World Journal of Gastroenterology

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World J Gastroenterol 2018 August 7; 24(29): 3281-3292

DOI: 10.3748/wjg.v24.i29.3281

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Prognostic significance of the fibrinogen-to-albumin ratio in gallbladder cancer patients

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Author contributions: Xu WY conceived the research, collected the clinical data and wrote the manuscript that led to the submission; Xu WY, Zhang HH, and Xiong JP helped to collect the clinical data and followed up with the patients; Lin JZ, Long JY, and Yang XB helped to analyze the data, Bai Y and Zheng YC revised the manuscript, Zhao HT and Sang XT provided financial support for this work; Zhao HT and Sang XT are co-corresponding authors, and they contributed equally to this work; all authors read and approved the final manuscript.

Supported by the National Key Project Research and Development Projects, No. S2016G9012; International Science and Technology Cooperation Projects, No. 2015DFA30650; and The Capital Special Research Project for Clinical Application, No. Z151100004015170.

Institutional review board statement: The publication of this manuscript has been reviewed and approved by the PUMCH Institutional Review Board.

Informed consent statement: All patients and their families signed informed consent statements before surgery, and the type of surgical procedure was performed according to the approved guidelines.

Conflict-of-interest statement: We declare that the authors have no conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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Received: April 20, 2018
Peer-review started: April 20, 2018
First decision: June 6, 2018
Revised: June 16, 2018
Accepted: June 27, 2018
Article in press: June 27, 2018
Published online: August 7, 2018

Abstract

AIM

To investigate the prognostic role of fibrinogen-to-albumin ratio (FAR) on patients with gallbladder cancer (GBC) in this study.

METHODS

One hundred and fifty-four GBC patients were retro-

spectively analyzed, who received potentially curative cholecystectomy in our institute from March 2005 to December 2017. Receiver operating characteristic curve (ROC curve) was used to determine the optimal cut-offs for these biomarkers. In addition, Kaplan-Meier survival analysis as well as multivariate analysis were applied for prognostic analyses.

RESULTS

ROC curve revealed that the optimal cut-off value for FAR was 0.08. FAR was significantly correlated with age (P = 0.045), jaundice (P < 0.001), differentiation (P = 0.002), resection margin status (P < 0.001), T stage (P < 0.001), TNM stage (P < 0.001), and CA199 (P < 0.001) as well as albumin levels (P < 0.001). Multivariate analysis indicated that the resection margin status [hazard ratio (HR): 2.343, 95% confidence interval (CI): 1.532-3.581, P < 0.001], TNM stage (P = 0.035), albumin level (HR = 0.595, 95%CI: 0.385-0.921, P = 0.020) and FAR (HR: 2.813, 95%CI: 1.765-4.484, P < 0.001) were independent prognostic factors in GBC patients.

CONCLUSION

An elevated preoperative FAR was significantly correlated with unfavorable overall survival in GBC patients, while an elevated preoperative albumin level was a protective prognostic factor for patients with GBC. The preoperative FAR could be used to predict the prognosis of GBC patients, which was easily accessible, cost-effective and noninvasive.

Key words: Gallbladder cancer; Fibrinogen; Albumin; Fibrinogen-to-albumin ratio; Prognosis; Survival

Core tip: The vital prognostic significance of fibrinogen and serum albumin has been confirmed in diverse malignancies, presenting host hemostasis and nutrition, respectively. Moreover, elevated plasma fibrinogen and reduced serum albumin levels are significantly related to shortened survival of cancer patients. It is reported that fibrinogen-to-albumin ratio (FAR) is more potent in predicting cancer patient prognosis than elevated fibrinogen or reduced serum albumin level alone. Nevertheless, there has been no study on the prognostic role of FAR in gallbladder cancer (GBC). Herein, we defined an elevated preoperative FAR, featured by noninvasiveness, cost-effectiveness and easily-accessible, which was a potential prognostic indicator for GBC.

Xu WY, Zhang HH, Xiong JP, Yang XB, Bai Y, Lin JZ, Long JY, Zheng YC, Zhao HT, Sang XT. Prognostic significance of the fibrinogen-to-albumin ratio in gallbladder cancer patients. *World J Gastroenterol* 2018; 24(29): 3281-3292 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i29/3281.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i29.3281

INTRODUCTION

Gallbladder cancer (GBC) is an uncommon malignancy among all types of cancer, but is the fifth most common gastrointestinal malignancy. Meanwhile, GBC is the most prevalent and aggressive cancer of the biliary tract[1-3]. Despite recent encouraging progress in the diagnosis and treatment of GBC, it is still a highly lethal disease, with overall 5-year survival rate under 5%[4]. Only surgical intervention renders probability of a long-term survival, however, most GBC patients generally present at late stage, with unresectable lesion. To be specific, fewer than 20% of cases are amenable to surgical treatment[5,6].

At present, a few clinicopathological parameters, such as clinical stage, performance status (PS), and pathological classification, have been demonstrated as independent survival predictors in patients harboring various types of common solid tumors[7]. Nevertheless, despite the wide application of high-resolution imaging systems, it is rather difficult to obtain accurate classification of clinical stage, and objective judgement of PS[8-10]. In addition, the pathological stage of tumor samples in these subjects is not as informative as that in untreated subjects[11]. In order to guarantee potent intense neoadjuvant therapy as well as regular follow-up in high-risk subjects, it is necessary to explore a simple and cost-effective predictor for the postoperative overall survival (OS) prior to surgery.

Accumulating evidence has demonstrated that nutritional deficiencies, hemostatic factors and systemic inflammatory response (SIR) are likely to be critically involved in the progression of human malignancies[12]. Fibrinogen plays an important regulatory role in both inflammation and cancer progression, including proliferation, angiogenesis as well as migration of tumor cells[13]. Serum albumin levels reflect the SIR of host and nutritional status[14-16]. Recently, accumulating researches have shown that both fibrinogen and serum albumin are important prognostic predictors in various cancers, and elevated plasma fibrinogen and lower serum albumin levels are significantly correlated with shorter survival in tumor patients[17-21].

From the results of the above studies, we can naturally hypothesize that the fibrinogen-to-albumin ratio (FAR) might be more powerful than elevated fibrinogen or lower serum albumin level in predicting the prognosis of patients with malignant tumors. In fact, Tan *et al*[22] have indicated that the preoperative FAR is an independent prognostic indicator for esophageal squamous-cell carcinoma (ESCC) patients, while Hwang *et al*[23] have indicated that the FAR is a more significant prognostic indicator than either indicator alone (elevated fibrinogen or lower serum albumin).

To our knowledge, there are no relevant studies concerning the prognostic significance of FAR in GBC patients. Herein, the study was designed to explore the prognostic roles of the preoperative FAR in GBC in terms of OS.

MATERIALS AND METHODS

Patients

Eligible patients were included in this study according to the following criteria: (1) patients with histological diagnosis of GBC; (2) GBC patients without other coexisting malignancies; (3) patients not undergoing other treatments before enrollment; (4) patients with complete clinical information and available follow-up data; and (5) patients aged > 18 years. The exclusion criteria were listed as follows: (1) patients with acute infection or chronic active inflammatory disease; (2) patients with collagen diseases, anemia and other diseases concerning the hematological system; (3) patients who received anticoagulant treatment or albumin transfusions before treatment; (4) patients with liver disease; and (5) patients with perioperative surgery-associated mortality. As a result, 154 GBC patients were retrospectively included and analyzed, who underwent potential curative resection at Peking Union Medical College Hospital of Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS & PUMC) from January 2005 to May 2017.

Data collection

Baseline clinicopathological characteristics, including age, gender, comorbidities, ABO blood group, pathological classifications, tumor differentiation, resection margin status, maximal tumor diameter, TNM stage, and preoperative CA199, fibrinogen, and albumin levels. Patient age referred to the age at diagnosis of primary GBC. The eighth edition of the American Joint Committee on Cancer (AJCC-8th) TNM classification was utilized for TNM stage.

Ethical statement

The study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital of CAMS & PUMC. All patients signed written informed consent. The study was carried out according to the ethical standard of the World Medical Association Declaration of Helsinki[24].

Fibrinogen and albumin measurements

Blood specimens were collected before breakfast within seven days before surgery, in order to assess the preoperative plasma fibrinogen and serum albumin concentrations. Afterwards, Datafai Fibrinogen (Sysmex Corporation, Kobe, Japan) and CA7000 analyzer (Sysmex Corporation, Kobe, Japan) were employed to assess fibrinogen level using the previously-mentioned Clauss method[25]. The normal reference values of plasma fibrinogen and serum albumin were 2-4 g/L and 35-51 g/L, respectively, according to relevant instructions.

FAR

FAR was defined by dividing the preoperative fibrinogen level by the preoperative serum albumin level.

Treatments and Follow up

All subjects received potential curative gallbladder resection at Peking Union Medical College Hospital of CAMS & PUMC. The extent of resection was classified as modified radical cholecystectomy or radical cholecystectomy and systemic therapy according to the extent of tumor invasion, which was identified by preoperative auxiliary examination results. Follow-up visits in our center were carried out every three months for the first two years, every six months for the third year and annually thereafter. The follow-up period was defined from the date of surgery to death or the last follow-up visit.

Statistical analysis

The continuous data with normal distribution were shown as the mean ± standard deviation (Kolmogorov-Smirnov test, $P > 0.05$), and those with abnormal distribution were expressed as the median (minimum-maximum). Frequencies and percentages were used for the categorical variables. Chi-square test or Fisher's exact test was utilized to assess differences in baseline clinicopathological characteristics between groups. OS referred to the duration from the date of surgery to death or the last follow-up visit. The optimal cut-off values of fibrinogen, albumin and FAR were identified by the receiver operating characteristic (ROC) curve. Kaplan-Meier method was used to generate the survival curves, followed by analysis by log-rank test. Additionally, multivariate Cox proportional hazards model was used to further assess those significant factors indicated by univariate analysis. SPSS version 24.0 (IBM Corp., Armonk, NY, United States) was utilized for statistical analysis. A two-sided $P < 0.05$ was considered as statistical significance, and 95% confidence intervals (CIs) were calculated.

RESULTS

Patient characteristics

All the 154 GBC patients in this study were treated at Peking Union Medical Hospital from January 2005 to May 2017. The median follow-up period was 17 mo. In total, 103 subjects died during the follow-up period, with an estimated median OS of 14.5 mo (range: 0.5-153.0 mo). The 1- and 2-year survival rates were 55.8% and 35.7%, respectively. The clinical data of all patients who met all criteria were analyzed. Among these patients, the median age at diagnosis was 64 years old (range: 29-85 years old), of whom, 98 (63.6%) were > 60 years old. Ninety-one (59.1%) patients were female. One hundred fifty (97.4%) patients were pathologically diagnosed with adenocarcinoma, three (1.9%) with adenosquamous cell carcinoma and one (0.6%) with papillary carcinoma. Ninety-four (61.0%) patients were histologically diagnosed with moderately or well-differentiated disease. Fifty-eight (37.7%) patients harbored a positive resection margin. According to the

Table 1 Baseline characteristics of 154 gallbladder cancer patients who underwent potential curative cholecystectomy *n* (%)

Characteristic	Patients (*n* = 154)
Age (yr)	64 (29-85)
⩽ 60	56 (36.4)
> 60	98 (63.6)
Sex	
Male	63 (40.9)
Female	91 (59.1)
Cholecystolithiasis	
Absent	79 (51.3)
Present	75 (48.7)
Diabetes	
Absent	116 (75.3)
Present	38 (24.7)
Jaundice	
Absent	129 (83.8)
Present	25 (8.9)
Blood groups	
A	43 (27.9)
B	56 (36.4)
AB	9 (5.8)
O	46 (29.9)
Pathological types	
Adenosquamous carcinoma	3 (1.9)
Adenocarcinoma	150 (97.4)
Papillocarcinoma	1 (0.6)
Degree of differentiation	
Poor	60 (39.0)
Moderate-well	94 (61.0)
Resection margin status	
Negative	96 (62.3)
Positive	58 (37.7)
Maximum tumor diameter (cm)	3 (0.2-13)
⩽ 2.45	68 (44.2)
> 2.45	86 (55.8)
T stage	
Tis-T1a	10 (6.5)
T1b-T2b	29 (18.8)
T3	103 (66.9)
T4	12 (7.8)
N stage	
0	98 (63.6)
1	47 (30.5)
2	9 (5.8)
Distant metastasis	
Absent	142 (92.2)
Present	12 (7.8)
TNM stage	
0- Ⅰ stage	16 (10.4)
ⅡA-ⅡB stage	16 (10.4)
ⅢA-ⅢB stage	92 (59.7)
ⅣA-ⅣB stage	30 (19.5)
CA199 (U/mL)	69.3 (0.6-10524)
⩽ 39	66 (42.9)
> 39	88 (57.1)
Fibrinogen concentration (g/L)	3.54 (1.71-7.47)
⩽ 3.47	75 (48.7)
> 3.47	79 (51.3)
Albumin levels (g/L)	41.0 (20.0-50.0)
⩽ 40.5	78 (50.6)
> 40.5	76 (49.4)
FAR	0.09 (0.04-0.25)
⩽ 0.08	71 (46.1)
> 0.08	83 (53.9)

FAR: Fibrinogen to albumin ratio.

TNM staging, most patients (59.7%) were classified as stage ⅢA-ⅢB. The detailed information of baseline characteristics of patients was shown in Table 1.

The optimal cut-off value of the preoperative fibrinogen concentration, albumin level and FAR for survival analysis

The ROC curves of OS were generated to validate the optimal cut-off values for the preoperative fibrinogen concentration, albumin level and FAR (Figure 1). The median plasma fibrinogen concentration in all patients was 3.54 g/L (range: 1.71-7.47 g/L) (Table 1). As shown in Figure 1A, the area under the curve (AUC) was recorded as 0.735 (95%CI: 0.654-0.816), and the optimal cut-off value of preoperative fibrinogen concentration for OS was 3.47 g/L, with the highest sensitivity and specificity of 0.709 and 0.721, respectively. Based on this cut-off, there were 75 patients (48.7%) with a fibrinogen concentration ⩽ 3.47 g/L, and 79 patients (51.3%) with a fibrinogen concentration > 3.47 g/L (Table 2).

The median serum albumin level in all patients was 41.0 g/L (range: 20.0-40.0 g/L) (Table 1). As shown in Figure 1B, the AUC was recorded as 0.648 (95%CI: 0.562-0.735), and the optimal cut-off value of the preoperative albumin level for OS was 40.5 g/L, with the highest sensitivity and specificity of 0.647 and 0.605, respectively. Based on this value, 76 patients (49.4%) had an albumin level ⩽ 40.5 g/L, and 78 patients (50.6%) had an albumin level > 40.5 g/L (Table 3).

The median FAR in all patients was 0.09 (range: 0.04-0.25) (Table 1). As shown in Figure 1C, the AUC was recorded as 0.783 (95%CI: 0.707-0.859), and the optimal cut-off value of the preoperative FAR for OS was 0.08, with the highest sensitivity and specificity of 0.779 and 0.765, respectively. Based on this value, 71 patients (46.1%) harbored a FAR value ⩽ 0.08, and 83 patients (53.9%) had a FAR value > 0.08 (Table 4).

Correlations of the preoperative fibrinogen concentration, albumin level and FAR with clinicopathological factors

As shown in Table 2, based on the optimal cut-off value for the preoperative fibrinogen concentration, all patients could be divided into the low-value group (⩽ 3.47 g/L) or the high-value group (> 3.47 g/L). Higher preoperative fibrinogen concentration was significantly correlated with jaundice (P = 0.003), degree of differentiation (P = 0.048), resection margin (P = 0.003), T stage (P < 0.001), TNM stage (P = 0.011), CA199 level (P = 0.005) as well as FAR (P < 0.001). However, there were no significant associations of the preoperative fibrinogen concentration with age, gender, cholecystolithiasis, diabetes, ABO blood group, pathological type, tumor size, N stage, distant metastasis or albumin level (P > 0.05). The survival curve stratified by the fibrinogen concentration indicated that GBC subjects with a fibrinogen concentration > 3.47 g/L had shorter OS than those with a fibrinogen concentration ⩽ 3.47 g/L (Figure 2A).

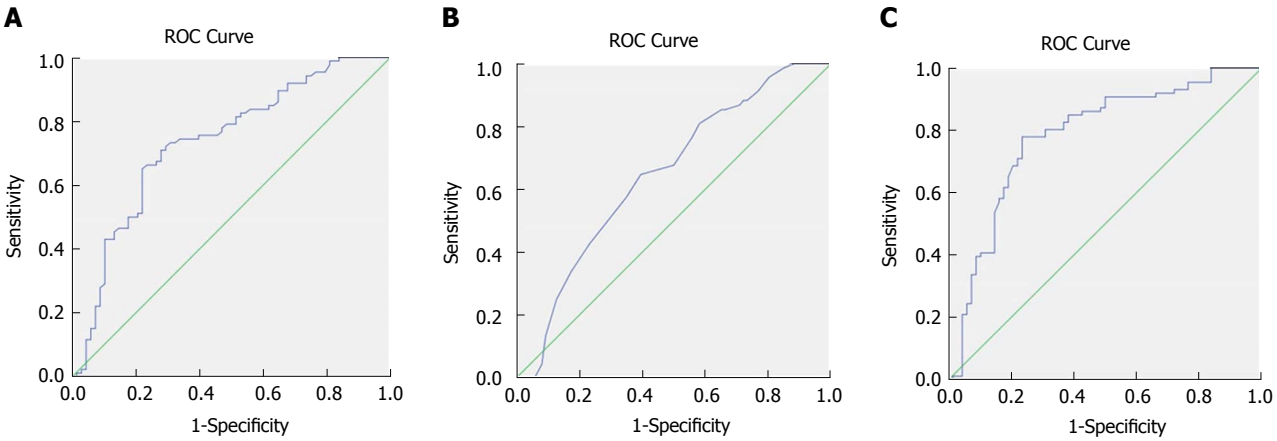

Figure 1 Receiver operating characteristics curve analysis based on fibrinogen (A), albumin (B), and fibrinogen to albumin ratio (C) for overall survival. A: The area under the ROC curve (AUC) indicates the diagnostic power of preoperative plasma fibrinogen concentration. In this model, the optimum cut-off point for fibrinogen concentration was 3.47 g/L, AUC was 0.735 (95%CI: 0.654-0.816), with a sensitivity of 0.709 and a specificity of 0.721 by the Youden index; B: The AUC indicates the diagnostic power of preoperative plasma albumin level. In this model, the optimum cut-off point for albumin level was 40.5 g/L, AUC was 0.648 (95%CI: 0.562-0.735), with a sensitivity of 0.647 and a specificity of 0.605 by the Youden index; C: The AUC indicates the diagnostic power of preoperative FAR. In this model, the optimum cut-off point for FAR was 0.08, AUC was 0.783 (95%CI: 0.707-0.859), with a sensitivity of 0.779 and a specificity of 0.765 by the Youden index. ROC: Receiver operating characteristics curve.

As shown in Table 3, based on the optimal cut-off value for the preoperative albumin level, all patients could be categorized into the low-value group (≤ 40.5 g/L) or high-value group (> 40.5 g/L). Higher preoperative albumin levels were significantly associated with jaundice ($P < 0.001$), ABO blood group ($P = 0.046$), degree of differentiation ($P = 0.047$), resection margin status ($P = 0.008$), T stage ($P = 0.021$), TNM stage ($P = 0.007$), CA199 levels ($P = 0.006$) as well as FAR ($P < 0.001$). The survival curve stratified by the albumin level showed that GBC patients with an albumin level > 40.5 g/L had longer OS than those with an albumin level ≤ 40.5 g/L (Figure 2B).

As shown in Table 4, based on the optimal cut-off value for the preoperative FAR, all patients could be grouped into the low-value group (≤ 0.08) or high-value group (> 0.08). A higher preoperative FAR was significantly correlated with age ($P = 0.045$), jaundice ($P < 0.001$), degree of differentiation ($P = 0.002$), resection margin status ($P < 0.001$), T stage ($P < 0.001$), TNM stage ($P < 0.001$), CA199 level ($P < 0.001$) as well as albumin level ($P < 0.001$). The survival curve stratified by the FAR showed that GBC patients with a FAR > 0.08 harbored worse OS compared to those with a FAR ≤ 0.08 (Figure 2C).

Univariate and multivariate analysis results

Univariate and multivariate analyses for OS prediction in GBC patients are shown in Tables 5 and 6. In the univariate Cox analysis, jaundice (HR: 2.598, 95%CI: 1.644-4.106, $P < 0.001$), degree of differentiation (HR: 1.527, 95%CI: 1.031-2.261, $P = 0.035$), resection margin status (HR: 3.683, 95%CI: 2.468-5.496, $P < 0.001$), T stage ($P < 0.001$), N stage ($P < 0.001$), distant metastasis (HR: 2.550, 95%CI: 1.388-4.684, $P = 0.003$), TNM stage ($P < 0.001$), CA199 level (HR: 3.125, 95%CI: 2.010-4.858, $P < 0.001$), fibrinogen concentration (HR: 2.795, 95%CI: 1.853-4.214, $P < 0.001$), albumin level (HR: 0.391, 95%CI: 0.259-0.590, $P < 0.001$) and FAR (HR: 4.626, 95%CI: 2.987-7.165, $P < 0.001$) were significant prognostic factors for OS in GBC patients (Table 5), whereas age, gender, cholecystolithiasis, diabetes, ABO blood group, pathological type and maximal tumor diameter were not significant predictors of OS ($P > 0.05$; Table 5). In the multivariate Cox regression analysis, resection margin status (HR: 2.343, 95%CI: 1.532-3.581, $P < 0.001$, TNM stage ($P = 0.035$), and FAR (HR: 2.813, 95%CI: 1.765-4.484, $P < 0.001$) were revealed as independent risk factors for poor OS in GBC patients, and the albumin level (HR: 0.595, 95%CI: 0.385-0.921, $P = 0.020$) was correlated with favorable OS in patients with GBC (Table 6).

Although the multivariate analysis showed that both FAR and albumin level were independent risk factors for the prognosis of GBC patients (Table 6), the AUC of FAR (0.783) was greater than that (0.648) of the albumin level (Figure 1B and C), indicating that the prognostic value of FAR was more powerful than that of the albumin level.

DISCUSSION

In this study, we demonstrate FAR is a significantly independent prognostic indicator for GBC. To our knowledge, it is the first research concerning the prognostic significance of FAR in patients with GBC. Although both FAR and serum albumin level were revealed to be significant prognostic indicators, the AUC of FAR was greater than that of the serum albumin level, and the *P* value of FAR was smaller than that of the serum albumin level.

In our study, a greater FAR was found to be correlated with a series of important clinicopathological indicators

Table 2 Correlation between fibrinogen concentration and clinicopathological characteristics in gallbladder cancer patients *n* (%)

Characteristics	Fibrinogen concentration		*P* value
	≤ 3.47 g/L (*n* = 75)	> 3.47 g/L (*n* = 79)	
Age (yr)			
≤ 60	31 (20.1)	25 (16.2)	0.243
> 60	44 (28.6)	54 (35.1)	
Sex			
Male	33 (21.4)	30 (19.5)	0.513
Female	42 (27.3)	49 (31.8)	
Cholecystolithiasis			
Absent	38 (24.7)	41 (26.6)	0.878
Present	37 (24.0)	38 (24.7)	
Diabetes			
Absent	57 (37.0)	59 (38.3)	0.850
Present	18 (11.7)	20 (13.0)	
Jaundice			
Absent	68 (44.2)	61 (39.6)	0.029
Present	7 (4.5)	18 (11.7)	
Blood groups			
A	19 (12.3)	24 (15.6)	0.145
B	33 (21.4)	23 (14.9)	
AB	2 (1.3)	7 (4.5)	
O	21 (13.6)	25 (16.2)	
Pathological types			
Adenosquamous carcinoma	0 (0)	3 (1.9)	0.142
Adenocarcinoma	75 (48.7)	75 (48.7)	
Papillocarcinoma	0 (0)	1 (0.6)	
Degree of differentiation			
Poor	23 (14.9)	37 (24.0)	0.048
Moderate-well	52 (33.8)	42 (27.3)	
Resection margin status			
Negative	56 (36.4)	40 (26.4)	0.003
Positive	19 (12.3)	39 (25.3)	
Maximum tumor diameter (cm)			
≤ 2.45	34 (22.1)	34 (22.1)	0.871
> 2.45	41 (26.6)	45 (29.2)	
T stage			
Tis-T1a	8 (5.2)	2 (1.3)	< 0.001
T1b-T2b	22 (14.3)	7 (4.5)	
T3	43 (27.9)	60 (39.0)	
T4	2 (1.3)	10 (6.5)	
N stage			
N0	50 (32.5)	48 (31.2)	0.748
N1	21 (13.6)	26 (16.9)	
N2	4 (2.6)	5 (3.2)	
Distant metastasis			
Absent	69 (44.8)	73 (47.4)	0.925
Present	6 (3.9)	6 (3.9)	
TNM stage			
0- Ⅰ stage	12 (7.8)	4 (2.6)	0.011
ⅡA-ⅡB stage	12 (7.8)	4 (2.6)	
ⅢA-ⅢB stage	39 (25.3)	53 (34.4)	
ⅣA-ⅣB stage	12 (7.8)	18 (11.7)	
CA199 (U/mL)			
≤ 39	41 (26.6)	25 (16.2)	0.005
> 39	34 (22.1)	54 (35.1)	
Albumin levels (g/L)			
≤ 40.5	32 (20.8)	44 (28.6)	0.111
> 40.5	43 (27.9)	35 (22.7)	
FAR			
≤ 0.08	59 (38.3)	12 (7.8)	< 0.001
> 0.08	16 (10.4)	67 (43.5)	

FAR: Fibrinogen to albumin ratio.

Table 3 Correlation between albumin levels and clinicopathological characteristics in gallbladder cancer patients *n* (%)

Characteristics	Albumin levels		*P* value
	≤ 40.5g/L (*n* = 76)	> 40.5 g/L (*n* = 78)	
Age (yr)			
≤ 60	22 (14.3)	34 (22.1)	0.067
> 60	54 (35.1)	44 (28.6)	
Sex			
Male	28 (18.2)	35 (22.7)	0.330
Female	48 (31.2)	43 (27.9)	
Cholecystolithiasis			
Absent	34 (22.1)	45 (29.2)	0.147
Present	42 (27.3)	33 (21.4)	
Diabetes			
Absent	53 (34.4)	63 (40.9)	0.136
Present	23 (14.9)	15 (9.7)	
Jaundice			
Absent	54 (35.1)	75 (48.7)	< 0.001
Present	22 (14.3)	3 (1.9)	
Blood groups			
A	20 (13.0)	23 (14.9)	0.046
B	34 (22.1)	22 (14.3)	
AB	6 (7.9)	3 (3.8)	
O	16 (21.1)	30 (19.5)	
Pathological types			
Adenosquamous carcinoma	0 (0)	3 (1.9)	0.137
Adenocarcinoma	75 (48.7)	75 (48.7)	
Papillocarcinoma	1 (0.6)	0 (0.0)	
Degree of differentiation			
Poor	36 (23.4)	24 (15.6)	0.047
Moderate-well	40 (26.0)	54 (35.1)	
Resection margin status			
Negative	39 (25.3)	57 (37.0)	0.008
Positive	37 (24.0)	21 (13.6)	
Maximum tumor diameter (cm)			
≤ 2.45	36 (23.4)	32 (20.8)	0.516
> 2.45	40 (26.0)	46 (29.9)	
T stage			
Tis-T1a	2 (1.3)	8 (5.2)	0.021
T1b-T2b	9 (5.8)	20 (13.0)	
T3	58 (37.7)	45 (29.2)	
T4	7 (4.5)	5 (3.2)	
N stage			
N0	45 (29.2)	53 (34.4)	0.403
N1	25 (16.2)	22 (14.3)	
N2	6 (3.9)	3 (1.9)	
Distant metastasis			
Absent	67 (43.5)	75 (48.7)	0.077
Present	9 (5.8)	3 (1.9)	
TNM stage			
0- Ⅰ stage	3 (1.9)	13 (8.4)	0.007
ⅡA-ⅡB stage	6 (3.9)	10 (6.5)	
ⅢA-ⅢB stage	46 (29.9)	46 (29.9)	
ⅣA-ⅣB stage	21 (13.6)	9 (5.8)	
CA199 (U/mL)			
≤ 39	24 (15.6)	42 (27.3)	0.006
> 39	52 (33.8)	36 (23.4)	
Fibrinogen concentration (g/L)			0.111
≤ 3.47g/L	32 (20.8)	43 (27.9)	
> 3.47 g/L	44 (28.6)	35 (22.7)	
FAR			
≤ 0.08	21 (13.6)	50 (32.5)	< 0.001
> 0.08	55 (35.7)	28 (18.2)	

FAR: Fibrinogen to albumin ratio.

Table 4 Correlation between FAR and clinicopathological characteristics in gallbladder cancer patients *n* (%)

Characteristics	FAR		*P* value
	≤ 0.08 (*n* = 71)	> 0.08 (*n* = 83)	
Age (yr)			
≤ 60	32 (20.8)	24 (15.6)	0.045
> 60	39 (25.3)	59 (38.3)	
Sex			
Male	30 (19.5)	33 (21.4)	0.870
Female	41 (26.6)	50 (32.5)	
Cholecystolithiasis			
Absent	37 (24.0)	42 (27.3)	0.873
Present	34 (22.1)	41 (26.6)	
Diabetes			
Absent	56 (36.4)	60 (39.0)	0.357
Present	15 (9.7)	23 (14.9)	
Jaundice			
Absent	67 (43.5)	62 (40.3)	< 0.001
Present	4 (2.6)	21 (13.6)	
Blood groups			
A	22 (14.3)	21 (13.6)	0.148
B	28 (18.2)	28 (18.2)	
AB	1 (0.6)	8 (5.2)	
O	20 (13.0)	26 (16.9)	
Pathological types			
Adenosquamous carcinoma	0 (0)	3 (1.9)	0.173
Adenocarcinoma	71 (46.1)	79 (51.3)	
Papillocarcinoma	0 (0)	1 (0.6)	
Degree of differentiation			
Poor	18 (11.7)	42 (27.3)	0.002
Moderate-well	53 (34.4)	41 (26.6)	
Resection margin status			
Negative	55 (35.7)	41 (26.6)	< 0.001
Positive	16 (10.4)	42 (27.3)	
Maximum tumor diameter (cm)			
≤ 2.45	37 (24.0)	31 (20.1)	0.075
> 2.45	34 (22.1)	52 (33.8)	
T stage			
Tis-T1a	8 (5.2)	2 (1.3)	< 0.001
T1b-T2b	24 (15.6)	5 (3.2)	
T3	36 (23.4)	67 (43.5)	
T4	3 (1.9)	9 (5.8)	
N stage			
N0	48 (31.2)	50 (32.5)	0.623
N1	19 (12.3)	28 (18.2)	
N2	4 (2.6)	5 (3.2)	
Distant metastasis			
Absent	68 (44.2)	74 (48.1)	0.145
Present	3 (1.9)	9 (5.8)	
TNM stage			
0- Ⅰ stage	14 (9.1)	2 (1.3)	< 0.001
ⅡA-ⅡB stage	14 (9.1)	2 (1.3)	
ⅢA-ⅢB stage	35 (22.7)	57 (37.0)	
ⅣA-ⅣB stage	8 (5.2)	22 (14.3)	
CA199 (U/mL)			
≤ 39	43 (27.9)	23 (14.9)	< 0.001
> 39	28 (18.2)	60 (39.0)	
Fibrinogen concentration (g/L)			
≤ 3.47g/L	59 (38.3)	16 (10.4)	< 0.001
> 3.47 g/L	12 (7.8)	67 (43.5)	
Albumin levels (g/L)			
≤ 40.5g/L	21 (13.6)	55 (35.7)	< 0.001
> 40.5 g/L	50 (32.5)	28 (18.2)	

of GBC patients, such as resection margin status, TNM stage and albumin level, which were independent risk factors for OS in GBC, indicating that an elevated FAR might be associated with aggressiveness and systemic progression of GBC.

Relatively few previous studies have probed into the prognostic significance of FAR in patients with malignant tumors. To date, there are only two studies performed in the context of breast cancer[23] and ESCC[22]. In line with our findings, the optimal cut-off value of FAR for ESCC patients was also 0.08. However, the optimal cut-off value of FAR in breast cancer was 0.071, which is slightly lower than that in ESCC patients and in GBC subjects in our study. Together, the inconsistent findings indicate that the optimal FAR cut-off value varies in different malignancies. Although the exact cause and underlying mechanism of these differences remain unknown, they might be related to the different biological behaviors of different tumors and gender-associated hormone difference. Hence, more studies are needed to further verify these conclusions.

Inconsistent with these previous two studies, our study indicates that the preoperative albumin level is also an independent risk factor for OS in GBC patients, and an elevated albumin level is a favorable prognostic factor for GBC patients. Several studies have demonstrated that lower serum albumin levels could lead to deteriorated diseases and a greater risk of poor prognosis in patients with gastric cancer[26], ovarian cancer[27] and upper urinary tract urothelial carcinoma[12]. However, to our knowledge, it is the first study to assess the prognostic significance of preoperative serum albumin in GBC.

Accumulating studies have demonstrated the effect of activated coagulation with fibrinolysis, malnutrition and inflammation during carcinogenesis, cancer progression and metastasis[28-31]. Although the prognostic value of the preoperative FAR has been established in patients with malignant tumors[22,23], the real mechanisms underlying this association remains largely undefined. Our observations are supported by several previous experimental and clinical researches. As a P-globulin and pro-inflammatory protein, fibrinogen can be synthesized by malignant tumor cells apart from hepatic cells, which participates in extracellular matrix (ECM) formation[32-34]. Fibrinogen can promote tumor progression *via* regulation of tumor cell growth by binding to vascular endothelial growth factor (VEGF) as well as platelet-derived growth factor (PDGF)[33-35]. An experimental study has demonstrated that fibrinogen can induce epithelial-mesenchymal transition (EMT) to enhance the migration and invasion ability of tumor cells via modulation of the expression of vimentin and E-cadherin[36]. Another experimental study performed in fibrinogen-deficient mice indicates that fibrinogen-free internal environment can suppress the spread of tumor cells and the subsequent establishment of micro-metastases[37]. A previous study[38] also showed that fibrinogen could facilitate tumor cell metastasis by suppressing natural killer (NK) cell-mediated apoptosis. Fibrinogen has

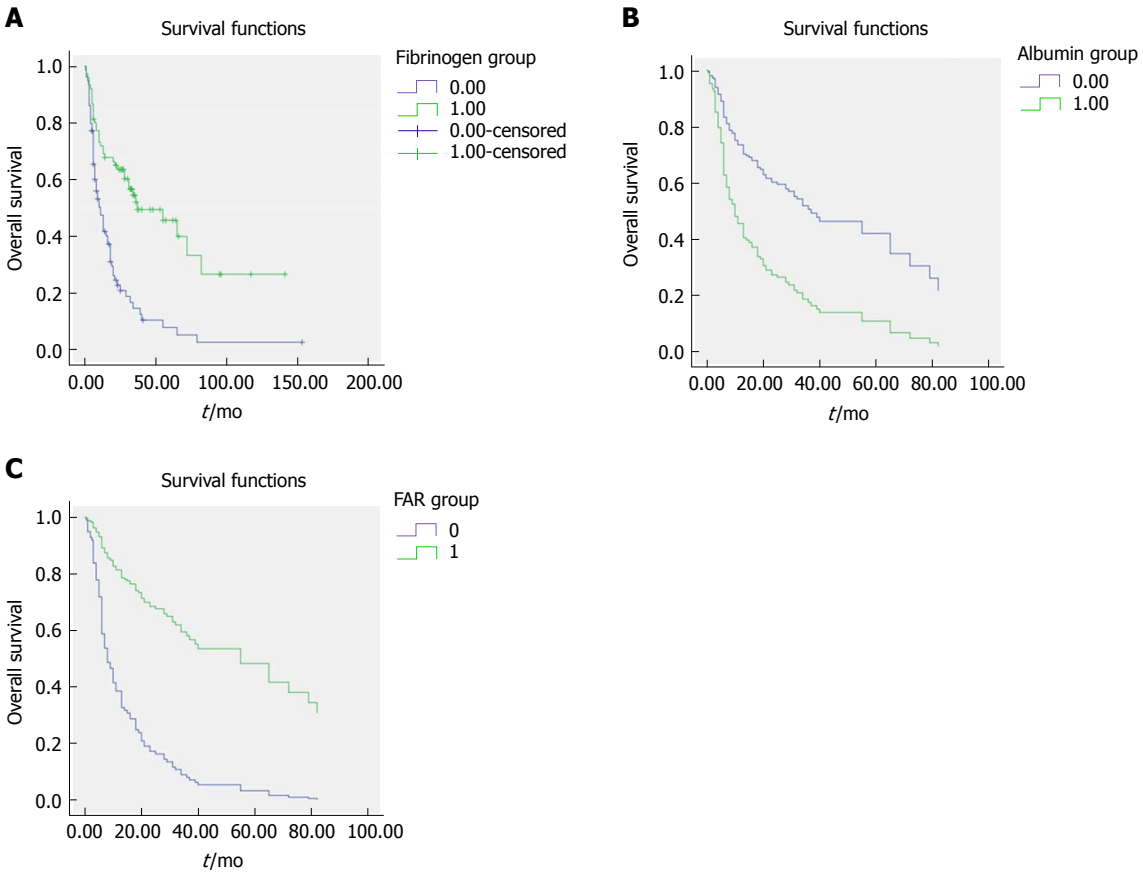

Figure 2 Survival curve according to the presence of preoperative fibrinogen concentration (A), albumin level (B), and fibrinogen to albumin ratio (C). A: Data compares fibrinogen concentration > 3.47 g/L *vs* ≤ 3.47 g/L group ($P < 0.05$). The number 1 for ≤ 3.47 g/L group, number 2 for > 3.47g/L group; B: Data compares albumin level > 40.5 g/L *vs* ≤ 40.5 g/L group ($P < 0.05$). The number 0 for albumin level > 40.5 g/L group, number 1 for albumin level ≤ 40.5 g/L group; C: Data compares FAR > 0.08 *vs* ≤ 0.08 group ($P < 0.05$). The number 1 for FAR > 0.08 group, number 0 for FAR ≤ 0.08 g/L group. FAR: Fibrinogen to albumin ratio.

also been demonstrated to be critically involved in the tumorigenesis and tumor progression *via* aggravation of cell proliferation, suppression of apoptosis and stimulation of angiogenesis as well as hematogenous metastasis[33,34,39-41]. The albumin level can not only reflect the malnutrition status of host, but also implicate the existence of inflammation. Malnutrition is commonly detected in cancer patients, which might lead to multiple negative outcomes, including compromised immune function, insensitive therapeutic response as well as reduced OS[42]. As part of the SIR to tumor or from tumor itself, inflammatory mediators are secreted, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 as well as acute-phase reactants. IL-6 has been suggested to modulate VEGF secretion from glioblastoma cells, and the latter can result in vascular permeability, contributing to declined serum albumin levels[43,44]. Proinflammatory cytokines, such as TNF-α, IL-1 and IL-6 can downregulate the hepatic synthesis of albumin[45-48]. Therefore, albumin level might be used to reflect tumor prognosis. Taken together, FAR could be considered as a prognostic factor for GBC patients.

There are certain limitations in this study. To begin with, this study was a retrospective, small-sample, single-center one, hence, there might be a selection bias. Secondly, due to the small sample size, we were unable to perform further subgroup analysis according to different models, such as the TNM stage model, treatment model and distant metastasis model. Thirdly, our findings lacked external verification, which requires further investigation. Fourth, although the cut-off values were calculated by ROC curves, they were based on a relatively small sample; as such, other cut-off values may be more accurate in the case of increased sample size. In this study, we mainly focused on the prognostic significance of the preoperative FAR, while changes in the postoperative FAR have not been studied; thus, the prognostic value of the postoperative FAR was not assessed. Therefore, more well-designed, prospective and large-sample multi-center studies are warranted to further verify the present conclusions.

In conclusion, the preoperative FAR is a significant and powerful negative prognostic indicator for OS in GBC patients, and the preoperative serum albumin level is a favorable prognostic factor for OS in GBC patients, and the predictive power of FAR is greater than that of the albumin level. As a simple, convenient and cost-effective indicator, FAR, defined as the fibrinogen-to-albumin ratio, could easily be applied in the clinical setting via routine preoperative laboratory tests to predict the

Table 5 Univariate analysis of overall survival in gallbladder cancer patients

Characteristics	HR (95%CI)	*P* value
Age (yr)	1.473 (0.973-2.230)	0.067
≤ 60		
> 60		
Sex	0.995 (0.670-1.477)	0.981
Male		
Female		
Cholecystolithiasis	1.198 (0.814-1.764)	0.360
Absent		
Present		
Diabetes	1.028 (0.651-1.623)	0.906
Absent		
Present		
Jaundice	2.598 (1.644-4.106)	< 0.001
Absent		
Present		
Blood groups	-	0.113
A		
B		
AB		
O		
Pathological types	-	0.165
Adenosquamous carcinoma		
Adenocarcinoma		
Papillocarcinoma		
Degree of differentiation	1.527 (1.031-2.261)	0.035
Poor		
Moderate-well		
Resection margin status	3.683 (2.468-5.496)	< 0.001
Negative		
Positive		
Maximum tumor diameter (cm)	1.101 (0.744-1.630)	0.631
≤ 2.45		
> 2.45		
T stage	-	< 0.001
Tis-T1a		
T1b-T2b		
T3		
T4		
N stage	-	< 0.001
0		
1		
2		
Distant metastasis	2.550 (1.388-4.684)	0.003
Absent		
Present		
TNM stage	-	< 0.001
0- I stage		
ⅡA-ⅡB stage		
ⅢA-ⅢB stage		
ⅣA-ⅣB stage		
CA199 (U/mL)	3.125 (2.010-4.858)	< 0.001
≤ 39		
> 39		
Fibrinogen concentration (g/L)	2.795 (1.853-4.214)	< 0.001
≤ 3.47		
> 3.47		
Albumin levels (g/L)	0.391(0.259-0.590)	< 0.001
≤ 40.5		
> 40.5		
FAR	4.626(2.987-7.165)	< 0.001
≤ 0.08		
> 0.08		

FAR: Fibrinogen to albumin ratio; HR: Hazard ratio; CI: Confidence interval.

Table 6 Multivariate analysis for overall survival in gallbladder cancer patients

Characteristics	HR (95%CI)	Wald	*P* value
Resection margin status	2.343 (1.532-3.581)		< 0.001
Negative			
Positive			
TNM stage		8.595	0.035
ⅡA-ⅡB stage/0-1stage	1.209 (0.287-5.095)	0.067	0.796
ⅢA-ⅢB stage/0-1 stage	3.401 (1.033-11.202)	4.051	0.044
ⅣA-ⅣB stage/0-1 stage	4.014 (1.142-14.107)	4.696	0.030
FAR	2.813 (1.765-4.484)		< 0.001
≤ 0.08			
> 0.08			
Albumin levels (g/L)	0.595 (0.385-0.921)		0.020
≤ 40.5			
> 40.5			

FAR: Fibrinogen to albumin ratio; HR: Hazard ratio; CI: Confidence interval.

prognosis of GBC patients. However, more related studies are warranted to validate these conclusions.

ARTICLE HIGHLIGHTS

Research background

Although gallbladder cancer (GBC) is a relatively rare hepato-biliary malignancy with a low incidence, it is generally insidious and progresses rapidly. Most GBC patients are diagnosed at an advanced stage, losing the chance of surgical intervention, which is considered to yield an optimal therapeutic effect. Despite the great advance in surgical techniques in recent years, the prognosis remains very poor. Therefore, it is urgent to explore a clinically simple, convenient and cost-effective prognostic indicator to detect and identify high-risk patients with GBC, on whom, appropriate surgical treatment can be performed as soon as possible. In recent years, a variety of studies have shown that the increased plasma fibrinogen concentration representing coagulation function of the body and the declined plasma albumin concentration indicating nutrient state of the body are independent risk factors for poor prognosis of malignant tumor patients. Integrating the results of studies on fibrinogen-to-albumin ratio (FAR) in the prognosis of patients with esophageal cancer and breast cancer, we naturally speculate that FAR might be significantly more effective than single elevated plasma fibrinogen concentration or reduced plasma albumin concentration in predicting the prognosis of GBC patients.

Research motivation

Hence, the present was mainly designed to determine and verify the role of high FAR in the prognosis of surgically-treated GBC patients. We aimed to detect a simple, convenient and cost-effective prognostic biomarker for GBC patients undergoing surgical treatment, which could facilitate the selection and identification of GBC patients suitable for surgical resection for clinical surgeons. Notably, this would be beneficial to both surgeons and GBC patients. Our findings would provide clinical evidence and research directions for other large-scale, multi-center randomized controlled trials in the future.

Research objectives

The main objective of our study was to determine whether high preoperative FAR was an independent risk factors for postoperative survival in GBC patients. As a result, we demonstrated that high preoperative plasma FAR value and low preoperative plasma albumin concentration were independent risk factors for poor post-operative prognosis of GBC patients. In addition, the prognostic effect of high preoperative FAR value was significantly stronger than the low preoperative plasma albumin concentration. Therefore, these above-described outcomes provided not only clinical direction for further clinical validation or relevant studies, but also clinical data for further researches concerning the

underlying mechanisms.

Research methods

First, the present study was a clinical retrospective one. A prearranged EXCEL data collection table was utilized to collect and organize the various variables, including epidemiological data, clinicopathological characteristics, and research-related target data. Moreover, the receiver operating characteristic (ROC) curve was used to obtain the optimal cut-off values for fibrinogen, albumin, and FAR. Continuous variables in normal distribution were shown as mean ± SD, and continuous variables without normal distribution were expressed as medians (range: minimum-maximum). Categorical variables were expressed as percentages or frequencies. Variables from the EXCEL table were further imported into the SPSS 24.0 statistical software for statistical analysis. Of note, the statistical methods used in our study were different from those used in previous studies of survival analysis regarding the prognosis of cancer patients. To begin with, the ROC curve was used to identify the optimal cut-off value of fibrinogen, albumin, and FAR in this study, which was more reasonable and more scientific than the traditional methods, which used the mean value of the targeted or identified biomarkers based on previous studies. It was because the cut-off value identified by this method was significantly associated with the overall survival of the targeted population. Secondly, most of the previous studies on postoperative prognosis of GBC patients only focused on single index, such as plasma fibrinogen or plasma albumin. However, in this study, we used the plasma FAR, representing the division of high fibrinogen and low albumin, which contributed to the more significant prognostic effect of the index, and effectively inhibited the influence of confounding factors. Together, the method was more scientific and harbored higher statistical efficiency.

Research results

In this study, we demonstrated that high preoperative plasma FAR and low preoperative plasma albumin concentration were independent risk factors for poor postoperative outcome in GBC patients. To the best of our knowledge, this is the first study indicating that high preoperative plasma FAR is an unfavorable prognostic biomarker for GBC patients undergoing surgical intervention. Additionally, it also verifies the role of low preoperative plasma albumin in predicting the worse prognosis of GBC patients receiving surgery. Nevertheless, our study is a retrospective study but not a prospective study, which might lead to a systematic bias. Moreover, the sample size in our study is relatively small, and it is a single-center study, and these defects would attenuate the statistical effectiveness of our conclusions. Nevertheless, the study was conducted in China, which did not include GBC patients from other ethnic groups and countries, thereby affecting the clinical applicability and generalizability of the results. Therefore, more multiple-center, large-scale prospective studies enrolling GBC patients from different races and countries are necessary to further verify the conclusions of this study.

Research conclusions

At present, accumulating studies have confirmed that high preoperative plasma fibrinogen concentration and low preoperative plasma albumin concentration are independent risk factors for poor prognosis of GBC patients. In addition, some studies have further validated that high preoperative plasma FAR is an independent risk factor for poor prognosis of patients with esophageal cancer and breast cancer, and its predictive ability is significantly more potent than that of single biomarkers, such as high plasma fibrinogen and low plasma albumin. Therefore, we naturally speculated that FAR, representing the body's coagulation function and the body's nutritional status, might be an independent risk factor for predicting postoperative adverse outcomes of GBC patients, which has been confirmed in our study. Our study was the first to reveal the prognostic effect of FAR in GBC patients, and we also used the ROC curve as a novel method to identify the optimal cut-off value for the prognostic index studied. The potential mechanism for our conclusion might be indicated as follows: fibrinogen, as a coagulation factor, was associated with the growth, progression and metastasis of cancer cells, while albumin was correlated with the nutrient status and immune function of the body. Therefore, the high preoperative plasma fibrinogen and low preoperative albumin are both unfavorable prognostic factors for GBC patients. The FAR can enhance and magnify the prognostic effect of the single index such as fibrinogen and albumin. Collectively, our research provides a simple, convenient and cost-effective prognostic indicator to help clinicians to more efficiently screen and identify high-risk GBC patients in clinical practice, and to facilitate patients to adopt better surgical methods and optimal follow-up strategy in the future.

Research perspectives

In the present study, it is indicated that the plasma FAR, incorporating two biomarkers, harbors a significantly better prognostic impact on surgically-treated GBC patients compared to a single prognostic indicator, such as plasma albumin or plasma fibrinogen. In the future, more large-scale, multiple-center and prospective studies, including GBC patients from other races and countries, should be conducted to further investigate and verify the conclusion derived from our study. Additionally, more basic experiments exploring the potential mechanisms are also necessary in the future.

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ISSN 1007-9327