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ORIGINAL ARTICLE

High level of preoperative serum fibrinogen is a predictor of poor prognosis in patients with esophageal squamous cell carcinoma

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Abstract

Objective This study aimed to elucidate the association between the level of preoperative serum fibrinogen (PSF) and the prognosis of patients with esophageal squamous cell carcinoma (ESCC).

Methods From January 2010 to December 2016, all patients diagnosed with ESCC who underwent surgery in Qingdao Municipal Hospital were analyzed retrospectively. Moreover, the fibrinogen levels of all patients were assessed before surgery, and hyperfibrinogenemia was diagnosed when the fibrinogen level was ≥4.0 g/L. The impact of PSF on disease-free survival (DFS) and overall survival (OS) was analyzed using the log-rank method and Cox proportional hazards regression model. *P* value less than 0.05 was considered statistically significant.

Results A total of 336 patients were finally analyzed, and approximately 102 patients (30.36%) were diagnosed with hyperfibrinogenemia before surgery. Hyperfibrinogenemia was associated with older age (≥ 70 years) (*P* = 0.012), advanced pathological T stage (*P* = 0.003), and lymph node involvement (*P* = 0.024). Univariate analysis showed that patients with hyperfibrinogenemia had shorter DFS (1.96 years *vs.* 3.64 years, *P* = 0.001) and OS (2.27 years *vs.* 4.15 years, *P* < 0.001) than patients without hyperfibrinogenemia. Multivariate analysis confirmed that PSF was an independent factor affecting DFS (risk ratio [RR]: 1.35, 95% confidence interval [CI]: 1.02–1.79, *P* = 0.038) and OS (RR: 1.37, 95% CI: 1.03–1.83, *P* = 0.034) in patients with ESCC.

Conclusion For patients with operable ESCC, hyperfibrinogenemia had poor prognosis. Moreover, PSF is an independent prognostic factor for operable ESCC.

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Key words: esophageal squamous cell carcinoma; biomarker; prognosis; serum fibrinogen

Esophageal squamous cell carcinoma (ESCC), with high morbidity and mortality, is prevalent in East Asia [1–2]. Although patients diagnosed with early-stage ESCC underwent radical resection, their 5-year survival rate was still poor [3]. Postoperative recurrence and metastasis were the main factors affecting the survival of ESCC [3]. At present, a significant prognostic biomarker for ESCC is not yet available in clinical practice; thus, it was dispensable to determine the potential prognostic biomarkers for patients with ESCC.

Fibrinogen, which is a coagulation factor, is mainly synthesized by hepatocytes. A previous study had reported that tumor escape involving fibrinogen was an important pathway for tumor recurrence and metastasis [5]. Some studies demonstrated that preoperative serum fibrinogen (PSF) can be used as a prognostic factor in common malignant tumors, such as in gastric cancer [6], lung cancer [7], and colorectal cancer [8]. However, the significance of PSF in predicting the prognosis of ESCC remains unclear. Some studies indicated that PFS was an independent prognostic predictor of esophageal cancer; however [9], some studies had contradicting results [10]. Therefore, this study was designed to analyze the association between the PSF and the pathological characteristics of ESCC and elucidate the association between the PFS and prognosis of ESCC.

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Materials and methods

Study design

From January 2010 to December 2016, all patients with esophageal cancer who underwent surgery in Qingdao Municipal Hospital were included in this study. Pathological stage was determined according to the 8th edition American Joint Committee on Cancer (AJCC) staging system[10]. The inclusion criteria were as follows: (1) patients with pathologically diagnosed ESCC, (2) patients with serum fibrinogen level assessed before surgery, (3) patients undergoing radical resection, and (4) patients with complete follow-up data after surgery. On the contrary, the exclusion criteria were as follows: patients who died during the perioperative period and patients diagnosed with concomitant disease influencing serum fibrinogen levels. Patients were followed up until December 2019.

A 5 mL fasting venous blood collected before surgery was provided for testing, and fibrinogen level test was performed within 30 min after blood collection using the Clause method. According to the test, hyperfibrinogenemia was diagnosed if the fibrinogen level was ≥4.0 g/L, and patients with fibrinogen level < 4.0 g/L were considered to have normal fibrinogen level.

Statistical analyses

The association between the level of PSF and clinicopathological characteristics was compared using the chi-squared test and Mann-Whitney *U* test. Moreover, univariate survival analysis was performed using log-rank test, and the Kaplan-Meier curve was used to draw the survival curve. Multivariate analysis was performed using Cox proportional hazards regression model. *P* value less than 0.05 was considered statistically significant. All statistical analysis was performed using the Statistical Package for the Social Sciences software version 22.0.

Results

Patients' characteristics

Finally, a total of 336 patients diagnosed with ESCC were included in this study. The oldest and youngest patients were aged 82 and 39 years, respectively, and the median age was 63 years. Among these patients, 249 were male and 87 were female. According to the 8th edition of the AJCC staging system, 56, 136, and 144 patients were categorized as stage I, stage II, and stage III, respectively.

The fibrinogen levels of all patients were assessed before operation, and the median preoperative fibrinogen level of all patients was 3.4 g/L (range, 1.1–9.6 g/L). Moreover, 102 patients (30.36%) were diagnosed with hyperfibrinogenemia (≥4.0 g/L), and 234 patients (69.64%) were diagnosed as normal according to the diagnostic criteria.

Preoperative serum fibrinogen level and clinical characteristics

In this study, we found that older patients (≥ 70 years) had higher PSF than younger patients (43.48% *vs.* 26.97%, $P = 0.012$), as shown in Table 1. Further analysis confirmed that pathological T stage ($P = 0.003$) and N stage ($P = 0.024$) as prognostic factors were significantly associated with PSF. Fig. 1 also shows that patients with hyperfibrinogenemia were more likely to be diagnosed with advanced pathological T stage and to had more metastatic lymph nodes compared to patients without hyperfibrinogenemia.

Survival analysis

The median time for disease-free survival (DFS) was 2.81 years, and univariate analysis indicated that patients with hyperfibrinogenemia had poorer DFS than patients without hyperfibrinogenemia (1.96 years *vs.* 3.64 years, $P = 0.001$), as shown in Table 2 and Fig. 2. Multivariate analysis confirmed that patients with hyperfibrinogenemia had 35.0% higher risk of disease progression than patients without hyperfibrinogenemia (risk ratio [RR]: 1.35, 95% confidence interval [CI]: 1.02–1.79, $P = 0.038$), as shown in Table 3.

Table 1 Clinical characteristics and level of PSF in 336 patients with ESCC

Variables	*n*	Preoperative serum fibrinogen level		*P*
		≥ 4.0 g/L (*n*,%)	< 4.0 g/L (*n*,%)	
Gender				0.104
Male	249	82 (32.93)	167 (67.07)	
Female	87	20 (23.50)	67 (76.50)	
Age (years)				0.012
< 70	267	72 (26.97)	195 (73.03)	
≥ 70	69	30 (43.48)	39 (56.52)	
Tumor location				0.300
Upper	27	9 (33.33)	18 (66.67)	
Middle	221	61 (27.60)	160 (72.40)	
Lower	88	32 (36.36)	56 (63.64)	
Differentiation				0.421
G1	97	30 (30.93)	67 (69.07)	
G2	158	52 (32.91)	106 (67.09)	
G3	81	20 (24.69)	61 (75.31)	
Pathological T stage				0.003
T1 + T2	115	23 (20.00)	92 (80.00)	
T3 + T4	221	79 (35.75)	142 (64.25)	
Pathological N stage				0.024
N0	171	42 (24.56)	129 (75.44)	
N1 + N2 + N3	165	60 (36.36)	105 (63.64)	
Pathological TNM stage				0.003
Stage I	56	12 (21.43)	44 (78.57)	
Stage II	136	32 (23.53)	104 (76.47)	
Stage III	144	58 (40.28)	86 (59.72)	

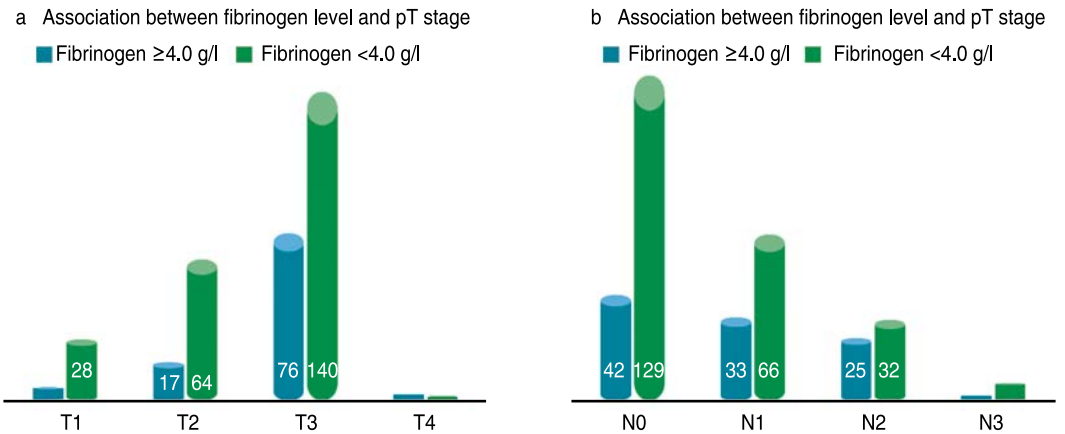

Fig. 1 Association between PSF and pathological T/N stage. (a) Association between PSF and pathological T stage; (b) Association between PSF and pathological N stage

Table 2 Univariate analysis of prognosis in patients with ESCC

Variables	DFS			OS		
	Median	95% CI	*P*	Median	95% CI	*P*
Gender			0.086			0.104
Male	2.71	2.10–3.31		3.33	2.68–3.98	
Female	3.45	1.30–5.60		3.64	0.88–6.40	
Age (years)			0.514			0.412
< 70	3.00	2.26–3.75		3.64	2.72–4.56	
≥ 70	2.39	1.52–3.25		2.88	2.18–3.58	
Tumor location			0.968			0.967
Upper	2.26	2.04–2.49		3.40	0.79–6.02	
Middle	2.96	2.30–3.61		3.49	2.99–3.99	
Lower	2.31	0.77–3.86		3.23	1.15–5.32	
Differentiation			0.317			0.399
G1	3.04	1.56–4.51		3.58	1.64–5.52	
G2	2.29	1.66–2.93		3.06	2.24–3.88	
G3	3.64	2.14–3.48		4.13	3.05–5.20	
Pathological T stage			< 0.001			0.001
T1	7.16	1.92–12.40		7.47	3.15–12.17	
T2	5.39	2.07–8.72		4.22	2.71–9.18	
T3	2.10	1.62–2.58		2.56	1.85–3.28	
T4	1.19	0.58–1.81		1.66	1.22–2.11	
Pathological N stage			< 0.001			< 0.001
N0	4.64	2.65–6.63		5.10	4.67–5.53	
N1	2.96	2.02–3.89		3.33	2.77–3.89	
N2	1.11	0.94–1.29		1.49	1.32–1.67	
N3	0.98	0.25–1.71		1.04	0.86–1.22	
Pathological TNM stage			< 0.001			< 0.001
Stage I	5.39	2.24–8.55		5.84	4.41–9.18	
Stage II	3.80	2.16–5.43		5.56	3.90–7.23	
Stage III	1.53	0.97–2.09		1.80	1.34–2.26	
Preoperative serum fibrinogen level			0.001			<0.001
≥ 4.0 g/L	1.96	1.29–2.62		2.27	1.44–3.09	
< 4.0 g/L	3.64	2.82–4.46		4.15	3.03–5.28	

For patients with ESCC, the median time for overall survival (OS) was 3.40 years. Survival analysis revealed that the median OS for patients with hyperfibrinogenemia was 2.27 years, which was significantly shorter than

that of patients with normal PSF (4.15 years) (Fig. 3). Multivariate analysis confirmed that PSF was an independent factor affecting OS (RR: 1.37, 95% CI: 1.03–1.83, $P = 0.034$) in patients with ESCC.

Discussion

Hyperfibrinogenemia was observed in esophageal cancer, and whether PSF can be an independent prognostic predictor for esophageal cancer remains controversial [6, 9]. In this study, approximately 30.4% of patients with ESCC were diagnosed with hyperfibrinogenemia before surgery, indicating that PSF might be a potential biomarker for operable ESCC.

The molecular mechanism of fibrinogen in tumorigenesis is still unclear. Fibrinogen is normally secreted by liver cells and is also recognized as a coagulant and inflammatory factor [12]. The recent study demonstrated that cancer cell can also synthesize fibrinogen, and fibrinogen has been shown to participate in the process of tumorigenesis, development, metastasis, and implantation [13–14].

The serum tumor biomarkers were widely used to predict the survival of patients with ESCC and to assess the therapeutic effects of certain treatments. It has been reported that cytokeratin 19 fragment (CYFRA 21-1) level was significantly associated with T stage ($P = 0.019$) and N stage ($P = 0.019$). Some studies also confirmed that CYFRA 21-1 can be used to assess the effect of radiotherapy [15]. Our study indicated that PSF would be useful for predicting the survival of patients with ESCC, and the level of PSF was significantly associated with pathological T stage, pathological N stage, and pathological TNM stage.

Moreover, whether PSF can be used to predict the prognosis of esophageal cancer remains controversial. This study was designed to investigate the prognostic value of coagulation in patients with ESCC. Based on the result of the recent study, the level of PSF was significantly higher in patients with ESCC than that in normal individuals, but it was not a prognostic indicator for ESCC (hazard ratio [HR]: 1.165, 95% CI: 0.790–1.717, $P = 0.441$) [5]. Another study, which comprised 1305 patients with ESCC, regarding this issue yielded a positive result. According to the study's survival analysis, patients with hyperfibrinogenemia had poor DFS ($P \leq 0.001$) and OS ($P \leq 0.001$), and the study's multivariate analysis revealed that PSF was an independent prognostic factor for patients with ESCC [9]. A meta-analysis comprising 2865 patients with esophageal cancer from 11 studies was designed to analyze the prognostic role of PSF in esophageal cancer. This meta-analysis demonstrated that high PSF was significantly associated with poor DFS (HR: 1.51, 95% CI: 1.16–1.97, $P < 0.001$) and OS (HR: 1.76, 95% CI: 1.28–2.42, $P < 0.001$) based on multivariate

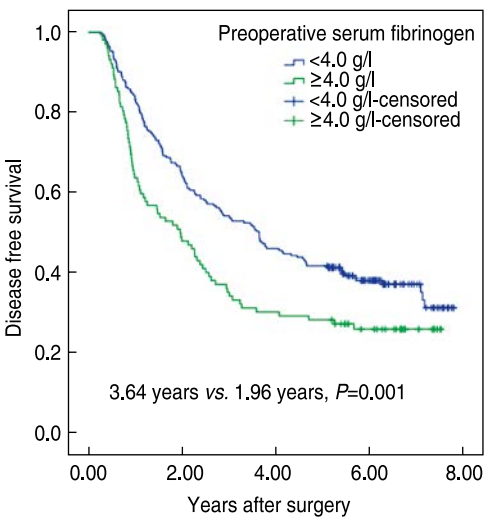

Fig. 2 Survival curve of DFS in patients with ESCC based on PSF

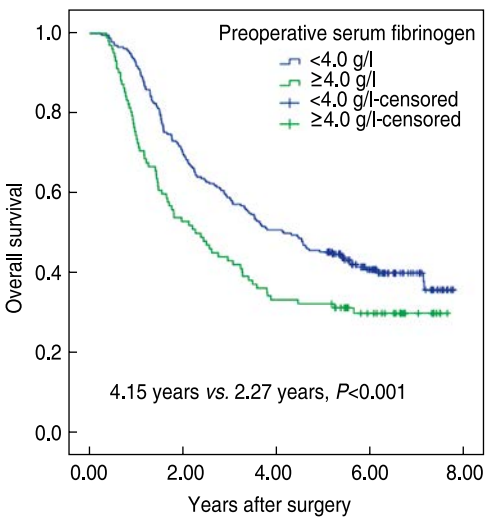

Fig. 3 Survival curve of OS in patients with ESCC based on PSF

Table 3 Multivariate analysis of prognosis in patients with ESCC

Variables	DFS			OS		
	RR	95% CI	*P*	RR	95% CI	*P*
Pathological T stage	1.31	1.05–1.64	0.017	1.35	1.07–1.71	0.011
Pathological N stage	1.54	1.32–1.80	< 0.001	1.57	1.35–1.84	< 0.001
Preoperative serum fibrinogen level	1.35	1.02–1.79	0.038	1.37	1.03–1.83	0.034

analysis [16]. Our study confirmed once again that PSF was a prognostic factor for patients with ESCC.

In conclusion, these results suggested that hyperfibrinogenemia was significantly associated with pathological T stage and N stage in patients with ESCC. PSF may be a serum prognostic biomarker for patients with ESCC.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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