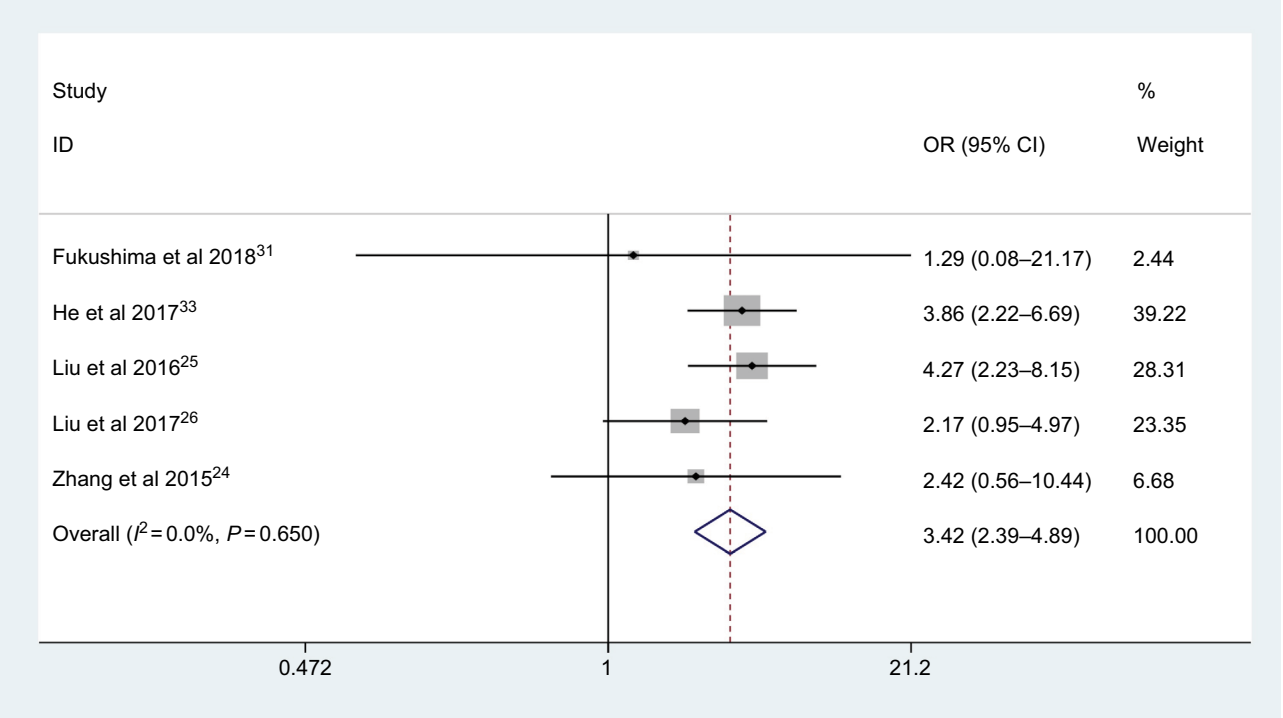

Figure 8 Meta-analysis of the association between AGR and pN status.
Abbreviation: AGR, albumin-to-globulin ratio.

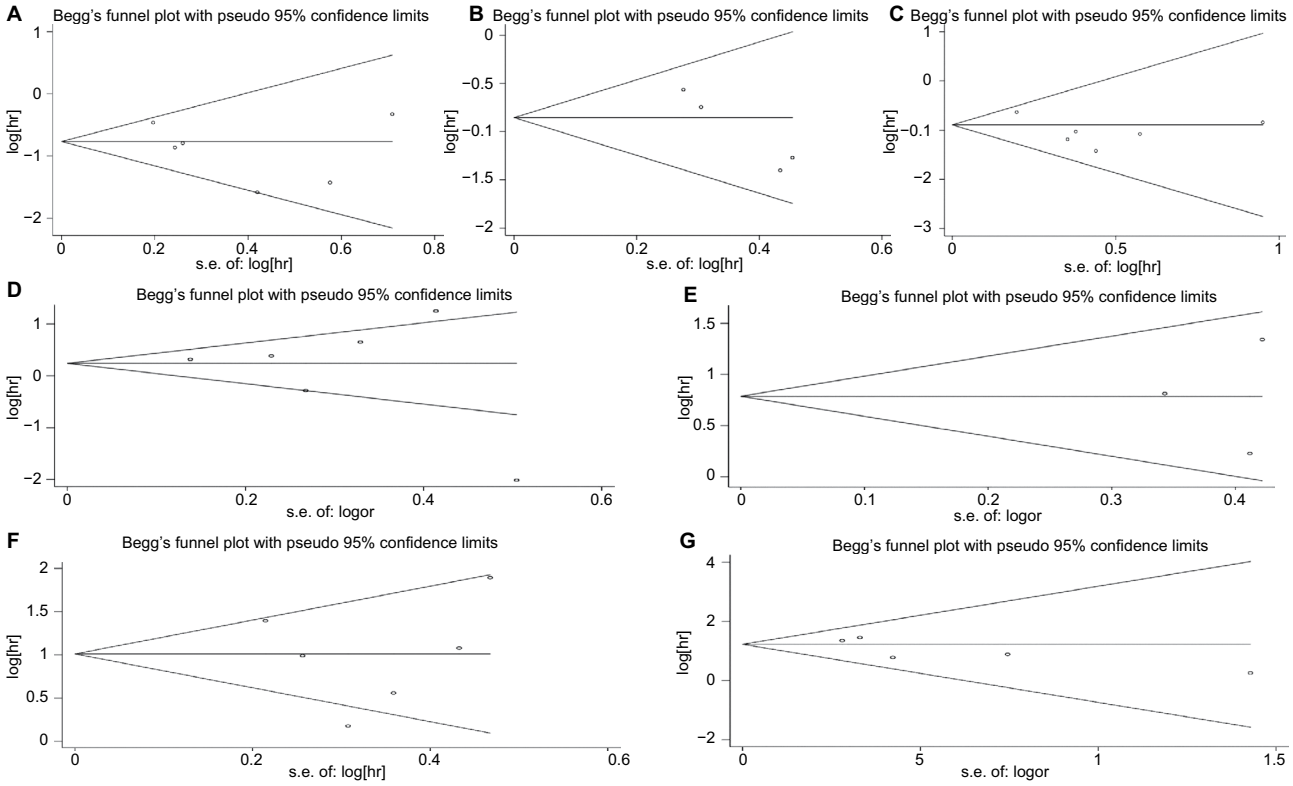

Figure 9 Publication bias assessment for OS (**A**), CSS (**B**), EFS (**C**), tumor grade (**D**), LVI (**E**), pT (**F**) and pN (**G**).
Abbreviations: CSS, cancer-specific survival; EFS, event-free survival; LVI, lymphovascular invasion; OS, overall survival.

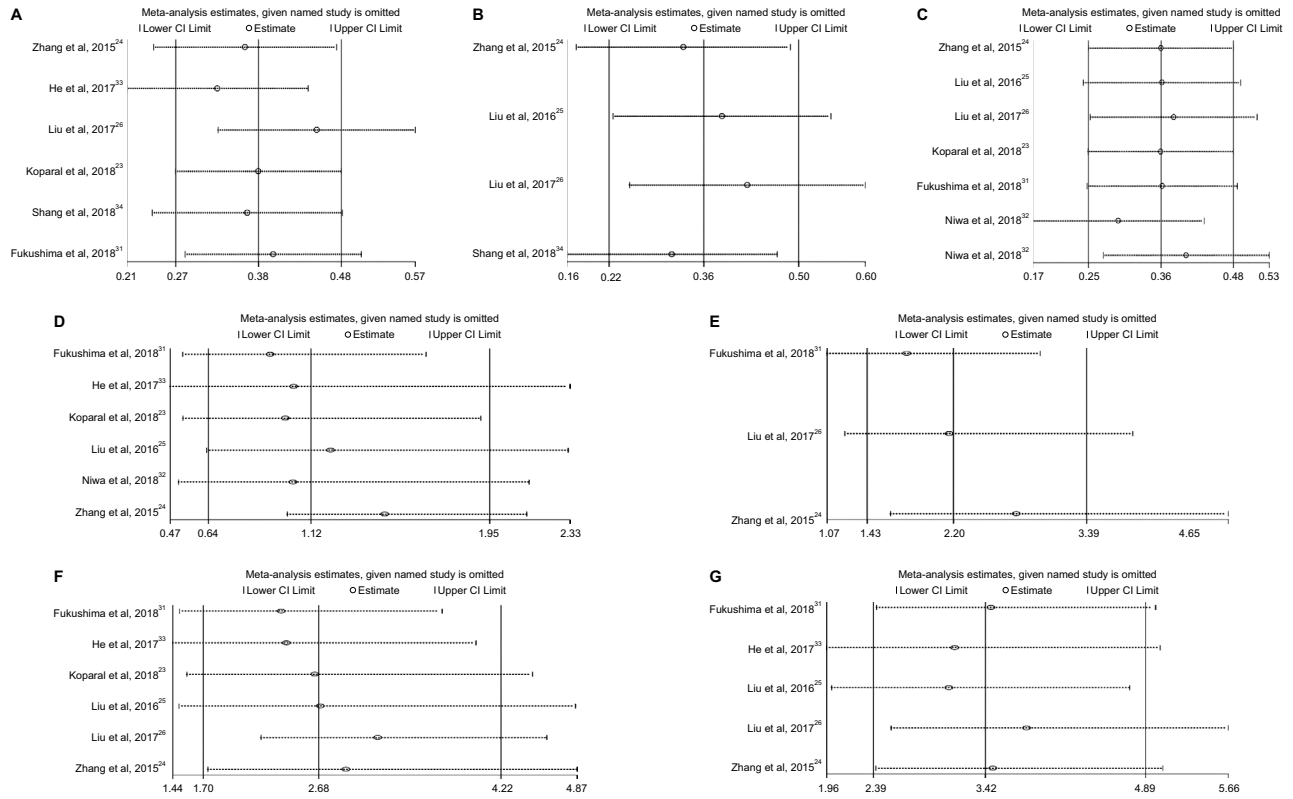

Figure 10 Sensitivity analysis for OS (**A**), CSS (**B**), EFS (**C**), tumor grade (**D**), LVI (**E**), pT (**F**) and pN (**G**).
Abbreviations: CSS, cancer-specific survival; EFS, event-free survival; LVI, lymphovascular invasion; OS, overall survival.

function and to assess subjects' nutritional status.[42–44] Besides, it plays multiple crucial roles in physiological activities, such as maintaining intravascular permeability stress and as a free radical scavenger.[45,46] Many previous studies also investigated the association between ALB and cancer. Serum albumin levels in cancer patients were significantly lower than in those without cancer,[46,47] and low albumin levels often mean poor nutritional status, and imply weakened several immune defense systems. Furthermore, albumin was considered as an important inflammatory response marker,[48] low albumin level was related to enhanced inflammatory response to the tumor and increased cytokine release, including interleukin(IL)–6 and tumor necrosis factor(TNF)-α, all of these might be surrogates for more aggressive tumor behaviors.[49,50] On the other hand, albumin has shown related antitumor and antioxidant effects; it could stabilize cell growth and DNA replication and inhibit the proliferation and growth of tumor cells.[51–53] Low albumin levels could also decrease the response to treatment in cancer patients,[54,55] and its clinical role as an unfavorable prognostic biomarker was also reported in various human malignancies.[56,57]

Referring to the nonalbumin proteins, they are also named as globulin (total protein – albumin). It comprises many different proinflammatory proteins, such as CRP, complement components, interleukins, immunoglobulins and so on. Prior studies had reported that inflammatory proteins were associated with tumor prognosis and progression, and displayed the predictive significance in different human cancers. For example, patients with elevated preoperative CRP had a poor survival in UTUC,[58–60] and high complement 3 levels were shown to be related to poor prognosis in patients with colorectal cancer,[61]and an increased preoperative gamma globulin levels predicted poor survival in lung cancer.[62] In addition, the globulins were shown to be closely related with chronic inflammation. Some serum globulins, such as IL-6, IL-8, TNF-α, VEGF, they were all inflammation-related factors, and played important roles in the tumor occurrence and progression. These inflammatory factors could promote the proliferation, invasion, metastasis of tumor cell, as well as subvert the host immune response, and contribute to the tumor drug resistance.[63,64] Overall, albumins and globulins are related with nutrition status, immuno-inflammatory reactions in the human body as well as the tumor progression and development. And the AGR takes both the ALB and GLB levels into account, it may more precisely and comprehensively reflect the body's nutritional and inflammatory states. It could be a significant prognostic biomarker that helpful to predict the clinical outcomes in cancers.

As far as we know, our study is the first meta-analysis to evaluate the prognostic significance of the AGR in patients with urologic cancers. We found that a low pretreatment AGR was closely related to worse clinical outcomes in cancers of the urinary system. A low pretreatment AGR was significantly related to shorter OS, worse CSS and inferior EFS in urologic cancers. And there were significant differences in the lymphovascular invasion, pT status and pN status among low and high AGR groups.

However, several limitations in the present meta-analysis should be taken into consideration. First, all included studies were designed retrospectively, and the number of total sample size included was relatively small. Second, studies enrolled were all involved in Asian ethnicity groups; this might limit the generalization of our conclusions; the prognostic value of AGR in more populations are needed for further confirmation. Third, the cutoff values for low AGR were different in those studies with a slight range from 1.24 to 1.68, a unified cutoff value is necessary before it could be really applied in clinical practices. The heterogeneity observed may be the inclusion of a small number of studies covering three different types of urologic tumor, each with their own particular morphologic, pathologic and clinical characteristics. Fourth, negative results were usually harder to be published than positive results, this might lead to some data missing, the number of studies exploring the relationship between AGR and some clinical features was small or none. Finally, some other factors, such as age, treatment strategy or clinical stages, also could affect the patient survival, and medication used and accompanied diseases of the patients could also influence the level of albumin and globulin.

In conclusion, our meta-analysis synthetically established a connection between pretreatment AGR and patients with urinary system cancers. A low AGR was significantly related to worse long-term survival and advanced clinicopathologic features. AGR would serve as a valuable and noninvasive prognostic marker in urologic cancers. Nevertheless, larger and prospective multicenter research trials should be conducted to validate the clinical application of pretreatment AGR in urologic cancers.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Relevant data for AGR and clinicopathologic features

Tumor grade				
	High grade		**Low grade**	
Study	Low AGR	High AGR	Low AGR	High AGR
Fukushima et al 2018[1]	31	22	15	37
He et al 2017[2]	166	195	205	329
Koparal et al 2018[3]	32	29	37	64
Liu et al 2016[4]	35	40	119	102
Niwa et al 2018[5]	53	96	59	156
Zhang et al 2015[6]	5	37	73	72
Lymphovascular invasion				
	Low AGR		High AGR	
Study	yes (+)	no (–)	yes (+)	no (–)
Fukushima et al 2018[1]	26	20	15	44
Liu et al 2017[7]	40	70	16	63
Zhang et al 2015[6]	13	65	15	94
pT status				
	pT3/4		pTa-2	
Study	Low AGR	High AGR	Low AGR	High AGR
Fukushima et al 2018[1]	25	9	21	50
He et al 2017[2]	83	35	288	489
Koparal et al 2018[3]	18	10	51	83
Liu et al 2016[4]	69	33	85	109
Liu et al 2017[7]	42	27	68	52
Zhang et al 2015[6]	21	19	57	90
pN status				
	Low AGR		High AGR	
Study	Positive (+)	Negative (–)	Positive (+)	Negative (–)
Fukushima et al 2018[1]	1	45	1	58
He et al 2017[2]	47	324	19	505
Liu et al 2016[4]	49	105	14	128
Liu et al 2017[7]	24	86	9	70
Zhang et al 2015[6]	5	73	3	106

Abbreviation: AGR, albumin-to-globulin ratio.

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