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ORIGINAL RESEARCH

Relationship Between Fibrinogen to Albumin Ratio and Prognosis of Gastrointestinal Stromal Tumors: A Retrospective Cohort Study

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Objective: The fibrinogen to albumin ratio (FAR) is an important parameter that reflects the coagulation state, systemic inflammation, and nutritional status of a patient and plays an essential role in tumor progression. Here, we evaluate the prognostic significance of FAR in gastrointestinal stromal tumor (GIST) patients that underwent radical surgery.

Methods: We retrospectively analyzed the data of 227 GIST patients that underwent radical surgery in Beijing Hospital from October 2004 to July 2018. We drew a curve of receiver operating characteristics to confirm the optimal critical values for hemoglobin (Hb), prognostic nutrition index (PNI), and FAR. Cox regression analysis and the Kaplan–Meier method were used to assess the prognostic factors.

Results: The FAR optimal critical value for postoperative recurrence-free survival (RFS) was 0.09. Many significant factors, including approach, the location and size of the tumor, mitotic index, risk classification, Hb levels, PNI, and recurrence, affect FAR. Multivariate analysis indicated that for patients with GISTs who underwent surgery, the tumor location (hazard ratio [HR]=3.393, 95% confidence interval [CI]: 1.539–7.479, P=0.002), mitotic index (HR=4.788, 95% CI: 1.836–12.486, P=0.001), tumor rupture (HR=10.954, 95% CI: 2.170–55.296, P=0.004), and FAR (HR=3.093, 95% CI: 1.303–7.339, P=0.010) were independent factors affecting RFS. Moreover, the FAR remained of prognostic significance for GIST stratified by subgroup analysis.

Conclusion: Preoperative FAR is a reliable marker for evaluating the prognosis of GIST, the prognostic ability of FAR is significantly better than Hb and PNI.

Keywords: fibrinogen to albumin ratio, prognostic nutrition index, hemoglobin, prognosis, gastrointestinal stromal tumors

Introduction

In the digestive system, gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors, with an annual incidence rate of 10–15 cases per one million people. Their malignant potential varies, ranging from mild benign lesions to fatal sarcomas. The primary treatment for resectable GISTs is margin negative complete resection. However, tumor relapse is still not uncommon after radical resection, particularly in high-risk patients.[1,2] After recurrence, the median time to survive is less than two years, and the prognosis of GISTs is still poor.[1,3] At present, the current parameters applied to predict and stratify the risk of tumor recurrence mainly include the size of the tumor, primary tumor site, mitotic index, and tumor rupture.[4] However, these parameters require obtaining postoperative tumor specimens. Hence, it is

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necessary to probe for some economical, non-invasive, and convenient methods for predicting the prognosis of GIST patients as well as for screening patients in the high and middle category for adjuvant or even neoadjuvant therapy.

Several studies have demonstrated that a hypercoagulable state, systemic inflammation, and malnutrition are critically involved in the progression of tumors.[5–7] Tumor-related inflammation blood parameters such as prognostic nutritional index (PNI) and hemoglobin (Hb) are significantly correlated with the prognosis of patients with GISTs.[8,9] Fibrinogen not only exerts an enormous function on inflammation and coagulation, but also participates in regulating cell proliferation, angiogenesis, and tumor cell migration.[10,11] Albumin levels are key factors in assessing nutritional status and systemic inflammatory response.[12] Moreover, many researchers have reported that preoperative FAR is upregulated in various cancer types, such as gastric, esophageal, and gallbladder cancer, and may indicate a poor prognosis.[13–15]

According to the above study, it can be speculated that FAR may be an important prognostic indicator for GISTs patients. Consequently, we retrospectively studied the prognostic FAR value in patients who had a radical operation with GIST.

Materials and Methods

Patients

The clinical and pathological parameters of 227 GIST patients that underwent curative surgical resection from October 2004 to July 2018 at Beijing Hospital were retrospectively included and analyzed. All of the patients were pathologically diagnosed with GISTs. The inclusion criteria were (1) patients with complete clinicopathological parameters and follow-up records; (2) patients with no neoadjuvant therapy before surgery; (3) patients ≥18 years of age. The exclusion criteria were (1) patients with connective tissue disease and hematological diseases; (2) patients with other tumors; (3) patients with active inflammation; (4) patients who were treated with anticoagulants or albumin transfusions within 3 months before surgery; and (5) patients with R1 or R2 resection. The Beijing Hospital Medical Ethics Committee approved the study. Written informed consent was obtained from all patients before surgery.

Data Collection

The clinicopathological data obtained include sex, age, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, surgical approach, the location and the size of the tumor, tumor rupture, risk classification, mitotic index (number of mitoses/50 high-power fields), Hb, total lymphocyte count, fibrinogen, levels of albumin, and adjuvant imatinib treatment. Hb, total lymphocyte count, fibrinogen, and albumin levels were collected within 7 days before surgery.

FAR was calculated as fibrinogen (g/L)/albumin (g/L). PNI was measured as serum albumin (g/dl) + 5 × total lymphocyte count (10^9/L).[16]

Follow-Up

The patients were followed-up once every 3 months in the first 2 years, once every 6 months in the next 3 years, and annually thereafter. The deadline for follow-up was September 20, 2019. The follow-up program included abdominopelvic and chest magnetic resonance imaging (MRI) or computed tomography (CT) scan along with endoscopy and bone marrow scan when necessary. As the primary endpoint, the recurrence-free survival (RFS) refers to the period from surgery to the tumor recurrence.

Statistical Analyses

This study used the operating characteristics of receivers (ROC) to assess the FAR diagnostic value and determine the optimal critical point by estimating the Youden index (sensitivity + specificity-1). The exact test of fishers or Chi-square test was utilized to assess the relationship between FAR and clinicopathological parameters. The curves of Kaplan-Meier survival were plotted, and the Log rank test was conducted to study the statistical distinction between groups. Both univariate and multivariate analyses were utilized to ascertain the prognostic value of various clinicopathological data.

Results

Clinicopathological Characteristics

Of the 227 GIST patients included in the study, 124 (54.6%) were male, and 103 (45.4%) were female. The median age was 62 years (range: 18–83 years), and the median BMI was 23.8 kg/m^2 (range: 16.4–36.6 kg/m2). 130 (57.3%) patients underwent open surgery and 97 (42.7%) patients underwent laparoscopic surgery. The median tumor size was 5 cm (range: 0.5–29 cm). According to the revised risk classification system of National Institute of Health (NIH), of the total 227 patients, 41 (18.1%) were very low risk, 73 (32.2%)

Table 1 Correlation Between the FAR and Clinicopathological Characteristics

Factor	Total (n=227)	FAR<0.09 (n=146)	FAR≥0.09 (n=81)	P value
Sex				
Male	124 (54.6%)	78 (62.9%)	46 (37.1%)	0.626
Female	103 (45.4%)	68 (66%)	35 (34%)	
Age (yr)				
<60	95 (41.9%)	67 (70.5%)	28 (29.5%)	0.098
≥60	132 (58.1%)	79 (59.8)	53 (40.2%)	
BMI (kg/m^2)				
<24	117 (51.5%)	69 (59%)	48 (41%)	0.083
≥24	110 (48.5%)	77 (70%)	33 (30%)	
ECOG score				
0–2	221 (97.4%)	143 (64.7%)	78 (35.3%)	0.669
3	6 (2.4%)	3 (50%)	3 (50%)	
Approach				
Open	130 (57.3%)	74 (56.9%)	56 (43.1%)	0.007
Laparoscopy	97 (42.7%)	72 (74.2%)	25 (25.8%)	
Tumor location				
Gastric	159 (70%)	110 (69.2%)	49 (30.8%)	0.019
Extra-gastric	68 (30%)	36 (52.9%)	32 (47.1%)	
Tumor rupture				
No	224 (98.7%)	145 (64.7%)	79 (35.3%)	0.290
Yes	3 (1.3%)	1 (33.3%)	2 (66.7%)	
Tumor size (cm)				
<5	134 (59%)	101 (75.4%)	33 (24.6%)	<0.001
≥5	93 (41%)	45 (48.4%)	48 (51.6%)	
Mitotic index (×50 HPF)				
<5	129 (56.8%)	94 (72.9%)	35 (27.1%)	0.002
≥5	98 (43.2%)	52 (53.1%)	46 (46.9%)	
Risk classification				
Very low, low	114 (50.2%)	87 (76.3%)	27 (23.7%)	<0.001
Intermediate, high	113 (49.8%)	59 (52.2%)	54 (47.8%)	
Hb(g/L)				
<126.5	102 (44.9%)	54 (52.9%)	48 (47.1%)	0.001
≥126.5	125 (55.1%)	92 (73.6%)	33 (26.4%)	
PNI				
<47.53	82 (36.1%)	32 (39%)	50 (61%)	<0.001
≥47.53	145 (63.9%)	114 (78.6%)	31 (21.4%)	
Adjuvant imatinib				
No	176 (77.5%)	116 (65.9%)	60(34.1%)	0.352
Yes	51 (22.5%)	30 (58.8%)	21 (41.2%)	
Recurrence				
No	196 (86.3%)	138 (70.4%)	58 (29.6%)	<0.001
Yes	31 (13.7%)	8 (25.8%)	23 (74.2%)	

were low risk, 40 (17.6%) were intermediate risk, and 73 (32.2%) were high risk. The median Hb level was 129 g/L (range: 38–168 g/L), and the median preoperative PNI level was 48.85 (range: 33.45–61.90). The median preoperative FAR level was 0.08 (range: 0.04–0.27). The median preoperative fibrinogen was 3.06 g/L (range: 1.22–10.36 g/L), and 39 (17.2%) was higher than the upper limit of normal (4.00 g/L). The median preoperative albumin was 40 g/L (range: 23–48 g/L), and 79 (34.8%) was below the lower limit of normal (40 g/L). Among the 113 patients of the moderate/high-risk group, 51 (45.1%) patients received adjuvant imatinib treatment following surgery (Table 1).

ROC Analysis

According to the analysis of the ROC curve, 0.09 is the best FAR critical value (AUC: 0.767; 95% CI

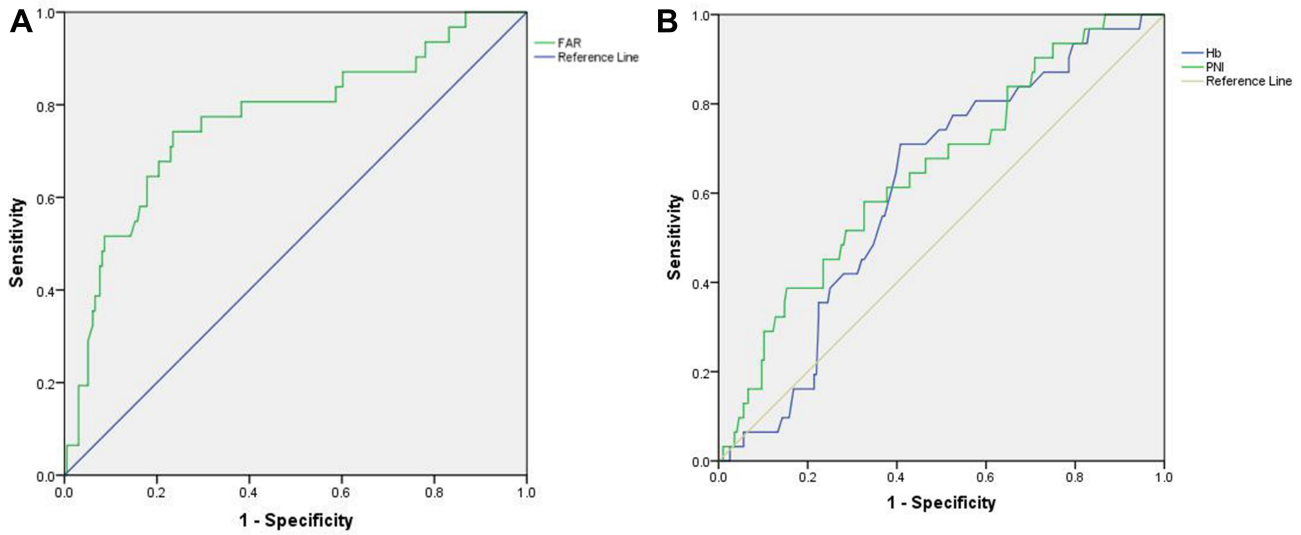

Figure 1 Optimal critical points of FAR (**A**), Hb and PNI (**B**) were applied using ROC curves.
Abbreviations: FAR, fibrinogen to albumin ratio; Hb, hemoglobin; PNI, prognostic nutritional index; ROC, receiver operating characteristics.

0.577–0.673; p<0.001) (Figure 1A). According to this value as a critical criterion, 81 patients (35.7%) were classified as high FAR group (≥0.09) and 146 patients (64.3%) were classified as a low FAR group (<0.09). The best critical values for Hb and PNI were 127 (AUC: 0.613; 95% CI: 0.518–0.707; p=0.044) and 47.53 (AUC: 0.649; 95% CI: 0.547–0.750; p=0.008) (Figure 1B).

Relationship Between the FAR and Clinicopathological Parameters

The correlation between preoperative FAR and the clinical and pathological parameters are presented in Table 1. Higher FAR was notably correlated with approach (P=0.007), size of the tumor (P<0.001), location of the tumor (P=0.019), mitotic index (P=0.002), risk classification (P<0.001), Hb levels (P=0.001), and PNI (P<0.001). However, there were no visible associations of FAR with sex, age, BMI, ECOG score or tumor rupture (Ps>0.05).

Survival Analysis

On the whole, one-year, three-year and five-year RFS rates were 96.8%, 88.5%, and 82.9%, respectively. The curves of Kaplan-Meier survival stratified by the FAR indicated that the RFS of the high FAR group is shorter than that of the low FAR group. One-year, three-year and five-year RFS rates for the high FAR group were 92.4%, 77.9%, and 67.1%, respectively, and 99.2%, 94.8%, and 93.3% for the low FAR group; overall, there is statistical significance in group differences (P<0.001, Figure 2). The RFS of patients with higher Hb or PNI was remarkably longer than that of patients with lower Hb or PNI (p=0.001, p=0.006, Figure 2).

In Table 2, univariate analysis demonstrated that approach, tumor location, tumor rupture, tumor size, the mitotic index, Hb level, PNI, and FAR were important prognostic factors affecting RFS in GIST patients. In the multivariate analysis, tumor location (HR =3.393, 95% CI: 1.539–7.479, p=0.002), tumor rupture (HR =10.954, 95% CI: 2.170–55.296, p=0.004), the mitotic index (HR =4.788, 95% CI: 1.836–12.486, p=0.001), and FAR (HR =3.093, 95% CI: 1.303–7.339, p=0.010) were independent prognostic factors for RFS, while the approach, tumor size, Hb level, and PNI were not.

To further examine the relationship between the preoperative FAR and RFS, we evaluated the prognostic significance of FAR by subgroup analyses. A shorter RFS was found in patients in the high FAR group who were part of either the very low/low/intermediate-risk classification subgroup or the high-risk classification subgroup (P=0.018 and P=0.020, respectively) (Figure 3).

Discussion

During clinical work, the main prognostic factor for GIST patients is NIH risk classification, but it must be obtained from postoperative specimens, and it is impossible to evaluate the patient's prognosis and guide treatment before surgery. Thus, some researchers began to explore blood-based biomarkers. For example, Hb and PNI are independent prognostic factors in GIST patients. FAR has shown

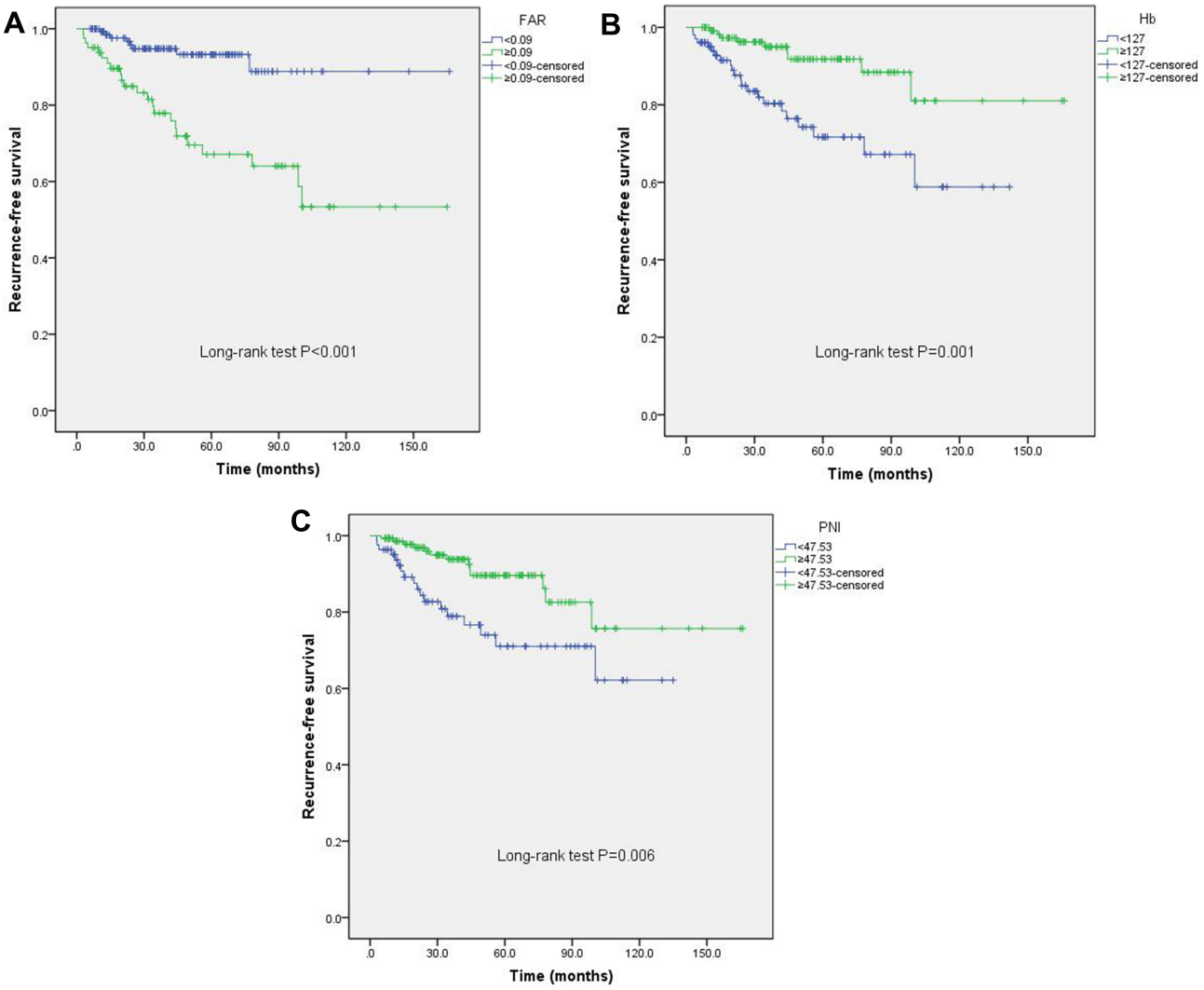

Figure 2 Kaplan–Meier curves for recurrence-free survival according to the FAR (**A**), Hb (**B**), and PNI (**C**).
Abbreviations: FAR, fibrinogen to albumin ratio; Hb, hemoglobin; PNI, prognostic nutritional index.

significant prognostic value in gastric cancer, esophageal squamous cell carcinoma, gallbladder cancer, and hepatocellular carcinoma.[14,15,17,18] Therefore, we speculated that FAR may have significant prognostic value in patients who went through radical surgery with GIST and proved this hypothesis through retrospective studies. According to the information we have, this is the first time that a study is assessing FAR's prognostic value in GIST patients.

Our study indicated that the optimal FAR critical value in GIST patients was 0.09, which is within the range of that in other digestive system tumors (range: 0.06–0.11).[14,15,17,18] The differences in the FARs between different digestive system tumors are slight; we speculate that these slight differences may be due to different biological behaviors of different tumors or the limitations of various studies. Moreover, Hb[8] and PNI[9] of GIST patients who had surgery in previous studies were demonstrated to be independent prognostic factors. However, our study showed significantly different results. First of all, the AUC of FAR has a higher value than PNI and Hb; at the same time, the p-value of FAR was also lower than Hb and PNI. Second, multivariate analysis revealed that FAR was an independent predictor, however, Hb and PNI were not. Therefore, the prognostic capability of FAR was significantly greater than that of Hb and PNI.

Our study also demonstrated that the FAR indicates that the tumor has more aggressive behavior which was related to the progression of GISTs, as a higher FAR was significantly related to the larger size of the tumor, higher risk classification and larger mitotic index, as well as a lower Hb level, lower PNI, and worse prognosis. These results further supported previous researches.[17] Moreover, subgroup

Table 2 Univariate and Multivariate Analysis of Clinicopathological Variables Related to Recurrence-Free Survival

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	*P*
Sex				
Male	1			
Female	0.835 (0.405–1.724)	0.626		
Age (yr)				
<60	1			
≥60	1.154 (0.559–2.380)	0.699		
BMI (kg/m^2)				
<24	1			
≥24	0.759 (0.372–1.549)	0.449		
ECOG score				
0–2				
3	1.553 (0.211–11.455)	0.666		
Approach				
Open	1		1	
Laparoscopy	0.203 (0.071–0.580)	0.003	0.709 (0.204–2.468)	0.589
Tumor location				
Gastric	1		1	
Extra-gastric	3.716 (1.824–7.569)	<0.001	3.393 (1.539–7.479)	0.002
Tumor rupture				
No	1		1	
Yes	10.612 (2.494–45.160)	0.001	10.954 (2.170–55.296)	0.004
Tumor size (cm)				
<5	1		1	
≥5	5.589 (2.406–12.983)	<0.001	1.932 (0.726–5.142)	0.187
Mitotic index (×50 HPF)				
<5	1		1	
≥5	6.642 (2.721–16.209)	<0.001	4.788 (1.836–12.486)	0.001
Hb (g/L)				
<126.5	1		1	
≥126.5	0.288 (0.133–0.627)	0.002	0.435 (0.170–1.117)	0.084
PNI				
<47.53	1		1	
≥47.53	0.384 (0.188–0.784)	0.009	1.827 (0.749–4.457)	0.185
FAR				
<0.09	1		1	
≥0.09	4.819 (2.146–10.822)	<0.001	3.093 (1.303–7.339)	0.01
Adjuvant imatinib				
No	1			
Yes	1.326 (0.590–2.981)	0.495		

analysis revealed that a higher FAR was related to shorter RFS of patients who were classified within the very low/low/intermediate and high-risk subgroups. The FAR can not only be used for prognosis evaluation of patients with GIST before the operation, but can also be considered to be added to the current risk classification system, to participate in further risk stratification of high-risk patients, and to guide neoadjuvant and adjuvant therapies which are more important for patients who cannot undergo surgery and obtain pathological specimens.

Several studies have indicated that fibrinogen may promote the progression of various tumors. As an important part of the coagulation system and acute-phase response protein, fibrinogen could upgrade pro-inflammatory cytokines in certain tumor cells, which promote the inflammatory response that is considered to supply a favorable tumor microenvironment for promoting tumor proliferation, invasion, and metastasis.[10,19-22] As an extracellular matrix protein, fibrinogen can induce the transition of epithelial mesenchyme to promote tumor cells migration and invasion, which involve modulation of the expression of E-cadherin and vimentin.[11,23] Another animal experiment using a mouse model of fibrinogen-deficiency showed that the internal environment without fibrinogen can inhibit the metastasis of tumor cells and can help the establishment of subsequent micrometastasis.[24] Fibrinogen also exerts an

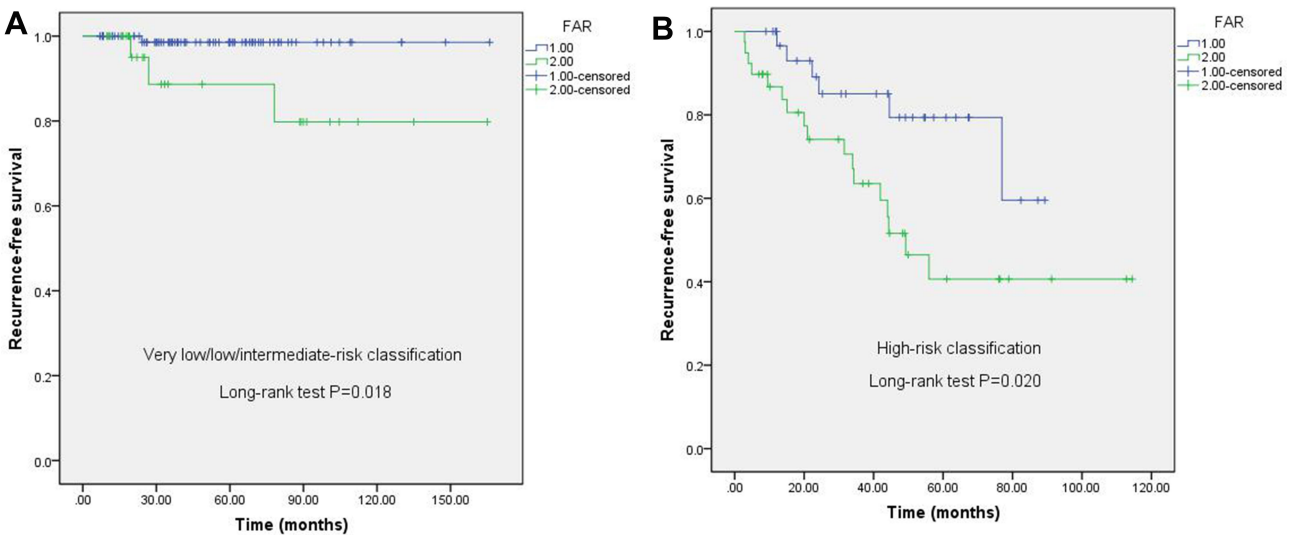

Figure 3 Prognostic data of the pretreatment FAR in different risk classification subgroups. (**A**) Very low/low/intermediate-risk classification subgroup; (**B**) high-risk classification subgroup.
Abbreviation: FAR, fibrinogen to albumin ratio.

enormous function on angiogenesis, which is critically involved in tumorigenesis and progression of the tumor. Besides, high fibrinogen levels can promote platelet adhesion to cancer cells, thereby facilitating the metastasis.[25] However, the exact molecular mechanism by which fibrinogen is involved in tumor progression requires further study.

As a chronic phase protein, albumin is considered to be a measure of systemic inflammation, liver function, and nutritional status. The relationship between albumin and tumors is complex, albumin can be considered both consequence and cause of the presence of an advanced tumor. On the one hand, advanced tumors lead to protein degradation including albumin mediated by the ubiquitin-proteasome pathway.[26] On the other hand, hypoalbuminemia promotes various tumor progression. Numerous researches have shown that it is a stabilizer for DNA proliferation and cell growth, and it exerts antioxidant functions on carcinogens and adjusted immune responses accordingly; which is of great significance in antitumor response.[27–29] Hypoalbuminemia caused by malnutrition and poor performance was shown to be related to postoperative complications and poor prognosis in patients with various tumors, especially in those with gastrointestinal tumors.[30–33]

For GISTs, the main molecular mechanism of tumorigenesis is that *c-KIT* gene mutation activates the phosphoinositide 3-kinase (PI3K) pathway, thereby regulating the cell cycle, making anti-apoptotic signals out of control, and stimulating tumor cell proliferation.[1,34] Moreover, the PI3K pathway can also promote the production of inflammatory cytokines, inflammatory cell recruitment and angiogenesis, which contributes to form a tumor environment favorable to tumor progression.[35] However, the molecular mechanism of inflammation and tumor interaction in GISTs needs to be further explored.

As an important therapy for GIST, adjuvant imatinib is believed to significantly improve the prognosis of GIST patients, however, its benefit was not shown in our multivariate analysis. The cases in this study were collected from 2004 to 2018, during which the indications and dosage of imatinib changed reasonably. Even to this day, the controversy about the specific use strategy of imatinib has not completely ended. We speculate that the above situation and insufficient follow-up time and the number of cases with adjuvant imatinib are possible reasons. Being a single-center retrospective study, the small sample size is a limitation of our research. In addition, because of adverse drug reactions or high drug costs, some of the intermediate and high-risk cases included in this study failed to receive standard adjuvant treatment.

Conclusion

The FAR is correlated with the progression of tumors. Also, it can be used as an independent indicator to predict RFS in GIST patients receiving radical surgery. Besides, our study indicated that the prognostic ability of FAR is significantly better than Hb and PNI. We recommend adding it to the current risk classification to further stratify high-risk patients and guide neoadjuvant therapy and adjuvant therapy. FAR as

an assessment tool to guide the future treatment of GIST still needs a large clinical prospective study for verification so that it can be applied to the patients' benefit.

Abbreviations

AUC, area under the curve; CI, confidence interval; CT, computed tomography; FAR, fibrinogen to albumin ratio; GIST, gastrointestinal stromal tumor; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; HR, hazard ratio; RFS, recurrence-free survival; ROC, receiver operating characteristics; PNI, prognostic nutrition index; PI3K, phosphoinositide 3-kinase.

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure

The authors report no conflicts of interest in this work.

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