

Prognostic significance of the ratio of fibrinogen and albumin in human malignancies: a meta-analysis

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Background and aim: Serum fibrinogen and albumin are two important factors in systemic inflammation and these two factors are related to tumor progression. This study aimed to comprehensively reveal the prognostic value of the ratio of fibrinogen and albumin in malignant tumors.

Methods: We systematically searched relevant studies in PubMed, Web of Science and Embase up to November 21, 2018. Hazard ratios (HRs) or odds ratio (ORs) for overall survival (OS)/disease-free survival (DFS), as well as relevant clinical data, were collected for analysis; all data analyses were performed by using STATA/SE 14.

Results: Twelve cohort studies were included in this meta-analysis, with a total of 5,088 cases including 9 different kinds of tumors recruited. The pooled results showed that high albumin/fibrinogen ratio (FAR) and low fibrinogen/albumin ratio (AFR) were significantly associated with poor OS (HR=1.50, 95% CI: 1.30–1.70). Subgroup analyses for OS were also performed based on the disease type, detection method, follow-up time and treatment. Similarly, high FAR or low AFR indicated a worse DFS in cancer patients (HR=1.86; 95% CI: 1.41–2.31). In addition, high FAR or low AFR was statistically significant in relation to deeper tumor infiltration (OR=2.81, 95%CI: 1.67–4.72), positive lymph node metastasis (OR=1.57, 95%CI: 1.23–2.02) and distant metastasis (OR=2.30, 95% CI: 1.36–3.89) as well as advanced clinical stage (OR=2.02, 95% CI: 1.17–3.47).

Conclusions: The ratio of fibrinogen and albumin could act as a promising prognostic marker in human malignant tumors. It might assist physicians to select optimal treatments by identifying the current status of the patient. Future multicenter clinical trials are needed to validate its applications.

Keywords: albumin/fibrinogen ratio, fibrinogen/albumin ratio, malignant tumor, prognosis

Introduction

Inflammation has been convincingly considered as an important hallmark of cancer.^{1,2} It participates in the initiation, progression, and metastasis of human cancer.^{3,4} Tumor-associated inflammatory factors are closely related to the prognosis in cancer patients.^{5,6} Thereof, a series of inflammation-related index systems, including the systemic immune-inflammation index (SII), prognostic nutritional index (PNI) and C-reactive protein/albumin ratio (CAR), were reported as useful predictors in a variety of human tumors.^{7–9} As novel inflammation-based markers, the combination with fibrinogen and albumin, namely, fibrinogen/albumin ratio (FAR) and albumin/fibrinogen ratio (AFR), were proposed and reported currently. The prognostic power of the

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ratio of fibrinogen and albumin was exhibited in several types of human cancers.^{10–13} For example, the patients with high FAR or low AFR had significantly worse survival than those with low FAR or high AFR in the breast, esophageal and gastric cancer;^{10–12} while the ratio of fibrinogen and albumin was found to be no significant impact on overall survival in patients with colorectal cancer.¹³ Besides, the findings on the relationship between the ratio of fibrinogen and albumin and clinicopathologic characteristics were reported but not inconsistent or even contradictory in these studies. Therefore, in order to provide a more accurate understanding of the prognostic significance of circulating FAR or AFR in cancer patients, we performed this systematic review and meta-analysis by pooling all those available data together. The links between the ratio of fibrinogen and albumin and clinicopathological features were further investigated in this study.

Materials and methods

Search strategy and study selection

The current meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁴ PubMed, Embase, and Web of Science were comprehensively searched (up to November 21, 2018) with the following search terms: “albumin-to-fibrinogen or albumin/fibrinogen or fibrinogen-to-albumin or fibrinogen/albumin” combining with “cancer or tumor or malignancy or carcinoma or neoplasms”. The search strategy is provided in the Supplementary material.

The inclusion criteria were as follows:

1. The correlation between serum AFR/FAR and overall survival (OS) or disease-free survival (DFS) of primary human malignancies were reported;
2. The assessment of hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) was available;
3. The full-articles were published in the English language.

The exclusion criteria were as follows:

1. Non-original articles (reviews, comments, editorials or conference abstracts, or case reports);
2. Articles without sufficient survival data for HRs;
3. Duplicated studies.

Data extraction and quality assessment

Three aspects of data were collected from the enrolled studies by two authors (Zhang Y and Xiao GL), independently:

1. Basic information: first author's name, publication year, original country, disease type, the number of enrolled patients, included period, prognostic index, detection method, cut-off value, treatment methods.
2. Clinicopathological features: the distribution of gender, age distribution, histological grade, lymph node metastasis, distant metastasis, tumor invasion depth, clinical stage.
3. Prognostic data: survival type and follow-up time, and due to all included studies reported the HRs for OS/DFS in univariate and/or multivariate analyses, the HRs and 95% CIs were directly used to combine the individual result and the HRs from multivariate analyses were preferred.

In this study, we focused on two prognostic indicators, AFR and FAR. By definition, these two ratio values are opposite to each other. In this meta-analysis, the HR greater than 1 indicated a worse prognosis in subjects with high FAR or low AFR.

We also assessed the quality of included studies, this method was detailed described in the article by Lin et al¹⁵. It contains predefined nine items, a study could get a final score from the lowest 0 and the highest 9 after assessment.

Statistical analysis

All data analysis was performed using STATA/SE 14.1. The synthesized HRs with 95% CIs were used to evaluate the prognostic significance of FAR and AFR on OS/DFS in cancer survivors. And the pooled odds ratio (ORs) with 95% CIs were used to explore the relationship between FAR or AFR and pathological features. Heterogeneity among the enrolled literature was assessed by Higgins I^2 statistics and Cochran's Q. A fixed-effects model was used for non-significant heterogeneity across studies ($I^2 < 50\%$ and $P > 0.1$), otherwise, a random-effects model was utilized. Begg's test, as well as visible plots, were applied to assess the possibility of publication bias. The stability of the overall results was tested by sensitivity analysis, it was conducted by deletion of individual studies one by one.

Results

Finally, a total of 12 publications with 5,088 cases were included in this meta-analysis,^{10–13,16–23} the detailed process of study assessment is shown in Figure 1. All these enrolled studies were retrospective design, and they were written in the English language and published in 2017 and 2018. Among them, eleven studies were carried out in P.R. China, and one in Korea. A total of nine different kinds of human malignant tumors were investigated: breast cancer (BC), esophageal squamous cell carcinoma (ESCC), gastric cancer (GC), hepatocellular carcinoma (HCC),

non-small cell lung cancer (NSCLC), colorectal cancer (CRC), gallbladder cancer (GBC), chronic lymphocytic leukemia (CLL), and soft tissue sarcoma (STS). Among those studies, seven articles reported the relationship between the AFR and OS, and five studies investigated the association between the FAR and prognosis of OS. Two studies focused on the prognostic value of AFR/FAR on DFS. The quality of all included studies was good with a median score of 8 (range 7–9, Figure 2, Table S1). Table 1 presents the main characteristics of all included studies.

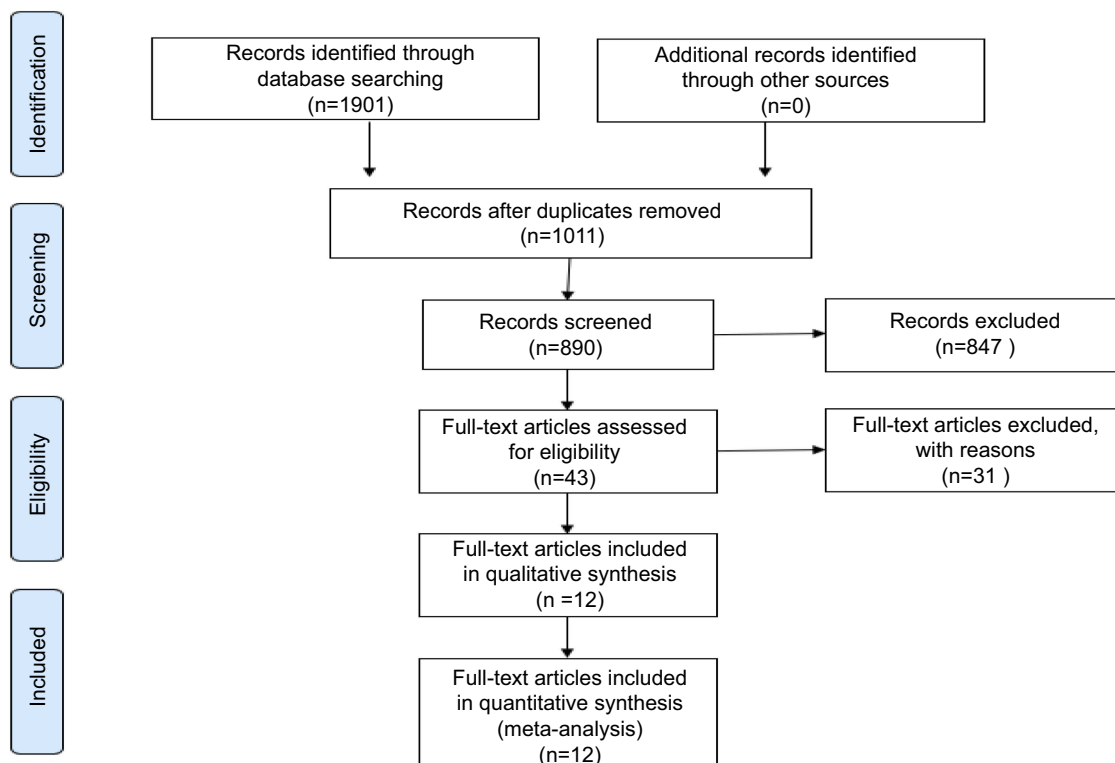


Figure 1 A flow diagram for the literature assessment process.

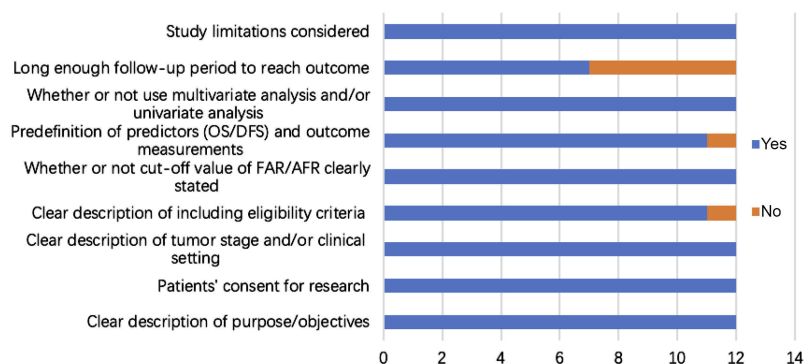


Figure 2 Quality assessment of 12 eligible cohort studies.

Abbreviations: OS, overall survival; DFS, disease-free survival; AFR, albumin/fibrinogen ratio; FAR, fibrinogen/albumin ratio.

Table 1 Characteristics of the included studies in this meta-analysis

Reference	Year	Country	Disease type	Patients (n)	Male/female	Included years	Age (years)*	Prognostic index	Detection method	Cut-off value	Survival type (analysis type)	Follow-up	Treatments	Stage
Hwang et al ¹⁰	2017	Korea	BC	793	0/793	2000–2016	54.1±12.3	FAR	ROC curve	7.1	OS (M)	≥5 years	With-surgery	I-II-III
Tan et al ¹¹	2017	China	ESCC	1135	888/247	2008–2010	58 (28–88)	FAR	X-tile software	0.08	OS (M)	≥5 years	With-surgery	NA
Zhang et al ¹²	2017	China	GC	360	261/99	2011–2013	58.24 ± 11.22	AFR	X-tile software	8.9	OS (M)	<5 years	With-surgery	II -III
Xu et al ¹⁶	2018	China	HCC	151	128/23	2006–2010	51 (22–78)	FAR	ROC curve	0.062	OS (M)	≥5 years	With-surgery	BCLC (0-A-B-C)
Chen et al ¹⁷	2018	China	NSCLC	529	312/217	2010–2015	62 (28–82)	AFR	ROC curve	9.67	OS (M), DFS (M)	≥5 years	With-surgery	I-II-III
Li et al ¹⁸	2018	China	NSCLC	412	317/95	2005–2014	60.33 ± 8.97	AFR	X-tile software	7.8	OS (M)	<5 years	Mixed	I-II-III-IV
Sun et al ¹³	2018	China	CRC	680	426/254	2008–2013	NA	AFR	X-tile software	9.2	OS (M)	<5 years	With-surgery	I-II-III
Xu et al ¹⁹	2018	China	GBC	154	63/91	2005–2017	64 (29–85)	FAR	ROC curve	0.08	OS (M)	≥5 years	With-surgery	I-II-III-IV
Zou et al ²⁰	2018	China	CLL	191	128/63	1995–2017	61 (23–86)	AFR	X-tile software	9.7	OS (M)	≥5 years	Untreated	Binet
Liang et al ²¹	2018	China	STS	310	174/136	1999–2013	39 (5–78)	FAR	ROC curve	0.0726	OS (M), DFS (U)	≥5 years	With-surgery	A-B-C stage I-II-III-IV
Gao et al ²²	2018	China	ESCC	153	128/25	2011–2013	61.93 ± 6.72	AFR	X-tile software	9.3	OS (M)	<5 years	With-surgery	0-I-II-III
Du et al ²³	2018	China	GBC	220	122/98	2009–2015	NA	AFR	X-tile software	15.45	OS (M)	<5 years	Mixed	Metastatic

Note: *Data shown as median (interquartile range) or mean ± standard deviation.

Abbreviations: BC, breast cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; GBC, gallbladder cancer; CLL, chronic lymphocytic leukemia; STS, soft tissue sarcoma; OS, overall survival; DFS, disease-free survival; AFR, albumin/fibrinogen ratio; FAR, fibrinogen/albumin ratio; ROC, receiver operating characteristic; M, multivariate analysis, U, univariate analysis, NA, not available.

The ratio of fibrinogen and albumin and OS

12 studies involving 5088 cases described the association between the ratio of fibrinogen and albumin and OS. No significant heterogeneity existed across studies ($I^2=30.7\%$, $P=0.145$), the fixed effects model was applied to merge the HRs and 95% CIs. The meta-analysis results showed that high FAR or low AFR was obviously correlated with poor survival

in cancer patients (HR=1.50, 95% CI: 1.30–1.70; $P<0.001$, Figure 3).

Furthermore, subgroup analyses were conducted based on the disease type, detection method, follow-up time and treatment. We found that high FAR or low AFR was closely correlated with shorter OS in gastrointestinal (GI) cancers (HR=1.40; 95% CI: 1.17–1.62; $P<0.001$) and non-GI cancers (HR=1.96; 95% CI: 1.49–2.42; $P<0.001$). For the

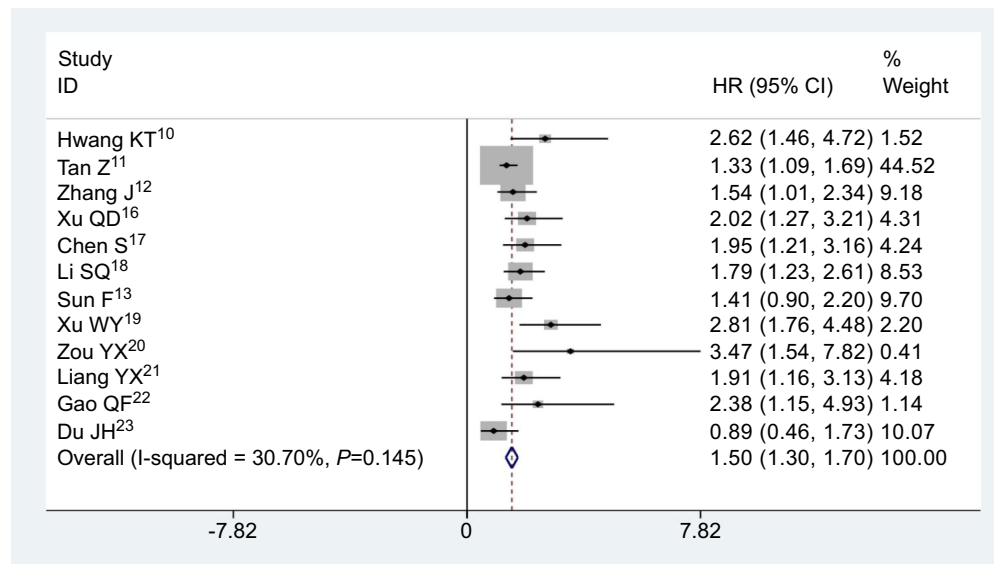


Figure 3 Pooled results for the correlation between the ratio of fibrinogen and albumin and OS in patients suffering from malignant tumors. **Abbreviations:** OS, overall survival; HR, hazard ratio; CI, confidence interval.

Table 2 Subgroup analysis for OS in the patient with malignant tumors

Stratified analysis	Studies (n)	Pooled results			Heterogeneity	
		HR	95% CI	P-value	I^2 (%)	P
Tumor type						
GI cancer	7	1.40	1.17–1.62	<0.001	37.6	0.142
Non-GI cancer	5	1.96	1.49–2.42	<0.001	0.0	0.780
Detection method						
ROC curve	5	2.13	1.64–2.63	<0.001	0.0	0.791
X-tile software	7	1.38	1.16–1.60	<0.001	11.4	0.342
Follow-up time						
<5 years	5	1.42	1.09–1.74	<0.001	18.4	0.297
≥5 years	7	1.56	1.30–1.81	<0.001	43.1	0.103
Treatment situation						
With-surgery	9	1.54	1.31–1.76	<0.001	20.3	0.262
Mixed	2	1.30	0.84–1.77	NS	71.7	0.060
Untreated	1	3.47	1.54–7.82	<0.001	–	–

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; GI, gastrointestinal; ROC, receiver operating characteristic, NS, not significant.

subgroup involving detection methods, it was observed that patients with high FAR or low AFR had a poorer OS in both groups using ROC curve (HR=2.13; 95% CI: 1.64–2.63; $P<0.001$) and X-tile software (HR=1.38; 95% CI: 1.16–1.60; $P<0.001$). Similarly, high FAR and low AFR were significantly related to shorter OS in group with follow-ups ≥ 5 years (HR=1.56; 95% CI: 1.30–1.81; $P<0.001$) and follow-ups <5 years (HR=1.42; 95% CI: 1.09–1.74; $P<0.001$). Obviously, high FAR and low AFR could serve as significant unfavorable factors in patients after curative resection (HR=1.54; 95% CI: 1.31–1.76; $P<0.001$). All results of subgroup analyses are presented in Table 2.

The ratio of fibrinogen and albumin and DFS

Only two studies reported the relationship between the ratio of fibrinogen and albumin and DFS, no significant heterogeneity was found among studies ($I^2=0.0\%$,

$P=0.707$), a fixed effects model was used to analyze the pooled HRs. As shown in Figure 4, the combined results indicated that the patients with high FAR or low AFR had a worse DFS (HR=1.86; 95% CI: 1.41–2.31; $P<0.001$).

The ratio of fibrinogen and albumin and clinicopathological features

The clinical relevance of the ratio of fibrinogen and albumin in tumor cases is presented in Table 3. High FAR and low AFR were found to be significantly correlated with deeper infiltration (OR=2.81, 95%CI: 1.67–4.72, $P=0.000$), positive lymph node metastasis (OR=1.57, 95%CI: 1.23–2.02, $P=0.000$), distant metastasis (OR=2.30, 95% CI: 1.36–3.89, $P=0.002$) and advanced clinical stage (OR=2.02, 95%CI: 1.17–3.47, $P=0.011$), whereas the high FAR or low AFR was not statistically significantly associated with histological grade (OR=1.29, 95%CI: 0.94–1.76, $P=0.115$).

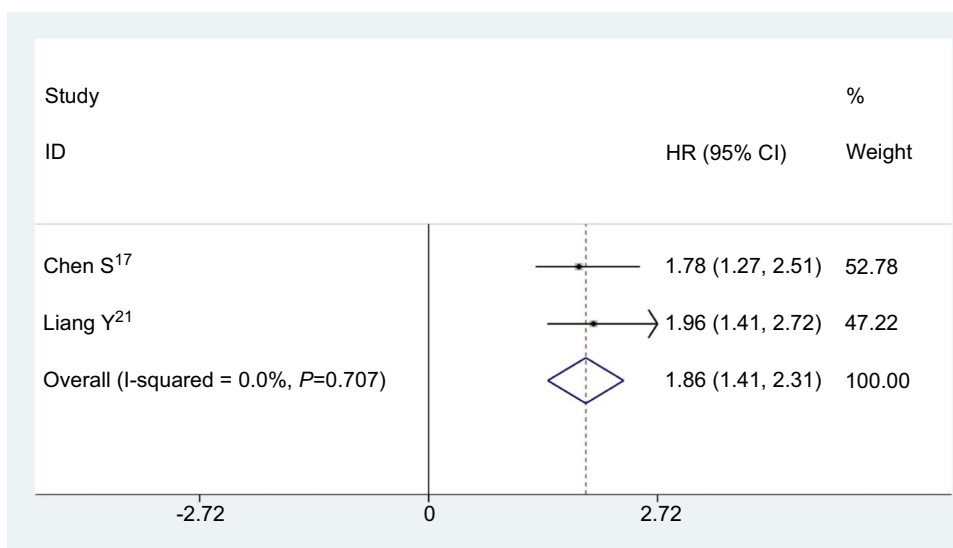


Figure 4 Pooled results for the correlation between the ratio of fibrinogen and albumin and DFS in cancer patients.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

Table 3 Results of the meta-analysis of clinicopathological characteristics

Clinicopathological parameter	Studies (n)	Pooled results			Heterogeneity		
		OR	95% CI	P-value	I^2 (%)	P	Model
Histological grade (G3/G4 vs.G1/G2)	8	1.29	0.94–1.76	0.115	67.0	0.004	Random
Infiltration (T3-4 vs Tis-I-2)	6	2.81	1.67–4.72	<0.001	73.6	0.002	Random
Lymph node metastasis (+ vs -)	7	1.57	1.23–2.02	<0.001	55.7	0.035	Random
Distant metastasis (+ vs -)	2	2.30	1.36–3.89	0.002	0.0	0.771	Fixed
Clinical stage (III-IV vs 0-I-II)	6	2.02	1.17–3.47	0.011	77.3	0.001	Random

Abbreviations: OR, odds ratio; CI, confidence interval.

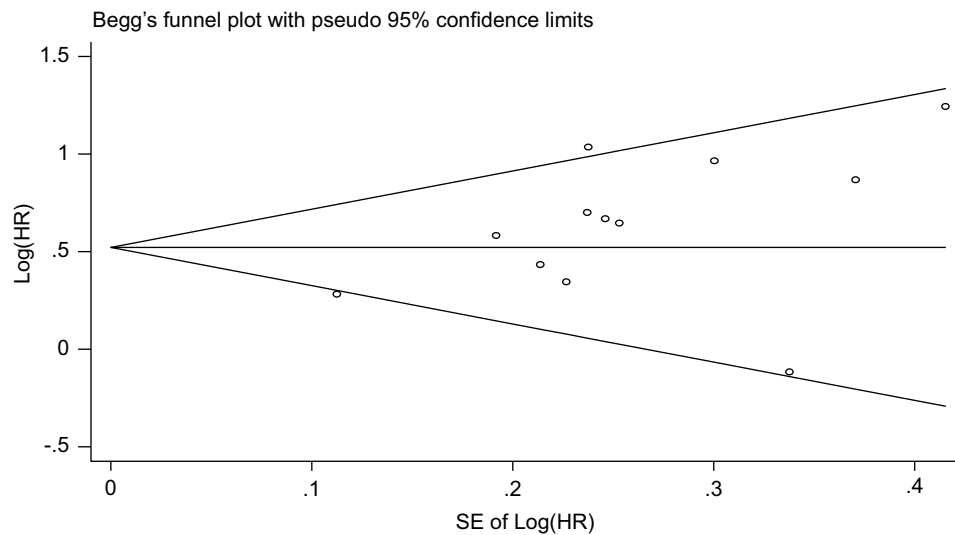


Figure 5 Begg's funnel plot for OS.
Abbreviations: OS, overall survival; HR, hazard ratio.

Publication bias

Begg's funnel plot was symmetrical (Figure 5) and Begg's test had a value of 0.086 ($P > 0.05$), which suggests the absence of publication bias.

Sensitivity analysis

Sensitivity analysis indicated that the overall results in this meta-analysis were stable and reliable (Figure 6).

Discussion

The relationships between FAR and AFR and prognosis were reported in previous studies, however, their prognostic and clinical-pathological values in cancer patients remains undetermined. Hence, we performed this meta-analysis for the first time to figure out the prognostic impact of this scoring system in cancers. We included 12 cohort studies with a total of 5088 cancer cases, and 9 different kinds of human malignancies were enrolled. By

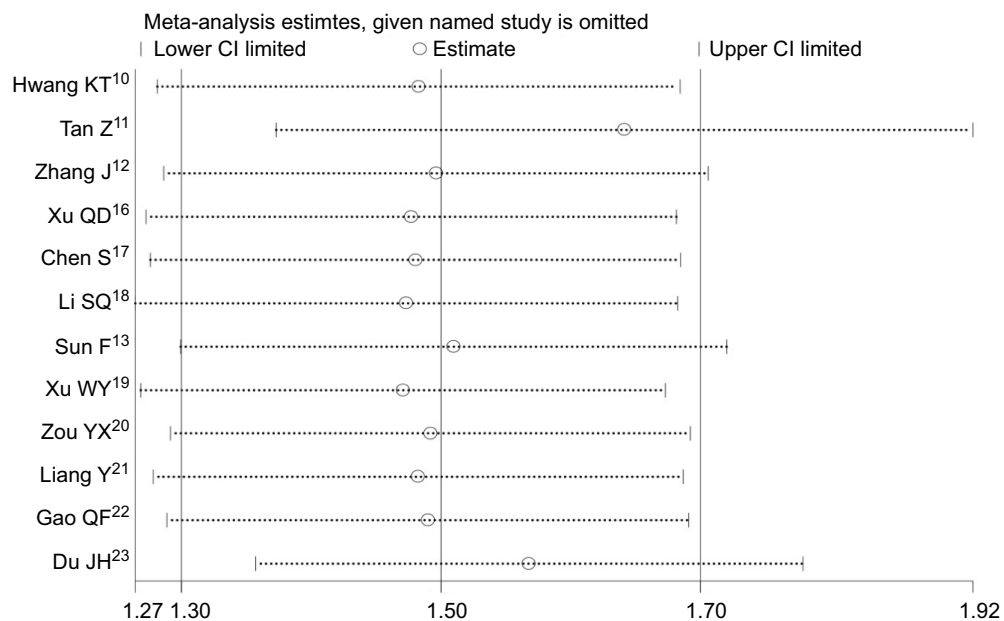


Figure 6 Sensitivity analysis test for OS.
Abbreviations: OS, overall survival; CI, confidence interval.

pooling all the available OS data from multivariate analyses, we found that patients with high FAR or low AFR had a significantly lower OS rate than those with low FAR or high AFR (HR=1.50, 95% CI: 1.30–1.70; $p<0.001$), and moreover, high FAR or low AFR was found to be an independent factor of unfavorable OS in patients with GI cancers or non-GI cancers, and there was clear evidence that high FAR and low AFR could be a significant predictor in long-term overall survival rate (≥ 5 years) or short-term survival rate (< 5 years) between the two groups. In addition, the ratio of fibrinogen and albumin might be an important predictor for DFS in cancers (HR=1.86; 95% CI: 1.41–2.31; $p<0.001$). Similarly, the significant associations between clinicopathological features and this scoring system were also found in tumor infiltration ($p<0.001$), lymph node metastasis ($p<0.001$), distant metastasis ($p=0.002$) and clinical stage ($p=0.011$).

Although the specific mechanism for the roles of this scoring system predicting cancer progression and prognosis remains incompletely understood, there are some potential explanations for this. Fibrinogen level was frequently observed elevated in serum of the cancer patients and hyper-fibrinogenemia was demonstrated to be related to unfavorable prognoses in multiple tumors, including liver cancer, lung cancer, esophageal cancer and urinary tract urothelial carcinoma.^{24–27} Fibrinogen is an important factor involved in hemostasis, and the coagulation system is often abnormally activated in cancer patients,^{2,28,29} and it could possess anti-cancer properties as a compound with sodium selenite.⁶ And as an acute-phase-response protein, fibrinogen could also reflect the status of the systemic inflammatory response, which was closely related to carcinogenesis.^{30–32} In addition, fibrinogen could regulate tumor cell growth as an extracellular matrix protein by binding to multiple growth factors,^{33–35} and enhance cell migration, invasion, and metastasis involving epithelial-mesenchymal transition.^{36–38} Fibrinogen also played a vital role in angiogenesis, which closely participated in the progression of cancer.^{39–42}

On the other side, albumin has been considered as an indicator that could objectively reflect the nutritional status, low serum albumin level often heralds malnutrition, and indicates weakened immunity in subjects.^{43–45} In addition, albumin is also a crucial factor that involved in the systemic inflammatory response, low concentration of albumin was shown to be related to the enhancement of inflammatory response to cancers and then release of

a series of cancer-related cytokines, which could contribute to tumor development.^{46–48} Furthermore, clinical studies showed that there was a significant association between albumin level and prognosis in various types of tumors, the low pretreatment serum albumin level yielded an unfavorable prognosis in cancers.^{49–51}

Several limitations in our meta-analysis should be carefully considered. First, the number of cohort studies that included was relatively small and the total sample size was also limited. Second, all included studies were carried out in two Asian countries, this might affect the applicability of our conclusions, more studies with different populations are required in the future. Third, we only included full-text articles published in the English language. Fourth, the prognostic roles of the ratio of fibrinogen and albumin in specific cancers were not investigated for the lack of sufficient data. Fifth, only two studies reported the data of DFS rate, and as a result, their impacts on DFS should be further confirmed. Last but not least, the cut-off of this scoring system varied among studies. As the limitations mentioned above, further researches should be embraced to verify and update our findings.

In summary, this meta-analysis systematically assessed the prognostic impact of the novel inflammation-based prognostic scores (FAR and AFR) on cancer patients. We found that high FAR and low AFR indicated worse prognosis and adverse clinical progression in tumors. And the prognostic validity of AFR and FAR should be globally checked for various cancer types, as these parameters can be easily obtained in a cheap and non-invasive manner, this might lead to their incorporation in official cancer management guidelines.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Literature search strategy in PUBMED

((albumin-to-fibrinogen[All Fields] OR albumin/fibrinogen[All Fields]) OR fibrinogen-to-albumin[All Fields]) OR fibrinogen/albumin[All Fields] AND (((("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR

"neoplasms"[All Fields] OR "tumor"[All Fields])) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "malignancy"[All Fields])) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields])) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields])) AND ("loattrfull text"[sb] AND ("0001/01/01"[PDAT]: "2018/11/21"[PDAT]) AND English[lang]).

Table 1. Study quality of the 12 eligible studies

Reference	Cancer type	Clear description of purpose/objectives	Patients' consent for research	Clear description of tumor stage and/or clinical setting	Clear description of including eligibility criteria or exclusion criteria	Whether or not cut-off value of FAR/AFR clearly stated	Predefinition of predictors (OS/DFS) and outcome measurements	Whether or not use multivariate analysis and/or univariate analysis	Long enough follow-up period to reach outcome	Study limitations considered	Quality score (0–9)
Hwang et al ¹	BC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Tan et al ²	ESCC	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
Zhang et al ³	GC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8
Xu et al ⁴	HCC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Chen et al ⁵	NSCLC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Li et al ⁶	NSCLC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8
Sun et al ⁷	CRC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8
Xu et al ⁸	GBC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Zou et al ⁹	CLL	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	7
Liang et al ¹⁰	STS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Gao et al ¹¹	ESCC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8
Du et al ¹²	GBC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8

Abbreviations: BC, breast cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; GBC, gallbladder cancer; CLL, chronic lymphocytic leukemia; STS, soft tissue sarcoma; OS, overall survival; DFS, disease-free survival; AFR, albumin/fibrinogen ratio; FAR, fibrinogen/albumin ratio.

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