

Original Article



High Preoperative Fibrinogen and Systemic Inflammation Response Index (F-SIRI) Predict Unfavorable Survival of Resectable Gastric Cancer Patients

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ABSTRACT

Purpose: This study was to investigate the prognostic significance of the preoperative fibrinogen and systemic inflammation response index (F-SIRI) in a Chinese cohort of resectable gastric cancer.

Materials and Methods: Baseline characteristics, preoperative fibrinogen levels and peripheral neutrophil, monocyte, and lymphocyte counts were retrospectively reviewed in 240 patients who underwent radical gastrectomy. The optimal cut-off values for fibrinogen and SIRI were defined as 4.0 g/L and 1.2. Then patients with hyperfibrinogenemia (≥ 4.0 g/L) and high SIRI (≥ 1.2) were assigned with an F-SIRI of 2 (both of these hematological abnormalities), 1 (one of these abnormalities), and 0 (neither abnormality), respectively. The prognostic value was examined by univariate and multivariate survival analysis.

Results: Preoperative F-SIRI was significantly correlated with tumor size, fibrinogen level, and adjuvant chemotherapy. Whereas there was no significant difference in age, gender, tumor location or other characteristics between groups. In addition, high preoperative F-SIRI was significantly associated with worse disease-free survival (DFS) (hazard ratio [HR], 2.299; 95% confidence interval [CI], 1.482–3.566; $P < 0.001$) and overall survival (OS) (HR, 2.461; 95% CI, 1.584–3.824; $P < 0.001$) by univariate survival analysis. Moreover, it remained an independent predictor for impaired DFS (HR, 2.023; 95% CI, 1.273–3.215; $P = 0.003$) and OS (HR, 2.341; 95% CI, 1.480–3.705; $P < 0.001$) in multivariate Cox regression analysis.

Conclusions: Preoperative F-SIRI could serve as a significantly prognostic marker for long-term survival in Chinese patients who underwent radical gastrectomy.

Keywords: Gastric cancer; Fibrinogen; Inflammation; Prognosis

INTRODUCTION

Gastric cancer is the fourth most common malignant disease and the second leading cause of cancer-related death worldwide [1]. Surgery is the only opportunity to cure, unfortunately, the rate of recurrence or distant metastasis in patients receiving radical gastrectomy remains high [2]. Although multimodal strategies are used to further improve the outcome, the 5-year survival rate is still less than 30%. Therefore, it is currently actively searching for more

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

effective therapeutics. However, there still lack reliable prognostic markers to guide clinical treatment decisions for individual patient.

Cancer-associated inflammation is a clear hallmark of malignancies that greatly contributes to the development and progression of cancer [3]. Fibrinogen, a glycoprotein produced by hepatocytes and a key regulator of the hemostatic system, plays an important role in coagulation, cell adhesion and systemic inflammatory responses [4]. In addition, elevated levels of fibrinogen have been observed in various malignancies including gastric cancer and significantly associated with tumor progression, invasion, distant metastasis, as well as poor survival [5-10].

Peripheral blood leukocytes are one of the indicators of inflammation response, including neutrophils, lymphocytes, and monocytes. Besides, several new inflammation-based indexes have been established to predict the prognosis of patients with malignancies, such as platelet-lymphocyte ratio, neutrophil-lymphocyte ratio (NLR) and lymphocyte-monocyte ratio (LMR) [11-13]. Fibrinogen and NLR (F-NLR) have been used to predict the prognosis of esophageal squamous cell carcinoma patients after esophagectomy, and have shown a good predictive effect [14]. Recently, the systemic inflammation response index (SIRI), which is calculated primarily based on peripheral neutrophil, lymphocyte and monocyte counts, has been identified as a reliable prognostic factor for gastric adenocarcinoma [15].

Therefore, we proposed a prognostic index based on preoperative fibrinogen and SIRI (F-SIRI) and to examine whether it could more accurately predict the long-term survival for resectable gastric cancer cases. The purpose of this study was to investigate the correlation of the preoperative F-SIRI with clinicopathological variables and its prognostic significance in patients with resectable gastric cancer.

MATERIALS AND METHODS

Patients

Between January 2007 and December 2016, a consecutive cohort of 300 patients with gastric cancer who underwent radical gastrectomy at the First Affiliated Hospital of Anhui Medical University in Hefei (Anhui, People's Republic of China) were retrospectively reviewed. Patients were excluded if they had a history of neoadjuvant chemotherapy and/or radiotherapy, and had diseases or received anticoagulants that would affect the hemostatic system. In addition, we also excluded subjects without preoperative information of hemostasis and patients died of causes other than gastric cancer. Furthermore, cases with malignancies other than gastric cancer, acute or chronic concurrent non-cancerous diseases, concurrent distant metastasis, or those who were lost during follow-up period were also excluded. Finally, a total of 240 eligible patients were enrolled in the present study.

This study was approved by the independent Ethics Committee at The First Affiliated Hospital of Anhui Medical University (Quick-PJ 2020-07-16) and was performed in accordance with the ethical standards of the World Medical Association Declaration of Helsinki. And written consent was obtained from all included patients.

Treatment and follow-up

All included patients underwent radical gastrectomy with lymphadenectomy. Adjuvant chemotherapy was delivered to those with high risk of local recurrence or distant metastasis.

Routine blood and biochemical tests, tumor markers, ultrasound/computed tomography and upper gastrointestinal endoscopy were regularly evaluated after surgery. Disease-free survival (DFS) was defined as the time interval from the date of diagnosis to local recurrence/distant metastasis or to the last follow-up, overall survival (OS) was calculated from the date of diagnosis to death from cancer or to the most recent follow-up.

Clinical and laboratory variables

Patient's baseline characteristics, preoperative fibrinogen levels, neutrophils, lymphocytes and monocytes, as well as other parameters were retrospectively reviewed and collected from the electronic medical records. Stages were classified according to the American Joint Committee on Cancer (AJCC)/International Union Against Cancer tumor-node-metastasis (TNM) staging system (the 8th edition). The long diameter measured with the general post-operative pathological specimen was determined as the tumor size. The locations of primary tumor were divided into upper, middle, lower and diffuse stomach, respectively. The degree of differentiation was categorized into poorly/not differentiated and moderately/well differentiated.

Blood specimens were obtained within one week before surgery. Plasma fibrinogen levels were tested by an automatic coagulation analyzer (Sysmex CS-5100; Sysmex Corporation, Kobe, Japan). The counts of neutrophil, lymphocyte and monocyte were examined using an automated hematology analyzer (Sysmex XN-9000, Sysmex Corporation).

Definition of Fibrinogen and SIRI Index (F-SIRI)

SIRI was calculated as follows: $SIRI = \text{neutrophil count} \times \text{monocyte count} / \text{lymphocyte count}$. According to the manufacturer's instructions, the normal range of plasma fibrinogen concentration was 2.0–4.0 g/L, and plasma concentrations above 4.0 g/L were defined as hyperfibrinogenemia [16]. Therefore, the optimal cut-off value for preoperative fibrinogen was defined as 4.0 g/L. Meanwhile, the optimal cut-off value for SIRI was determined as 1.2 by X-tile 3.6.1 software (Yale University, New Haven, CT, USA). Patients with elevated fibrinogen (≥ 4.0 g/L) and SIRI (≥ 1.2) were allocated an F-SIRI of 2, those with only one of these 2 abnormalities were assigned an F-SIRI of 1, and those with neither of the 2 abnormalities were allocated an F-SIRI of 0.

Statistical analysis

All statistical analyses were carried out using SPSS 22.0 (SPSS IBM, Chicago, IL, USA). The correlation between variables was determined by Pearson's χ^2 test. Survival curves were calculated by the Kaplan-Meier method, and differences were compared with log-rank test. Cox proportional hazards regression models were utilized to perform univariate and multivariate analysis and hazard ratios (HRs) for parameters respecting to DFS and OS were calculated. HRs with 95% confidence intervals (CIs) and 2-sided P-value were reported. A 2-sided $P < 0.05$ was considered to be with statistical significance.

RESULTS

Patient characteristics

Two hundred and forty patients were enrolled in the present study. The baseline characteristics were shown in **Table 1**. The median age at diagnosis was 60.5 years (ranged, 22.0–86.0 years). The cohort consisted of 163 males (67.9%) and 77 females (32.1%).

Table 1. Patient baseline characteristics and their correlations with preoperative F-SIRI (n=240)

Clinicopathologic characteristics	Patients	F-SIRI score			P-value
		0	1	2	
Age (yr)					0.172
<60	115 (47.9)	74 (52.9)	29 (32.2)	12 (21.1)	
≥60	125 (52.1)	66 (47.1)	61 (67.8)	45 (78.9)	
Gender					0.936
Man	163 (67.9)	96 (68.6)	45 (66.2)	22 (68.7)	
Woman	77 (32.1)	44 (31.4)	23 (33.8)	10 (31.3)	
Tumor location					0.568
Upper	102 (42.5)	55 (39.3)	33 (48.5)	14 (43.8)	
Middle	43 (17.9)	28 (20.0)	9 (13.3)	6 (18.7)	
Lower	52 (21.7)	35 (25.0)	12 (17.6)	5 (15.6)	
Diffuse	43 (17.9)	22 (15.7)	14 (20.6)	7 (21.9)	
Tumor size (cm)					0.001
<5	102 (42.5)	74 (52.9)	18 (26.5)	10 (31.3)	
≥5	138 (57.5)	66 (47.1)	50 (73.5)	22 (68.7)	
Degree of differentiation					0.968
Well/moderate	58 (24.2)	33 (23.6)	17 (25.0)	8 (25.0)	
Poor/undifferentiated	282 (75.8)	107 (76.4)	51 (75.0)	24 (75.0)	
T stage					0.689
T1/T2	43 (17.9)	26 (18.6)	13 (19.1)	4 (12.5)	
T3/T4	197 (82.1)	114 (81.4)	55 (80.9)	28 (87.5)	
N stage					0.109
N0	42 (17.5)	26 (18.6)	10 (14.7)	6 (18.8)	
N1	66 (27.5)	43 (30.7)	17 (25.0)	6 (18.8)	
N2	74 (30.8)	43 (30.7)	25 (36.8)	6 (18.8)	
N3	58 (24.2)	28 (20.0)	16 (23.5)	14 (43.6)	
TNM stage					0.129
I	26 (10.8)	18 (12.9)	7 (10.3)	1 (3.1)	
II	40 (16.7)	22 (15.7)	11 (16.2)	7 (21.9)	
III	174 (72.5)	100 (71.4)	50 (73.5)	24 (75.0)	
Lymph node status					0.773
Negative	42 (17.5)	26 (18.6)	10 (14.7)	6 (18.8)	
Positive	198 (82.5)	114 (81.4)	58 (85.3)	26 (81.2)	
Adjuvant chemotherapy					0.039
No	50 (20.8)	22 (15.7)	17 (25.0)	11 (34.4)	
Yes	190 (79.2)	118 (84.3)	51 (75.0)	21 (65.6)	
SIRI					>0.050
<1.20	210 (87.5)	140 (100)	38 (55.9)	0 (0)	
≥1.20	30 (12.5)	0 (0)	30 (44.1)	32 (100)	
Preoperative fibrinogen level (g/L)	3.360 (1.19–7.15)	2.955 (1.19–3.99)	4.060 (1.84–5.83)	4.635 (4.03–7.15)	<0.001

Values are presented as number (%) or median (range). The bold numbers in the tables are P-values with statistical significance (<0.05).

F-SIRI = fibrinogen and systemic inflammation response index; TNM = tumor-node-metastasis; SIRI = systemic inflammation response index.

According to the 8th edition AJCC staging criteria, 26 (10.8%) patients were classified with stage I, 40 (16.7%) patients were stage II, and 174 (72.5%) patients were stage III diseases. Lymph node metastasis was positive in 198 (82.5%) of the patients. Four fifths (190, 79.2%) of the cases received adjuvant chemotherapy (**Table 1**).

Correlation between preoperative F-SIRI and clinicopathologic variables

Of the enrolled 240 patients, 140 (58.3%) were assigned an F-SIRI of 0, 68 (28.3%) had an F-SIRI of 1 and 32 (13.3%) had an F-SIRI of 2 (**Table 1**). The analysis demonstrated that preoperative F-SIRI was significantly correlated with tumor size, adjuvant chemotherapy and fibrinogen levels (P=0.001, P=0.039 and P<0.001, respectively). However, there was no significant difference in age, gender, tumor location, degree of differentiation, depth of invasion, lymph node status or TNM stage between groups (**Table 1**).

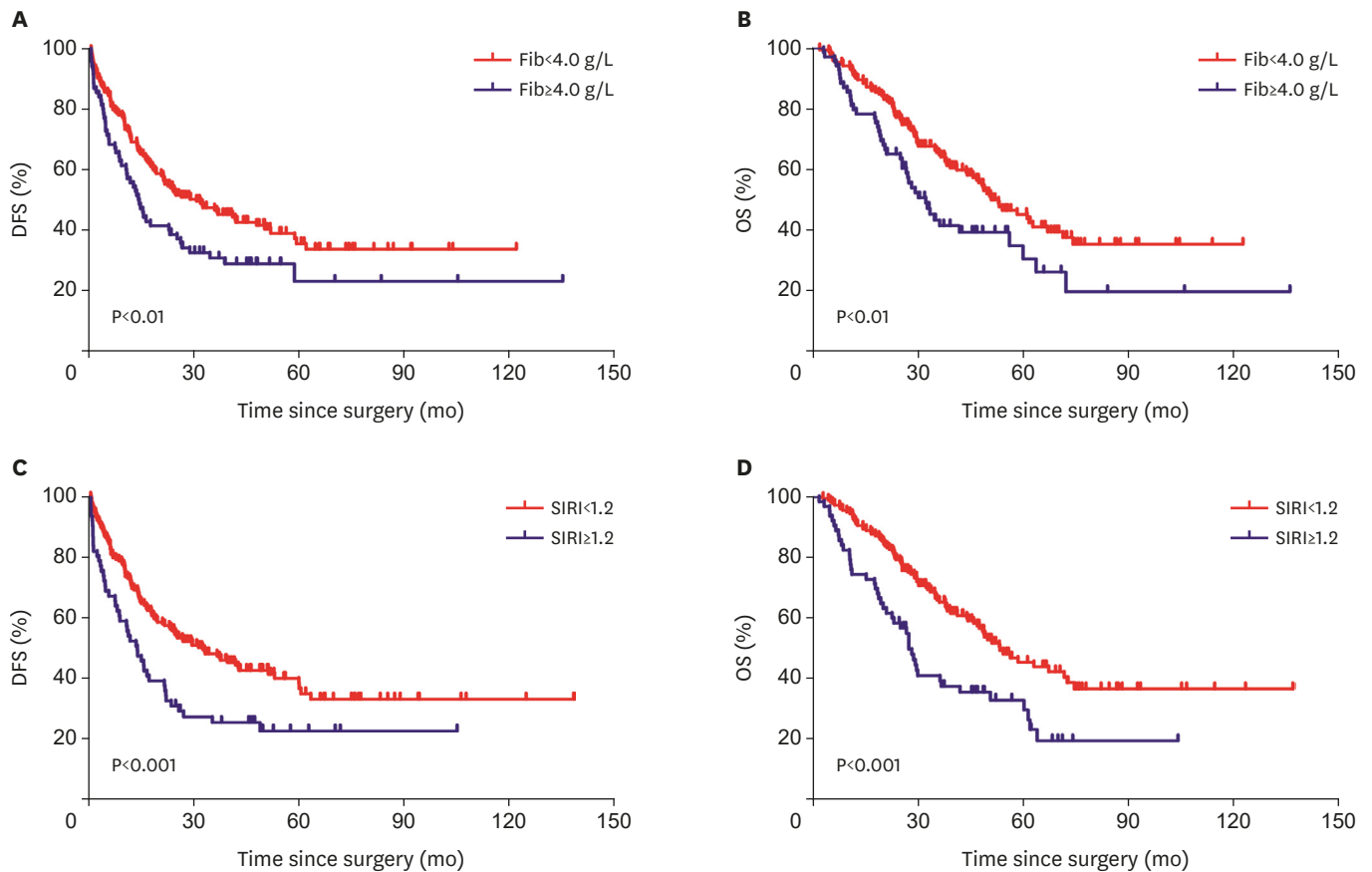


Fig. 1. Kaplan-Meier survival curves of (A), DFS and (B), OS stratified by preoperative fibrinogen levels; (C), DFS and (D), OS stratified by SIRI in 240 resectable gastric cancer patients (with log-rank test).

DFS = disease-free survival; OS = overall survival; SIRI = systemic inflammation response index.

Prognostic Impact of preoperative fibrinogen or SIRI

The patients with low fibrinogen values ($<4.0\text{g/L}$) had a better DFS and OS than those with high fibrinogen values ($P < 0.01$; **Fig. 1A and B**). Similarly, low SIRI (<1.2) was associated with prolonged DFS and OS in resectable gastric cancer patients ($P < 0.001$; **Fig. 1C and D**).

Prognostic significance of preoperative F-SIRI in resectable gastric cancer

A Cox univariate model for DFS revealed that high preoperative F-SIRI was significantly associated with impaired DFS (HR, 2.299; 95% CI, 1.482–3.566; $P < 0.001$; **Fig. 2A**). Age ($<60/\geq 60$ years), tumor size ($<5/\geq 5$ cm), depth of invasion (T1–2/T3–4), lymph node involvement (negative/positive), TNM stage (I–II/III), adjuvant chemotherapy (yes/no), SIRI ($<1.2/\geq 1.2$) and fibrinogen ($<4.0/\geq 4.0$ g/L) were other significant prognostic parameters identified by univariate analysis ($P < 0.05$). On multivariate analysis, preoperative F-SIRI (HR, 2.023; 95% CI, 1.273–3.215; $P = 0.003$) remained an independent prognostic indicator for DFS. TNM stage (HR, 2.464; 95% CI, 1.810–3.356; $P < 0.001$) and adjuvant chemotherapy (HR, 0.213; 95% CI, 0.154–0.294; $P < 0.001$) were other independent prognostic factors (**Table 2**).

In addition, univariate analysis of OS indicated that patients with high preoperative F-SIRI tended to have unfavorable OS (HR, 2.461; 95% CI, 1.584–3.824; $P < 0.001$; **Table 2; Fig. 2B**). Moreover, other parameters including age, tumor size, depth of invasion, lymph node involvement, TNM staging, adjuvant chemotherapy, fibrinogen and SIRI could also significantly predict OS

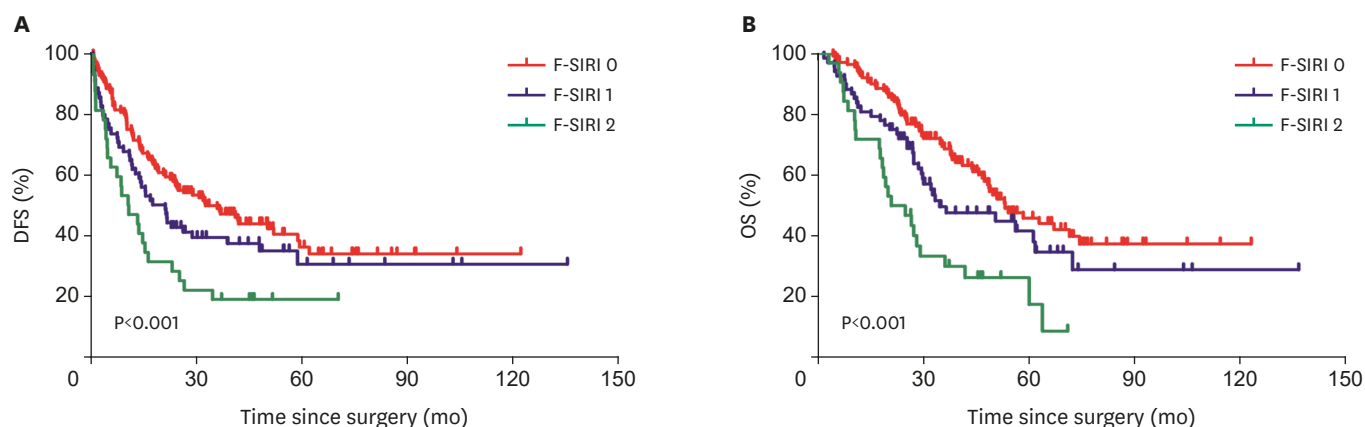


Fig. 2. Kaplan-Meier survival curves of (A), DFS and (B), OS stratified by preoperative F-SIRI in 240 resectable gastric cancer patients (with log-rank test). F-SIRI = fibrinogen and systemic inflammation response index; DFS = disease-free survival; OS = overall survival.

($P < 0.05$). Furthermore, high preoperative F-SIRI could also serve as an independent predictor for OS (HR, 2.341; 95% CI, 1.480–3.705; $P < 0.001$) after adjusting for other confounding factors. As expected, depth of invasion (HR, 2.002; 95% CI, 1.058–3.791; $P = 0.033$), lymph node involvement (HR, 3.286; 95% CI, 1.771–6.098; $P < 0.001$), as well as adjuvant chemotherapy (HR, 0.358; 95% CI, 0.242–0.529; $P < 0.001$) were also significant independent predictors for OS (Table 3).

DISCUSSION

This study evaluated the prognostic significance of preoperative F-SIRI in a Chinese cohort of resectable gastric cancer patients. The results showed that preoperative F-SIRI was significantly associated with systemic inflammatory response and clinical outcomes, indicating that patients with high preoperative F-SIRI had a higher risk of local recurrence and/or distant metastasis, and had a poorer prognosis. To the best of our knowledge, this study was the first one reporting the prognostic value of preoperative F-SIRI which was established based on preoperative fibrinogen and peripheral neutrophil, lymphocyte and monocyte counts in resectable gastric cancer.

Since 2011, cancer-related inflammation has been recognized as an important the seventh important marker of cancer [3]. In addition, there is increasing evidence suggesting that local immune responses and systemic inflammation could promote tumor growth, deterioration and metastasis, and are closely associated with long-term survival [17-19]. Results from several studies have indicated that gastric cancer patients with elevated plasma fibrinogen are closely associated with unfavorable prognosis [10,20]. Moreover, Yu and his colleagues [8] found that hyperfibrinogenemia was significantly associated with tumor progression and was an independent indicator for poor prognosis in patients with gastric cancer. Furthermore, Yu et al. [9] suggested that preoperative serum fibrinogen levels were positively correlated with advanced tumor stage and survival rates in patients with advanced gastric cancer, and they were also independent risk factors for survival in such cases. These findings indicate that fibrinogen is a promising marker for predicting tumor behavior and outcome in conventional blood tests.

Recently, Qi et al. [21] first proposed that SIRI, which was determined based on neutrophil, monocyte and lymphocyte counts could serve as an independent predictor of postoperative recurrence and survival in patients with pancreatic cancer. Besides, its prediction ability was

Table 2. Clinicopathological factors, F-SIRI, and DFS: univariate and multivariate analysis (n=240)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (yr)			0.036			0.165
<60	Ref.			Ref.		
≥60	1.453	1.024–2.060		1.293	0.900–1.857	
Gender			0.968			NI
Man	Ref.					
Woman	1.008	0.696–1.458				
Tumor location			0.154			NI
Diffuse	Ref.					
Upper	0.694	0.429–1.122				
Middle	0.522	0.318–0.859				
Lower	0.898	0.559–1.440				
Tumor size			0.001			0.094
<5	Ref.			Ref.		
≥5	1.910	1.314–2.775		1.409	0.944–2.104	
Differentiation			0.715			NI
Well/moderate	Ref.					
Poor/undifferentiated	1.080	0.714–1.633				
Depth of invasion			0.001			0.022
T1/T2	Ref.			Ref.		
T3/T4	2.685	1.481–4.868		2.132	1.117–4.073	
Lymph node involvement			<0.001			<0.001
Negative	Ref.			Ref.		
Positive	2.889	1.593–5.239		3.586	1.921–6.694	
TNM stage			<0.001			NI
I/II	Ref.					
III	2.926	1.813–4.723				
Adjuvant chemotherapy			<0.001			<0.001
No	Ref.			Ref.		
Yes	0.302	0.207–0.442		0.219	0.147–0.328	
SIRI			<0.001			NI
<1.20	Ref.					
≥1.20	1.964	1.363–2.828				
Fibrinogen			0.012			NI
<4	Ref.					
≥4	1.594	1.107–2.296				
F-SIRI score			<0.001			0.003
0/1	Ref.			Ref.		
2	2.299	1.482–3.566		2.023	1.273–3.215	

The bold numbers in the tables are P-values with statistical significance (<0.05).

F-SIRI = fibrinogen and systemic inflammation response index; TNM = tumor-node-metastasis; DFS = disease-free survival; HR = hazard ratio; CI = confidence interval; SIRI = systemic inflammation response index; NI = not included; Ref. = reference.

shown to be greater than that of the NLR and LMR and was associated with chemoresistance, higher serum inflammatory cytokine/chemokine levels and shorter outcomes [21]. In addition, Li et al. [15] evaluated the prognostic value of SIRI in patients with gastric cancer who received radical gastrectomy. The results showed that SIRI was an independent predictor for DFS and disease-specific survival, and was closely related to age, tumor size, TNM staging, lymphatic vessel and peripheral invasion. Meanwhile, patients with low SIRI could benefit from postoperative adjuvant chemotherapy and had a better prognosis [15]. Moreover, Geng and his colleagues [22] demonstrated that SIRI could predict postoperative survival of patients with esophageal squamous cell carcinoma and survival analysis indicated that the median OS in patients with SIRI ≤1.2 was significantly higher than that in patients with SIRI >1.2 (P<0.05). Furthermore, the nomogram including SIRI could predict OS more accurately compared with the TNM staging system.

Table 3. Clinicopathological factors, F-SIRI, and OS: univariate and multivariate analysis (n=240)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (yr)			0.012			0.065
<60	Ref.			Ref.		
≥60	1.565	1.102–2.222		1.404	0.979–2.014	
Gender			0.484			NI
Man	Ref.					
Woman	0.876	0.605–1.269				
Tumor location			0.152			NI
Diffuse	Ref.					
Upper	0.678	0.419–1.097				
Middle	0.529	0.322–0.869				
Lower	0.885	0.551–1.421				
Tumor size			0.001			0.189
<5	Ref.			Ref.		
≥5	1.891	1.302–2.748		1.309	0.876–1.958	
Differentiation			0.367			NI
Well/moderate	Ref.					
Poor/undifferentiated	1.210	0.800–1.829				
Depth of invasion			0.001			0.033
T1/T2	Ref.			Ref.		
T3/T4	2.770	1.528–5.022		2.002	1.058–3.791	
Lymph node involvement			<0.001			<0.001
Negative	Ref.			Ref.		
Positive	2.998	1.653–5.439		3.286	1.771–6.098	
TNM stage			<0.001			NI
I/II	Ref.					
III	3.082	1.910–4.973				
Adjuvant chemotherapy			<0.001			<0.001
No	Ref.			Ref.		
Yes	0.440	0.301–0.643		0.358	0.242–0.529	
SIRI			<0.001			NI
<1.20	Ref.					
≥1.20	1.999	1.387–2.881				
Fibrinogen			0.005			NI
<4	Ref.					
≥4	1.681	1.166–2.424				
F-SIRI score			<0.001			<0.001
0/1	Ref.			Ref.		
2	2.461	1.584–3.824		2.341	1.480–3.705	

The bold numbers in the tables are P-values with statistical significance (<0.05).

F-SIRI = fibrinogen and systemic inflammation response index; TNM = tumor-node-metastasis; OS = overall survival; HR = hazard ratio; CI = confidence interval; SIRI = systemic inflammation response index; NI = not included; Ref. = reference.

Therefore, we proposed that preoperative F-SIRI might predict survival more accurately in gastric cancer patients who underwent radical gastrectomy. The results of the present study show that there was no significant difference in the lymph node status or the TNM stage between the groups, probably because lymph node involvement was mainly a reflection of aggressive tumor behavior and not closely associated with systemic inflammatory response [23]. Moreover, F-SIRI was not related to the depth of invasion, thus requiring further study. In addition, univariate analysis showed that preoperative fibrinogen and SIRI were both prognostic factors and multivariate analysis indicated that F-SIRI was an independent prognostic predictor for DFS (HR, 2.023; 95% CI, 1.273–3.215; P=0.003) and OS (HR, 2.341; 95% CI, 1.480–3.705; P<0.001). Besides, patients with SIRI ≥1.2 would have a worse outcome after curative resection compared with those, which was consistent with the results of the previous 2 studies [15,22]. Furthermore, the median DFS and OS of patients with an

F-SIRI of 0, 1, and 2 differed significantly, suggesting that patients with an F-SIRI of 2 had more malignant tumors than those with F-SIRI of 0 or 1. Thus, F-SIRI could serve as a good indicator and tool for monitoring the general inflammation and predicting the survival of gastric cancer patients.

In conclusion, although the present study were mainly limited to the lack of measurements of other inflammatory parameters, retrospective single-center design and small sample size, the results showed that preoperative F-SIRI could serve as a novel and promising marker for predicting long-term survival, to help more accurate risk classification and design optimal treatment strategies for resectable gastric cancer patients. However, further studies with large cohort are still needed to verify these findings.

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