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Original Article

Prognostic Impact of Plasma Fibrinogen Changing in Patients with Resectable Pancreatic Cancer

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ABSTRACT

Introduction: Previous studies have indicated that hyperfibrinogenemia is a predictor of poor prognosis in various tumors. However, little information is available on the prognostic impact of preoperative hyperfibrinogenemia and its changing pattern in resectable pancreatic ductal adenocarcinoma (PDAC) patients.

Methods: This retrospective study examined 102 PDAC patients who underwent curative surgery at Omori Medical Center, Toho University School of Medicine (Tokyo, Japan) between 2004 and 2016. Among these, 44 (43.1%) reported preoperative hyperfibrinogenemia.

Results: Preoperative hyperfibrinogenemia was associated with an independent prognostic factor for patient survival. The cumulative 5-year overall survival time rate in the normal fibrinogen and hyperfibrinogen groups was 44.8% and 31.2%, respectively, with a significant difference between the two groups (P = 0.047). The prognostic factors in PDAC patients revealed preoperative hyperfibrinogenemia of ≥400 mg/dL (P = 0.017). The cumulative 5-year overall survival rates were 57.3% and 9.1% in the normalization and non-normalization groups, respectively, with a significant difference between the two groups (P = 0.008). In multivariate analysis, the prognostic factors in patients with preoperative hyperfibrinogenemia revealed a postoperative fibrinogen level of ≥400 mg/dL (P = 0.001).

Conclusions: Preoperative hyperfibrinogenemia was the risk factor for reducing overall survival in PDAC patients. Among the patients with hyperfibrinogenemia, the non-normalization group after surgery revealed to be a high-risk group for poor prognosis.

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KEYWORDS: hyperfibrinogenemia, pancreatic cancer, prognosis

Introduction

Although radical surgical resection offers a cure, the recurrence rate after surgery remains high in pancreatic cancer.[1–3] Reportedly, tumor size and lymph node involvement are considered to be poor prognostic factors after

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pancreatic cancer resection.[4–6] Owing to the inadequacy of pathological staging to predict patients' prognosis, identifying a biomarker that can detect high-risk groups to predict prognosis is imperative.

Previous studies have reported that hyperfibrinogenemia is a poor prognostic factor in various cancers and is associated with tumor progression.[7–11] Reportedly, hyperfibrinogenemia is a phenomenon in which fibrinogen causes various plasma components, including fibrinogen, to accumulate in the stroma of tumors, converting fibrinogen to crosslinked fibrin for the coagulation/procoagulant activity of malignant cells and/ or tumor-infiltrating macrophages.[12, 13] In addition, leaky blood vessels facilitate the passage of fibrinogen, and fibrinogen deposits are produced by the tissue factor spoken on the tumor endothelium. These processes permit invasion and metastasis to promote the growth of metastases.[14] Recent studies have proved that fibrinogen levels, which also reflect the degree of systemic inflammation, is related to tumor progression in non-resectable PDAC.[8, 15–18] However, little information is available on the prognostic impact of preoperative hyperfibrinogenemia and the changing pattern of hyperfibrinogenemia in resectable PDAC patients.

This study aims to investigate the correlation among preoperative hyperfibrinogenemia, changing pattern of hyperfibrinogenemia, clinicopathological factors, and survival in resectable PDAC patients.

Materials and Methods

Patients

All consecutive patients with a pathological diagnosis of pancreatic cancer during the study period who underwent pancreatectomy, R0 and R1, were enrolled in this study. The exclusion criteria of this study were as follows: (a) PDAC derived from an intraductal papillary-mucinous neoplasm or a mucinous cystic neoplasm, (b) other rare pancreatic malignancies, (c) apparent inflammatory diseases, (d) a history of thrombosis, (e) treatment with drugs that might affect the coagulation/fibrinolytic system, (f) severe jaundice that might affect carbohydrate antigen 19-9 (CA19-9) levels, or (g) treatment-related death.

In this study, we examined 111 consecutive PDAC patients who underwent pancreatic resection. Among these, we excluded 9 patients for various reasons listed above (R2 resection, $n = 5$; acute obstructive cholangitis, $n = 1$; history of thrombosis, $n = 2$; severe jaundice, $n = 1$). Finally, we enrolled 102 patients in the present study. Patients' information was obtained from a common database of PDAC patients who underwent tumor resection to attain cure at Omori Medical Center, Toho University School of Medicine (Tokyo, Japan) between 2004 and 2016.

Surgery, adjuvant chemotherapy, and follow-up methods

This retrospective, observational study examined PDAC patients who underwent pancreatectomy. In this study, lymph nodes were harvested by standard lymphadenectomy (D2) according to the Classification of Pancreatic Carcinoma of Japan Pancreas Society.[19] While gemcitabine or tegafur/gimeracil/oteracil-based chemotherapy was usually initiated within 10 weeks after surgery as adjuvant therapy, adjuvant chemotherapy was not performed if patients could not fully recover from surgery.

In this study, we used computed tomography, endoscopic sonography, endoscopic retrograde cholangiopancreatography, or percutaneous transhepatic cholangiography to assess local or distant tumor extension. Computed tomography determined the preoperative resectability status. A tumor was considered unresectable if it was associated with distant metastases, including liver metastases or peritoneal dissemination, or the presence of superior mesenteric artery encasement of greater than 180°, any celiac abutment, and aortic invasion or encasement. There was no patient who received neoadjuvant therapy during this study period.

This retrospective study was approved by the Ethical Committee of our university with number 26-256. All the patients were followed up until the end of August 2018 or death.

Study design

We examined the patients' clinicopathological factors, including patients' demographics, tumor characteristics, and survival, which were compared between patients in the high- and low-plasma fibrinogen groups, and prognostic factors. In addition, various biological features were evaluated. The cut-off values for carcinoembryonic antigen (CEA) and CA19-9 were fixed following the manufacturer's instructions with 5.0 ng/mL and 37 U/mL, respectively.

We further categorized patients with preoperative hyperfibrinogenemia into two groups based on the postoperative fibrinogen status: normalization and non-normalization within 3 months after surgery. The clinicopathological factors, including patients' demographics, tumor characteristics, and survival, were compared between

Table 1 Comparisons between plasma fibrinogen levels according to clinicopathological factors and various biomarkers

Variables		Number of patients (n = 102)	Fibrinogen level Mean ± SD (mg/dl)	P value [a]	Number of patients with hyperfibrinogenemia (%) [b]	P value [c]
Gender	Male	50	405 ± 106	0.389	26 (52.0)	0.076
	Female	52	392 ± 93		18 (34.6)	
Age (year)	<65	32	393 ± 104	0.748	15 (46.9)	0.607
	≥65	70	402 ± 98		29 (41.4)	
Tumor size (mm)	<40	87	399 ± 101	0.709	36 (41.3)	0.390
	≥40	15	398 ± 94		8 (53.3)	
Tumor depth	T1-2	13	355 ± 90	0.046	4 (30.8)	0.328
	T3-4	89	405 ± 99		40 (44.9)	
Nodal status	Negative	45	366 ± 95	0.002	15 (33.3)	0.074
	Positive	57	425 ± 96		29 (50.9)	
Stage	I, II	85	390 ± 96	0.065	33 (38.8)	0.049
	III, IV	17	443 ± 108		11 (64.7)	
WBC count (cells/μl)	<8500	92	396 ± 99	0.499	39 (42.4)	0.646
	≥8500	10	420 ± 109		5 (50.0)	
Platelet count (cells/μl)	$<25.0\times10^4$	76	385 ± 89	0.080	29 (38.2)	0.084
	$\geq25.0\times10^4$	26	437 ± 120		15 (57.7)	
CRP (mg/dl)	≤0.2	72	376 ± 87	0.001	26 (36.1)	0.027
	>0.2	30	455 ± 106		18 (60.0)	
Prothrombin time (%)	<100	54	399 ± 100	0.765	24 (44.4)	0.777
	≥100	48	398 ± 101		20 (41.7)	
Activated partial thromboplastin time (s)	<30	44	392 ± 91	0.499	17 (38.6)	0.423
	≥30	58	404 ± 106		27 (46.5)	
CA19-9 (ng/ml)	≤37	39	397 ± 87	0.524	19 (48.7)	0.371
	>37	63	400 ± 107		25 (39.7)	
Carcinoembryonic antigen (ng/ml)	≤5.0	75	395 ± 94	0.630	32 (42.7)	0.873
	>5.0	27	409 ± 116		12 (44.4)	

SD, Standard deviation; WBC, white blood cell; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19-9
a. Mann-Whitney U test
b. A plasma fibrinogen level of ≥400 mg/dl was the cutoff for hyperfibrinogenemia
c. Fisher's exact probability test

Table 2 Logistic regression analysis of relations between hyperfibrinogenemia and biomarkers

Variables		Multivariate		
		H.R. [a]	95% CI [b]	P value [c]
Stage	I-II	1		0.307
	III-IV	1.489	0.672-2.962	
CRP (mg/dl)	≤0.2	1		0.124
	>0.2	1.601	0.875-2.843	

CRP, C-reactive protein; CI, confidence interval
a. Adjusted hazards ratio
b. Adjusted 95% confidence interval
c. Logistic regression analysis

these two groups. Univariate and multivariate analyses were used to evaluate the prognostic impact.

Plasma fibrinogen levels after surgery were re-evaluated in patients with hyperfibrinogenemia. Furthermore, patients with normal fibrinogen levels after surgery were defined as the "normalization group." However, other

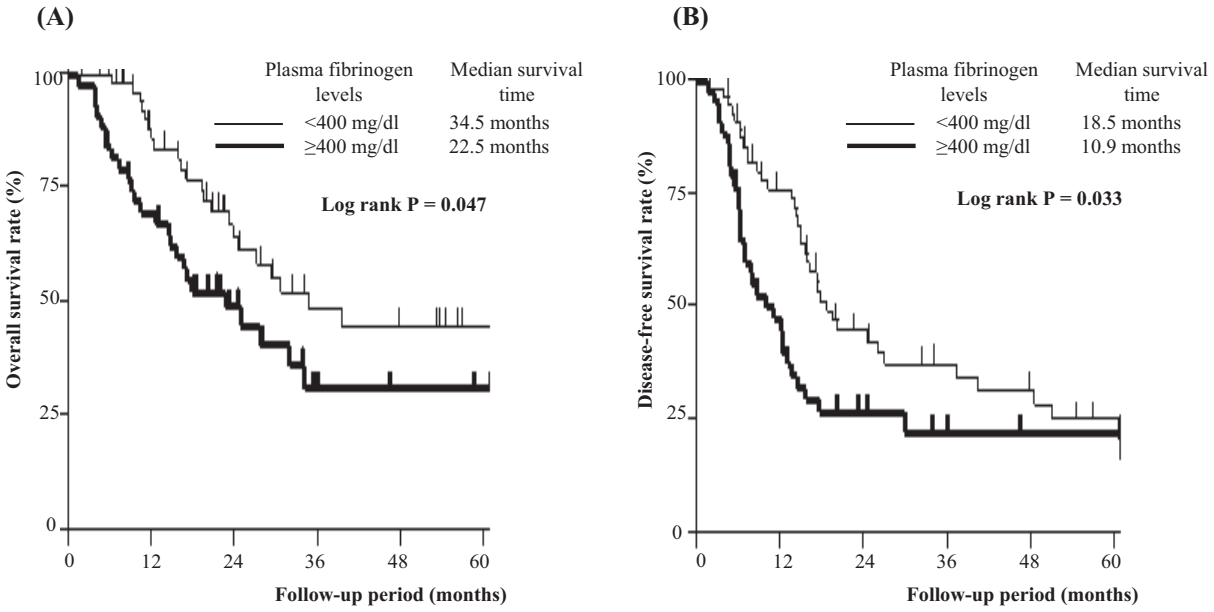

Fig. 1 (A) The overall ($P = 0.047$; log-rank test) and (B) disease-free survival of patients according to the plasma fibrinogen levels of < 400 and ≥ 400 mg/dL ($P = 0.033$; log-rank test).

patients who demonstrated hyperfibrinogenemia even after surgery were defined as the "non-normalization group."

Definitions of parameters

The final stage of pancreatic cancer was pathologically assessed according to the tumor-node-metastasis classification system of malignant tumors of the International Union against Cancer, 8th edition.[20] The evaluated margins routinely included the pancreatic transection, superior mesenteric artery, posterior, and proximal bile duct margins. Surgical margins were considered positive if infiltrating adenocarcinoma was present along the pancreatic transection line or dissected peripancreatic soft tissue margins. R0 or R1 resection was defined as the absence or presence of cancer cells along the margin.[19]

For the first 3 years after surgery, patients were followed up every 1-3 months. Follow-up visits comprised a physical examination, laboratory tests, and evaluation of tumor markers. Then, the patients were followed up by computed tomography every 6 months or at the time of abnormal laboratory data. After 3 years, patients were followed up every 6 months. "Disease-free survival" was defined as no new lesions found on computed tomography.

Data collection

We used a standard flow sheet to collect data on preoperative parameters, operative variables, pathological parameters, postoperative treatment, and survival to create a dedicated database. The overall survival time for each patient was calculated from the time of surgery. While the survival time after surgery and cause of death were recorded for patients who died, the postoperative survival time and recurrence status were recorded for survivors.

Blood tests were routinely performed with venous samples collected before surgery. We regularly measured plasma fibrinogen and various markers before (samples collected within 7 days before surgery) and after (samples collected within 3 months after surgery) surgery. In addition, plasma fibrinogen levels were evaluated during routine workups to exclude coagulation disorders or the presence of acute infections before cancer diagnostic interventions or treatment. In this study, fibrinogen levels were re-evaluated after surgery in all the patients. In addition, plasma fibrinogen levels were measured with 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).[21] Based on the institutional standards and the reference range of clinical criterion at our hospital, plasma fibrinogen levels higher than 400 mg/dL were defined as hyperfibrinogenemia.[22, 23]

Statistical analyses

Statistical analysis was performed using the JMP statistical software (version 12; SAS Institute, Cary, NC, USA).

Table 3 Univariate and multivariate analysis of risk factors for overall survival in 102 patients

Variables		Number of patients (n = 102)	Univariate	Multivariate		
			P value [a]	H.R. [b]	95% CI [c]	P value [d]
Gender	Male	50	0.472			
	Female	52				
Age (year)	＜65	32	0.431			
	≥65	70				
Tumor size (mm)	＜40	87	＜0.001	1		0.087
	≥40	15		1.999	0.900-4.302	
Tumor depth	T1-2	13	0.258			
	T3-4	89				
Nodal status	Negative	45	0.397			
	Positive	57				
Stage	I-II	85	0.226			
	III-IV	17				
CRP (mg/dl)	≤0.2	72	0.092			
	＞0.2	30				
Fibrinogen level (mg/dl)	＜400	58	0.047	1		0.017
	≥400	44		2.018	1.130-3.624	
WBC count (/μl)	＜8500	92	0.474			
	≥8500	10				
Platelet count (/μl)	＜25.0×10^4	76	0.543			
	≥25.0×10^4	26				
CA19-9 (ng/ml)	≤37	39	0.036	1		0.578
	＞37	63		1.217	0.608-2.465	
Carcinoembryonic antigen (ng/ml)	≤5.0	75	0.012	1		0.022
	＞5.0	27		2.144	1.118-3.995	
Adjuvant chemotherapy	No	23	0.272			
	Yes	79				
Residual tumor	R0	72	0.005	1		0.062
	R1	30		1.917	0.966-3.732	

WBC, white blood cell; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19-9; CI, confidence interval
a. Log-rank test
b. Adjusted hazards ratio
c. Adjusted 95% confidence interval
d. Logistic regression analysis

Serum biomarker levels were expressed as the mean ± standard deviation. Comparisons between unpaired groups for these variables were performed with the Mann-Whitney *U* test. In addition, survival rates were calculated using the Kaplan-Meier product limit estimate. Differences between groups regarding survival were analyzed using the log-rank test. Furthermore, significant predictors identified by the univariate analysis were assessed by multivariate analysis using the Cox proportional hazards model. We considered $P < 0.05$ as statistically significant.

Results

Relations between plasma fibrinogen levels and clinicopathological factors

Among the 102 patients, 44 (43.1%) were diagnosed with preoperative hyperfibrinogenemia. Our patient cohort comprised 50 males (49.0%) and 52 females (51.0%), with a median age of 71 (range, 33-85) years.

Table 1 showed that the plasma fibrinogen levels were significantly associated with the depth and nodal status of the tumor but not with patient's sex or tumor size. Various coagulation mediators, such as prothrombin time (PT) and activated partial thromboplastin time (APTT), and serum tumor markers, such as CA19-9 and CEA, were not signifi-

Table 4 Comparison between normalization group and non-normalization group among patients with preoperative hyperfibrinogenemia

Variables		Number of patients (n = 44)	Normalization (n = 20) (%)	Non-normalization (n = 24) (%)	P value [a]
Gender	Male	26	10 (50%)	16 (67%)	0.263
	Female	18	10 (50%)	8 (33%)	
Age (year)	<65	15	4 (20%)	11 (46%)	0.068
	≥65	29	16 (80%)	13 (54%)	
Tumor size (mm)	<40	36	15 (75%)	21 (87%)	0.284
	≥40	8	5 (25%)	3 (13%)	
Tumor depth	T1, 2	4	1 (5%)	3 (13%)	0.376
	T3, 4	40	19 (95%)	21 (87%)	
Nodal status	Negative	15	8 (40%)	7 (29%)	0.451
	Positive	29	12 (60%)	17 (71%)	
Stage	I-II	33	15 (75%)	18 (75%)	1.000
	III-IV	11	5 (25%)	6 (25%)	
Surgical procedure	PD	34	16 (80%)	18 (75%)	0.156
	DP	6	1 (5%)	5 (21%)	
	TP	4	3 (15%)	1 (4%)	
Operation time (min)	<480	14	6 (30%)	8 (33%)	0.813
	≥480	30	14 (70%)	16 (67%)	
Blood loss (ml)	<1000	19	7 (35%)	12 (50%)	0.316
	≥1000	25	13 (65%)	12 (50%)	
Vascular resection	(−)	39	16 (80%)	23 (96%)	0.093
	(+)	5	4 (20%)	1 (4%)	
CRP (mg/dl)	≤0.2	26	14 (70%)	12 (50%)	0.176
	>0.2	18	6 (30%)	12 (50%)	
CA19-9 (ng/ml)	≤37	19	6 (30%)	13 (54%)	0.104
	>37	25	14 (70%)	11 (46%)	
Postoperative CA19-9 (ng/ml)	≤37	32	16 (80%)	16 (67%)	0.319
	>37	12	4 (20%)	8 (33%)	
Carcinoembryonic antigen (ng/ml)	≤5.0	32	14 (80%)	18 (75%)	0.711
	>5.0	12	6 (20%)	6 (25%)	
Postoperative Carcinoembryonic antigen (ng/ml)	≤5.0	37	18 (90%)	19 (79%)	0.319
	>5.0	7	2 (10%)	5 (21%)	
Residual tumor	R0	29	14 (70%)	15 (62%)	0.600
	R1	15	6 (30%)	9 (38%)	

a. Fisher's exact probability test

cantly associated with hyperfibrinogenemia. Stage and C-reactive protein (CRP) levels were demonstrated to be significantly associated with hyperfibrinogenemia. In multivariate analysis, stage (P = 0.307) and CRP levels (P = 0.124) were not significantly associated with hyperfibrinogenemia (Table 2).

Correlation between plasma fibrinogen levels and patients' survival

In this study, the median survival time and cumulative 5-year overall survival rate for the entire cohort of 102 patients were 29.1 months and 32.9%, respectively. Kaplan-Meier analysis was performed for overall and disease-free survival (Fig. 1). While the median observation period in the normal fibrinogen group (<400 mg/dL) was 27 months, it was 21 months in the hyperfibrinogen group (≥400 mg/dL). In the normal fibrinogen group, the median survival time and cumulative 5-year overall survival rate were 34.5 months and 44.8%, respectively; however, in the hyperfibrinogen group, these values were 22.5 months and 31.2%, respectively, with a significant difference in the survival rate between the two groups (P = 0.047). In the normal fibrinogen group, the median survival time and cumulative 5-year overall survival rate were 18.5 months and 25.4%, respectively; however, in the hyperfibrinogen

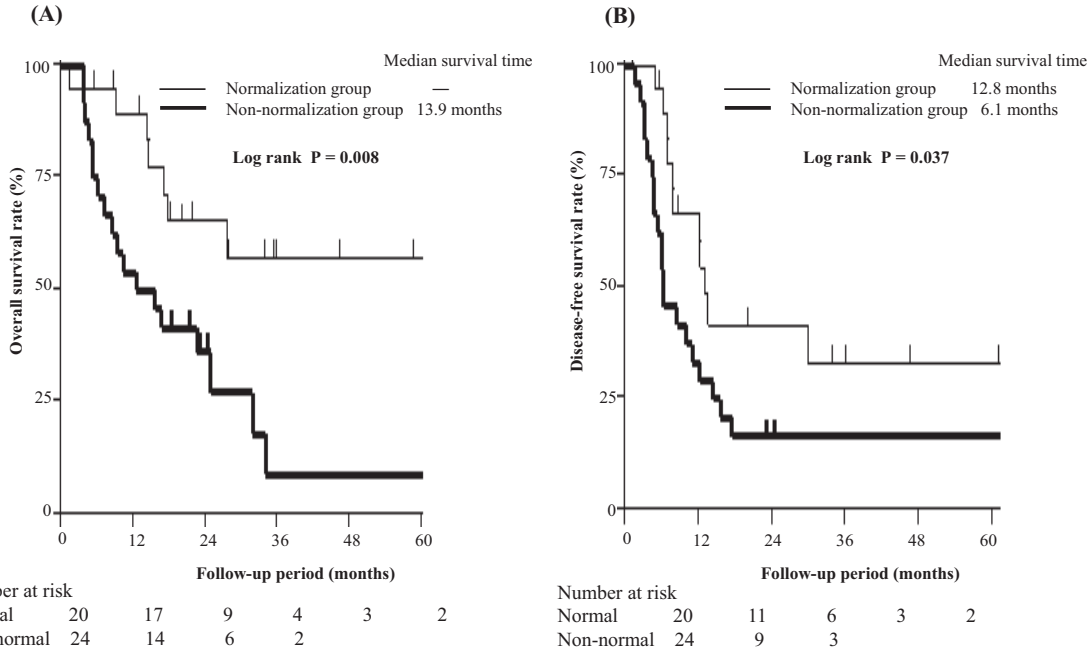

Fig. 2 (A) The overall ($P = 0.008$; log-rank test) and (B) disease-free survival of patients according to the status of postoperative fibrinogen levels (normalization and non-normalization groups; $P = 0.037$; log-rank test).

group, these values were 10.9 months and 22.4%, respectively, with a significant difference in the survival rate between the two groups ($P = 0.033$).

Univariate and multivariate analyses of risk factors for poor prognosis

In this study, univariate analysis identified the presence of preoperative CA19-9 value (>37 U/mL), fibrinogen level (≥400 mg/dL), CEA level (>5 ng/mL), and residual tumor R1 as significant predictors of a poor prognosis (Table 3). Multivariate analysis demonstrated that hyperfibrinogenemia (≥400 mg/dL; $P = 0.017$; hazard ratio [HR], 2.018; 95% confidence interval [CI]: 1.130-3.624) and serum CEA level (>5.0 ng/dL; $P = 0.022$; HR, 2.144; 95% CI: 1.118-3.995) were independent risk factors for patients' poor survival.

Comparison between the normalization and non-normalization groups in patients with preoperative hyperfibrinogenemia

Among patients with preoperative hyperfibrinogenemia, postoperative fibrinogen levels were significantly lower than preoperative fibrinogen levels (425.5 ± 123.5 U/mL vs. 488.6 ± 72.8 U/mL; $P = 0.005$; data not shown). Among the 44 patients with preoperative hyperfibrinogenemia, 20 (45%) were defined as the normalization group. A comparison between the normalization and non-normalization groups revealed no significant differences in clinicopathological factors, surgical procedures, perioperative surgical factors, and serum markers between the two groups (Table 4).

Comparison between the normalization and non-normalization group survival

The median follow-up in this study was 17 months (range: 1.5-112 months). The median survival time and cumulative 5-year overall survival rate for the entire cohort of 44 patients were 22.5 months and 31.2%, respectively. While the median observation period in the normalization group was 20 months, it was 17 months in the non-normalization group. The cumulative 5-year overall survival rate was 57.3% in the normalization group and 9.1% in the non-normalization group, with a significant difference in the survival rate between the two groups ($P = 0.008$; Fig. 2A). The median survival time and cumulative 5-year disease-free survival rate were 12.8 months and 33.3%, respectively, in the normalization group and 6.1 months and 16.6%, respectively, in the non-normalization group, with a significant difference in the survival rate between the two groups ($P = 0.037$; Fig. 2B).

Univariate and multivariate analysis of risk factors for survival in patients with preoperative hyperfibrinogenemia

Table 5 summarizes the prognostic factors in patients with preoperative hyperfibrinogenemia. Univariate analysis identified the presence of tumor size ≥40 mm, postop-

Table 5 Univariate and multivariate analysis of risk factors for survival in 44 patients with preoperative hyperfibrinogenemia

Variables		Number of patients (n = 44)	Univariate	Multivariate		
			P value [a]	H.R. [b]	95% CI [c]	P value [d]
Gender	Male	26	0.746			
	Female	18				
Age (year)	<65	15	0.588			
	≥65	29				
Tumor size (mm)	<40	36	0.002	1		0.025
	≥40	8		5.777	1.255-26.67	
Tumor depth	T1-2	4	0.508			
	T3-4	40				
Nodal status	Negative	15	0.620			
	Positive	29				
UICC stage	I-II	33	0.117			
	III-IV	11				
CRP (mg/dl)	≤0.2	26	0.072			
	>0.2	18				
Postoperative Fibrinogen level (mg/dl)	<400	20	0.008	1		0.001
	≥400	24		4.405	1.742-12.92	
WBC count (/μl)	<8500	39	0.715			
	≥8500	5				
Platelet count (/μl)	$<25.0\times10^4$	29	0.953			
	$\geq25.0\times10^4$	15				
CA19-9 (ng/ml)	≤37	19	0.416			
	>37	25				
Postoperative CA19-9 (ng/ml)	≤37	32	0.002	1		0.262
	>37	12		1.939	0.587-5.677	
Carcinoembryonic antigen (ng/ml)	≤5.0	32	0.056			
	>5.0	12				
Postoperative Carcinoembryonic antigen (ng/ml)	≤5.0	37	0.012	1		0.981
	>5.0	7		1.020	0.231-5.216	
Adjuvant chemotherapy	No	9	0.278			
	Yes	35				
Residual tumor	R0	29	0.008	1		0.008
	R1	15		3.139	1.351-7.339	

WBC, white blood cell; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19-9; CI, confidence interval
a. Log-rank test
b. Adjusted hazards ratio
c. Adjusted 95% confidence interval
d. Logistic regression analysis

erative CA19-9 value >37 U/mL, postoperative hyperfibrinogenemia ≥400 mg/dL, and residual tumor R1 as significant predictors of poor prognosis. In addition, the multivariate analysis performed using the Cox proportional hazard regression model identified the presence of postoperative fibrinogen level ≥400 mg/dL (P = 0.001; HR, 4.405; 95% CI: 1.742-12.92), tumor size ≥40 mm (P = 0.025; HR, 5.777; 95% CI: 1.255-26.67), and residual tumor R1 (P = 0.008; HR, 3.139; 95% CI: 1.351-7.339) as independent predictors of poor prognosis.

Table 6 presents initial recurrence sites and rate of recurrence within 1 year after surgery. A comparison of the normalization and non-normalization groups revealed no significant differences in initial recurrence sites, such as the liver, lymph nodes, lung, peritoneum, and local, between the two groups. However, the recurrence rate within 1 year after surgery was 25% in the normalization group and 59% in the non-normalization group, with a significant difference in the recurrence rate between the two groups (P = 0.024).

Table 6 Initial recurrence site and rate of recurrence within 1 year of surgery

Variables	Number of patients (n = 44)	Normalization group (n = 20)	Non-normalization group (n = 24)	P value [a]
Initial recurrence with multiple organs (n, %)	3 (7%)	2 (10%)	1 (4%)	0.444
Initial recurrence site				
Liver (n, %)	12 (27%)	4 (20%)	8 (33%)	0.318
Lymph nodes (n, %)	15 (34%)	6 (30%)	9 (38%)	0.600
Lung (n, %)	2 (5%)	1 (5%)	1 (4%)	0.895
Peritoneum (n, %)	3 (7%)	1 (5%)	2 (8%)	0.658
Local (n, %)	2 (5%)	1 (5%)	1 (4%)	0.895
Recurrence within 1 year (n, %)	19 (45%)	5 (25%)	14 (59%)	0.024

a. Fisher's exact probability test

Discussion

In our present study, preoperative hyperfibrinogenemia was reported in 43% of the PDAC patients. Plasma fibrinogen levels were significantly associated with CRP levels and the depth and nodal status of the tumor. In multivariate analysis, hyperfibrinogenemia was an independent risk factor to reduce patents' overall survival. Moreover, the postoperative non-normalization group revealed significantly poorer survival than that in the normalization group.

Regarding the malignant potential of hyperfibrinogenemia, Tsuru et al. have reported that Arg-Gly-Asp-containing peptides derived from the C-terminal portion of plasma fibrinogen enhance new blood vessel growth and increase vascular endothelial growth factor levels in patients with hepatocellular carcinoma.[24] Zhang et al. have reported that hyperfibrinogenemia might promote cell motility by inducing the epithelial-mesenchymal transition by the p-AKT-p-mTOR pathway.[25] Perhaps these fibrinogen functions might underlie its malignant potential observed in previous studies.[8, 15–18] Although these three studies established a correlation between hyperfibrinogenemia and advanced tumor stage, our multivariate analysis did not observe any significant association between hyperfibrinogenemia and tumor progression. Such discrepancy might be attributed to differences in the distribution of tumor stages. Although the present study focused on surgically resected cases, all previous studies have mainly focused on unresectable advanced PDAC and concluded that plasma fibrinogen level is correlated with tumor progression, metastases, and overall survival. Considering these findings, whether hyperfibrinogenemia is either the cause or outcome of tumor progression remains unknown, which might be the basis of distant metastasis. Of note, the independent prognostic impact of hyperfibrinogenemia was the key finding of this study.

Preoperative plasma fibrinogen levels might decrease to a normal range after complete tumor cell clearance. However, in some cases, plasma fibrinogen levels remain above the upper limit of the normal range. Because hyperfibrinogenemia was associated with the epithelial-mesenchymal transition of cancer cells to metastasized cancer cells, we hypothesized that postoperative hyperfibrinogenemia was related to residual cancer cells. As the postoperative plasma fibrinogen levels in this study did not decrease in patients with recurrence, persistent hyperfibrinogenemia indicates that microscopic residual cancer cells release thrombin, increasing plasma fibrinogen levels.[16] Importantly, the normalization group of patients with preoperative hyperfibrinogenemia was revealed to have good prognosis. Although Shimada et al. have reported that complications after radical surgery for gastrointestinal cancers were associated with patient prognosis; of note, postoperative complications were not associated with the changing pattern of plasma fibrinogen levels in this study.[26]

The limitation of this study was that we enrolled only patients who underwent radical surgery. Previous studies focusing mainly on unresectable PDAC have reported the association between tumor stage and plasma fibrinogen levels. However, we could not confirm such tendency in our study. Perhaps this discrepancy could reflect the differences in the proportion of resectable PDAC. The monitoring of fibrinogen levels can detect high-risk patients for recurrence even after radical surgery. Perhaps non-normalized plasma fibrinogen levels after surgical treat-

ment might predict tumor recurrence and poor prognosis. Based on the perioperative changing pattern of plasma fibrinogen levels, the appropriate identification of patients who need neoadjuvant chemotherapy to reduce recurrence might be possible. Moreover, the cut-off values were fixed following the manufacturer's instructions to avoid confusion due to the differences in the cut-off values before and after surgery.

In conclusion, we found that preoperative hyperfibrinogenemia was associated with inflammatory mediators and tumor progression on univariate analysis in resectable PDAC patients. We also found that preoperative hyperfibrinogenemia was associated with poor survival on multivariate analysis. Moreover, the non-normalization group among patients with preoperative hyperfibrinogenemia was revealed to be a high-risk group for poor prognosis. Hence, the perioperative monitoring of fibrinogen levels might be a potential tool to predict poor prognosis in PDAC patients.

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