

Prognostic significance of preoperative plasma fibrinogen levels in primary gastrointestinal stromal tumours: a retrospective cohort study

Shibo Song

Beijing Hospital <https://orcid.org/0000-0001-6326-0852>

Xianglong Cao

Beijing Hospital

Hongda Pan

Fudan University Shanghai Cancer Center

Maolin Hu

Beijing Hospital

Qiuxia Yan

Beijing Hospital

Jinghai Song

Beijing Tongren Hospital

Hua Yang

Beijing Hospital

Gang Zhao

Beijing Hospital

Gang Xiao (✉ xiaogangbeijing@163.com)

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Abstract

Background Improved prediction of prognosis for gastrointestinal stromal tumours (GISTs) has become increasingly important since the introduction of small molecule tyrosine kinase inhibitors. Here, we aimed to evaluate the prognostic significance of preoperative plasma fibrinogen (Fib) levels in patients with primary GISTs and to analyse their correlations with clinicopathological characteristics. **Methods** A total of 201 previously untreated patients with primary GISTs who had undergone radical surgery at our institution between October 2004 and July 2018 were enrolled. Patient demographics, clinicopathological characteristics, preoperative plasma Fib levels and recurrence-free survival (RFS) were analysed. The optimal cut-off value for Fib levels was calculated using time-dependent receiver operating characteristic curve analysis. RFS, the primary endpoint, was calculated by the Kaplan–Meier method and compared by the log-rank test. Univariate and multivariate Cox regression models were calculated. **Results** Patients in the high Fib group had a shorter RFS than those in the low Fib group ($P < 0.001$). In multivariate analysis, high preoperative plasma Fib levels were detected as an independent adverse prognostic factor ($P = 0.008$, hazard ratio 3.136, 95% CI 1.356–7.256). Furthermore, high preoperative plasma Fib levels also indicated a poor prognosis within the modified National Institutes of Health (mNIH) high-risk subgroup ($P = 0.041$). In addition, preoperative plasma Fib levels showed a positive correlation with several prognostic factors and even a linear relationship with tumour size (Spearman correlation coefficient $[r] = 0.411$, $P < 0.001$). **Conclusions** High preoperative plasma Fib levels may indicate a poor prognosis in patients with primary GISTs. As a cost-effective biomarker, preoperative assessment of plasma Fib levels may help to further risk stratify patients with mNIH high-risk GISTs and instruct the application of targeted therapy.

Background

Gastrointestinal stromal tumours (GISTs) are rare but the most common mesenchymal neoplasms in the gastrointestinal (GI) tract, with an annual incidence of approximately 10 per million people [1, 2]. The malignant potential of GISTs ranges from benign tumours to rapidly progressing sarcomas [3].

The only well-recognized curative treatment for primary GISTs is radical resection [4]. However, the recurrence rate remains high after curative resection alone, especially for high-risk patients, who have a greater than 50% chance of recurrence at 2 years [5]. Fortunately, the introduction of small molecule tyrosine kinase inhibitors (TKIs) revolutionized the treatment strategies and greatly improved the prognosis of patients with GISTs [4, 6]. The well-recognized indications for TKIs are inoperable or metastatic GISTs and GISTs with a moderate or high risk of recurrence after resection [4]. However, all the current popularized risk-stratification schemes are based only on tumour-specific factors after resection [7–11]. Therefore, in this era of adjuvant TKI therapy, it is urgent to find some preoperative factors of prognosis and perfect the current risk-stratification schemes to improve the prediction of prognosis and instruct the application of targeted therapy early in the treatment setting.

In addition to tumour-specific factors, hypercoagulation is thought to be associated with several developmental processes of tumours, such as tumour angiogenesis, invasion, progression, and

metastasis [12, 13]. Fibrinogen (Fib) is one of the most significant indicators of coagulation [12, 14]. In the last few years, high preoperative Fib levels have been found to be associated with poor prognosis in various solid tumours [15-21]. However, to our knowledge, there are few studies on the relationship between Fib and the prognosis of patients with GISTs, and their results have been controversial [22, 23]. Furthermore, no studies have explored whether Fib correlates with prognosis within different recurrent risk subgroups. Hence, there is limited evidence confirming the prognostic ability of Fib in GISTs.

In the present study, we analysed the preoperative plasma Fib levels in 201 patients with primary GISTs who had undergone radical surgery, seeking to evaluate their prognostic significance in the overall cohort and subgroups, and further analysed their correlation with clinicopathological prognostic factors.

Methods

Patients

We retrospectively reviewed the medical records of 237 consecutive patients with primary GISTs who had undergone surgery at Beijing Hospital between October 2004 and July 2018. A total of 201 patients were enrolled in this study. This retrospective study was approved by the institutional review board of Beijing Hospital.

Participants in the present study met the following inclusion criteria: 1) postoperatively confirmed GIST; 2) R0 resection; 3) available plasma Fib level data within 7 days before operation; and 4) age > 18 years. The exclusion criteria were as follows: 1) 6 months or less of follow-up data; 2) preoperative imatinib treatment; 3) coexistent haematological disorders, including splenectomy, thromboembolism, or anticoagulant therapy within 3 months before operation; 4) blood transfusion or inflammatory disorders within 2 weeks before operation; 5) synchronous metastasis or other malignancies; and 6) acute or chronic liver disease.

Preoperative operability was assessed by using abdominal/pelvic computed tomography or magnetic resonance imaging. Patients were regularly followed up every 3–6 months for 3–5 years and then annually. The follow-up was conducted by telephone and regular outpatient rechecks. During the follow-up, physical examinations, laboratory tests, imaging and endoscopy were performed. The date of last follow-up visit, recurrence, or death were recorded. The latest follow-up date was February 15, 2019.

Plasma fibrinogen

Data on preoperative plasma Fib levels were retrospectively obtained from blood coagulation analysis before breakfast within 7 days prior to surgery. Plasma Fib levels were measured by the Clauss clotting method using the automatic blood coagulation analyser ACL TOP™ 700 (Instrumentation Laboratory, Werfen Group, America) according to the manufacturer's instructions, with its matching thrombin reagent.

Pathological assessment and tumour grading

The diagnosis of GISTs was well recognized by histopathologic examination of resection specimens according to the Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumour [24]. Tumour location, size, rupture, and mitotic index (number of mitoses per 50 high-power fields [HPFs]) were recorded. The malignant potential for each GIST was based on the modified National Institutes of Health (mNIH) risk classification [7].

Statistical analysis

The optimal cut-off value for preoperative Fib levels was calculated using time-dependent receiver operating characteristic (ROC) curve analysis. Continuous values were assessed using Student's t-test or the Mann-Whitney U-test, and categorical data were compared by the χ^2 test, Fisher's exact test or the Mann-Whitney U-test, as appropriate. Spearman's rank correlation coefficients were used to examine associations between two continuous variables. Recurrence-free survival (RFS) was defined as a composite endpoint of local recurrence, distant metastasis, or death from any cause, whichever came first. RFS curves were calculated by the Kaplan–Meier product limit method and then compared using the log-rank test. Univariate and multivariate Cox proportional hazard regression models were constructed to identify associations with RFS. All tests were two-sided, and $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 20.0 and R software.

Results

ROC curve analysis

A ROC curve for preoperative plasma Fib levels and the prediction of 5-year RFS is shown in Figure 1. The area under the ROC curve of Fib was 0.665. Based on the 5-year RFS, the optimal cut-off value of 3.48 g/L had the highest sensitivity (56.5%) and specificity (74.0%). Patients were categorized into groups of H-Fib (> 3.48 g/L) and L-Fib (≤ 3.48 g/L) according to the cut-off value.

Patient demographics and clinicopathological features

Patient demographics and clinicopathological features are summarized in Table 1. There were 110 males (54.73%) and 91 females (45.27%), with a median age of 61 years (range 26–83 years) at surgery. The most frequent location was the stomach (145, 72.14%), followed by the jejunum and ileum (25, 12.44%), duodenum (13, 6.47%), colon and rectum (11, 5.47%), and extragastrointestinal sites (7, 3.48%). The median tumour size was 4.2 cm (range 0.7–22.0 cm), and the majority of patients (65.17%) had a mitotic index of $\leq 5/50$ HPFs. All 201 patients had no evidence of tumour rupture at the time of surgery. According to the mNIH risk classification [7], 99 patients (49.25%) were classified in the very low/low-risk group, and 102 patients (50.75%) were classified in the moderate/high-risk group. Among the 102 patients, 36 patients (35.29%) received adjuvant imatinib treatment following surgery.

Associations between preoperative plasma fibrinogen levels and clinicopathological factors

According to the cut-off value of 3.48 g/L, patients were divided into two groups: 141 patients were in the H-Fib group, and 60 patients were in the L-Fib group (Table 1). Significantly, patients in the H-Fib group were more likely to be older ($P = 0.002$) and have a larger tumour size ($P \leq 0.001$), a greater mitotic index ($P \leq 0.001$) and a higher mNIH risk classification ($P \leq 0.001$) than those in the L-Fib group. Other features, including sex, cardiovascular diseases (CVDs), diabetes, GI bleeding, body mass index (BMI), plasma albumin (Alb) levels, Eastern Cooperative Oncology Group (ECOG) performance status, adjuvant imatinib treatment and tumour location, were similarly distributed between both groups. The preoperative plasma Fib levels showed a positive correlation with tumour size (Figure 2a, $P \leq 0.001$), mitotic index (Figure 2b, $P \leq 0.001$) and mNIH risk classification (Figure 2c, $P \leq 0.001$) and even were linearly correlated with tumour size (Figure 2d, Spearman correlation coefficient [r] = 0.411, $P < 0.001$).

Survival analyses

The median follow-up time was 45 months (range 7–174 months). Among the 201 patients, 23 patients showed recurrence or metastasis, and 3 patients died from other causes during the study before recurrence or metastasis. For the overall population, the 1-, 3- and 5-year RFS rates were 96.9%, 89.5% and 84.7%, respectively. Patients in the H-Fib group had a shorter RFS than those in the L-Fib group (Figure 3, $P \leq 0.001$). The 5-year RFS in the H-Fib group was 68.1%, compared to 92.7% in the L-Fib group.

In univariate analysis, Fib (hazard ratio [HR]: 4.239; 95% CI: 1.882–9.548; $P \leq 0.001$), Alb (hazard ratio [HR]: 0.891; 95% CI: 0.825–0.964; $P = 0.004$), tumour location, tumour size and mitotic index were found to be associated with RFS (Table 2). Moreover, the multivariate analysis identified Fib (HR: 3.136, 95% CI: 1.356–7.256, $P = 0.008$), tumour location and mitotic index as independent predictive factors of RFS (Table 2). High preoperative plasma Fib levels were detected as an independent adverse prognostic factor.

To further demonstrate the prognostic significance of Fib, we performed subgroup analysis stratified by mNIH risk, tumour size, tumour location, adjuvant imatinib treatment and age. High preoperative plasma Fib levels still indicated a worse prognosis for patients within the mNIH high-risk subgroup (Figure 4a, $P = 0.041$) but not for the remaining patients (Figure 4b, $P = 0.091$). Preoperative plasma Fib levels were not significantly associated with prognosis for patients with tumours > 5 cm (Figure 4c, $P = 0.063$) and patients with tumours ≤ 5 cm (Figure 4c, $P = 0.156$). In addition, high preoperative plasma Fib levels indicated a poor prognosis for patients with GISTs regardless of the primary tumour location (Figure 4e and 4f) or age (Figure 4g and 4h). In other subgroup analyses, significant prognostic significance of preoperative plasma Fib levels was shown in patients who did not receive adjuvant imatinib treatment (Figure 4i and 4j).

Discussion

The present study demonstrated that high preoperative plasma Fib levels were significantly associated with poor RFS in patients with primary GISTs who underwent radical surgery and explored its possible cut-off value (3.48 g/L) to predict RFS. To the best of our knowledge, this study represents the largest

dedicated series published, focusing on the prognostic significance of preoperative plasma Fib levels in patients with primary GISTs. Furthermore, we found, for the first time, that high preoperative plasma Fib levels still indicated a poor RFS in patients with mNIH high-risk GISTs. In addition, our study showed a positive correlation between preoperative plasma Fib levels and well-recognized prognostic factors, including tumour size, mitotic index, and mNIH risk classification.

In our study, the correlation between high preoperative plasma Fib levels and poor prognosis was further verified, which is consistent with previous studies on GISTs [22, 23]. However, the cuff-off value (3.48 g/L) is inconsistent with the study by Cai et al. (3.24 g/L) [23]. Obviously, given the heterogeneity of different populations, it is impossible to determine the ideal threshold for Fib in small or retrospective studies. Although Lu et al first observed a correlation between high preoperative plasma Fib levels and poor prognosis in patients with GISTs, their sample size was small (n = 91), the follow-up time was shorter (median follow-up time: 2 years), and no subgroup analysis was performed [22]. Cai et al recently reported a similar result with a larger sample size (n = 170), but their databases overlapped with those of Lu et al, and the median follow-up time was not given [22, 23]. In addition, our results are consistent with previous studies in patients with different malignancies [15-21]. Some researchers found that Fib was positively correlated with the neutrophil-lymphocyte ratio (NLR), and others found that the combination of Fib and NLR could better predict prognosis, but the specific mechanisms remain unclear [19, 25, 26]. Moreover, some animal experiments have suggested that Fib is an important factor in the metastatic potential of tumour cells [27, 28]. Some studies have indicated that, in addition to antithrombotic functions, heparins and derivatives also exert critical antimetastatic effects by interfering with P-selectin-mediated cell binding [29, 30]. As a biomarker of nutritional status, Alb has been recognized as a prognostic factor in some kinds of tumours [31-34]. However, in the present study, although preoperative Alb levels were found to be associated with RFS in the univariate analysis, they were not detected as an independent predictive factor in the multivariate analysis. In the present study, tumour size was not observed to be an independent prognostic factor, which may be due to the limited sample size, the exclusion of patients who received preoperative imatinib treatment or non-radical resection, or other factors obscuring the prognostic significance. Since the survival analyses were conducted in the overall population, prognostic benefits of adjuvant imatinib treatment were not observed. However, in our study, adjuvant imatinib treatment significantly improved the prognosis of patients with mNIH moderate/high-risk GISTs (P = 0.015), which is consistent with previous studies [4, 6].

In the mNIH high-risk subgroup analysis, for the first time, preoperative plasma Fib levels were detected to be a significant prognostic factor, which would help to further risk stratify patients with mNIH high-risk GISTs and instruct the application of targeted therapy. However, correlations were not significant within the very-low/low/moderate-risk subgroup analysis, which may be due to the limited number of endpoint events and the shorter follow-up time. Although there was no significant correlation between Fib and RFS in subgroups of different tumour sizes, a trend was observed that high Fib indicated poor RFS, which may require a larger sample size and a continuous follow-up time to further determine. Preoperative plasma Fib levels were a significant prognostic factor for GISTs in both stomach and non-stomach, which may indicate that plasma Fib levels were not significantly associated with the tumour locations. For patients

without adjuvant imatinib treatment, high preoperative plasma Fib levels indicated a significantly poor prognosis. However, in the subgroup with adjuvant imatinib treatment, a correlation was not observed between Fib and RFS, which may be due to the prognostic benefits from imatinib treatment or the limited sample size.

Our study showed a positive correlation between the preoperative plasma Fib levels and several prognostic factors, including tumour size, mitotic index, and mNIH risk classification, which is similar to the study by Cai et al [23]. Furthermore, we even observed a linear correlation between preoperative plasma fibrinogen levels and tumour size, which indirectly indicates Fib's prognostic significance. Previous studies have reported that the plasma concentrations of some coagulation factors, such as Fib, increase progressively with age [35]. We also found that patients in the H-Fib group were older than patients in the L-Fib group, which was consistent with previous studies [23, 35]. However, in our study, for patients with GISTs, the correlation between age and the preoperative plasma Fib levels was not strong (Spearman correlation coefficient [r] = 0.198, P = 0.005). Furthermore, in our study, regardless of age, high preoperative plasma Fib levels indicated a poor prognosis for patients with GISTs. Therefore, the impact of ageing could not cover up the correlation between preoperative plasma Fib levels and the malignant degree of GISTs.

The molecular mechanisms by which tumour cells interact with the haemostatic system are yet to be uncovered. Several possible mechanisms were proposed to explain the complex correlation. On the one hand, tumour cells activate the haemostatic system in multiple ways. Tumour cells not only directly activate the coagulation cascade by producing many procoagulant proteins (tissue factor, heparanase, cancer procoagulant, and tissue factor-positive microparticles) but also stimulate the procoagulant properties of the host's haemostatic cells (endothelial cells, platelets, and leukocytes), thereby increasing plasma Fib levels [36, 37]. We also cannot exclude that the pathophysiological mechanism of hypercoagulation may be secondary to the tumour-derived systemic inflammatory response and/or intra-abdominal infectious disease [36-39]. Indeed, all of the procoagulant mechanisms elicited by tumour tissues, as well as the patient's general and clinical thrombotic risk factors, contribute to the occurrence of hypercoagulation in patients with cancer [37]. On the other hand, Fib could also promote tumour progression in return. In the tumour microenvironment, Fib could influence the development of tumours through complex interactions with multiple integrin or non-integrin Fib receptors (e.g., cadherins, $\alpha\text{IIb}\beta\text{3}$, $\alpha\text{V}\beta\text{3}$, $\alpha\text{X}\beta\text{2}$, $\alpha\text{M}\beta\text{2}$, $\alpha\text{5}\beta\text{1}$, $\alpha\text{V}\beta\text{1}$, and Toll-like receptors), which mediate innate immune cell function, tumour cellular proliferation, migration, and apoptosis [40-46]. For example, Fib has been suggested to be a bridging molecule between tumour cells and vascular endothelial growth factor, which could stimulate angiogenesis and promote tumour proliferation [46]. All of these possible mechanisms promote a positive feedback loop between tumour progression and hypercoagulation.

As a cost-effective biomarker, Fib is easily detected with conventional coagulation analysis before surgery. Accordingly, the evaluation of Fib levels would be clinically useful for indicating the malignant potential and prognosis in combination with imaging and pathological features.

There are several limitations in the present study. First, a selection bias cannot be excluded because it was a retrospective study of a single institution. The exclusion of patients who did not undergo radical surgery, as well as the inclusion of patients with adjuvant imatinib treatment, had an effect on the prognosis of the overall cohort. Second, due to the limited follow-up time, the inclusion of patients with adjuvant imatinib treatment and the high survival of patients with GISTs, we did not analyse OS as the endpoint of this study. Third, genetic mutation analysis was not conducted in most patients because of the high cost, which limits further studies.

Conclusions

High preoperative plasma Fib levels may indicate poor prognosis in patients with primary GISTs who underwent radical surgery. As a cost-effective biomarker, preoperative assessment of plasma Fib levels may help to further risk stratify patients with mNIH high-risk GISTs and instruct the application of targeted therapy. However, larger prospective studies and further molecular biological experiments are warranted to confirm our results.

Abbreviations

GISTs: gastrointestinal stromal tumours; GI: gastrointestinal; TKIs: tyrosine kinase inhibitors; Fib: fibrinogen; HPFs: high-power fields; mNIH: modified National Institutes of Health; ROC: receiver operating characteristic; AUC: area under the ROC curve; RFS: recurrence-free survival; CI: confidence interval; Alb: albumin; CVDs: cardiovascular diseases; BMI: body mass index; ECOG score: Eastern Cooperative Oncology Group score; HR: hazard ratio

Declarations

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Authors' contributions

SBS designed the study, analysed the data, and wrote the manuscript. GX assisted in the study design, data interpretation and revision. XLC, HDP, JHS, and GZ contributed to the study design and revision. MLH, QXY and HY contributed to the data collection and analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Beijing Hospital with Approval Letter No. 2019BJYYEC-030-01 and was granted an exemption from requiring informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Patient demographics and clinicopathological features

Variable	Total (n=201)	L-Fib (n=141) Fib ≤ 3.48 g/L	H-Fib (n=60) Fib > 3.48 g/L	P-value
Age (years)*	61 (52, 70)	60.00 (50.00, 67.50)	63.50 (57.25, 72.00)	0.002^a
Sex				
Male	110 (54.73%)	74 (52.48%)	36 (60.00%)	0.327 ^b
Female	91 (45.27%)	67 (47.52%)	24 (40.00%)	
CVDs				
No	111 (55.22%)	80 (56.74%)	31 (51.67%)	0.508 ^b
Yes	90 (44.78%)	61 (43.26%)	29 (48.33%)	
Diabetes				
No	175 (87.06%)	125 (88.65%)	50 (83.33%)	0.304 ^b
Yes	26 (12.94%)	16 (11.35%)	10 (16.67%)	
GI bleeding				
No	160 (79.60%)	116 (82.27%)	44 (73.33%)	0.150 ^b
Yes	41 (20.40%)	25 (17.73%)	16 (26.67%)	
BMI (kg/m ²)*	24.22 ± 3.38	24.34 ± 3.57	23.94 ± 2.89	0.442 ^c
Alb (g/L)*	40.00 (38.00, 42.00)	41.00 (39.00, 43.00)	40.00 (37.25, 42.00)	0.052 ^a
ECOG score				
1–2	196 (97.51%)	137 (97.16%)	59 (98.33%)	1.000 ^d
3–4	5 (2.49%)	4 (2.84%)	1 (1.67%)	
Tumour location				
Stomach	145 (72.14%)	104 (73.76%)	41 (68.33%)	0.425 ^b
Non-stomach	56 (27.86%)	37 (26.24%)	19 (31.67%)	
Tumour size (cm)				
≤ 2	37 (18.41%)	33 (23.40%)	4 (6.67%)	□ 0.001^a
≤ 5	90 (44.78%)	69 (48.94%)	21 (35.00%)	
≤ 10	44 (21.89%)	30 (21.28%)	14 (23.33%)	
> 10	30 (14.93%)	9 (6.38%)	21 (35.00%)	
Mitotic index (/50 HPFs)				
≤ 5	131 (65.17%)	102 (72.34%)	29 (48.33%)	□ 0.001^a
≤ 10	32 (15.92%)	22 (15.60%)	10 (16.67%)	
> 10	38 (18.91%)	17 (12.06%)	21 (35.00%)	
mNIH risk classification				
Very low	36 (17.91%)	32 (22.70%)	4 (6.67%)	□ 0.001^a
Low	63 (31.34%)	50 (35.46%)	13 (21.67%)	
Moderate	37 (18.41%)	25 (17.73%)	12 (20.00%)	
High	65 (32.34%)	34 (24.11%)	31 (51.67%)	

Postoperative imatinib				
No	165 (82.09%)	118 (83.69%)	47 (78.33%)	0.365 ^b
Yes	36 (17.91%)	23 (16.31%)	13 (21.67%)	

Notes: Continuous variables were expressed as means \pm standard deviations or medians (25th–75th percentile), and categorical variables were presented as frequency (%), as appropriate. Continuous values were assessed using Student’s t-test or the Mann-Whitney U-test, and categorical data were compared by the χ^2 test, Fisher’s exact test or the Mann-Whitney U-test, as appropriate. * Continuous value, ^a the Mann-Whitney U-test, ^b the χ^2 test, ^c Student’s t-test, ^d Fisher’s exact test.

Abbreviations: Fib, fibrinogen; CVDs, cardiovascular diseases; GI, gastrointestinal; BMI, body mass index; Alb, albumin; ECOG score, Eastern Cooperative Oncology Group score; mNIH risk classification, modified National Institutes of Health risk classification.

Table 2 Univariate and multivariate Cox regression analyses for RFS (n = 201)

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Alb (> 3.48 vs \leq 3.48 g/L)	4.239	1.882–9.548	\square 0.001	3.136	1.356–7.256	0.008
Age (> 60 vs \leq 60 years)	1.174	0.542–2.544	0.684			
Sex (male vs female)	0.842	0.381–1.859	0.670			
Diabetes (yes vs no)	0.612	0.266–1.407	0.248			
Hypertension (yes vs no)	0.502	0.119–2.134	0.352			
Bleeding (yes vs no)	1.492	0.627–3.505	0.365			
BMI (kg/m ²)	0.959	0.852–1.080	0.492			
Fib (g/L)	0.891	0.825–0.964	0.004			
ECOG score (>2 vs \leq 2)	1.991	0.268–14.812	0.501			
Primary site (non-stomach vs stomach)	4.088	1.884–8.871	\square 0.001	4.287	1.924–9.550	< 0.001
Primary tumor size (>5 vs \leq 5 cm)	5.363	2.251–12.785	\square 0.001			
HPF index (> 5 vs \leq 5/50 HPFs)	8.501	3.360–21.507	\square 0.001	6.088	2.335–15.871	\square 0.001
Postoperative imatinib (yes vs no)	0.593	0.177–1.982	0.396			

Notes: Univariate and multivariate Cox proportional hazard regression models were performed to identify associations with RFS. Factors found significant in univariate analysis were included in a forward stepwise multivariate Cox proportional hazards regression model with entry criteria of $P \leq 0.05$ and removal criteria of $P > 0.1$.

Abbreviations: Fib, fibrinogen; CVDs, cardiovascular diseases; GI, gastrointestinal; BMI, body mass index; Alb, albumin; ECOG score, Eastern Cooperative Oncology Group score; HPFs, high-power fields; HR, hazard ratio; CI, confidence interval; RFS, recurrence-free survival.

Figures

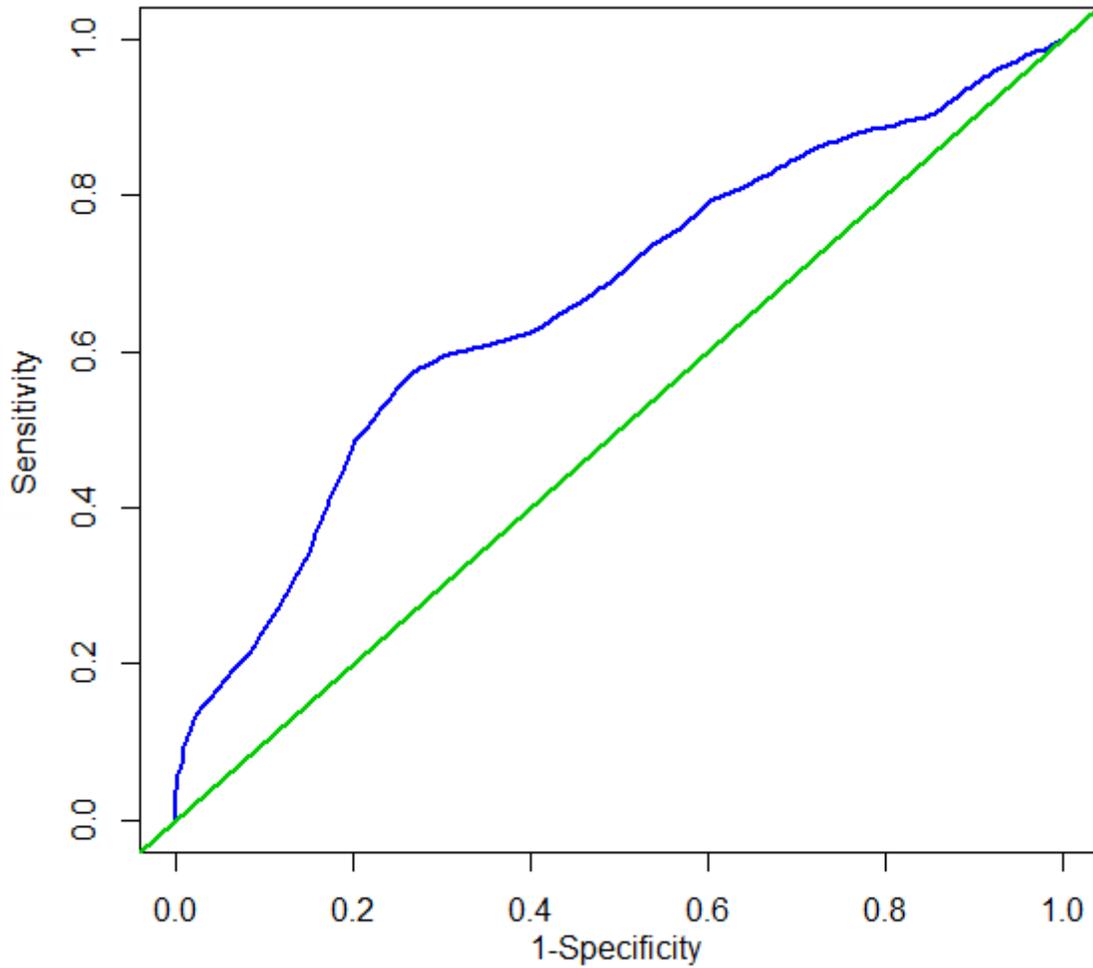


Figure 1

ROC curve for preoperative plasma Fib levels to predict 5-year RFS. Notes: The area under the ROC curve of Fib was 0.665. Fib = 3.48 g/L had the highest sensitivity (56.5%) and specificity (74.0%).

Abbreviations: ROC, Receiver operating characteristic; Fib, fibrinogen; RFS, recurrence-free survival

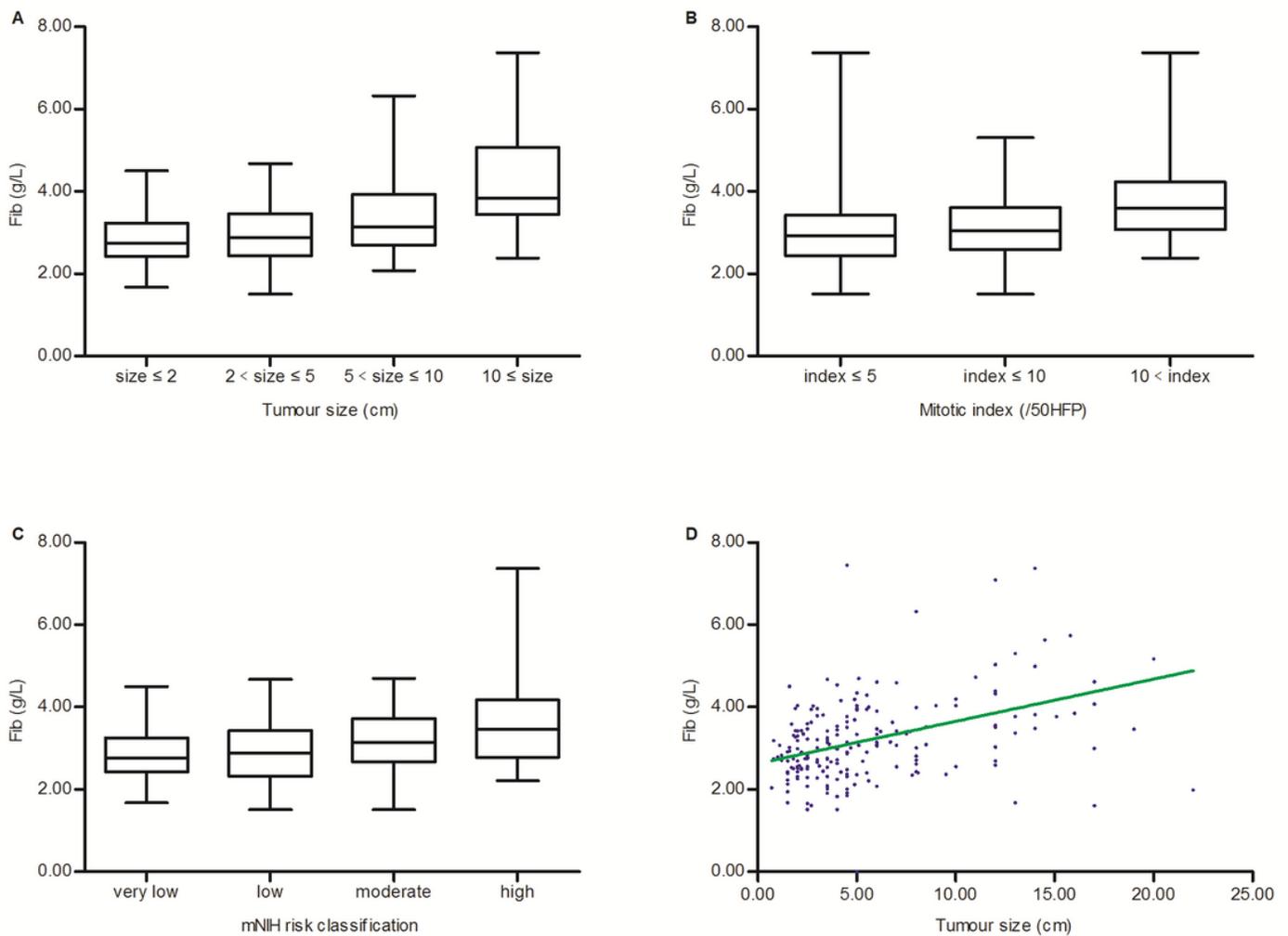


Figure 2

Associations between preoperative plasma Fib levels and several prognostic factors Notes: (a) Preoperative Fib levels in patients with GISTs in terms of primary tumour size. Kruskal-Wallis test: $P \leq 0.001$. (b) Preoperative Fib levels in patients with GISTs in terms of mitotic index. Kruskal-Wallis test: $P \leq 0.001$. (c) Preoperative Fib levels in patients with GISTs in terms of the modified National Institutes of Health (mNIH) risk classification. Kruskal-Wallis test: $P \leq 0.001$. (d) Tumour size is positively associated with preoperative plasma Fib levels (Spearman correlation coefficient $[r] = 0.411$, $P \leq 0.001$). Abbreviations: Fib, fibrinogen; GISTs, gastrointestinal stromal tumours; HPFs, high-power fields; mNIH risk classification, modified National Institutes of Health risk classification.

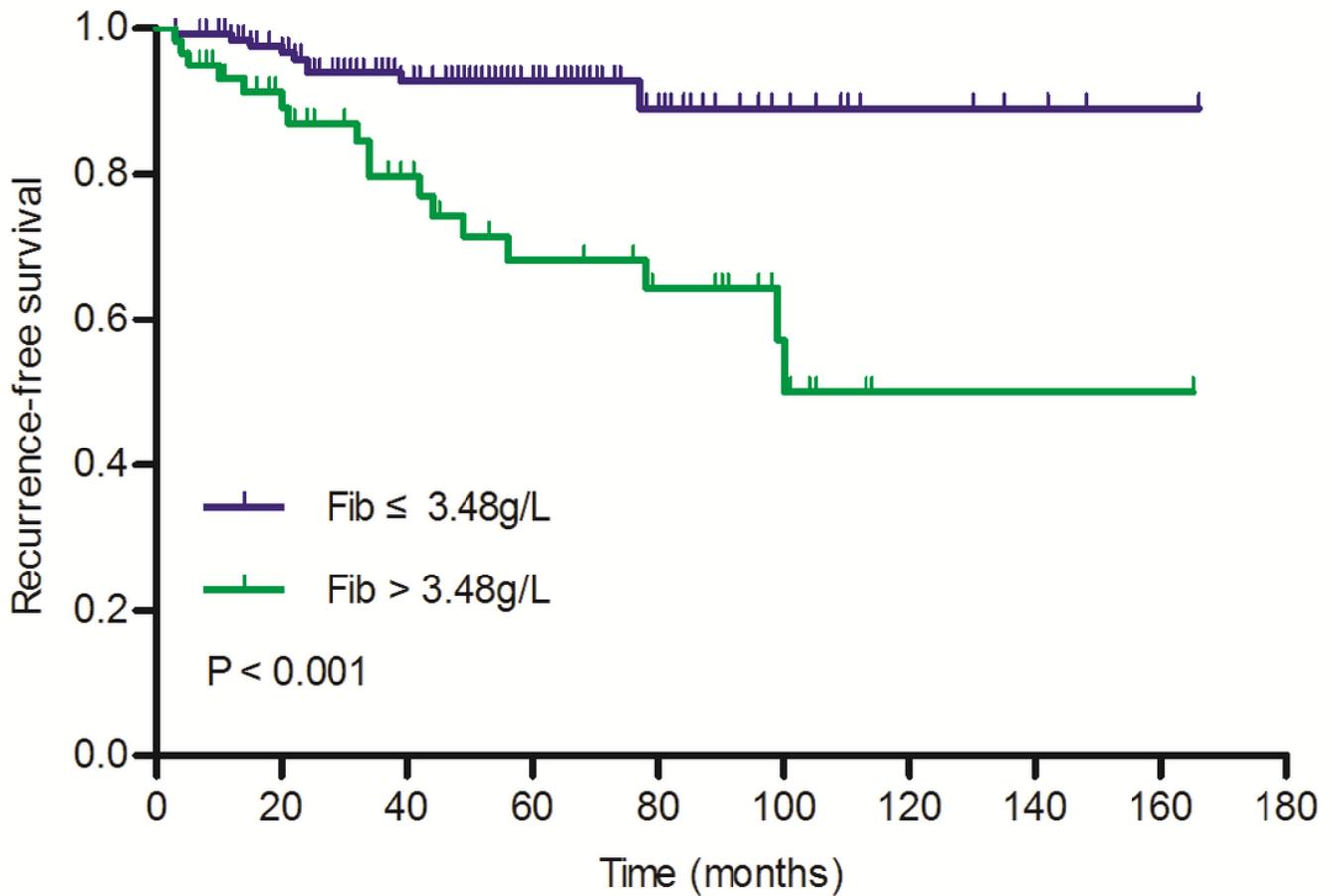


Figure 3

RFS curve analysis for patients with GISTs based on the preoperative plasma Fib levels. Notes: RFS curves were calculated by the Kaplan–Meier product limit method and then compared using the log-rank test. High preoperative plasma Fib level was significantly associated with shorter RFS. Abbreviations: RFS, recurrence-free survival; GISTs, gastrointestinal stromal tumours; Fib, fibrinogen.

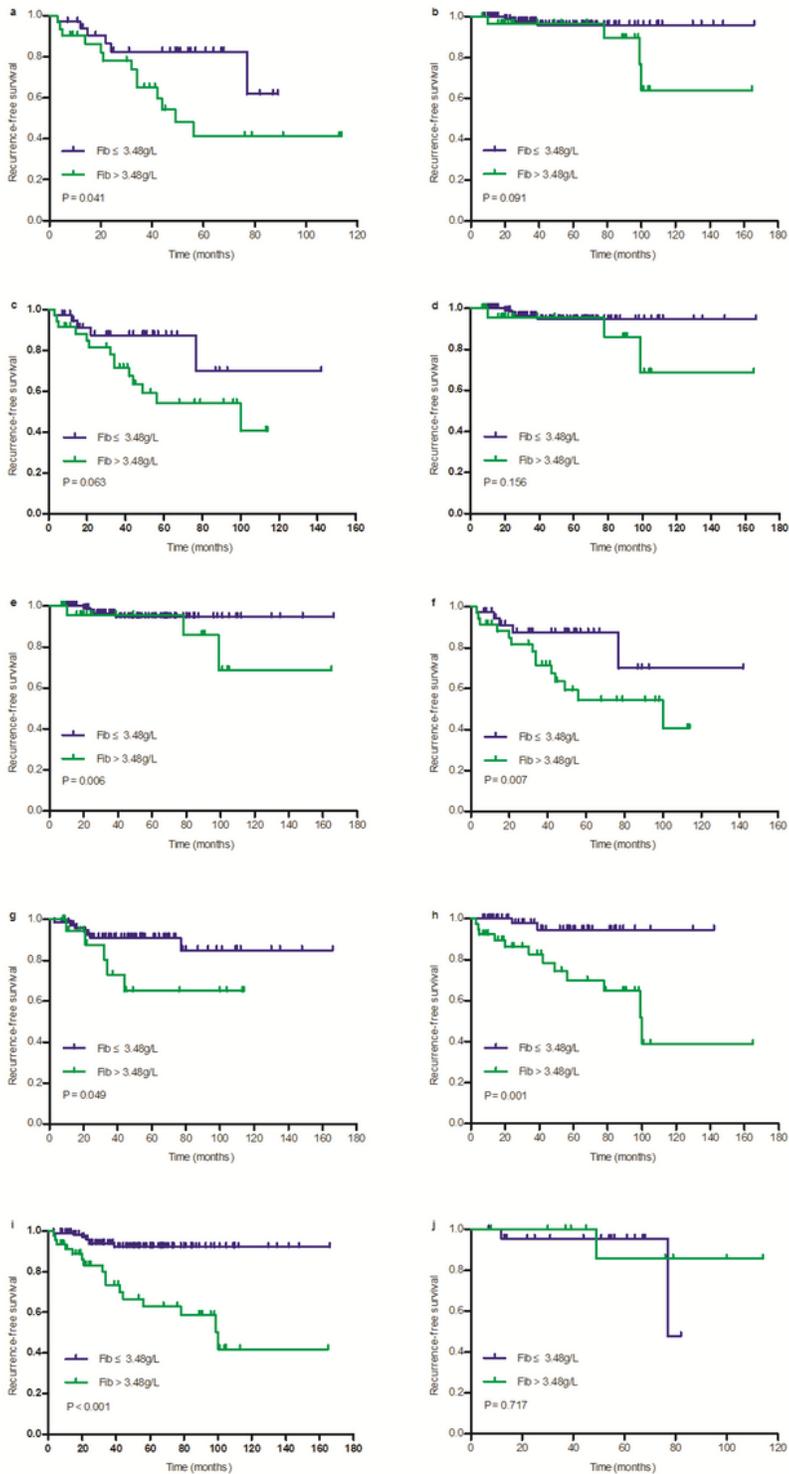


Figure 4

RFS curve analyses based on the preoperative plasma Fib levels in subgroups. Notes: (a) 65 patients with mNIH high-risk GISTs ($P = 0.041$), (b) 136 patients with mNIH very low/low/moderate-risk GISTs ($P = 0.091$), (c) 74 patients with tumours > 5 cm ($P = 0.063$), (d) 127 patients with tumours ≤ 5 cm ($P = 0.156$), (e) 145 patients with GISTs at stomach ($P = 0.006$), (f) 56 patients with GISTs at non-stomach ($P = 0.007$), (g) 99 patients ≤ 60 years ($P = 0.049$), (h) 102 patients > 60 years ($P = 0.001$), (i) 165 patients

without adjuvant imatinib treatment ($P \leq 0.001$), (j) 36 patients with adjuvant imatinib treatment ($P = 0.717$). Abbreviations: RFS, recurrence-free survival; Fib, fibrinogen; mNIH risk classification, modified National Institutes of Health risk classification; GISTs, gastrointestinal stromal tumours.