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***Retrospective Study***

**Role of fibrinogen and D-dimer-fibrinogen ratio in resectable gastrointestinal stromal tumors**

Cai HX*et al*. FIB, DFR and Prognosis of GIST

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**Abstract**

***AIM***

To investigate the prognostic value of preoperative fibrinogen concentration (FIB) and D-dimer-fibrinogen ratio (DFR) in gastrointestinal stromal tumors (GIST).

***METHODS***

The purpose of this study was to retrospectively analyze 170 patients who were admitted to our hospital from January 2010 to December 2015. The optimal cutoff value of related parameters was estimated by receiver operating characteristic (ROC) curve analysis. The recurrence free survival (RFS) rate was evaluated by Kaplan-Meier curves. Univariate analysis and multivariate Cox regression models were used to analyze the prognostic factors of GIST. The relationship between the FIB, D-dimer, DFR, platelets (PLT), and the clinicopathological features of GIST is described by chi-square test or nonparametric rank sum test (Mann-Whitney test).

***RESULTS***

InROC analysis, the optimal cutoff value of FIB, D-dimer, DFR, and PLT was 3.24 g/L, 1.24 mg/L, 0.354, and 197.5 (× 109/L), respectively. Univariate analysis and the Kaplan-Meier survival curve showed that FIB, D-dimer, DFR, PLT, National Institutes of Health (NIH) risk category, tumor size, tumor location, and mitotic index were relevant to the 3-year and 5-year survival rate of patients (*P* < 0.05). Cox multivariate regression analysis illustrated that FIB (*RR*: 0.108, 95%CI: 0.031­0. 373), DFR (*RR*: 0.319, 95%CI: 0.131­0. 777), and NIH risk category (*RR*: 0.166, 95%CI: 0.047­0.589) were independent prognostic factors of the RFS rate (*P* < 0. 05). Moreover, FIB, D-dimer, DFR, and PLT were correlated with the clinical features of GIST.

***CONCLUSION***

FIB, D-dimer, DFR and PLT are all related to the prognosis of GIST. Moreover, FIB and DFR may be independent risk factors for predicting the prognosis of resectable GIST.

**Key words:** Fibrinogen; D-dimer;D-dimer-fibrinogen ratio; Prognosis; Gastrointestinal stromal tumor

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**Core tip**: For patients with gastrointestinal stromal tumors (GIST), postoperative recurrence and metastasis are the main factors affecting survival. Moreover, recurrence and metastasis mainly occurred in moderate and high-risk patients. Therefore, it is necessary to screen these patients for adjuvant treatment at an early stage. Fibrinogen (FIB) and D-dimer were reported to be associated with the prognosis of many tumors. The purpose of this study was to investigate the value of preoperative FIB, D-dimer, the D-dimer–fibrinogen ratio (DFR), and platelets in the prognosis of GIST. The results showed that FIB and DFR were independent risk factors for predicting prognosis of primary resectable GIST.

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**INTRODUCTION**

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasms originating from the gastrointestinal tract[1-2]. GIST may occur anywhere in the digestive tract, including outside the gastrointestinal tract[[1](#_ENREF_1" \o "Goh, 2016 #3)]. The incidence of GIST is 60%-70% in the stomach, and 30% in the small intestine[[3](#_ENREF_3)].However, GIST occurring in areas such as colon, rectum and esophagus is rare.The main treatment for primary localized GIST is complete resection and marginal negative[[1](#_ENREF_1" \o "Goh, 2016 #3)]. However, the recurrence or metastasis of the original disease after the operation is an obstacle to prolonging the survival period. It was reported that approximately 50% of the patients who undergo surgery alone will have tumor recurrence, and the median survival after recurrence is less than 2 years**[**[**4**](#_ENREF_4)**]**. Unfortunately,if GIST recurs or is metastatic, the value of the operation is low. In addition, the expert consensus on gastrointestinal stromal tumors in China indicated that patients in the intermediate category or high category who met the 2008 revision risk classification standard should carry out corresponding auxiliary treatment[3]. Therefore, early screening of middle and high category patients with adjuvant therapy can significantly improve the prognosis of patients. However, the current accepted risk classification criteria for predicting the prognosis of GIST patients require pathological results to be obtained. In this case, it is important to develop some simple, noninvasive methods to accurately screen high-risk populations of GIST and provide early adjuvant therapy to improve their prognosis.

Thrombocytopenia and coagulation abnormalities are very common in cancer patients. Research showed that cancer was a prothrombotic state, and much evidence points to a role for the fibrinogen-platelet axis in tumor biology[4]. Fibrinogen (FIB) is a glycoprotein produced mainly by liver cells, which is an important coagulation factor and contributes to the regulation of blood coagulation pathways[5]. Moreover, FIB can promote cell adhesion and inflammation in the process of coagulation. Additionally, recent evidence suggests that tumors with elevated FIB levels are more likely to develop to invasion and metastasis[6-7], including esophageal, stomach and colorectal carcinomas[8].In the coagulation system, FIB can be transformed into fibrin by thrombin, and the end product D-dimer of fibrin is increased in cases such as colorectal cancer, lymph node metastasis and vascular invasion[9]**.** In addition, it was reported that the combination of FIB and the neutrophil‑-lymphocyte ratio could predict tumor progression and prognosis in gastric cancer patients[8]. At the same time, D-dimer can also predict the prognosis of metastatic gastric cancer after chemotherapy[10].

Based on the above results, we hypothesized that plasma FIB, D-dimer, and platelet count (PLT) may be associated with clinical outcomes in patients with cancer. However, as far as we know, studies assessing the prognostic value of plasma FIB, D-dimer and PLT in patients with GIST are rarely reported.

The aim of this study was to investigate the relationship between preoperative FIB, D-dimer, the D-dimer-FIB ratio (DFR), PLT values and clinicopathologic characteristics and to evaluate the prognostic value of these markers in GIST.

**MATERIALS AND METHODS**

***Patients and clinicopathologic parameters***

The research institution of this study was the First Affiliated Hospital of Xi'an Jiaotong University. One hundred and seventy patients with GIST were treated in our department from January 1, of 2010 to December 31, 2015. Clinicopathological parameters and follow-up data were assessed for all the GIST patients (91 men and 79 women) who received initial curative surgical resection. All the patients were pathologically confirmed as GIST. The demographic data and clinicopathologic features of each patient were collected. The average age of the patients was 61 years.

All enrolled patients must met the following criteria: (1) The first diagnosis was primary resectable GIST; (2) complete blood test results can be obtained before treatment; (3) surgical treatment was performed, and imatinib was not treated preoperatively; and (4) there were complete postoperative follow-up data.

Patients with hematological diseases, other tumor types, the use of coagulation and anticoagulation drugs for 8 wk, the blood test results are not complete, or with myocardial infarction, cerebral infarction and other diseases were excluded.

The assessment of preoperative assessment of GIST was by abdominal or pelvic CT, magnetic resonance imaging (MRI) or gastrointestinal endoscopy or endoscopic ultrasound examination. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, and all the patients signed an informed consent before the operation.

We collected demographic data on all patients in the study, including patient demographics (age, gender), clinical and pathological features, comorbidities, FIB, D-dimer, PLT, operative factors (type of surgery and extent of lymph node dissection) and tumor characteristics (location, size, lymph node metastasis, mitotic number, distant metastasis and risk category).

Preoperative plasma FIB, D-dimer, PLT and other laboratory data collection are the closest to the results of a test of the time of surgery. It was most important that all the laboratory data were obtained from each patient before breakfast. No evidence of infection of venous blood was collected. The D-dimer-FIB ratio (DFR) was calculated as D-dimer (mg/L) divided by fibrinogen concentration (g/L).

***Follow-up assessments***

Patients were followed up 1 time every 3 mo for 2 years, 1 time every 6 mo between 2 and 5 years, and once a year after 5 years. Follow-ups were either by outpatient or inpatient review, or by contacting patients or their relatives by telephone. For the follow-up of GIST patients after surgery, chest and abdominal CT scan, abdominal (liver and adrenal) B Ultrasound scan, bone marrow scan and endoscopic biopsy, and positron emission computerized tomography (PET) to exclude recurrence and metastasis were utilized. According to the follow-up program, all patients were followed up with the deadline of December 1, 2016 or the death of the patient. Patients who are visible on the imaging of the metastatic recurrence or death as the end point events.

***Statistical analysis***

The frequency and percentage are used to represent the patient's baseline characteristics. The optimal values of FIB, D-dimer, DFR and PLT were determined by receiver operating characteristic (ROC) curves[[1](#_ENREF_1)]. The patients were divided into high and normal groups by this optimal value. The area under the curve can be determined by the ROC curve, and the confidence interval (CI) of 95% can be determined. The correlation of tests, including binary classification variables, was performed using the Chi-square test or nonparametric rank sum test (Mann-Whitney test). Recurrence free survival (RFS) was defined as the time from the postoperative to clinical or imaging evidence of recurrence for the first time. The Kaplan-Meier method was used to estimate the survival curve of RFS, and the log-rank test was used to evaluate the difference between groups. Univariate analysis was used to analyze the risk factors influencing the prognosis of GIST RFS. A multivariate Cox proportional hazards regression model was used to identify the independent risk factors affecting RFS, calculate the risk ratio (RR) and the corresponding 95%CI. The meaningful indicators found in univariate analysis were further evaluated by a multivariate Cox proportional hazards regression model (Forward stepwise method – conditional Likelihood Ratio). The Cox regression equation was as follows: *h* (*t, x*) = *h0* (*t*) *exp* (β1x1 + β2x2 + … + βpxp). Where, *x* is covariate with time, *h* (*t, x*) is a risk function that is the individual with a covariate x function of risk on the t moment, *h0* (*t*)is the baseline hazard function, and β I ( I = 1, 2,…, p) is population regression. The prognostic index (PI) model was as follows: PI = β1x1 + β2x2 + … + β p x p.

All data were statistically analyzed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, United States). All trials were bilateral, and *P* values below 5% were considered statistically significant.

**RESULTS**

***ROC analysis***

The optimal cutoff value of FIB, D-dimer, DFR, and PLT was determined using ROC curves. The area under the ROC curve for FIB, D-dimer, DFR and PLT was 0.758 (95%CI: 0.666­0. 850; *P* < 0.01), 0.739 (95%CI: 0.629­0. 850; *P* < 0.01), 0.709 (95%CI: 0.596­0. 822; *P* = 0.001), and 0.625 (95%CI: 0.517­0. 733; *P* = 0.050), respectively (Figure 1). For all GIST patients, FIB = 3.24 g/L, D-dimer = 1.24 mg/L, DFR = 0.354, and PLT = 197.5 (× 109/L) had the highest sensitivity (87.5%, 70.8%, 66.7%, 75%) and specificity (61.6%, 76%, 80.1%, 51.4%), respectively (Table 1).

***Baseline patient characteristics***

All 170 patients in this study were confirmed by pathology as GIST. The age of the study population ranged from 19 to 80 years, with a median age of 61 years. In all patients, there were 91 male cases, accounting for 53.5%, slightly more men than women; the male to female ratio was 1.15:1. The most common site of the GIST was stomach (122 cases), accounting for 71.76%, followed by the small intestine (20%; 34/170), colon and rectum (5.88%; 10/170), pelvic cavity (1.76%; 3/170) and esophagus (0.59%; 1/170). The median diameter of tumors in this study was 5 cm, with a minimum of 0.5 cm and a maximum of 29 cm. According to the revised NIH (National Institutes of Health) risk category of 2008[10], of the total 170 patients, 18 patients were at very low risk (10.59%), 65 patients were at low risk (38.24%), 37 patients were at intermediate risk (21.76%), and 50 patients were at high risk (29.41%). The mitotic count was more than 5/50 high power field (HPF) in 125 patients (73.53%). There were 48 (55.17%, 48/87) patients receiving adjuvant imatinib following surgery in the intermediate and high risk categories. During follow-up, 24 patients showed recurrence or metastasis; 15 patients suffered from GIST related deaths; and 1 patient died in a car accidents. The 3- and 5-year survival rates of RFS in 170 patients with GIST were 85% and 75% respectively.

***Univariate analysis of prognostic factors***

Of the 170 patients in this study, the median RFS survival time was 32 mo (1 mo to 80 mo) postoperatively. Univariate analyses of demographic and clinicopathologic factors were performed to assess the prognostic factors associated with survival. Univariate analysis showed that gender (male and female) and age (61 years < and > 61 years) were not relevant to the prognosis of patients with GIST (all *P* > 0.05). In addition, other demographic and clinical pathology factors were risk factors that affected the prognosis of the patient. These risk factors included FIB (≥ 3.24 g/L *vs* < 3.24 g/L, *P <* 0.01), D-dimer (mer, D-dimerddit < 1.24 mg/L*, P <* 0.01), DFR (erddition, *P* < 0.354, *P <*0.01), PLT (≥ 197. 5 × 109/L *vs* <197.5 × 109/L, *P* = 0.014), mitotic index (emographPF *vs* > 5/50 HPF, *P <* 0.01), tumor size (tic index > 5 cm, *P <* 0.01), tumor location (gastric *vs* extragastric, *P =* 0.001) and NIH risk category (very low and low *vs* intermediate and high, *P <* 0.01). The results of these univariate analyses are shown in Table 2.

We divided the serum FIB level, D-dimer, DFR, and PLT into a normal group and a high group, respectively and investigated the relationship between the above parameters and the prognosis of GIST patients. We found that patients with high preoperative FIB, D-dimer, DFR, or PLT had a shorter RFS than did normal controls (Figure 2A-D). In the first 3 years, the survival time of patients who received the adjuvant imatinib was significantly longer than that of the untreated in the intermediate and high risk category group (Figure 2E).

In addition, extragastric tumors，larger than 5 cm，intermediate-high risk potential NIH risk category group, and mitotic image count above 5/50 HPF had a poorer prognosis (log-rank, *P* < 0.01) (Table 2).

This study also evaluated the prognostic value of FIB concentration combined with D-dimer in patients with GIST, as well as its clinical applicability and clinical value. We divided GIST patients into four groups based on the following criteria: Group 1: Low FIB and low D-dimer; Group 2: Low FIB and high D-dimer; Group 3: High FIB and low D-dimer; and Group 4: High FIB and high D-dimer. The prognosis of high FIB and high D-dimer group was worse than that of the low FIB and / or low D-dimer group (38% *vs* 95% *vs* 92% *vs* 82%, *P* ﹤0. 01,Figure 3).

***Multivariate analysis of prognostic factors***

To determine the independent risk factors for GIST patients, we used the Cox proportional hazard model to assess the outcome.

Multivariate analysis was used to further analyze the risk factors affecting the prognosis of GIST in univariate analysis. Factors in the multivariate analysis included FIB levels, D-dimer levels, DFR, PLT, tumor size, tumor location and NIH isk category. The results showed that FIB (RR: 0.131, 95%CI: 0.039-0.443, *P* = 0.001), DFR (RR: 0.334, 95%CI: 0.139-0.802, *P* = 0.014), and NIH risk category (RR: 0.206, 95%CI: 0.059-0.711, *P* = 0.012) were independent risk factors for the prognosis of GIST (Table 3).

The Cox regression formula for the present study was *h* (*t, x* ) = *h0* (*t*) *exp* (2.035 FIB + 1. 097 DFR + 1.582 NIH risk category). The PI of the present study was PI = 2.035 FIB + 1.097 DFR + 1.582 NIH risk category.

To exclude confounding the analyses by the treatment of GIST patients with the tyrosine kinas inhibitor imatinib, we recalculated the RFS of GIST by a hierarchy of whether patients received adjuvant imatinib or not after surgery.This multivariate analysis indicated that FIB, DFR, and NIH risk category (RR: 0.108, 95%CI: 0.031-0.373, *P* < 0. 01; RR: 0.319, 95%CI: 0.131-0.777, *P* = 0.012; RR: 0.166, 95%CI: 0.047-0.589, *P* = 0.005; respectively) were still independent risk factors associated with GIST prognosis, as shown in Table 4*.* The Cox proportional regression model was *h* (*t, x*) = *h0 (t)* *exp* (2.223 FIB + 1.141 DFR + 1.795 NIH risk category). The PI of the present study was PI = 2.223 FIB + 1.141 DFR + 1.795 NIH risk category.

***Correlation analysis between FIB, D-dimer, DFR, PLT levels and clinicopathologic factors in GIST patients***

The clinicopathologic features of high and low FIB, D-dimer, DFR and PLT GIST patients were analyzed and summarized in Tables 5-8, respectively. The results showed that age, sex, tumor location, tumor size, NIH risk category, and mitotic index were correlated with the above indexes (all *P* < 0.05). This finding indicated that the correlation between the above parameters and prognosis may be attributed to their correlation with tumor size, mitotic index, and NIH risk category.

**DISCUSSION**

It was reported that FIB could strongly predict the prognosis of various malignant tumors, such as lung, stomach and pancreatic cancer[11]. The D-dimer was related to the stage of the tumor in patients with prostate, lung, cervix, ovary, breast, or colorectal cancer[12-[[12](#_ENREF_10)14]. PLT was associated with the prognosis of epithelial ovarian carcinoma and pancreatic cancer[4,15]. However, the data for FIB, D-dimer, and PLT predicting the prognosis of primary resectable GIST are still very limited. We found only 1 study that examined the role of D-dimer in primary GISTs[16]. That study found that a baseline D-dimer level of greater than 1000 ng/mL was associated with total GIST survival rate and progression-free survival rate and was inversely proportional. Recently, another study found that high levels of FIB were associated with decreased overall survival (OS) and RFS in patients with GISTs[17]. However, as far as we know, there is little research on the value of these markers in the prognosis of patients with GIST.

In the present study, we have been explored the clinical association between FIB, D-dimer, DFR, PLT, and pathological features and the prognosis of GIST. Our purpose was to determine whether the above parameters could be associated with the prognosis of GIST. We found that preoperative plasma FIB, D-dimer, PLT, NIH risk category, tumor location, tumor size, and mitotic index were associated with RFS in GIST patients who underwent surgical excision. To eliminate the interference of various factors on the predicted results of FIB and D-dimer, we calculated the ratio of D-dimer to FIB (DFR) and found that DFR was also a prognostic indicator of GIST. In addition, we joined FIB and D-dimer and divided them into 4 groups to show that the prognosis of the high D-dimer and high FIB group was significantly poorer than others. By inputting the statistical significance index, which was found in the univariate analysis results into the Cox proportional hazards models, multiple factor regression analysis indicated that elevated FIB, DFR and high risk of NIH risk category were independent risk factors for poor prognosis of GIST. There was also a correlation between the preoperative FIB, D-dimer, DFR, PLT and the clinicopathologic features of GIST. If we can predict the prognosis of GIST by using hematology markers such as FIB, D-dimer, DFR, and PLT, especially FIB and DFR, the analysis will be more convenient. We can easily monitor and predict the recurrence and metastasis of patients.

It is well known that the failure of many cancer treatments is closely related to tumor metastasis. A positive correlation between coagulation and tumor metastasis was observed many years ago[18]**.** Coagulation system abnormalities are usually associated with tumor progression, and the coagulation cascade is often amplified in cancer patients. Approximately 50% of local tumor patients and most metastatic tumors have several coagulation factor abnormalities[9,19]**.** FIB is a plasma protein that plays an important role in the process of coagulation.

Some studies have shown that FIB is positively related to cancer progression[20]. The elevated FIB is associated with distant tumor metastasis, suggesting that FIB plays an important role in the adhesion of tumor and vascular metastasis of the target organ. In addition, FIB plays an important role in angiogenesis and tumor cell growth, which may be associated with the promotion of growth factor fusion and cell adhesion, proliferation and migration. Moreover, platelet fibrin malignancies play an important role in the early development of tumor cells, avoiding the host's autoimmune surveillance by providing protection[20]. Other research evidence indicates that the FIB fragment promotes tumor progression and metastasis by inhibiting tumor angiogenesis, binding and downregulating the expression of vascular endothelial cells[20]. However, the exact mechanism of the role of FIB in the progression of tumor remains unclear, and requires further study.

D-dimer is not only a product of fibrin degradation that is found in blood after the coagulation cascade but also a specific marker for fibrinolysis. Similarly, D-dimer is an important marker of coagulation abnormalities. Studies have indicated that coagulation disorders exist in 90% of cancer patients, such as shortened prothrombin and partial thromboplastin time, and increased factors II, V, VIII, IX, XI, XII, FIB and fibrin degradation products[13][[13](#_ENREF_12)][[11](#_ENREF_11)]. There are other studies to determine whether the level of D-dimer in disseminated intravascular coagulation (DIC), deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebral infarction and other thromboembolic events in patients was significantly increased[18].

In addition, we speculate that another cause of the increase in FIB and D-dimer may be related to the liver because the blood clotting related indicators are produced by the liver. Furthermore, it is not ruled out that the prognostic effect of FIB and DFR on GIST may be due to the correlation between these indexes and the clinicopathologic features of GIST.

The relationship between PLT and tumors can be understood to play a very important role in tumor vascular growth through various platelet-derived vascular growth factors, and platelet-derived transforming growth factor β (TGF-β) can coactivate TGF-β/S mad and NF-κB pathways in cancer cells, thus promoting tumor metastasis[21].

At present, the prognostic factors of GIST, such as mitotic count, tumor location, size, rupture, metastasis[2,22], all depend on postoperative pathological results. Biomarkers to screen for the recurrence or progression of GIST are still limited, but many studies support the prognosis of tumors prognosis using tumor biomarkers[[13](#_ENREF_13)]. For example, marker CA-153 is associated with the recurrence and metastasis of breast cancer, CEA is used to monitor the treatment of colorectal cancer and gastric cancer, and CA-199 is associated with ovarian cancer.

Moreover, in most hospitals, the tests for plasma FIB, D-dimer, and PLT have been included in conventional preoperative coagulation and routine blood tests, and the values are easy to obtain. Therefore, it is easy for clinicians to use FIB, D-dimer, and PLT as prognostic markers in GIST patients. Therefore, before an operation, we could roughly predict the prognosis of GIST by hematological indicators, to give early intervention therapy, and thus obtain a better prognosis. Especially for those patients who can't get pathological results, it is more significant to use these hematological indicators to predict the prognosis of GIST. Furthermore, combining these hematological parameters with the clinical features of GIST can significantly improve the prognostic efficacy of GIST.

This study has some limitations. First, it is a single center, retrospective, nonrandomized, controlled study. More forward-looking research is needed to verify the predictive value of these indicators. Second, its small sample size may cause some bias; therefore, a larger sample size study is required to further validate our results. Third**,** this study also includes a number of deleted cases that did not survive for 5 years after surgery, which may lead to bias in the survival analysis. Fourth, some of the NIH risk categories of high risk GIST patients in this study failed to receive adjuvant treatment or to complete adjuvant treatment as a result of their high drug costs or adverse drug reactions. Furthermore, we only analyzed the predictive value of these indicators in primary resectable and preoperative GIST without adjuvant medication, and the predictive value of these markers in adjuvant imatinib and nonoperative GIST needs further study.

However, considering the low cost and ease of operation of hematological testing, plasma FIB, D-dimer, DFR, and PLT should be considered as prognostic indicators for GIST patients, especially in developing countries. It is known that clinicians are better at screening patients requiring adjuvant therapy and formulating targeted general treatment and monitoring programs. Nevertheless, this finding also requires a large, forward-looking study to further confirm.

In light of these results, it is concluded that preoperative plasma FIB, D-dimer, DFR, and PLT can be used as effective hematological biomarkers for monitoring the prognosis of GIST patients that do not require special measuring devices. It was also indicated that clinicians should obtain FIB, D-dimer, DFR, and PLT values as part of routine care. In particular, the value of FIB and DFR in predicting the prognosis of GIST should be emphasized. These values should be added to the currently accepted preoperative risk categories, such as size, primary tumor site, and genetic mutation.

**ARTICLE HIGHLIGHTS**

***Research background***

It is well known that moderate and high-risk gastrointestinal stromal tumors (GIST) patients have a high recurrence rate and need adjuvant targeted therapy to improve prognosis. Therefore, early screening of this part of patients to give adjuvant treatment is particularly important. At present, the prediction of GIST is obtained by postoperative pathology, and there is no effective index to predict the prognosis of GIST before operation. The purpose of this retrospective study was to investigate the role of Fibrinogen (FIB), D-dimer–fibrinogen ratio(DFR) in the prognosis of GIST before operation.

***Research motivation***

The increase of blood coagulation indexes such as fibrinogen content and D-dimer before operation can predict the adverse prognosis of many kinds of cancer, but there is little discussion about the relationship between these indexes and GIST.

***Research objectives***

The retrospective study analyzed the role of FIB, D-dimer, DFR and platelets (PLT) in the prognosis of GIST before operation.

***Research methods***

This study included 170 patients with GIST who met the criteria. Collect the data of all the patients before and after operation, follow up and make statistical analysis. All data are analyzed using the SPSS 18.0 statistical software, *P* value below 0.05 has statistical difference.

***Research results***

In the present study, univariate analysis showed that FIB, D-dimer, DFR, PLT was correlated with 3-and 5-year survival rate of GIST patients. In addition, there is a correlation between the clinical features and FIB, D-dimer, DFR, PLT in GIST. Moreover, multivariate analysis showed that FIB and DFR had an independent effect on the prognosis of GIST patients.

***Research conclusions***

This retrospective study showed that FIB, D-dimer, DFR, PLT was the prognostic factor of GIST, but there was an independent correlation between FIB, DFR and GISTprognosis. These factors help to screen out high-risk patients early and to administer adjuvant intervention as soon as possible.

***Research perspectives***

For patients with GIST, the prognosis can be preliminarily estimated according to hematological indexes such as FIB, DFR before the operation, and adjuvant therapy can be given early to improve the prognosis of patients. Of course, the results of this study need to be further verified by a large sample size prospective study.

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A



B



**Figure 1** **Receiver operating characteristic curve for predicting recurrence free survival among 170 gastrointestinal stromal tumors patients.** A and B: Plasma fibrinogen (FIB) and D-dimer to FIB ratio (D-dimer/FIB) and platelet count. ROC: Receiver operating characteristic curves; RFS: Recurrence-free survival; GIST: Gastrointestinal stromal tumor.

**A**

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**Figure 2 Kaplan-Meier survival cures of high and normal groups of different indicators in 170 resected primary gastrointestinal stromal tumor patients. (**A) Fibrinogen (FIB) category, (B) D-dimer category, (C) D-dimer-fibrinogen ratio (DFR) category, (D) platelets (PLT) category, (E) adjuvant imatinib treatment of intermediate and high risk gastrointestinal stromal tumor patients.RFS of FIB, D-dimer, DFR, PLT, and risk category were significantly lower in the high group than in the low group (*P* < 0.05).FIB: Fibrinogen; DFR:D-dimer-fibrinogen ratio; RFS: Recurrence-free survival; GIST: Gastrointestinal stromal tumor.



**Figure 3 Recurrence-free survival of gastrointestinal stromal tumor patients, according to the combination of FIB and D-dimer.** The prognosis of the high fibrinogen and high D-dimer groups was worse than thatin theother groups. FIB: Fibrinogen; RFS: Recurrence-free survival; GIST: Gastrointestinal stromal tumor.

**Table 1 Area under the Curve**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Result Variable(s)** | **Area** | **Std. Error** | | ***P*-value** | **95%CI** |
| FIB (g/L)  D-dimer (mg/L)  D-dimer/FIB  PLT (109/L) | 0.758  0.739  0.709  0.625 | 0.047  0.056  0.058  0.055 | < 0.01  < 0.01  0.001  0.050 | | 0.666-0.850  0.629-0.850  0.596-0.822  0.517-0.733 |

FIB: Fibrinogen; CI: Confidence interval; PLT: Platelet count.

**Table 2 Clinicopathologic features and prognosis of univariate analysis in gastrointestinal stromal tumor patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristics** | **Number** | **3-year RFS (%)** | **5-year RFS (%)** | **95%CI** | ***P* value** |
| Gender |  |  |  |  |  |
| Male | 91 | 80 | 75 | 61.170-72.86 | 0.498 |
| Female | 79 | 90 | 80 | 56.828-65.996 |  |
| Age (yr) |  |  |  |  |  |
| < 61 | 78 | 85 | 81 | 58.018-66.650 | 0.406 |
| ≥ 61 | 92 | 83 | 78 | 61.508-73.445 |  |
| NIH risk category |  |  |  |  |  |
| Very low, low | 83 | 97 | 95 | 73.805-80.329 | < 0.01 |
| Intermediate, high | 87 | 80 | 65 | 50.488-62.245 |  |
| Tumor size (cm) |  |  |  |  |  |
| ≤ 5 | 97 | 95 | 95 | 75.130-80.262 | < 0.01 |
| > 5 | 73 | 63 | 55 | 49.388-63.256 |  |
| Tumor location |  |  |  |  |  |
| Gastric | 122 | 92 | 85 | 67.968-76.637 | 0.001 |
| Extragastric | 48 | 76 | 55 | 42.703-56.229 |  |
| FIB (g/L) |  |  |  |  |  |
| < 3.24 | 95 | 95 | 95 | 75.248-80.253 | < 0.01 |
| ≥ 3.24 | 75 | 65 | 50 | 48.878-62.958 |  |
| D-dimer（mg/L） |  |  |  |  |  |
| < 1.24 | 118 | 95 | 88 | 70.09-88.603 | < 0.01 |
| ≥ 1.24 | 52 | 65 | 55 | 46.163-62.647 |  |
| DFR |  |  |  |  |  |
| < 0.354 | 126 | 95 | 85 | 70.237-78.220 | < 0.01 |
| ≥ 0.354 | 44 | 70 | 50 | 43.262-61.237 |  |
| PLT (×109/L) |  |  |  |  |  |
| < 197.5 | 81 | 92 | 85 | 68.060-78.540 | 0.014 |
| ≥ 197.5 | 89 | 76 | 68 | 55.307-67.619 |  |
| Mitotic index |  |  |  |  |  |
| ≤ itot HPF | 125 | 95 | 90 | 70.431-77.808 | < 0.01 |
| > 5/50 HPF | 45 | 65 | 35 | 39.663-55.513 |  |
| Adjuvant imatinib1 |  |  |  |  |  |
| Yes | 48 | 70 | 55 | 48.468-64.287 | 0.940 |
| No | 39 | 75 | 55 | 41.127-64.055 |  |

1Intermediate and high risk gastrointestinal stromal tumor patients. GIST: Gastrointestinal stromal tumor; NIH: National institutes of health; FIB: Fibrinogen; RFS: Recurrence-free survival; DFR: D-dimer to FIB ratio (D-dimer/FIB); PLT: Platelet count.

**Table 3 Multivariate analysis of the significant variables determined by univariate analysis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **B** | **SE** | **Wald** | ***P*-value** | **RR (95%CI)** |
| FIB | -2.035 | 0.622 | 10.692 | 0.001 | 0.131 (0.039-0.443) |
| Risk | -1.582 | 0.633 | 6.249 | 0.012 | 0.206 (0.059-0.711) |
| DFR | -1.097 | 0.447 | 6.022 | 0.014 | 0.334 (0.139-0.802) |

FIB: Fibrinogen classification (FIB < 3.24 and FIB ≥ 3.24); Risk: Risk category (VERY low, low and intermediate, high risk); DFR: D-dimer to FIB classification (DFR fication, < 0.354); RR: Risk ratio; CI: Confidence interval.

**Table 4 Multivariate analysis of the significant variables determined by univariate analysis on the hierarchy of adjuvant imatinib.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | **B** | **SE** | **Wald** | ***P*-value** | **RR (95%CI)** |
| FIB | -2.223 | | 0.632 | 12.385 | 0.000 | 0. 108 (0.031-0.373) |
| Risk | -1.795 | | 0.645 | 7.736 | 0.005 | 0.166 (0.047-0.589) |
| DFR | -1.141 | | 0.454 | 6.325 | 0.012 | 0.319 (0.131-0.777) |

FIB: Fibrinogen classification (FIB < 3.24 and FIB ≥ 3.24); Risk: Risk category (very low, low and Intermediate, high risk); DFR: D-dimer to FIB ratio classification (DFR ficationatio < 0.354); RR: Risk ratio; CI: confidence interval.

**Table 5 Clinicopathologic characteristics of gastrointestinal stromal tumors patients grouped by fibrinogen preoperation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Low FIB (﹤3.24 g/L)** | **High FIB (≥ igh FIB)** | ***P* value** |
| Age |  |  | < 0.01 |
| > 61 | 78 | 0 |  |
| ≥ 10 | 17 | 75 |  |
| Gender |  |  | < 0.01 |
| Male | 91 | 0 |  |
| Female | 4 | 75 |  |
| Location |  |  | < 0.01 |
| Gastric | 95 | 27 |  |
| Nongastric | 0 | 48 |  |
| Tumor size |  |  | < 0.01 |
| ≤ 5 | 95 | 2 |  |
| > 5 | 0 | 73 |  |
| NIH risk category |  |  | < 0.01 |
| Very low | 18 | 0 |  |
| Low | 65 | 0 |  |
| Intermediate | 12 | 25 |  |
| High | 0 | 50 |  |
| Mitotic index |  |  | < 0.01 |
| ≤ 5/50 HPF | 95 | 30 |  |
| > 5/50 HPF | 0 | 45 |  |

FIB: Fibrinogen; HPF: High power field.

**Table6Clinicopathologic characteristics of gastrointestinal stromal tumors patients grouped by D-dimer preoperation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Low D-dimer (< 1.24 mg/L)** | **High D-dimer (≥ imer D-di)** | ***P* value** |
| Age |  |  | < 0.01 |
| < 61 | 78 | 0 |  |
| ≥ 10 | 40 | 52 |  |
| Gender |  |  | < 0.01 |
| Male | 91 | 0 |  |
| Female | 27 | 52 |  |
| Location |  |  | < 0.01 |
| Gastric | 118 | 4 |  |
| Nongastric | 0 | 48 |  |
| Tumor size |  |  | < 0.01 |
| ≤ 5 | 97 | 0 |  |
| > 5 | 21 | 52 |  |
| NIH risk category |  |  | < 0.01 |
| Very low | 18 | 0 |  |
| Low | 65 | 0 |  |
| Intermediate | 35 | 2 |  |
| High | 0 | 50 |  |
| Mitotic index |  |  | < 0.01 |
| ≤5/50 HPF | 118 | 7 |  |
| > 5/50 HPF | 0 | 45 |  |

NIH: National Institutes of Health; HPF: High power field.

**Table *7* Clinicopathologic characteristics of gastrointestinal stromal tumors patients grouped by D-dimer-fibrinogen ratio preparation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Low DFR (< 0.354)** | **High DFR (≥ igh D)** | ***P* value** |
| Age |  |  | < 0.01 |
| < 61 | 78 | 0 |  |
| ≥ 10 | 48 | 44 |  |
| Gender |  |  | < 0.01 |
| Male | 91 | 0 |  |
| Female | 35 | 44 |  |
| Location |  |  | < 0.01 |
| Gastric | 122 | 0 |  |
| Nongastric | 4 | 44 |  |
| Tumor size |  |  | < 0.01 |
| ≤ 5 | 97 | 0 |  |
| > 5 | 29 | 44 |  |
| NIH risk category |  |  | < 0.01 |
| Very low | 18 | 0 |  |
| Low | 65 | 0 |  |
| Intermediate | 37 | 0 |  |
| High | 6 | 44 |  |
| Mitotic index |  |  | < 0.01 |
| ≤ 5/50 HPF | 125 | 0 |  |
| > 5/50 HPF | 1 | 44 |  |

HPF: High power field; DFR: D-dimer to fibrinogen ratio.

**Table8 Clinicopathologic characteristics of of gastrointestinal stromal tumors patients grouped by platelets preoperation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Low PLT (< 197.5 × 109/L)** | **High PLT (≥ igh PLTr9/L)** | ***P* value** |
| Age |  |  | < 0.01 |
| < 61 | 78 | 0 |  |
| ≥ 10 | 3 | 89 |  |
| Gender |  |  | < 0.01 |
| Male | 81 | 10 |  |
| Female | 0 | 79 |  |
| Location |  |  | < 0.01 |
| Gastric | 81 | 41 |  |
| Nongastric | 0 | 48 |  |
| Tumor size |  |  | < 0.01 |
| ≤ 5 | 81 | 16 |  |
| > 5 | 0 | 3 |  |
| NIH risk category |  |  | < 0.01 |
| Very low | 18 | 0 |  |
| Low | 63 | 2 |  |
| Intermediate | 0 | 37 |  |
| High | 0 | 50 |  |
| Mitotic index |  |  | < 0.01 |
| ≤ 5/50 HPF | 81 | 44 |  |
| > 5/50 HPF | 0 | 45 |  |

NIH: National Institutes of Health; HPF: High power field.

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