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An elevated preoperative plasma fibrinogen level is associated with poor overall survival in Chinese gastric cancer patients

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ABSTRACT

Objective: To investigate the association between preoperative plasma fibrinogen level and overall survival (OS) in a cohort of Chinese gastric cancer patients who underwent gastrectomy.
Methods: A retrospective cohort study was conducted among 1090 gastric cancer patients treated between January 2003 and December 2011 who were eligible for inclusion criteria. Plasma fibrinogen level was routinely measured before surgeries. The optional cut-off value for fibrinogen level was estimated by receiver operating characteristic (ROC) curve analysis. OS was evaluated using Kaplan-Meier curve. Univariate and multivariate Cox regression models were performed to determine correlations between preoperative plasma fibrinogen level and OS.
Results: Enrolled subjects who returned for at least one follow-up visit had been followed for a median of 44.0 months (interquartile range, 62.0 months). An optimal cut-off value of 3.9 g/L was determined for preoperative plasma fibrinogen level. Lymph node dissection method, tumor location, invasion depth, lymph node metastasis, differentiation, distant metastasis, CA199 and plasma fibrinogen level remained statistically significant with OS in multivariate analysis. Plasma fibrinogen level was significantly associated with age, tumor size, lymph node dissection method, invasion depth, lymph node metastasis, TNM stage and CEA.
Conclusions: Elevated preoperative plasma fibrinogen was independently associated with poor prognosis and may serve as a clinically useful biomarker for risk assessment and treatment choice in Chinese gastric cancer patients.

1. Introduction

Gastric cancer is one of the leading causes of cancer death worldwide, with an estimated 951,600 new gastric cancer cases and 723,100 deaths occurring in 2012 [1]. China is the most affected country as nearly half of the global cases occurred in China [2]. Moreover, most of the Chinese patients are diagnosed in a locally advanced stage. Survival rates of gastric cancer patients are relatively low, with five-year survival rates of patients with localized disease (61%) decreasing to 25% among patients with regional lymph nodes metastasis, and to 4% following distant metastasis [3]. Early detection and subsequent proper treatment are crucial for enhancing the survival rates of gastric patients. Although the diagnosis of gastric cancer has been greatly improved over recent decades due to the availability of computed tomography and diagnostic laparoscopy, their diagnostic value was limited by cost, risk and inconvenience [4]. Therefore, development of noninvasive, sensitive and specific biomarkers that enable identifying people with high risk of gastric cancer would have potential clinical benefits.

There is rising evidence that supports the interactive relationship between activation of coagulation, fibrinolysis and tumor biology, such as tumor angiogenesis, invasion, progression and metastatic spread of malignant cells [5–7]. Accumulating data indicated that procoagulant factors were overexpressed in several tumors, and associated with tumor pathological stage, response to therapy and prognosis [8,9]. Approximately 50% of all cancer patients and over 90% of the patients with metastatic disease manifested with coagulation abnormalities [10,11]. Fibrinogen, a 340-kDa glycoprotein, that is synthesized by normal hepatocytes and converted to fibrin by activated thrombin, is one of the most important indicators of coagulation [12,13]. Fibrinogen plays a major role in the coagulation pathway, involving in platelet

Abbreviations: CEA, carcinoembryonic antigen; BMI, body mass index; IQR, inter-quartile range; ROC, receiver operating characteristic; OS, overall survival; HR, hazard ratios; CI, confidence intervals.

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aggregation, clot formation and contributing in the final step of coagulation cascade [14]. Recent studies have shown that elevated pre-treatment plasma fibrinogen level is associated with poor prognosis in various malignancies, such as lung cancer [15], breast cancer [16], prostate cancer [17], soft-tissue sarcoma [11], colorectal cancer [18], cervical cancer [19], renal cell carcinoma [20], B cell lymphoma [21], urothelial carcinoma [22], esophageal cancer [23,24], pancreatic cancer [25] and ovarian cancer [26].

Based on the results mentioned above, we hypothesized that plasma fibrinogen might be a good biomarker of clinical outcome among cancer patients. However, few studies with small sample size have assessed the prognostic significance of preoperative plasma fibrinogen level in gastric cancer patients as a predictor of survival after gastrectomy [27,28]. The aim of the present retrospective study was to investigate the association between preoperative plasma fibrinogen level and overall survival (OS) in a cohort of Chinese gastric cancer patients who underwent surgery.

2. Methods

2.1. Study design and participants

A retrospective cohort study was conducted among patients with gastric cancer who underwent gastrectomy between January 2003 and December 2011 at the department of General Surgery, Qingpu Branch of Zhongshan Hospital, Fudan University.

Eligibility for inclusion in the present study should meet the following inclusion criteria: 1) aged ≥18 years with histopathologically confirmed gastric cancer; 2) had gastrectomy plus lymphadenectomy (radical or non-radical); 3) no preoperative neoadjuvant therapies (including chemotherapy and radiotherapy); and 4) with available preoperative testing results for plasma fibrinogen level. Those participants who were pregnant or taking breastfeeding, had previous or other synchronous malignancies, died in the perioperative period, had a history of familial coagulopathy, active disseminated intravascular coagulation, or thromboembolism, were diagnosed with acute inflammatory disease, liver cirrhosis or chronic rental failure, or who had received either anticoagulant or anti-aggregate therapies, were excluded from this study.

The present study was performed in accordance with the Declaration of Helsinki and the study protocol was reviewed and approved by institutional review board of Zhongshan Hospital, Fudan University.

Table 1
Correlation between plasma fibrinogen level and clinicopathological characteristics among gastric cancer patients.

Variables		Participants (N = 1090)			Plasma fibrinogen level	
		Low-fibrinogen (≤3.9 g/L) (N = 840)	High-fibrinogen (>3.9 g/L) (N = 250)	*P* value[a]	median ± IQR	*P* value[b]
Gender	Male	615 (76.9)	185 (23.1)	0.81	3.12 ± 1.37	0.73
	Female	225 (77.6)	65 (22.4)		3.10 ± 1.30	
Age (Years)	<60	498 (79.7)	127 (20.3)	0.02	3.07 ± 1.35	<0.01
	≥60	342 (73.5)	123 (26.5)		3.27 ± 1.27	
BMI (Kg/m^2)	<18.5	111 (70.7)	46 (29.3)	0.06	3.17 ± 1.54	0.07
	[18.5, 20)	121 (72.9)	45 (27.1)		3.25 ± 1.27	
	[20,24)	360 (79.3)	94 (20.7)		3.07 ± 1.30	
	≥24	248 (79.2)	65 (20.8)		3.07 ± 1.34	
Family history	No	665 (75.9)	211 (24.1)	0.07	3.12 ± 1.35	0.23
	Yes	175 (81.8)	39 (18.2)		3.05 ± 1.42	
Tumor location	Upper	123 (73.7)	44 (26.3)	0.09	3.22 ± 1.38	0.04
	Middle	156 (72.9)	58 (27.1)		3.22 ± 1.42	
	Lower	561 (79.1)	148 (20.9)		3.07 ± 1.34	
Tumor size (cm)	<5.0	395 (88.4)	52 (11.6)	<0.01	2.85 ± 1.13	<0.01
	≥5.0	445 (69.2)	198 (30.8)		3.38 ± 1.39	
Lymph node dissection	Radical	678 (79.9)	171 (20.1)	<0.01	3.07 ± 1.27	<0.01
	Non-radical	162 (67.2)	79 (32.8)		3.50 ± 1.51	
Invasion depth	T1	103 (90.4)	11 (9.6)	<0.01	2.73 ± 0.97	<0.01
	T2	159 (88.3)	21 (11.7)		2.89 ± 1.20	
	T3	292 (74.5)	100 (25.5)		3.22 ± 1.38	
	T4	286 (70.8)	118 (29.2)		3.32 ± 1.39	
Lymph node metastasis	N0	305 (83.3)	61 (16.7)	<0.01	2.90 ± 1.23	<0.01
	N1	154 (76.6)	47 (23.4)		3.12 ± 1.41	
	N2	171 (74.0)	60 (26.0)		3.22 ± 1.31	
	N3	210 (71.9)	82 (28.1)		3.27 ± 1.35	
Distant metastasis	M0	812 (77.3)	238 (22.7)	0.28	3.12 ± 1.37	0.34
	M1	28 (70.0)	12 (30.0)		3.41 ± 1.38	
TNM stage	I	172 (89.6)	20 (10.4)	<0.01	2.73 ± 1.03	<0.01
	II	270 (80.1)	67 (19.9)		3.07 ± 1.43	
	III	371 (71.1)	151 (28.9)		3.30 ± 1.35	
	IV	27 (69.2)	12 (30.8)		3.49 ± 1.47	
Differentiation	Differentiated	185 (75.8)	59 (24.2)	0.60	3.21 ± 1.28	0.50
	Undifferentiated	655 (77.4)	191 (22.6)		3.11 ± 1.39	
CEA (ng/ml)	≤5	703 (79.0)	187 (21.0)	<0.01	3.12 ± 1.32	0.02
	>5	137 (68.5)	63 (31.5)		3.27 ± 1.74	
CA199 (U/ml)	≤37	687 (78.0)	194 (22.0)	0.14	3.10 ± 1.41	0.08
	>37	153 (73.2)	56 (26.8)		3.20 ± 1.34	

BMI: body mass index.
CEA: Carcinoembryonic antigen.
IQR: interquartile range.
[a] Using chi-squared test, $P < 0.05$ was considered statistically significant.
[b] Using Kruskal-Wallis test, $P < 0.05$ was considered statistically significant.