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ORIGINAL RESEARCH

Prognostic Value of Fibrinogen and Lymphocyte Count in Intermediate and High Risk Gastrointestinal Stromal Tumors

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Yinghao Guo[1,2,*]
Jinqiang Liu[1,3,*]
Wenming Zhang[1,4,*]
Shuao Xiao[1]
Gaozan Zheng[1]
Shushang Liu[1]
Man Guo[1]
Hongwei Zhang[1]
Fan Feng[1]

[1]Department of Digestive Surgery, Xijing Hospital of Digestive Diseases, The Fourth Military Medical University, Xi'an 710032, Shaanxi, People's Republic of China; [2]Health Company, 92667 Army of PLA, Qingdao 266100, Shandong, People's Republic of China; [3]Cadre's Sanitarium, 62101 Army of PLA, Xinyang 464000, Henan, People's Republic of China; [4]Department of General Surgery, Linxia People's Hospital, Linxia 731100, Gansu, People's Republic of China

*These authors contributed equally to this work

Purpose: Data about the prognostic value of fibrinogen concentration and absolute lymphocyte count for the prognosis of gastrointestinal stromal tumors (GISTs) were limited. Thus, the aim of the present study was to investigate the predictive value of preoperative fibrinogen concentration and absolute lymphocyte count in GISTs.

Patients and Methods: From March 2002 to December 2017, 143 intermediate and high risk GIST patients treated with R0 resection were enrolled in the present study. Clinicopathological characteristics were recorded. The optimal cut-off values of patients were calculated by X-tile software. Categorical variables were analyzed using Chi-square test or Fisher's exact test. Disease-free survival was analyzed by the Kaplan–Meier method and compared by a Log rank test.

Results: There were 71 males (49.65%) and 72 females. The median age was 56 years (range 19–86). The optimal cut-off value was 4.5 g/L for fibrinogen concentration (P=0.000) and 1.0×10^9/L for lymphocyte count (P=0.002). No significant association was found between lymphocyte level and clinicopathological features. However, elevated fibrinogen level was correlated with tumor location, tumor size and NIH risk category. Tumor size, fibrinogen concentration and lymphocyte count were independent risk factors for the prognosis of patients according to the multivariate analysis. The prognosis of patients with high fibrinogen concentration or low lymphocyte count was significantly worse than that with low fibrinogen concentration or high lymphocyte count. Further, combination of fibrinogen concentration and lymphocyte count could increase the prognostic value for GIST patients.

Conclusion: Fibrinogen concentration and absolute lymphocyte count were independent prognostic factors for intermediate and high risk GIST patients. The combination of fibrinogen concentration and absolute lymphocyte count could further increase the predictive value for the prognosis of GIST patients.

Keywords: gastrointestinal stromal tumors, GIST, mesenchymal tumor, fibrinogen, lymphocyte, prognosis

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract.[1] It typically arises from the digestive tract and rarely elsewhere in vivo. Although R0 resection remains the optimal treatment for localized GISTs, over 40% of patients will develop recurrence or metastasis after surgery.[2] Thus, precise assessment of the recurrence of GIST patients after surgery is critical for the administration of adjuvant therapy. Although the risk stratification systems have been revised and improved, their accuracy is not precise enough to

Correspondence: Hongwei Zhang; Fan Feng
Email zhanghwfmmu@126.com; surgeonfengfan@163.com

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predict the tumor recurrence.[3] In addition, with the application of artificial intelligence, new proposed systems and models have been developed, but their predictive capability should be validated and verified in prospective studies.[4] Hence, it's increasingly important to identify additional prognostic factors in order to aid the prognostic prediction and treatment of patients, especially for intermediate and high risk GIST patients.

Fibrinogen is an essential protein in the coagulation cascade and can be easily tested in the plasma. It was reported that fibrinogen could protect the circulating tumor cells (CTCs) from the attack of lymphocyte and natural killer cells.[5] This may partially explain the phenomenon that patients with elevated preoperative fibrinogen level was associated with tumor metastasis and resulted in poor prognosis in a variety of malignancies.[6,7]

The immune status is also very important for the prognosis of several solid tumors. Peripheral lymphocyte, as a simple and cost-effective parameter to reflect the immune status, plays a critical role in the cell-mediated antitumor immune response.[8] Although neutrophil-to-lymphocyte ratio has been well recognized as a prognostic factor in the recent years, the absolute count of lymphocyte has also been reported to be associated with the prognosis of tumors.[9]

However, the role of preoperative fibrinogen concentration and blood lymphocyte count in the prognosis of GISTs has rarely been investigated in GIST patients. Furthermore, the prognostic value of balance between preoperative fibrinogen concentration and absolute lymphocyte count on GIST patients has never been investigated. Given this situation, the present study aims to investigate both the individual and combined effects of preoperative fibrinogen concentration and absolute lymphocyte count on disease-free survival (DFS) in intermediate and high risk GIST patients.

Patients and Methods

This study was performed in the Xijing Hospital of Digestive Diseases affiliated to the Fourth Military Medical University. From March 2002 to December 2017, a total of 143 GIST patients were enrolled in our present study. The inclusion criteria were listed as follows: (1) histological confirmation of intermediate or high risk GISTs, (2) with R0 resection, (3) with complete clinicopathological and follow-up data. The exclusion criteria were: (1) with other malignant tumors, (2) with distant metastasis, (3) with preoperative imatinib therapy, (4) with inflammatory diseases, (5) with venous or arterial thromboembolism or anticoagulant treatment within 3 months before surgery, (6) with pregnancy, stroke or neurosurgery within 6 months before surgery. This study was approved by the Ethics Committee of Xijing Hospital, and written informed consent was obtained from all patients before surgery.

All the preoperative peripheral blood routine test and blood coagulation index were performed within 7 days prior to surgery. Fibrinogen concentration and absolute count of lymphocyte were recorded. Clinicopathological data including gender, age, tumor location, tumor size, mitotic index, histological type, National Institutes of Health (NIH) risk category and adjuvant therapy were collected. To evaluate the prognostic value of the combination of fibrinogen concentration and absolute count of lymphocyte for GIST patients. GIST patients were divided into four groups according to the levels of fibrinogen and lymphocyte: Group 1, patients with low fibrinogen concentration and high lymphocyte count; Group 2, patients with low fibrinogen concentration and low lymphocyte count; Group 3, patients with high fibrinogen concentration and high lymphocyte count; and Group 4, patients with high fibrinogen concentration and low lymphocyte count. DFS was calculated from the date of surgery to the date of recurrence or metastasis. The patients after surgery were followed up until December 2018.

Statistical Analysis

Data were processed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA). The optimal cut-off values of fibrinogen concentration and absolute count of lymphocyte for the prognosis of GISTs were calculated by X-tile software.[10] Patients were grouped by the level of fibrinogen concentration and absolute lymphocyte count. Categorical variables were analyzed using Chi-square test or Fisher's exact test. Survival between groups were analyzed by the Kaplan–Meier method and compared by a Log rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to assess time-to-event outcomes. The low fibrinogen concentration group and low lymphocyte count group were settled as "reference" group. A HR >1 indicated a worse prognosis in GISTs patients. Significant risk factors ($P<0.15$) for the prognosis of GISTs patients identified by univariate analysis were further assessed by multivariate analysis using the Cox regression proportional hazard model. A P value of 0.05 was considered statistically significant.

Results

The clinicopathological features of patients divided by fibrinogen concentration and absolute lymphocyte count were summarized in Table 1. There were 71 males (49.65%) and 72 females. The median age was 56 years (range 19–86). Tumor location, tumor size and NIH risk category were significantly associated with fibrinogen level (all P<0.05). No significant differences were found between clinicopathological features and absolute lymphocyte count (all P>0.05).

The cut-off value of fibrinogen concentration and absolute count of lymphocyte for the prognosis of GIST patients are shown in Figure 1. The optimal cut-off value was 4.5 g/L for fibrinogen (P = 0.000) and 1.0 × 10^9/L for lymphocyte (P = 0.002).

The median follow-up time was 51.73 months (range 9–124). Nineteen patients experienced recurrence or metastasis. The risk factors for the prognosis of GIST patients were analyzed using univariate analysis (Table 2). The results showed that tumor size, adjuvant therapy, fibrinogen concentration and lymphocyte count were risk factors for the prognosis of GIST patients (all P<0.05). However, only tumor size, fibrinogen concentration and lymphocyte count were independent risk factors for the prognosis of GISTs (Table 3, all P<0.05).

The DFS of GIST patients stratified by fibrinogen concentration and lymphocyte count were shown in Figure 2. The prognosis of patients with high fibrinogen concentration or low lymphocyte count were significantly lower than that with low fibrinogen concentration or high lymphocyte count.

Table 1 Comparison of Clinicopathological Features of GIST Patients According to Fibrinogen Concentration and Lymphocyte Count

Characteristics	Low Fibrinogen Concentration	High Fibrinogen Concentration	P	Low Lymphocyte Count	High Lymphocyte Count	P
Age						
≤60	77(83.7%)	15(16.3%)	0.923	21(22.8%)	71(77.2%)	0.538
>60	43(84.3%)	8(15.7%)		14(27.5%)	37(72.5%)	
Gender						
Male	58(81.7%)	13(18.3%)	0.472	20(28.2%)	51(71.8%)	0.308
Female	62(86.1%)	10(13.9%)		15(20.8%)	57(79.2%)	
Tumor location						
Stomach	87(88.8%)	11(11.2%)	0.041	22(22.4%)	76(77.6%)	0.707
Small intestine	27(71.1%)	11(28.9%)		11(28.9%)	27(71.1%)	
Other	6(85.7%)	1(14.3%)		2(28.6%)	5(71.4%)	
Tumor size (cm)						
≤5	54(94.7%)	3(5.3%)	0.000	14(24.6%)	43(75.4%)	0.878
>5, ≤10	55(84.6%)	10(15.4%)		15(23.1%)	50(76.9%)	
>10	11(52.4%)	10(47.6%)		6(28.6%)	15(71.4%)	
Mitotic rate						
≤5/50 HPF	28(90.3%)	3(9.7%)	0.203	11(35.5%)	20(64.5%)	0.267
>5/50 HPF,≤10/50 HPF	80(84.2%)	15(15.8%)		20(21.1%)	75(78.9%)	
>10/50 HPF	12(70.6%)	5(29.4%)		4(23.5%)	13(76.5%)	
Histologic type						
Spindle	113(84.3%)	21(15.7%)	0.546	35(26.1%)	99(73.9%)	0.211
Epithelioid	2(100%)	0(0.0%)		0(0.0%)	2(100%)	
Mixed	5(71.4%)	2(28.6%)		0(0.0%)	7(100%)	
NIH risk category						
Intermediate risk	58(93.5%)	4(6.5%)	0.006	16(25.8%)	46(74.2%)	0.746
High risk	62(76.5%)	19(23.5%)		19(23.5%)	62(76.5%)	
Adjuvant therapy						
Yes	50(79.4%)	13(20.6%)	0.189	13(20.6%)	50(79.4%)	0.343
No	70(87.5%)	10(12.5%)		22(27.5%)	58(72.5%)	

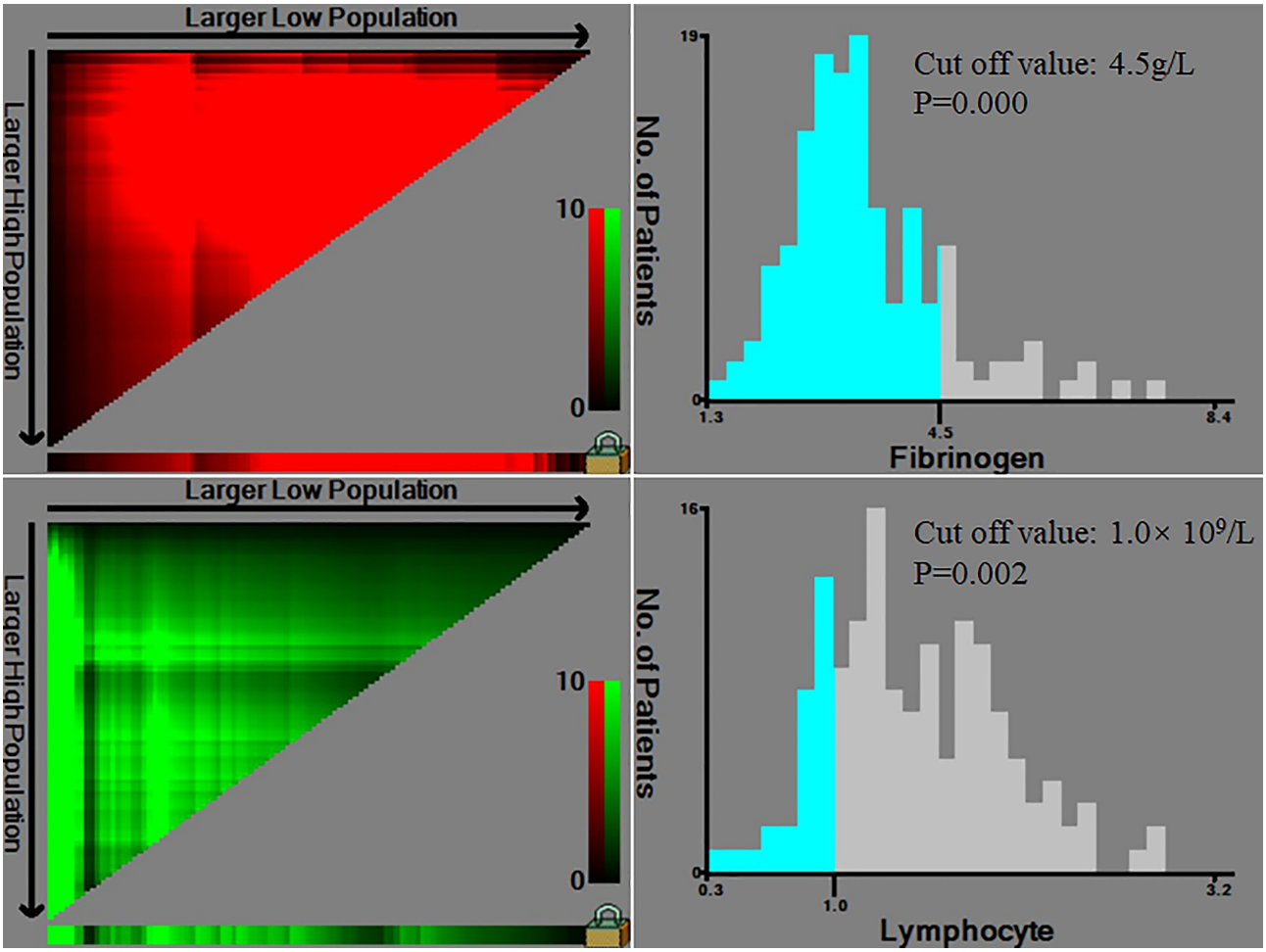

Figure 1 Calculation of cut-off value of fibrinogen concentration and absolute lymphocyte count by X-tile software.

Further, the prognostic value of the combination of fibrinogen concentration and absolute count of lymphocyte for GIST were also evaluated. The clinicopathological features of the four groups were summarized in Table 4. The results showed that tumor size and NIH risk category were significantly different between the four groups (P<0.05). The DFS of the four groups were shown in Figure 3. The results showed that combination of fibrinogen and absolute lymphocyte count could increase the predictive value for the prognosis of GIST patients.

Table 2 Univariate Analysis of Risk Factors for Disease-Free Survival of GIST Patients

Prognostic Factors	HR	95% CI	P value
Age	0.785	0.298–2.068	0.625
Gender	0.409	0.155–1.078	0.071
Tumor location	1.585	0.671–3.746	0.294
Tumor size	4.813	2.327–9.957	0.000
Mitotic rate	1.517	0.668–3.446	0.320
Histologic type	1.016	0.359–2.873	0.976
Adjuvant therapy	3.086	1.168–8.153	0.023
Fibrinogen	10.204	4.047–25.729	0.000
Lymphocyte	0.270	0.109–0.668	0.005

Abbreviations: HR, hazard ratio; CI, confidence interval.

Discussion

Blood coagulation index and peripheral blood routine test are preoperative routine tests which are simple,

Table 3 Multivariate Analysis of Risk Factors for Disease-Free Survival of GIST Patients

Prognostic Factors	HR	95% CI	P value
Gender	0.457	0.168–1.247	0.126
Tumor size	3.814	1.587–9.165	0.003
Adjuvant therapy	1.886	0.631–5.637	0.256
Fibrinogen	4.212	1.511–11.736	0.006
Lymphocyte	0.156	0.055–0.446	0.001

Abbreviations: HR, hazard ratio; CI, confidence interval.

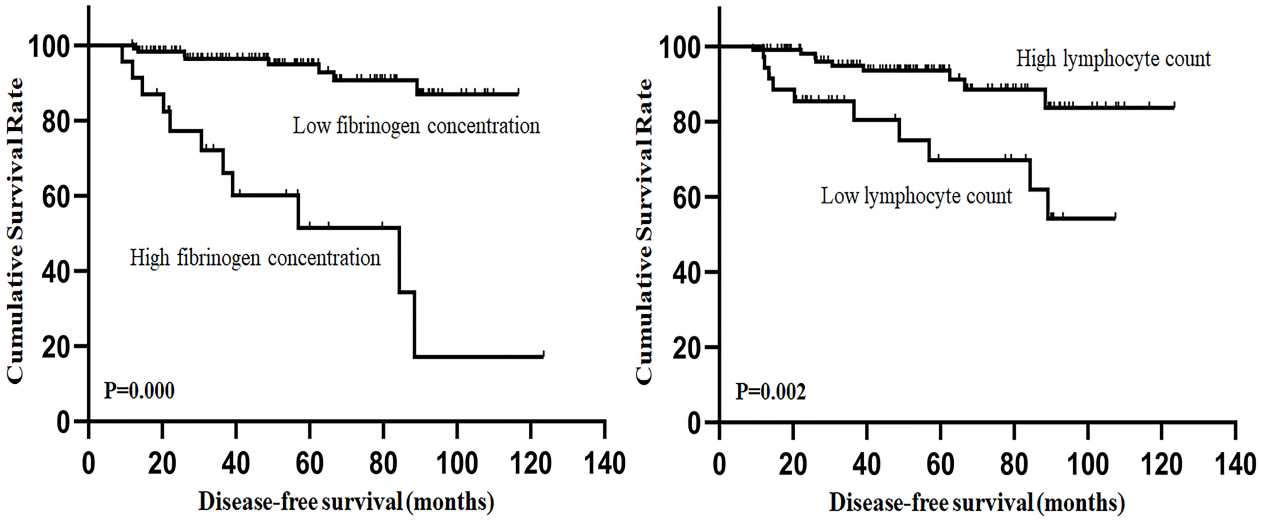

Figure 2 DFS of GIST patients stratified by fibrinogen concentration and absolute lymphocyte count.

convenient, reproducible, and cost-effective. However, data about the association between fibrinogen concentration and lymphocyte count and prognosis of GISTs were limited. Therefore, in the present study, we investigated the prognostic value of fibrinogen concentration and lymphocyte count in GIST patients. We found that elevated fibrinogen level was correlated with tumor location, tumor size and NIH risk category. High fibrinogen concentration and low lymphocyte count were independently associated with poor prognosis of intermediate and high risk GIST patients. Moreover, the combination of fibrinogen concentration and lymphocyte count improved prognosis prediction in intermediate and high risk GIST patients.

Lymphocytes play critical role in host immune response and possess potent antitumor activity in many tumors.[11,12] It reflects the degree of responsiveness of the immune status of the host. A series of studies have suggested that lymphopenia was independently associated with poor overall survival in some tumors.[13,14] Inversely, increased activated cytotoxic T lymphocytes were correlated with promising clinical outcomes in some tumors.[15] Besides, lymphocyte count was also used in some indexes such as prognostic nutritional index,[16] neutrophil to lymphocyte ratio[17] and platelet to lymphocyte ratio[18] to predict the prognosis of tumor patients, including GIST. However, the prognostic value of absolute lymphocyte count on GIST patients have never been investigated before. The present study, for the first time, demonstrated that high level of absolute lymphocyte count was associated with favorable prognosis of GIST patients.

As a major acute reactive phase protein and an important coagulation factor, fibrinogen present in plasma at high levels in the presence of malignancy.[19] Several potential mechanisms may explain this phenomenon. Sahni et al[20] found that fibrinogen can be synthesized by tumor cells. Yamaguchi et al[21] reported that the overproduction of inflammatory proteins (such as IL-6) by cancer cells may trigger the production of fibrinogen. Furthermore, Falanga et al[22] revealed that tumor growth is frequently associated with hemodynamic changes, tissue necrosis and acute phase response, which may result in subsequent increase in plasma fibrinogen levels. These may partially explain the findings in our present study that elevated fibrinogen concentration was positively associated with tumor size and NIH risk category of patients.

Over the past decade, growing evidences suggested that high pretreatment plasma fibrinogen levels were associated with poor prognosis in various types of tumor.[23–25] A meta-analysis containing 37 studies reported that fibrinogen concentration was significant predictor of poor survival in digestive malignancies.[26] Similarly, another meta-analysis, which contains 52 studies, found that increased pretreatment plasma fibrinogen concentration was significantly associated with decreased survival in patients with solid tumors.[27] However, the relationship between preoperative fibrinogen concentration and the prognosis of GIST patients was rare. Until now, only two studies investigated the correlation between plasma fibrinogen levels and prognosis of GIST patients. Lu et al[28] revealed that elevated fibrinogen level was correlated with a worse clinical outcome in GIST patients. Cai et al[29] also reported that fibrinogen

Table 4 Clinicopathological Features of GIST Patients According to the Four Groups

Characteristics	Low Fibrinogen Concentration High Lymphocyte Count	Low Fibrinogen Concentration Low Lymphocyte Count	High Fibrinogen Concentration High Lymphocyte Count	High Fibrinogen Concentration Low Lymphocyte Count	P
Age					
≤60	61(66.3%)	16(17.4%)	10(10.9%)	5(5.4%)	0.937
>60	32(62.7%)	11(21.6%)	5(9.8%)	3(5.9%)	
Gender					
Male	43(60.6%)	15(21.1%)	8(11.3%)	5(7.0%)	0.701
Female	50(69.4%)	12(16.7%)	7(9.7%)	3(4.2%)	
Tumor location					
Stomach	69(70.4%)	18(18.4%)	7(7.1%)	4(4.1%)	0.266
Small intestine	20(52.6%)	7(18.4%)	7(18.4%)	4(10.5%)	
Other	4(57.1%)	2(28.6%)	1(14.3%)	0(0.0%)	
Tumor size (cm)					
≤5	42(73.7%)	12(21.1%)	1(1.8%)	2(3.5%)	0.002
>5, ≤10	43(66.2%)	12(18.5%)	7(10.8%)	3(4.6%)	
>10	8(38.1%)	3(14.3%)	7(33.3%)	3(14.3%)	
Mitotic rate					
≤5/50 HPF	18(58.1%)	10(32.3%)	2(6.5%)	1(3.2%)	0.207
>5/50 HPF,≤10/50 HPF	66(69.5%)	14(14.7%)	9(9.5%)	6(6.3%)	
>10/50 HPF	9(52.9%)	3(17.6%)	4(23.5%)	1(5.9%)	
Histologic type					
Spindle	86(64.2%)	27(20.1%)	13(9.7%)	8(6.0%)	0.511
Epithelioid	2(100%)	0(0.0%)	0(0.0%)	0(0.0%)	
Mixed	5(71.4%)	0(0.0%)	2(28.6%)	0(0.0%)	
NIH risk category					
Intermediate risk	44(71.0%)	14(22.6%)	2(3.2%)	2(3.2%)	0.046
High risk	49(60.5%)	13(16.0%)	13(16.0%)	6(7.4%)	
Adjuvant therapy					
Yes	41(65.1%)	9(14.3%)	9(14.3%)	4(6.3%)	0.404
No	52(65.0%)	18(22.5%)	6(7.5%)	4(5%)	

concentration was an independent risk factor for predicting the prognosis of resectable GISTs. In accordance with previous studies, our present study with the largest sample size also confirmed the prognostic value of fibrinogen concentration in GIST patients.

The molecular mechanisms underlying the relationship between high plasma fibrinogen concentration and poor prognosis of tumors have not been fully elucidated. Yano et al[30] showed that fibrinogen may interact with integrin and non-integrin receptors of tumor cells to regulate proliferation or migration of tumor cells. Sahni et al[31] noted that fibrinogen may cooperate with vascular endothelial growth factor and stimulate endothelial cell proliferation and angiogenesis. Zhang et al[32] reported that fibrinogen could induce epithelial-mesenchymal transition through increasing vimentin expression and reducing E-cadherin expression, which confers capacity of invasion, migration, and multidrug resistance to tumor cells. Fibrinogen could also serve as a stable framework to support the formation of stroma tissue, which provides gas exchange and nutrient for the growing tumor cells.[33]

In addition to the biological effect, fibrinogen could also provide physical protection of tumor cells. Previous studies have already demonstrated the existence of circulating tumor cells in peripheral blood of GIST patients.[34] Fibrinogen can aggregate to form a dense layer around CTCs, which protects

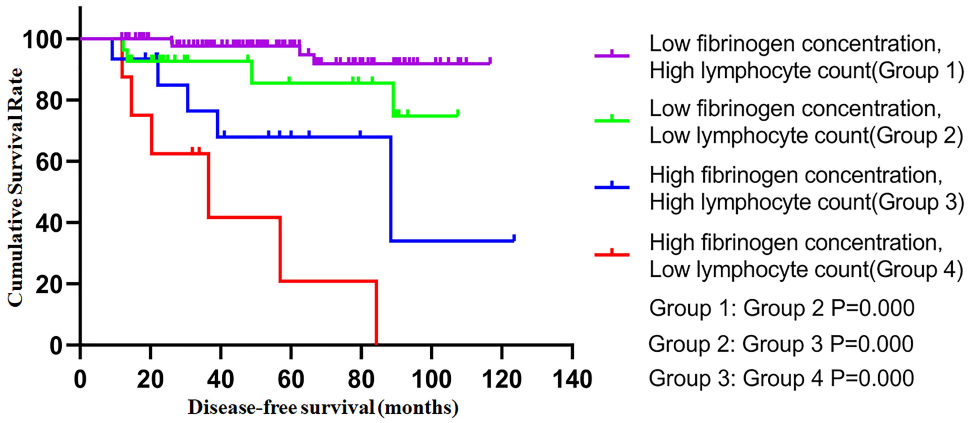

Figure 3 DFS of GIST patients according to the combination of fibrinogen concentration and absolute lymphocyte count.

CTCs from shear forces of the blood flow. It could also protect the CTCs from immune attack from T and NK cells.[5,35] Thus, we speculated that the balance between the fibrinogen concentration and peripheral lymphocyte count, to a large extent, would influence the prognosis of intermediate and high risk GIST patients. The findings in our present study were totally in consistent with our speculation. The results showed that patients with low fibrinogen concentration and high lymphocyte count have the best prognosis and that with high fibrinogen concentration and low lymphocyte count have the worst prognosis. We also found that the prognosis of patients with high fibrinogen concentration and high lymphocyte count was poorer than that with low fibrinogen concentration and low lymphocyte count, this may attribute to the dual role of fibrinogen on the tumor cells.

There are several limitations in our present study. First, it was a retrospective study in single institution's experience. Prospective and multi-center studies are needed to verify the predictive value of these parameters. Second, the sample size was not large enough, which may result in bias during analysis. Third, the prognostic value of fibrinogen and lymphocyte after surgery was not evaluated. Fourth, we only analyzed the predictive value of parameters in primarily localized GISTs. Whether these parameters have a predictive value in inoperable GISTs with imatinib therapy needs further investigation.

Conclusions

In conclusion, our present study indicated that fibrinogen concentration and absolute lymphocyte count were independent prognostic factors for intermediate and high risk GIST patients. The combination of fibrinogen concentration and absolute lymphocyte count could further increase the predictive value of prognosis of GISTs.

Abbreviations

GISTs, gastrointestinal stromal tumors; CTCs, circulating tumor cells; DFS, disease-free survival; NIH, National Institutes of Health.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Xijing Hospital, and written informed consent was obtained from all patients before surgery. This study was conducted in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest for this work.

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