Original Article

Combination of the platelet-to-lymphocyte ratio and fibrinogen may predict 5-year overall survival of patient in non-small cell lung cancer treated with surgery

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Background: Non-small cell lung cancer (NSCLC) is a major type of lung cancer with high incidence and mortality. Systemic inflammatory response (SIR) and an imbalance of the coagulation system are both associated with the tumor progression. However, few studies have investigated the prognostic utility of a combination of inflammation and the coagulation system in NSCLC. The combination of platelet-to-lymphocyte ratio (PLR) and fibrinogen (FIB) (PLR-FIB; defined as PLR × FIB) is an indicator reflecting SIR and coagulation concurrently, which have potentiality to predict prognosis of NSCLC.

Methods: This retrospective, single-center study included 314 NSCLC patients with surgery. According to a cutoff value for the PLR-FIB, we divided participants into a low-PLR-FIB group and a high-PLR-FIB group. We retrospectively collected the data on 314 patients and used univariate and multivariate analyses to investigate the relationship between the PLR-FIB and survival.

Results: Univariate analysis showed that adenosquamous carcinoma (ASC) (P=0.002), high PLR-FIB (P=0.023), and tumor-node-metastasis (TNM) stage III–IV (P<0.001) were associated with a poor outcome. On multivariate analysis, low PLR-FIB [hazard ratio (HR), 0.587; 95% confidence interval (CI): 0.359–0.985; P=0.044], and TNM stage I–II (HR, 0.380; 95% CI: 0.245–0.590; P<0.001) were independent factors of a better prognosis. ASC type was an independent prognostic factor of poor outcome (HR, 5.513; 95% CI: 1.895–16.034; P=0.002). There were no significant differences in patient demographics or clinical characteristics between the two PLR-FIB groups (P>0.05). The 5-year overall survival (OS) rates were 80.8% and 67.9% for the low-PLR-FIB group and high-PLR-FIB group, respectively (P=0.02).

Conclusions: Preoperative PLR-FIB was found to be an independent prognostic factor for 5-year overall survival in patients with NSCLC treated with surgery.

Keywords: Platelet-to-lymphocyte ratio (PLR); fibrinogen (FIB); non-small cell lung cancer (NSCLC); prognosis

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Introduction

Lung cancer, as one of the most common solid tumors worldwide, remains the leading cause of cancer death (1). Non-small cell lung cancer (NSCLC), including lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD), accounts for up to 85% of lung cancer cases (2). Surgical resection is the optimal treatment for early-stage lung cancer (3). However, there remains a large difference in the range of outcomes in NSCLC patients undergoing surgery. Tumor-node-metastasis (TNM) stage, histological type, and genetic markers used to predict overall survival (OS). Moreover, the evaluation of TNM staging is complex and the cost of genetic testing is high. It is thus of critical importance to identify a simple and cost-effective biomarker for NSCLC prognosis.

Many recent studies have shown that the systemic inflammatory response (SIR) plays a critical role in tumor progression and metastasis (4,5). The biomarkers associated with SIR, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and other inflammatory factors. PLR has been reported to be prognostic indicators for several malignant tumors, including NSCLC (6-13).

The coagulation and fibrinolysis system activated by tumor cells has been reported to be associated with tumor development, proliferation, invasion, and tumor angiogenesis (14). Thrombosis is the second-leading cause of mortality in patients with cancer (15). Fibrinogen (FIB), a 350-KDa glycoprotein, converted to fibrin by activated thrombin affects blood clotting, fibrinolysis, inflammatory response and neoplasia (16). Thrombocytosis, FIB, and the D-dimer levels have been reported as biomarkers for the prognosis of NSCLC (17-19). Moreover, high FIB, reflecting hypercoagulability, has been identified as a factor for predicting poor prognosis in patients with NSCLC (20-22).

Systemic inflammation and an imbalance of the coagulation system are both associated with the malignant tumor progression (23,24). However, Using PLR or FIB alone to predicting prognosis of cancer was controversial (25-28). Moreover, few studies have investigated the prognostic utility of a combination of SIR and the coagulation system in NSCLC. We thus hypothesized that the combination of PLR and FIB (PLR-FIB; defined as PLR × FIB), reflecting SIR and coagulation concurrently, would predict the outcome of patients with NSCLC. In this study, we investigated the association of preoperative PLR-FIB and OS in patients with NSCLC who underwent surgery. We present this article in accordance with the REMARK reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1730/rc).

Highlight box

Key findings

- The combination of platelet-to-lymphocyte ratio and fibrinogen (PLR-FIB) was found to be an independent prognostic factor of overall survival in non-small cell lung cancer (NSCLC), with little effect linked to the tumor-node-metastasis stage.

What is known and what is new?

- Systemic inflammation and an imbalance of the coagulation system are both associated with the progression of malignant tumors, including NSCLC. PLR and FIB have each been independently reported to be a prognostic biomarker of NSCLC.
- Few studies have investigated the combination of systemic inflammatory response and the coagulation system in NSCLC prognosis. We thus hypothesized that the PLR-FIB (defined as PLR × FIB) would be able to predict the outcome of patients with NSCLC.

What is the implication, and what should change now?

- Preoperative PLR-FIB is suggested to be a potential biomarker for predicting the outcome of patients with NSCLC treated with surgery.

Methods

Participants

This study examined 314 patients with NSCLC accepted for surgery in the period from December 2017 to December 2021 at Fujian Cancer Hospital, China. All participants were diagnosed via pathology and classified according to the 8th version of the International Association for Lung Cancer Research (IASLC) TNM system (29). Patients with autoimmune disease, hematological disease, infection, or a history of neoadjuvant therapy or immunotherapy were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent. The study was approved by the Ethics Committee of Fujian Cancer Hospital (No. K2023-249-01).

Study design

We employed a retrospective, single-center study design, in which data on demographics, underlying disease, smoking/alcohol history, pathologic type, TNM stage, surgery type,

length of hospitalization (days), complications, and laboratory results of the 314 participants were collected. The laboratory data (platelet count, lymphocyte count, FIB, lactate dehydrogenase, albumin) were collected within 1 week prior to surgery between 6 am and 10 am. The survival data were collected via medical records or telephone, with December 31, 2018, being the deadline of the follow-up.

Definition

PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. PLR-FIB was defined as the product of PLR and FIB. The cutoff value of PLR-FIB was 166.45, which was calculated as the predominant point on the receiver operating characteristic (ROC) curve [sensitivity, 76.8%; specificity, 36.6%; area under the ROC curve (AUC), 0.520, Figure S1]. PLR-FIB low and high were defined as ≤166.45 and >166.45, respectively. OS was defined as the time from the surgery to death or the last follow-up.

Statistical analysis

The independent-sample *t*-test was used to compare continuous variables between groups. Qualitative variables were analyzed using the chi-squared (χ^2) test. The cutoff value was set as the point on the ROC curves that was closest to the upper left-hand corner of the plot. Univariate and multivariate risk regressions were performed using Cox proportional hazards regression, and the strength of risk regression was measured using hazard ratios (HRs) and 95% confidence intervals (CIs). Parameters with P value less than 0.05 in the univariable analysis were selected for inclusion in multivariable analysis. The Kaplan-Meier curve was used to analyze OS, and the comparisons were determined with the log-rank test. A P value <0.05 (bilateral) was considered statistically significant. Data were analyzed as of 2022 with SPSS 23.0 software (IBM Corp., Armonk, NY, USA).

Results

Patients' characteristics

This study enrolled 314 participants, who were divided into a low-PLR-FIB group (n=104) and a high-PLR-FIB high group (n=210). There were 220 (70.1%) males and 94 (29.9%) females, with a median age of 59 (IQR, 52–65) years. The median body mass index (BMI) was 22.82 (IQR, 20.72–24.94) kg/m^2. The majority of participants did not have a history of alcohol intake (n=4, 1.3%) or complications after surgery (n=11, 3.5%). Less than half of the participants had a history of smoking (n=142, 45.2%) or underlying diseases (n=156, 49.7%). Among the cases, 173 (55.1%) were pathologically diagnosed as adenocarcinoma (ADC), 105 (33.4%) as squamous cell carcinoma (SCC), 11 (3.5%) as adenosquamous carcinoma (ASC), and 25 (8.0%) as other types. The most common surgery type in our sample was lobectomy (n=274, 87.3%). As shown in *Table 1*, there were no significant differences in patient demographics or clinical characteristics between the two PLR-FIB groups (P>0.05).

Univariate and multivariate analyses

The results of the univariate and multivariate analyses for 5-year OS are shown in *Table 2*. Univariate analysis demonstrated that ASC (P=0.002), high PLR-FIB (P=0.023), and TNM stage III–IV (P<0.001) were associated with a poor outcome. On multivariate analysis, low PLR-FIB (HR, 0.587; 95% CI: 0.350–0.985; P=0.044), and TNM stage I–II (HR, 0.380; 95% CI: 0.245–0.590; P<0.001) were independent factors for a better prognosis. In addition, ASC type was an independent prognostic factor for a poor outcome (HR, 5.513; 95% CI: 1.895–16.034; P=0.002).

Outcome

The median survival of the 314 participants was 57 (range, 32–71) months. The low-PLR-FIB group had a better OS than the high-PLR-FIB group (61.5 *vs.* 52.0 months, P=0.028; *Table 1*). The 5-year OS rates were 80.8% and 67.9% for the low-PLR-FIB group and high-PLR-FIB group, respectively (P=0.02; *Figure 1A*). According to Kaplan-Meier analysis, ADC type (P<0.0001; *Figure 1B*), and TNM stage I–II (P<0.0001; *Figure 1C*) had a better 5-year OS.

Discussion

NSCLC is a malignant tumor with the highest morbidity and mortality among cancers worldwide (1). It is of critical importance to establish a simple, effective and accurate prognosis in patients treated with surgery in order to provide the appropriate treatment after surgery.

Since the connection between inflammation and cancer was first reported in 1863 (30), the value of inflammatory biomarkers in the diagnosis and prognosis of malignant

Table 1 Baseline characteristics of the 314 participants

Variables	Overall (n=314)	PLR-FIB low (n=104)	PLR-FIB high (n=210)	P value
Gender				0.360
Male	220 (70.1)	69 (66.3)	151 (71.9)	
Female	94 (29.9)	35 (33.7)	59 (28.1)	
Age (years)	59.00 [52.00, 65.00]	59.00 [52.75, 64.25]	58.00 [51.25, 65.00]	0.987
BMI (kg/m^2)	22.82 [20.72, 24.94]	23.41 [21.25, 25.02]	22.62 [20.56, 24.84]	0.165
Length of hospitalization (days)	13.00 [11.00, 15.00]	13.00 [11.00, 15.00]	13.00 [11.00, 15.00]	0.769
LDH (U/L)	149.00 [132.00, 169.00]	148.50 [133.75, 169.25]	149.00 [128.25, 169.00]	0.689
ALB (g/L)	39.00 [36.00, 41.00]	39.00 [37.00, 41.00]	38.00 [35.00, 41.00]	0.045
Alcohol				>0.99
No	310 (98.7)	103 (99.0)	207 (98.6)	
Yes	4 (1.3)	1 (1.0)	3 (1.4)	
Smoking				0.473
No	172 (54.8)	60 (57.7)	112 (53.3)	
Yes	142 (45.2)	44 (42.3)	98 (46.7)	
Underlying disease				0.632
No	158 (50.3)	50 (48.1)	108 (51.4)	
Yes	156 (49.7)	54 (51.9)	102 (48.6)	
Complications				0.515
No	303 (96.5)	99 (95.2)	204 (97.1)	
Yes	11 (3.5)	5 (4.8)	6 (2.9)	
TNM				0.896
I–II	221 (70.4)	74 (71.2)	147 (70.0)	
III–IV	93 (29.6)	30 (28.8)	63 (30.0)	
Pathology				0.113
ADC	173 (55.1)	65 (62.5)	108 (51.4)	
SCC	105 (33.4)	33 (31.7)	72 (34.3)	
ASC	11 (3.5)	2 (1.9)	9 (4.3)	
Other	25 (8.0)	4 (3.8)	21 (10.0)	
Surgery type				0.675
Sublobectomy	11 (3.5)	4 (3.8)	7 (3.3)	
Lobectomy	274 (87.3)	93 (89.4)	181 (86.2)	
Pneumonectomy	26 (8.3)	7 (6.7)	19 (9.0)	
Other	3 (1.0)	0 (0.0)	3 (1.4)	
OS (months)	57.00 [32.00, 71.00]	61.50 [41.75, 72.00]	52.00 [29.25, 68.75]	0.028*
5-year OS rate (%)	73.9	80.8	67.9	0.02*

Data are presented as n (%) or median [IQR]. *, P<0.05. PLR-FIB, combination of PLR and FIB; PLR, platelet-to-lymphocyte ratio; FIB, fibrinogen; BMI, body mass index; LDH, lactate dehydrogenase; ALB, albumin; TNM, tumor-node-metastasis; ADC, adenocarcinoma; SCC, squamous cell carcinoma; ASC, adenosquamous carcinoma; OS, overall survival; IQR, interquartile range.

Table 2 Univariate and multivariate analysis for 5-year OS

Variables	Univariate analysis for OS			Multivariate analysis for OS		
	HR	95% CI	P value	HR	95% CI	P value
Age (≤49, >49 years)	0.730	0.516–1.032	0.075			
Gender (male, female)	1.274	0.981–1.655	0.069			
BMI (≤20.1, >20.1 kg/m^2)	0.776	0.565–1.066	0.118			
Smoking (no, yes)	0.879	0.708–1.092	0.244			
Underlying disease (no, yes)	1.203	0.966–1.499	0.099			
Complications (no, yes)	0.664	0.438–1.007	0.054			
Pathology (other, SCC, ADC, ASC)			<0.001*			<0.001*
Other	Ref.	Ref.		Ref.	Ref.	
SCC	0.884	0.373–2.095	0.780	1.361	0.565–3.276	0.492
ADC	1.284	0.535–3.077	0.576	0.848	0.355–2.022	0.709
ASC	5.422	1.874–15.689	0.002*	5.513	1.895–16.034	0.002*
ALB (≤25.9, >25.9 g/L)	0.222	0.000–509.839	0.703			
LDH (≤170.5, >170.5 U/L)	0.802	0.637–1.010	0.060			
PLR (≤30.4, >30.4)	0.503	0.299-1.216	0.603			
FIB (≤3.25, >3.25 g/L)	0.789	0.501-1.240	0.304			
Hospitalization (≤12, >12 days)	0.958	0.771–1.191	0.701			
PLR-FIB (low, high)	0.742	0.574–0.959	0.023*	0.587	0.350–0.985	0.044*
TNM (I–II, III–IV)	0.403	0.261–0.622	<0.001*	0.380	0.245–0.590	<0.001*

*, P<0.05. OS, overall survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SCC, squamous cell carcinoma; ADC, adenocarcinoma; ASC, adenosquamous carcinoma; ref., reference; ALB, albumin; LDH, lactate dehydrogenase; PLR, platelet-to-lymphocyte ratio; FIB, fibrinogen; PLR-FIB, combination of PLR and FIB; TNM, tumor-node-metastasis.

tumors has been confirmed numerous studies. Cancer immunosurveillance is mediated by $CD4^+$ and $CD8^+$ T cells (31). Lymphocytes produce cytokines that activate antitumor immunity, which plays an important role in cancer immunosurveillance (32). The epithelial-mesenchymal transition (EMT), which drives metastasis during the progression of NSCLC, has been associated with the exclusion of immune cells critical to the immune response to cancer, and a significantly lower infiltration of $CD4^+$ T cells or $CD4^+$ and $CD8^+$ T cells has been found in patients with LUAD or LUSC (33). Platelets contribute to cancer progression by releasing growth factors that promote tumor cell proliferation and angiogenesis (34-36). By reflecting the combined effect of lymphocytes and platelets, PLR has shown to have potential in predicting the prognosis of various malignant tumors, including NSCLC (37-39). Several meta-analyses have reported that a low PLR is associated with better outcomes in lung cancer (40-43).

The relationship between thrombosis and cancer was first reported by Armand Trousseau in 1865 (24). Thrombosis is not only a common complication for cancer patients, but is also associated with tumor progression (14,15). FIB, an acute phase reaction protein, increases in concentration during the course of hyperfibrinolysis. It has been reported that FIB can protect tumor cells from natural killer (NK) cell-mediated cytotoxicity by aggregating around tumor cells and forming dense fibrin layers (44,45). A tumor cell fate study conducted by Palumbo *et al.* showed that FIB contributed to the sustained adhesion and survival of tumor cells in lung cancer (46). In patients with NSCLC, FIB was reported to be an independent prognostic factor for *EGFR* gene mutation status and lymphatic metastasis (47). In Sheng *et al.*'s study of operable NSCLC

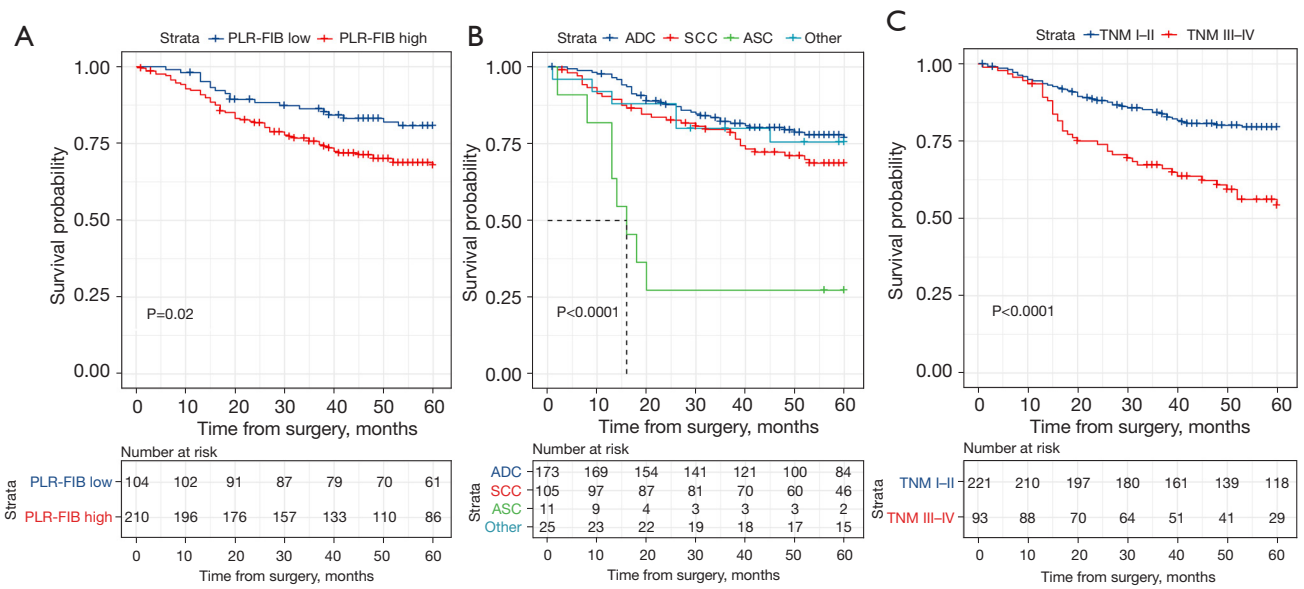

Figure 1 OS. (A) OS between the PLR-FIB groups. (B) OS among the pathological types. (C) OS between the TNM I–II and TNM III–IV groups. PLR-FIB, combination of PLR and FIB; PLR, platelet-to-lymphocyte ratio; FIB, fibrinogen; SCC, squamous cell carcinoma; ADC, adenocarcinoma; ASC, adenosquamous carcinoma; TNM, tumor-node-metastasis; OS, overall survival.

patients, those with a higher FIB level had an elevated risk of disease progression (HR, 1.49; 95% CI: 1.07–2.05) and death (HR, 1.64; 95% CI: 1.06–2.53) compared to patients with a normal FIB level (22). In another study, a high FIB level (plasma FIB >5 g/L) was associated with incomplete resection in patients with NSCLC (48).

In our study, PLR-FIB, which reflects systemic inflammation and thrombosis, was shown to be a novel prognostic biomarker in patients with NSCLC. According to univariate and multivariate analyses, PLR-FIB was an independent prognostic biomarker of NSCLC. A low PLR-FIB was associated with a better 5-year OS (HR, 0.586; 95% CI: 0.349–0.984; P=0.043). According to the comparison of the clinical characteristics, there was no significant difference in TNM stage between the low- and high-PLR-FIB groups. However, PLR as well as FIB have been respectively reported to be related to the TNM stage in previous studies (49,50). PLR-FIB might be a prognostic factor with little combined effect on the TNM stage. Furthermore, PLR-FIB can be obtained easily with a routine blood test and is cost-effective. Thus, we recommend the use of preoperative PLR-FIB to predict patient outcome in NSCLC.

Some limitations of this study should be mentioned. First, as we employed a retrospective, single-center design and enrolled just 314 participants, so the sample size was not sufficiently large to definitively support our conclusions. Second, this study only investigated the association of PLR-FIB with OS; however, progression-free survival may also be an important endpoint for evaluating the prognostic value of PLR-FIB. Third, the participants were enrolled in this study from 2007 to 2012, and the results might have been biased by the relatively large time span. As treatment has changed and neoadjuvant and adjuvant treatment including programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1) antibodies are now common standards in NSCLC stage II and IIIA, it would be interesting whether PLR-FIB remains a prognostic factor in this new era or therapy. Therefore, we will consider including progression-free survival and a greater number of cases in future research. A large, multicenter, prospective study is needed to validate our findings.

Conclusions

PLR-FIB is an independent prognostic factor for OS in patients with NSCLC and had little effect in terms of TNM stage. Preoperative PLR-FIB may be a potential biomarker

for predicting surgically treated NSCLC patients' outcome.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1730/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1730/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1730/coif). W.M.B. received honoraria for lectures or educational events from AstraZeneca, Boehringer, Novartis, MSD, BMS, Lilly, Pfizer and Roche. W.M.B. received support for attending meetings and/or travel from Boehringer, Roche and AstraZeneca. W.M.B. served on advisory board of AstraZeneca, Boehringer, Novartis, MSD, Lilly Pharma, BMS, and Roche. W.M.B. received equipment, material, drugs, medical writing, gifts or other services from Boehringer for medical writing. W.M.B.'s patent application EP21183549.1 (method for predicting a clinical response towards an immune checkpoint inhibitor based on pretreatment therewith) was filed with regard to the results of this study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent. The study was approved by the Ethics Committee of Fujian Cancer Hospital (No. K2023-249-01).

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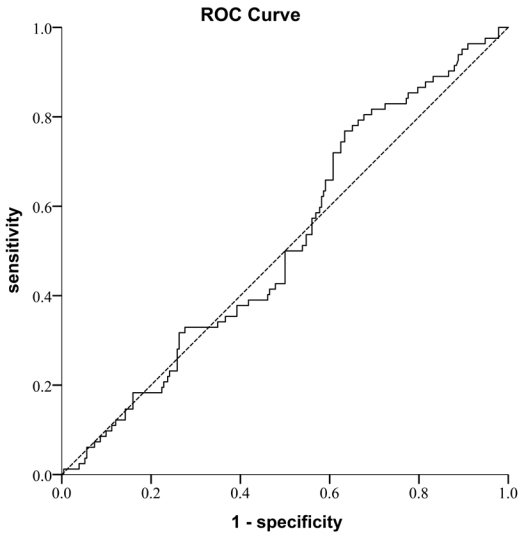

Figure S1 ROC curve for PLR-FIB. ROC, receiver operating characteristic; PLR-FIB, combination of PLR and FIB; PLR, platelet-to-lymphocyte ratio; FIB, fibrinogen.

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