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Hyperfibrinogenemia is associated with various inflammatory mediators and poor prognosis in patients with gastric cancer.

Takashi Suzuki[1], Hideaki Shimada[1], Tatsuki Nanami[1], Yoko Oshima[1], Satoshi Yajima[1], Masaaki Ito[1], Naohiro Washizawa[1], Hironori Kaneko[1]

1. Department of Surgery, School of Medicine, Toho University, 6-11-1 Omori-nishi, Ota-ku, Tokyo 142-8541, Japan

Correspondence to Dr. Hideaki Shimada

E-mail: hideaki.shimada@med.toho-u.ac.jp

TEL: 81-03-3762-4151, FAX: 81-03-3298-4348

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Abstract

Purpose: Although hyperfibrinogenemia have been reported to be associated with poor prognosis in various cancers, clinical significance in gastric cancer has not been well analyzed. This study aimed to assess the clinicopathological significance and prognostic value of hyperfibrinogenemia in patients with gastric cancer.

Methods: Plasma fibrinogen levels were measured before surgery in 315 patients with gastric cancer. The clinicopathological significance of hyperfibrinogenemia and the relationship with several biomarkers (WBC, CRP, platelet count, PT and APTT) were evaluated. Post-operative plasma levels were compared to pre-operative levels. The multivariate prognostic value of hyperfibrinogenemia was determined using the Cox proportional hazards model.

Results: Tumor progression was significantly associated with hyperfibrinogenemia. CRP and platelet counts were also significantly associated with hyperfibrinogenemia. Plasma fibrinogen levels significantly decreased after radical surgery. Adjusting for TNM factors, multivariate analysis indicated that hyperfibrinogenemia was an independent prognostic factor of poor patient survival (hazard ratio = 2.607, 95% confidence interval = 1.180–5.761, $P = 0.018$).

Conclusion: Preoperative hyperfibrinogenemia was associated with tumor progression, inflammatory mediators and poor overall survival in patients with gastric cancer.

Introduction

Fibrin or fibrinogen was identified as one of the major components of the tumor stroma enveloping tumor cells [1]. Hyperfibrinogenemia has frequently been found to be associated with various malignancies [2–8]. As a consequence of hyperfibrinogenemia, various plasma components, including fibrinogen, can accumulate in the tumor stroma, where fibrinogen can be converted to cross-linked fibrin by the coagulant/procoagulant activities of malignant cells [8] and/or by tumor-infiltrating macrophages [9]. Several studies have reported that hyperfibrinogenemia is associated with poor prognosis and tumor progression [2–5, 7]. Although there is evidence that tumor cells secrete humoral factors that may eventually lead to hyperfibrinogenemia, the pathogenesis of hyperfibrinogenemia in gastric cancer has not yet been clarified [10, 11]. Although increasing evidence suggests that fibrinogen expression and inflammation are associated with poor prognosis of various cancers [2, 3, 4, 8], the association between the plasma fibrinogen concentrations and gastric cancer prognosis has only been examined by univariate analysis [10, 11]. Therefore, we analyzed inflammatory mediators in 315 patients with primary gastric adenocarcinoma before surgery to identify correlations between inflammatory mediators and hyperfibrinogenemia. Possible correlations between fibrinogen levels and several biomarkers, i.e., WBC count, CRP level, prothrombin time, activated partial thromboplastin time, CEA, CA19-9, CA125, and D-dimer, were also analyzed. Finally, the prognostic significance of hyperfibrinogenemia was assessed after adjusting for the selected clinicopathological variables by multivariate

analysis.

Methods

Patients

Laboratory data and clinicopathological parameters of 315 patients with histologically confirmed primary gastric adenocarcinoma who underwent surgery at Toho University Hospital (Tokyo, Japan) between 2008 and 2013 were retrospectively reviewed. The patient population comprised 212 men (67.3%) and 103 women (32.7%), with a median age of 69 years (range, 33–93 years). The study protocol was approved by the institutional review board of Toho University (IRB #26-256).

After surgery, all patients were classified according to the 14th edition (3rd English edition) of the Japanese Classification of Gastric Carcinoma [12]. The distribution of patients according to their cancer stages was as follows: stage I, 146; stage II, 71; stage III, 65; and stage IV, 33. All patients classified in stage IV had distant lymph node metastasis but no organ metastasis. All patients underwent either total or subtotal gastrectomy with standard lymphadenectomy. All patients were regularly followed-up until July 2015 or death. The follow-up period ranged from 0 months to 88 months (median, 28 months).

Blood sample analysis for fibrinogen levels and other biomarkers

Venous blood samples were collected before treatment initiation. Among the 315 patients, serum CEA was analyzed in 293 patients, serum CA19-9 in 290, serum CA125 in 165, active partial thromboplastin time in 314, D-dimer in 231, and fibrin/fibrinogen degradation products in 235. Hyperfibrinogenemia status was re-analyzed in some patients after surgery. Repeated freezing and thawing of samples was avoided. Each sample was centrifuged at 3000 g for 5 min and then frozen at −80°C until the time of the assay. Plasma fibrinogen levels were measured using a previously established solid phase human fibrinogen immunoassay enzyme-linked immunosorbent assay kit (reagent: Coagpia®Fbg; analyzer: Automated Coagulation Analyzer CP3000®, Sekisui Medical Co., Tokyo, Japan) [13]. Patients were divided into groups of high and low plasma fibrinogen levels using three cut-off values (300, 350, and 400 mg/dl), according to institutional standards [14] and previous publications [2, 3, 10, 11]. We also used cut-off values for WBC count (9000 cells/mm^3) and CRP levels (0.2 mg/ml), in accordance with institutional standards.

Statistical Analyses

Serum biomarker levels are expressed as means + standard deviations. Comparisons between unpaired groups for these variables were conducted using the Mann–Whitney *U* test. Overall survival was calculated using the Kaplan–Meier product limit estimate. Survival differences between groups were determined using the log-rank test.

Significant predictors identified by univariate analysis were assessed by multivariate analysis using the Cox proportional hazards model. All statistical analyses were performed using EZR statistical software [15]. Two-sided *P*-values of <0.05 were considered statistically significant.

Results

Comparisons of clinicopathological factors between the high and low plasma fibrinogen level groups

Plasma fibrinogen levels were significantly associated with age, stage, tumor size, tumor depth, nodal involvement, and liver metastasis presence, but not with gender or histology (Table 1). According to the three cut-off plasma fibrinogen levels, frequency of hyperfibrinogenemia according to clinicopathological factors were also compared (Table 2). The hyperfibrinogenemia was consistently associated with nodal involvement, tumor depth, and large tumor size using any of the three cut-off levels (Table 2).

A receiver operating characteristic curve was constructed to assess plasma fibrinogen cut-off levels to differentiate advanced tumors from T1N0 or T2N0 tumors. The best cut-off value was found to be 347 mg/dl, similar to 350 mg/dl (Figure 1). We assessed, based on Table 2, how much differences were observed in frequencies of hyperfibrinogenemia between stage I/II and stage III/IV. We found that the biggest deference was observed when we used 350mg/dl as a cut-off value. We also assessed, based on Figure 2, how much differences were observed in

prognostic impact of hyperfibrinogenemia. We found that the biggest deference was observed when we used 350mg/dl as a cut-off value. Therefore, we used 350 mg/dl as the cut-off value for plasma fibrinogen levels for further analyses.

Association between hyperfibrinogenemia, pathological factors and biomarkers

Various inflammatory mediators were significantly associated with hyperfibrinogenemia (Table 3). The frequencies of hyperfibrinogenemia were significantly associated with following parameters; large tumor, deep tumor, positive lymph node, high WBC, high CRP, high platelet and high APTT (Table 2 and 3). Therefore, we evaluated contribution of all these seven parameters for hyperfibrinogenemia by multivariate analysis (Table 4). Multivariate analysis showed that CRP levels ($P < 0.001$) and platelet count ($P = 0.044$) were independent risk factors for hyperfibrinogenemia.

Prognostic impact of plasma fibrinogen levels

Of 65 patients who died by the end of July 2015, 59 (90.8%) succumbed to gastric cancer. Hyperfibrinogenemia, as defined by any of the three cut-off values, was consistently associated with poor patient survival (Figure 2). Based on the survival curves obtained after dividing the patients into low-risk groups, a plasma fibrinogen level of 350

mg/dl seemed to be the best cut-off value to identify high-risk patients with poor prognoses (Figure 2). Univariate analysis revealed that survival was significantly worse in the high fibrinogen level group than in the low fibrinogen level group ($P < 0.001$), and large tumors (>50 mm), deep tumors (>T3), and lymph node metastasis or peritoneal metastasis were significant prognostic factors for poor overall survival (Table 5). In multivariate analysis, not only tumor depth and nodal status but also hyperfibrinogenemia were selected as independent poor prognostic factors for patients with gastric adenocarcinoma rather than (Table 5).

Postoperative plasma fibrinogen levels of patients with preoperative hyperfibrinogenemia

Among a total of 122 patients with hyperfibrinogenemia, plasma fibrinogen levels were re-examined in 32 patients at 6–12 months after surgery. Postoperative plasma fibrinogen levels were significantly lower than preoperative levels (Figure 3a, $P < 0.001$). Among these 32 patients, disease recurred in 7. In a representative case, out of these 7 recurrent cases, the changing plasma fibrinogen levels after radical surgery until tumor recurrence is shown in Figure 3b. Plasma fibrinogen levels decreased after surgery but then began to increase at the time of lymph node recurrence.

Discussion

In the present study, we found that an increase in plasma fibrinogen levels was associated with tumor progression,

high CRP levels, and poor prognosis. Although previous reports defined hyperfibrinogenemia as a plasma fibrinogen level of 300 to 400 mg/dl, we defined it as >350 mg/dl. When we used a cut-off level of >350 mg/dl, hyperfibrinogenemia was present in 122 (38.7%) of the 315 patients. The frequency of hyperfibrinogenemia in the present study was relatively lower than that reported for other types of solid tumors [2–8]: 55% for esophageal cancer [2], 50% for pancreatic cancer [3], 42% for hepatocellular carcinoma [4], 43% for breast cancer [5], and 77% for colon cancer [6]. However, but frequency of hyperfibrinogenemia in gastric cancer was relatively higher than prostate cancer (12%) [7]. This can be partly explained by the lower frequency of advanced tumors in the present series of patients with gastric cancer.

The results of this study identified hyperfibrinogenemia as an independent prognostic indicator of poor patient survival when adjusted for tumor stage. Other cut-off values (300 and 400 mg/dl) were not selected as independent prognostic factors (data not shown). Based on the interactions between IL-6, platelets, and cancer cells [16], hyperfibrinogenemia may promote lymph node metastasis [17]. The pathophysiological mechanism of hyperfibrinogenemia may be secondary to tumor-associated elevations of circulating inflammatory mediators and/or intra-abdominal infectious disease [18, 19]. We also analyzed several other biomarkers such as FDP, D-Dimer, CEA, CA19-9 and CA125 in those parameters lacking many data. Actually, FDP and D-Dimer were significantly associated with hyperfibrinogenemia, however CEA, CA19-9 and CA125 were not (supplemental Table 1). Because

hyperfibrinogenemia is an independent prognostic factor of reduced patient survival, patients with hyperfibrinogenemia may be candidates for neoadjuvant chemotherapy to reduce tumor recurrence. A total of 76 (62%) of the 122 patients with hyperfibrinogenemia had lymph node metastases. For such patients, D2 lymph node dissection should be applied even for tumors clinically negative for lymph node metastases. As inflammatory mediators are also associated with prognosis, combinatory assessment could be helpful to identify high-risk patients for recurrence even after curative surgery.

Post-operative plasma fibrinogen levels should decrease if cancer cells were one of the causes of hyperfibrinogenemia. Although plasma fibrinogen levels were monitored only in some patients, we found that the levels significantly decreased after surgery. Although plasma fibrinogen levels after recurrence were monitored only in some patients, we found that the levels increased at the time of diagnosis of recurrent disease. Because post-operative plasma fibrinogen levels were available for only some patients to assess this interaction, further analyses are needed to identify underlying mechanisms to arrive at a conclusion.

In conclusion, hyperfibrinogenemia was significantly associated with tumor load and patients' overall survival, indicating its usefulness as a clinical biomarker. Preoperative assessment of plasma fibrinogen levels may be useful to predict tumor stage and patients' overall survival.

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Conflict of interest

The authors have no conflict of interest to declare.

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Figure Legends

Figure 1. Receiver operating characteristic curve of plasma fibrinogen levels to differentiate stage I (T1N0 and T2N0) disease.

Figure 2. Survival curves according to various plasma fibrinogen cut-off levels. Thick lines represent the survival curves of patients with high plasma fibrinogen levels. Thin lines represent the survival curves of patients with low plasma fibrinogen levels.

Figure 3. Postoperative plasma fibrinogen levels of patients with preoperative hyperfibrinogenemia. a. Median and standard deviation of plasma fibrinogen levels before and after surgery. b. Representative pattern of changing plasma fibrinogen level after surgery until recurrence.

Table 1. Comparisons of plasma fibrinogen levels according to clinicopathological factors.

Variables		Number of patients (total=315)	Mean +SD	*P* value
Gender	Female	103	332±81	0.279
	Male	212	343±89	
Age	≦65	114	326±88	0.019
	> 65	201	347±85	
Histology*	Differentiated	163	342±90	0.883
	Poorly differentiated	148	336±82	
Tumor*	≦50mm	197	321±77	<0.001
size	> 50mm	103	369±94	
Tumor	T1-2	161	315±75	<0.001
depth	T3-4	154	364±91	
Nodal	Negative	174	321±81	<0.001
status	Positive	141	362±87	
Liver	Negative	310	338±86	0.033
metastasis	Positive	5	423±74	
Peritoneal	Negative	303	336±83	0.054
metastasis	Positive	12	411±126	
Residual tumor	R0	273	333±83	0.005
	R1	42	378±100	
Stage	Stage Ⅰ/Ⅱ	217	327±82	<0.001
	stageⅢ/Ⅳ	98	366±91	

P values were calculated by Mann-Whitney *U*-test.
* Not include unknown cases

Table 2. Frequency of hyperfibrinogenemia according to clinicopathological factors based on three cut-off levels.

Variables		Number of patients (Total=315)	Number of patients with hyperfibrinogemia (>400mg/dl)	*P* value[a]	Number of patients with hyperfibrinogemia (>350mg/dl)	*P* value[a]	Number of patients with hyperfibrinogemia (>300mg/dl)	*P* value[a]
Gender	Female	103	19(18.4%)	0.384	33(32.0%)	0.109	64(62.1%)	0.804
	Male	212	50(23.6%)		89(42.0%)		135(63.7%)	
Age	≦65	114	21(18.4%)	0.321	38(33.3%)	0.150	61(53.5%)	0.011
	> 65	201	48(23.9%)		84(41.8%)		138(68.7%)	
Histology*	Differentiated	163	38(23.3%)	0.490	64(39.3%)	0.816	101(62%)	0.725
	Poorly differentiated	148	29(19.6%)		56(37.8%)		95(64.2%)	
Tumor*	≦50mm	197	29(14.7%)	<0.001	55(27.9%)	<0.001	111(56.3%)	0.004
size	> 50mm	103	34(33%)		59(57.3%)		76(73.8%)	
Tumor	T1-2	161	22(13.7%)	<0.001	39(24.2%)	<0.001	85(52.8%)	<0.001
depth	T3-4	154	47(30.5%)		83(53.9%)		114(74%)	
Nodal	Negative	174	28(16.1%)	0.006	46(26.4%)	<0.001	95(54.6%)	<0.001
status	Positive	141	41(29.1%)		76(53.9%)		104(73.8%)	
Liver	Negative	310	66(21.3%)	0.072	118(38.1%)	0.076	194(62.6%)	0.162
metastasis	Positive	5	3(60%)		4(80%)		5(100%)	
P factor	Negative	302	64(21.1%)	0.145	113(37.3%)	0.066	189(62.6%)	0.546
	Positive	12	5(41.7%)		8(66.7%)		9(75%)	
Residual tumor	R0	273	53(19.4%)	0.009	96(35.2%)	0.001	167(61.2%)	0.085
	R1	42	7(31.8%)		12(54.5%)		15(68.2%)	
Stage	Stage Ⅰ / Ⅱ	217	38(17.5%)	0.008	68(31.3%)	<0.001	127(58.5%)	0.012
	stage Ⅲ / Ⅳ	98	31(31.6%)		54(55.1%)		72(73.5%)	

P values were calculated by Fisher's exact probability test.

* No include unknown cases

Table 3. The associations between hyperfibrinogenemia and various biomarkers.

Variables		Number of patients (Total=315)	Mean+SD	*P* value[a]	Number of patients with hyperfibrinogemia	*P* value[b]
WBC	≦9,000/μL	298	336±83	0.005	110(36.9%)	0.009
	＞9,000/μL	17	397±116		12(70.6%)	
CRP*	≦0.2mg/dl	215	308±64	<0.001	49(22.8%)	<0.001
	＞0.2mg/dl	98	405±88		72(73.5%)	
Pletelet	≦400×10^9/L	306	337±86	0.002	114(37.3%)	0.003
	＞400×10^9/L	9	413±58		8(88.9%)	
PT	≦14.0sec.	312	338±86	0.029	119(38.1%)	0.057
	＞14.0sec.	3	468±68		3(100%)	
APTT*	≦40.0sec.	298	336±84	0.005	110(36.9%)	0.006
	＞40.0sec.	15	394±116		11(73.3%)	

a. *P* values were calculated by Mann-Whitney *U*-test.
b. *P* values were calculated by Fisher's exact probability test.
* Not include unknown cases

Table 4. Logistic regression analysis of relations between hyperfibrinogenemia and various biomarkers.

Variables		Odds ratio	95%CI[a]	Multivariate P value[b]
Tumor size	≦50mm	1.580	0.801-3.110	0.188
	＞50mm			
Tumor depth	T1-2	1.480	0.668-3.260	0.335
	T3-4			
Nodal status	Negative	1.940	0.918-4.110	0.083
	Positive			
WBC	≦9,000/μL	2.450	0.619-9.680	0.202
	＞9,000/μL			
CRP	≦0.2mg/dl	8.350	4.490-15.50	<0.001
	＞0.2mg/dl			
Platelet	≦400×10^9/L	11.200	1.070-117.0	0.044
	＞400×10^9/L			
APTT	≦40.0sec.	1.650	0.357-7.630	0.521
	＞40.0sec.			

Adjusted 95% confidence interval
P values were calculated by Logistic regression analysis

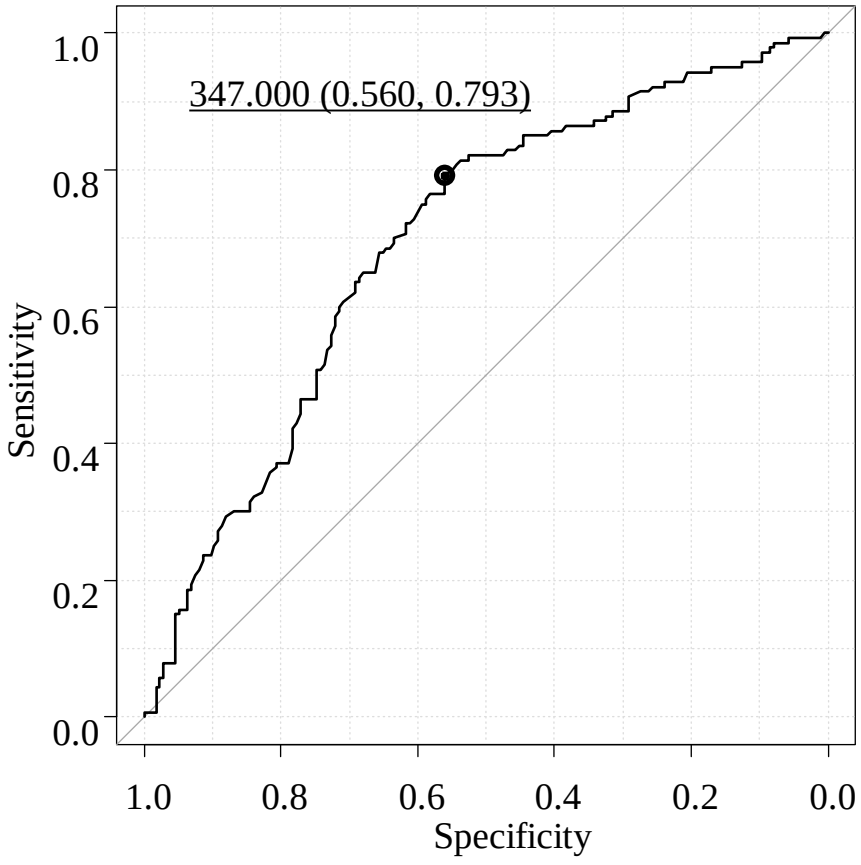
Table 5. Univariate and multivariate analysis of risk factors for patients' survival.

Variables		Univariate P value[a]	H.R.[b]	95%CI[c]	Multivariate P value[d]
Gender	Female	0.155	0.627	0.309-1.274	0.197
	Male				
Age	≦65	0.936	0.904	0.434-1.882	0.788
	＞65				
Tumor size	≦50mm	<0.001	0.895	0.426-1.884	0.771
	＞50mm				
Tumor depth	T1-2	<0.001	4.178	1.141-15.30	0.031
	T3-4				
Nodal status	Negative	<0.001	5.183	1.479-18.16	0.01
	Positive				
Peritoneal status	Negative	<0.001	2.502	0.924-6.778	0.071
	Positive				
Fibrinogen	≦350mg/dl	<0.001	2.607	1.180-5.761	0.018
	＞350mg/dl				

a. Log-rank test.
b. Adjusted hazards ratio
c. Adjusted 95% confidence interval
d. Cox proportional hazards model

Figure 1

a.


347.000 (0.560, 0.793)
Sensitivity
Specificity
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0.8
0.6
0.4
0.2
0.0

b.

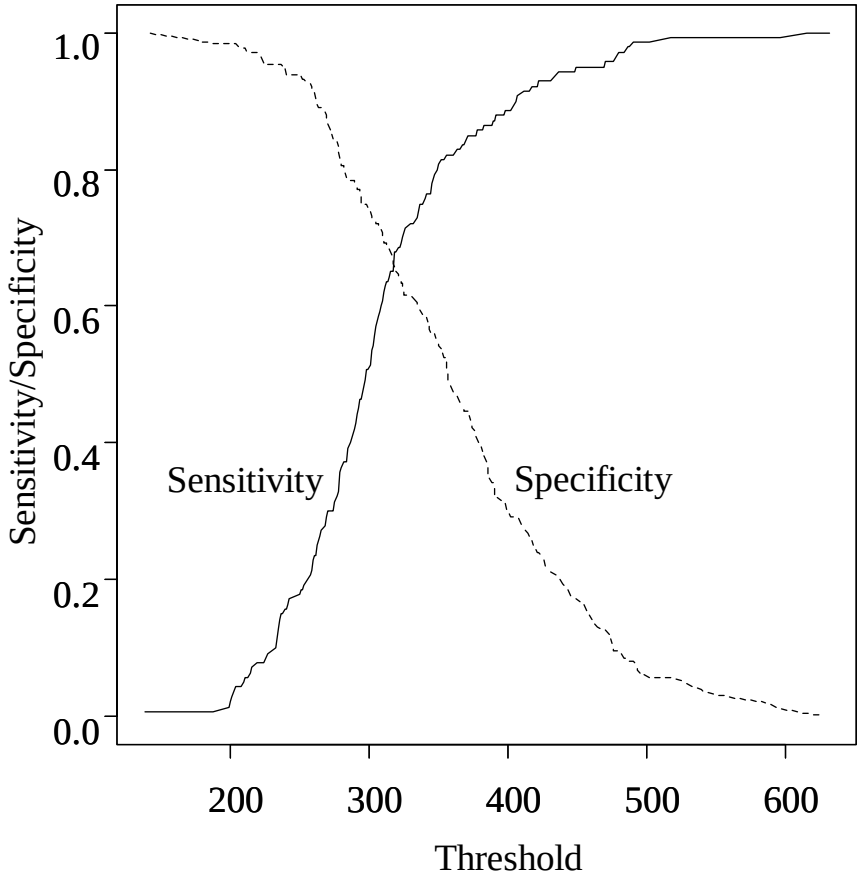

Sensitivity/Specificity
Threshold
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0
200
300
400
500
600

Figure 2

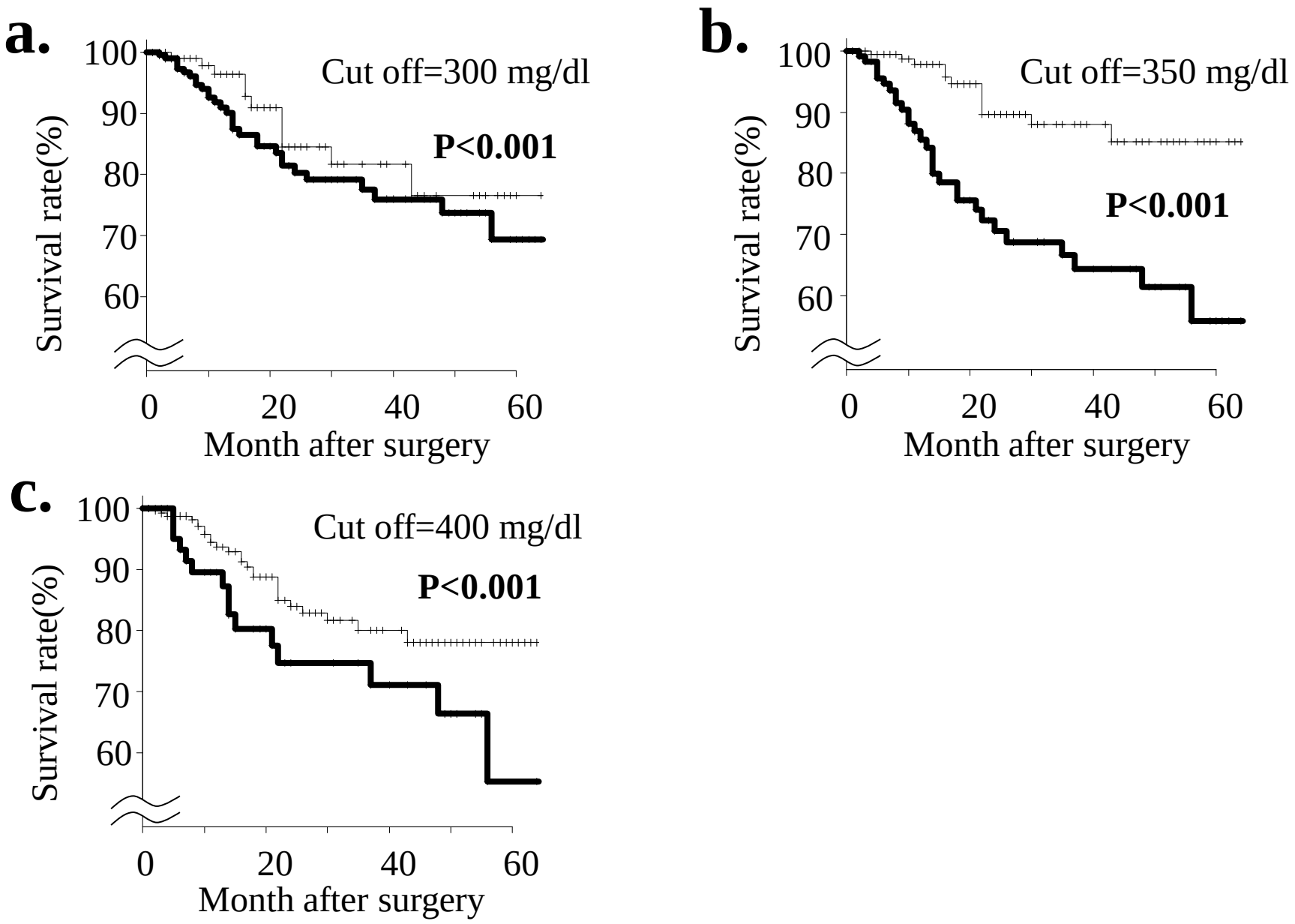
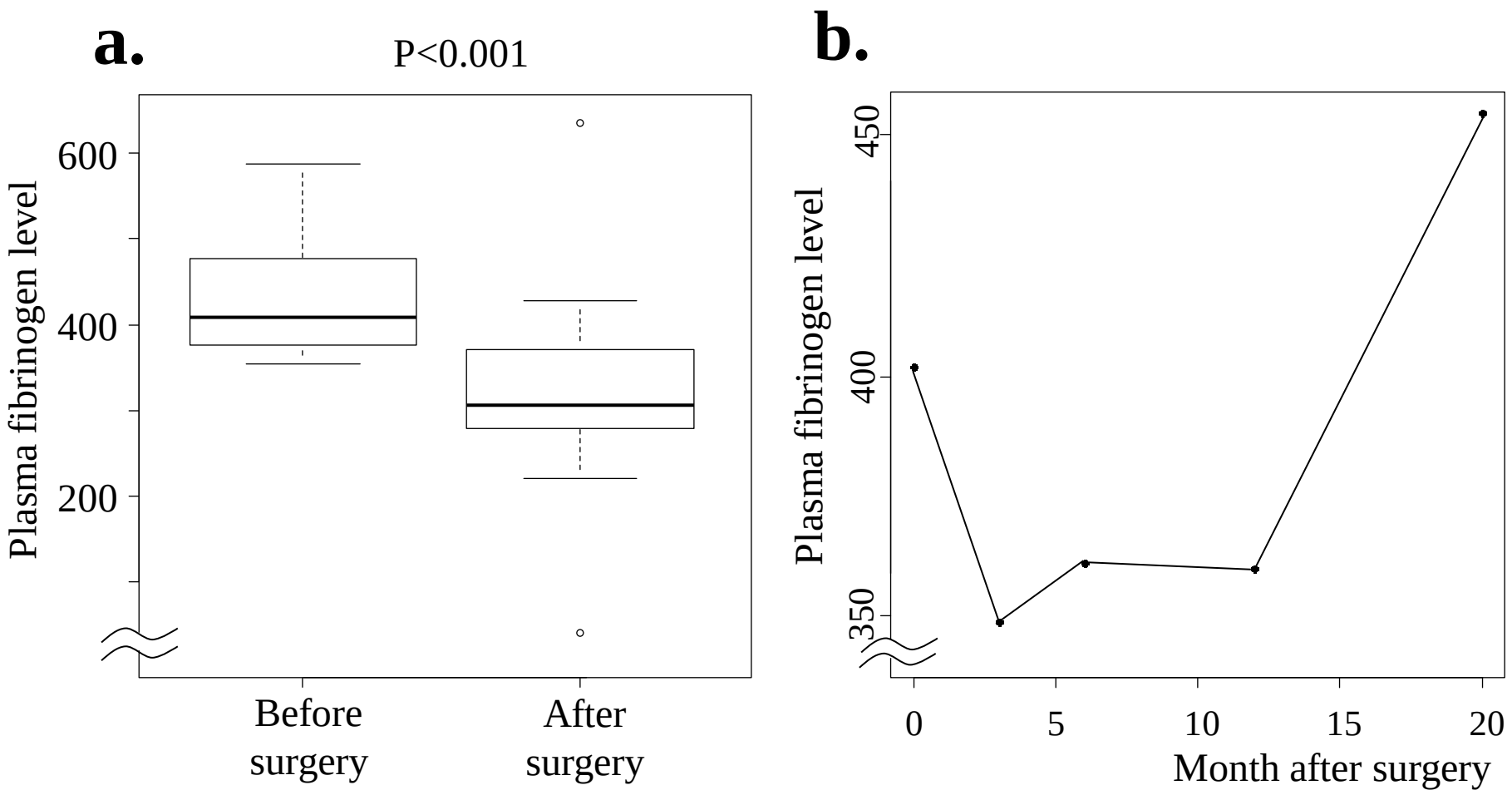

a.
Cut off=300 mg/dl
P<0.001
Survival rate(%)
100
90
80
70
60
0
20
40
60
Month after surgery
b.
Cut off=350 mg/dl
P<0.001
Survival rate(%)
100
90
80
70
60
0
20
40
60
Month after surgery
c.
Cut off=400 mg/dl
P<0.001
Survival rate(%)
100
90
80
70
60
0
20
40
60
Month after surgery

Figure 3


a.
P<0.001
Plasma fibrinogen level
600
400
200
Before surgery
After surgery
b.
Plasma fibrinogen level
450
400
350
0
5
10
15
20
Month after surgery