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ORIGINAL ARTICLE

Prognostic significance of combined fibrinogen concentration and neutrophil-to-lymphocyte ratio in patients with resectable non-small cell lung cancer

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ABSTRACT

Objective: Cancer-associated inflammation and coagulation cascades play vital roles in cancer progression and survival. In this study, we investigated the significance of the combination of preoperative fibrinogen and the neutrophil-to-lymphocyte ratio (NLR) in predicting the survival of patients with non-small cell lung cancer (NSCLC).

Methods: We retrospectively enrolled 589 patients with NSCLC who underwent surgery. The univariate and multivariate Cox survival analyses were used to evaluate the prognostic indicators, including the combination of fibrinogen and NLR (F-NLR). The cut-off values for fibrinogen, NLR, and clinical laboratory variables were defined by the receiver operating characteristic (ROC) curve analysis. According to the ROC curve, the recommended cut-off values for fibrinogen and the NLR were 3.48 g/L and 2.30, respectively. Patients with both a high NLR ($\geq$ 2.30) and hyperfibrinogenemia ($\geq$ 3.48 g/L) were given a score of 2, whereas those with one or neither were scored as 1 or 0, respectively.

Results: Our results showed that F-NLR was an independent prognostic indicator for disease-free survival (DFS) [hazard ratio (HR), 1.466; 95% confidence interval (CI), 1.243–1.730; $P < 0.001$] and overall survival (OS) (HR, 1.512; 95% CI, 1.283–1.783; $P < 0.001$). The five-year OS rates were 66.1%, 53.5%, and 33.3% for the F-NLR = 0, F-NLR = 1, and F-NLR = 2, respectively ($P < 0.001$). Correspondingly, their five-year DFS rates were 62.2%, 50.3%, and 30.4%, respectively ($P < 0.001$). In the subgroup analyses of the pathological stages, the F-NLR level was significantly correlated with DFS and OS in stage I and IIIA cancers.

Conclusions: Preoperative F-NLR score can be used as a valuable prognostic marker for patients with resectable early-stage NSCLC.

KEYWORDS Non-small cell lung cancer; neutrophil-to-lymphocyte ratio; fibrinogen; prognosis

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 80% of all cases[1]. Despite the recent improvements in treatment and diagnosis of lung cancer, its prognosis remains unsatisfactory, with a low five-year survival rate of about 15% at diagnosis. Currently, the new strategy in tumor therapy focuses on using a suitable prognostic factor to make the appropriate risk classification of patients with tumors and to design subsequent treatment. Although multiple studies have found a large number of prognostic indicators for patients with NSCLC, the majority of these indicators are not available preoperatively.

Cancer-related inflammation plays an important role in tumor progression and survival[2]. Cancer-related inflammation, as the 7th hallmark of cancer, promotes the proliferation and invasion of tumor cells and accelerates metastasis[3]. Moreover, most systemic symptoms associated with cancer, including weight loss, cachexia, and anemia, are stimulated by inflammation[4]. The neutrophil-to-lymphocyte ratio (NLR), as a representative index, can be considered a useful marker to assess the inflammatory response[5]. An increased NLR promotes tumor progression and relates to poor prognoses in a variety of cancers, such as NSCLC, esophageal cancer, and gastric cancer[6-8]. In terms of the systemic inflammatory response, the coagulation cascade also plays a pivotal role in tumor progression and metastasis[9].

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Liver-produced fibrinogen is an important acute phase protein. Fibrinogen, as a key factor in the coagulation cascade, is converted into fibrin under the action of activated thrombin. Hyperfibrinogenemia is involved in cancer aggressiveness in various types of malignancies[10-12]. Recently, several studies analyzed a novel prognostic index, that is, the combination of fibrinogen and NLR (F-NLR). F-NLR has been found to be a significant prognostic factor in different types of cancers, such as gastric cancer, esophageal carcinoma, and NSCLC[13-16].

The present study aimed to evaluate the clinical significance of a novel prognostic system based on fibrinogen concentration and NLR in patients with NSCLC undergoing complete resection. This study also assessed the association between the three F-NLR groups and the clinicopathologic characteristics or the clinical laboratory variables.

Materials and methods

Patients

We performed a retrospective study of patients with NSCLC who underwent complete surgical resection at the Tianjin Medical University Cancer Institute and Hospital between January 2006 and December 2009. The major inclusion criteria were pathological confirmation of primary NSCLC and complete surgical resection. The exclusion criteria were as follows: preoperative treatment (including chemotherapy or radiotherapy), residual tumor cells in the surgical edge, continuous anticoagulant therapy, hematological disease, autoimmune disease, and infection. Patients with intravenous or arterial embolization within 3 months before the surgery were also excluded. Based on the inclusion and exclusion criteria, 589 patients were enrolled in our study. This study was approved by the Ethical Committees of Tianjin Medical University Cancer Institute and Hospital. Prior to the treatment, and written informed consent from all participants were acquired.

Based on the medical records, we collected the patients' clinicopathologic parameters and laboratory inspections, such as age, sex, histopathology, TNM stage, and blood cell count. Tumor stages were determined according to the 7th edition of the TNM classification[17].

F-NLR definition

Hematological indexes, including lymphocyte count, neutrophil count, and fibrinogen concentration, were obtained from the routine blood test administered a week prior to the surgery. The neutrophil count divided by the lymphocyte count was defined as the NLR. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values for the preoperative fibrinogen concentration and NLR. According to the ROC curve analysis, the most appropriate cut-off point for NLR was 2.30, with an area under the curve of 0.635. Therefore, we recommended 2.30 as the cut-off value for NLR. Similarly, the optimal point based on the ROC curve showed a cut-off value of 3.48 g/L for fibrinogen, with an area under the curve of 0.595. Consequently, we defined 3.48 g/L as the optimal cut-off value for fibrinogen.

Based on these cut-off values, we calculated the F-NLR score. Patients with both a high NLR ($\geq$ 2.30) and hyperfibrinogenemia ($\geq$ 3.48 g/L) were given a score of 2. Patients with either high NLR ($\geq$ 2.30) or hyperfibrinogenemia ($\geq$ 3.48 g/L) were given a score of 1. Patients without either abnormality were scored 0.

Statistical analysis

Chi-square and Kruskal-Wallis tests were applied to evaluate the differences between the three F-NLR groups and the clinicopathologic characteristics or clinical laboratory variables. Continuous variables are presented as mean ± SD. We carried out the ROC curve analysis to select the appropriate cut-off values for NLR, fibrinogen, and the clinical laboratory variables. These clinical laboratory variables included fibrinogen, lactate dehydrogenase (LDH), D-dimer, neutrophil ratio, monocyte ratio, lymphocyte ratio, white blood cell (WBC) count, platelet count, hemoglobin (Hb), and alkaline phosphatase (ALP). The outcomes of this study were disease-free survival (DFS) and overall survival (OS). DFS was defined as the time in months from the date of surgery to the date of first progression or last follow-up. OS was defined as the time in months from the date of surgery to the date of death or last follow-up. Survival analysis was performed using the Kaplan-Meier survival curve. Univariate and multivariate analyses, which were carried out by Cox regression models, were used to determine the prognostic factors. SPSS version 18.0 (SPSS Inc., Chicago, IL) was utilized for statistical analyses. A P value of < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 589 patients who were pathologically diagnosed

with NSCLC were included in this study. All patients underwent surgery for early-stage NSCLC. **Tables 1** and **2** illustrate the relationship of the clinicopathologic variables and clinical laboratory parameters with patients grouped by their F-NLR score. The present study included 390 (66.2%) men and 199 (33.8%) women, ranging 24–82 years (median

Table 1 Correlation between preoperative F-NLR and clinicopathologic characteristics of patients with NSCLC

	F-LMR score, *n*(%)			*P*
	0	1	2	
Age, years				0.005
≤ 60	115 (55.6)	60 (39.0)	120 (52.6)	
> 60	92 (44.4)	94 (61.0)	108 (47.4)	
Gender				0.006
Female	84 (40.6)	55 (35.7)	60 (26.3)	
Male	123 (59.4)	99 (64.3)	168 (73.7)	
Smoking				0.014
Yes	121 (58.5)	108 (70.1)	161 (70.6)	
No	86 (41.5)	46 (29.9)	67 (29.4)	
Tumor location				0.496
Right	121 (58.5)	87 (56.5)	142 (62.3)	
Left	86 (41.5)	67 (43.5)	86 (37.7)	
Lesion				<0.001
Peripheral	178 (86.0)	108 (70.1)	138 (60.5)	
Central	29 (14.0)	46 (29.9)	90 (39.5)	
Resection type				<0.001
Pneumonectomy	10 (4.8)	18 (11.7)	41 (18.0)	
Lobectomy	197 (95.2)	136 (88.3)	187 (82.0)	
Pathological stage				<0.001
I	131 (63.3)	71 (46.1)	76 (33.3)	
II	18 (8.7)	33 (21.4)	69 (30.3)	
IIIA	58(28.0)	50 (32.5)	83 (36.4)	
Histology				<0.001
SqCC	62 (30.0)	74 (48.1)	137 (60.1)	
Adenocarcinoma	122 (58.9)	53 (34.4)	66 (28.9)	
Others	23 (11.1)	27 (17.5)	25 (11.0)	
Lymph node metastasis				0.028
Yes	71 (34.3)	64 (41.6)	107 (46.9)	
No	136 (65.7)	90 (58.4)	121 (53.1)	
Tumor size, cm				<0.001
<4	128 (61.8)	64 (41.6)	67 (29.4)	
≥4	79 (38.2)	90 (58.4)	161 (70.6)	

NSCLC: non-small cell lung cancer; SqCC: squamous cell carcinoma; F-NLR: combination of fibrinogen concentration and neutrophil to lymphocyte ratio.

Table 2 Correlation between preoperative F-NLR and clinical laboratory characteristics of patients with NSCLC

Variables	F-NLR=0 (*n*=207)	F-NLR=1 (*n*=154)	F-NLR=2 (*n*=228)	*P*
Age, years	59.3±9.4	62.6±9.5	60.0±9.3	0.001
Maximum tumor diameter (cm)	3.3±1.4	4.4±1.8	5.1±2.4	<0.001
NLR	1.6±0.4	1.7±0.4	3.2±1.0	<0.001
Fibrinogen (g/L)	2.8±0.4	4.3±0.6	4.1±1.0	<0.001
Neutrophil ratio (%)	53.8±6.5	55.8±6.2	67.3±4.8	<0.001
Monocyte ratio (%)	7.6±2.3	7.9±2.1	7.9±2.2	0.333
Lymphocyte ratio (%)	35.2±6.1	33.5±6.7	22.3±4.3	<0.001
D-dimer (mg/L)	0.16±0.09	0.21±0.27	0.20±0.17	0.119
WBC count ($\times 10^3/\mu L$)	6.1±1.6	7.0±1.9	7.4±1.5	<0.001
PLT ($\times 10^9/L$)	225.6±63.1	265.5±80.9	252.7±72.4	<0.001
ALP (U/L)	70.4±23.4	77.5±22.7	78.0±31.6	<0.001
Hb (g/L)	140.2±18.2	138.0±13.4	137.8±14.6	0.269
LDH (U/L)	178.3±53.6	180.3±47.8	185.4±55.4	0.284
Survival period (months)	51.3±22.7	44.7±24.4	37.6±25.6	<0.001

F-NLR: combination of fibrinogen concentration and neutrophil to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; WBC: white blood cell; PLT: platelet count; ALP: alkaline phosphatase; Hb: hemoglobin; LDH: lactate dehydrogenase.

age: 60 years). The allocation of the F-NLR score was as follows: F-NLR = 0, 207 (35.1%) patients; F-NLR = 1, 154 (26.2%) patients; and F-NLR = 2, 228 (38.7%) patients. A total of 278, 120, and 191 patients presented with pathological stages I, II, and IIIA, respectively. The median and mean follow-up periods were 44 and 44.3 months, respectively. The five-year OS rate in the entire study population was 50.3%.

Correlation between the clinicopathologic variables or clinical laboratory parameters and F-NLR

The association between the F-NLR and clinicopathologic indexes of patients with NSCLC is shown in **Table 1**. We found significant correlation of F-NLR with age ($P = 0.005$), gender ($P = 0.006$), smoking ($P = 0.014$), lesion ($P < 0.001$), resection type ($P < 0.001$), pathological stage ($P < 0.001$), histology ($P < 0.001$), lymph node metastasis ($P = 0.028$), and tumor size ($P < 0.001$).

The clinical laboratory variable distribution in the three F-NLR groups is presented in **Table 2**. Significant differences among these three groups were demonstrated in the following indexes: age ($P = 0.001$), maximum tumor diameter ($P < 0.001$), NLR ($P < 0.001$), fibrinogen ($P < 0.001$), neutrophil ratio ($P < 0.001$), lymphocyte ratio ($P < 0.001$), WBC count ($P < 0.001$), platelet count ($P < 0.001$), ALP ($P < 0.001$), and survival period ($P < 0.001$).

Survival analysis of F-NLR

We performed the Kaplan-Meier analysis and log-rank test to determine the survival differences among the three groups classified by F-NLR score. The five-year DFS rate and the median survival in patients with F-NLR = 2 were significantly lower than those in patients with F-NLR = 1 or F-NLR = 0 [30.4% *vs.* 50.3% or 62.2% (22.5 *vs.* 36.0 or 42.0 months), $P < 0.001$; **Figure 1A**]. The five-year OS rates were 66.1%, 53.5%, and 33.3%, and the median survival times were 51.0, 46.0, and 33.0 months for F-NLR = 0, F-NLR = 1, and F-NLR = 2, respectively ($P < 0.001$, **Figure 1B**). When the pathological stages (I, II, and IIIA) were analyzed separately, the DFS and OS of patients with F-NLR = 0 were higher than those with F-NLR = 1 or F-NLR = 2 in stages I and IIIA (stage I: $P < 0.001$ for DFS, $P < 0.001$ for OS, **Figures 2A** and **2B**; stage IIIA: $P = 0.001$ for DFS, $P < 0.001$ for OS, **Figures 2E** and **2F**). However, no significant relationship was observed between F-NLR and prognosis in patients with stage II NSCLC ($P = 0.149$ for DFS and $P = 0.139$ for OS, **Figures 2C** and **2D**). Further analyses were conducted in subgroups (adenocarcinoma and squamous carcinoma). We demonstrated that patients with F-NLR = 0 displayed a higher DFS and OS than those with F-NLR = 1 or F-NLR = 2 in the adenocarcinoma and squamous carcinoma subgroups

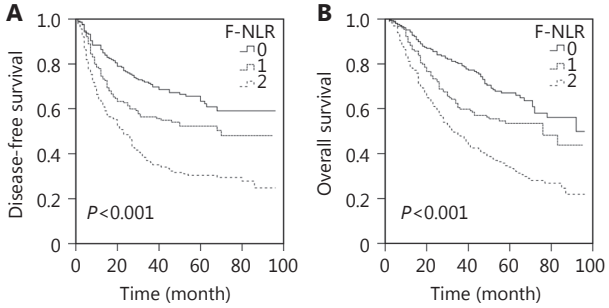

Figure 1 Survival curves of patients with non-small cell lung cancer (NSCLC) (stages I-IIIA) in the combination of fibrinogen and neutrophil-to-lymphocyte ratio (F-NLR). (A) Disease-free survival (DFS) curve of patients with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P > 0.001$). (B) Overall survival (OS) curve of patients with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P > 0.001$).

(adenocarcinoma: $P < 0.001$ for DFS, $P < 0.001$ for OS, **Figures 3A** and **3B**; squamous carcinoma: $P < 0.001$ for DFS, $P < 0.001$ for OS, **Figures 3C** and **3D**).

Univariate and multivariate analyses of variables are shown in **Tables 3** and **4**, respectively. Based on the cut-off values, we separated the patients into different groups. Univariate analysis demonstrated that lesion ($P = 0.023$ for DFS and $P = 0.014$ for OS), resection type ($P = 0.041$ for DFS and $P = 0.038$ for OS), pathological stage ($P < 0.001$ for DFS and $P < 0.001$ for OS), tumor size ($P < 0.001$ for DFS and $P < 0.001$ for OS), adjuvant radiotherapy ($P = 0.001$ for DFS and $P = 0.004$ for OS), F-NLR score ($P < 0.001$ for DFS and $P < 0.001$ for OS), NLR ($P < 0.001$ for DFS and $P < 0.001$ for OS), fibrinogen ($P < 0.001$ for DFS and $P < 0.001$ for OS), LDH ($P = 0.003$ for DFS and $P = 0.005$ for OS), D-dimer ($P < 0.001$ for DFS and $P = 0.002$ for OS), neutrophil ratio ($P < 0.001$ for DFS and $P < 0.001$ for OS), monocyte ratio ($P = 0.008$ for DFS and $P = 0.006$ for OS), lymphocyte ratio ($P < 0.001$ for DFS and $P < 0.001$ for OS), WBC count ($P = 0.007$ for DFS and $P = 0.008$ for OS), ALP ($P = 0.002$ for DFS and $P = 0.003$ for OS), and Hb ($P = 0.022$ for DFS and $P = 0.040$ for OS) were correlated with DFS and OS.

Multivariate analysis of independent prognostic indicators

To determine the independent predictive indexes, further Cox multivariate analysis, which included the variables

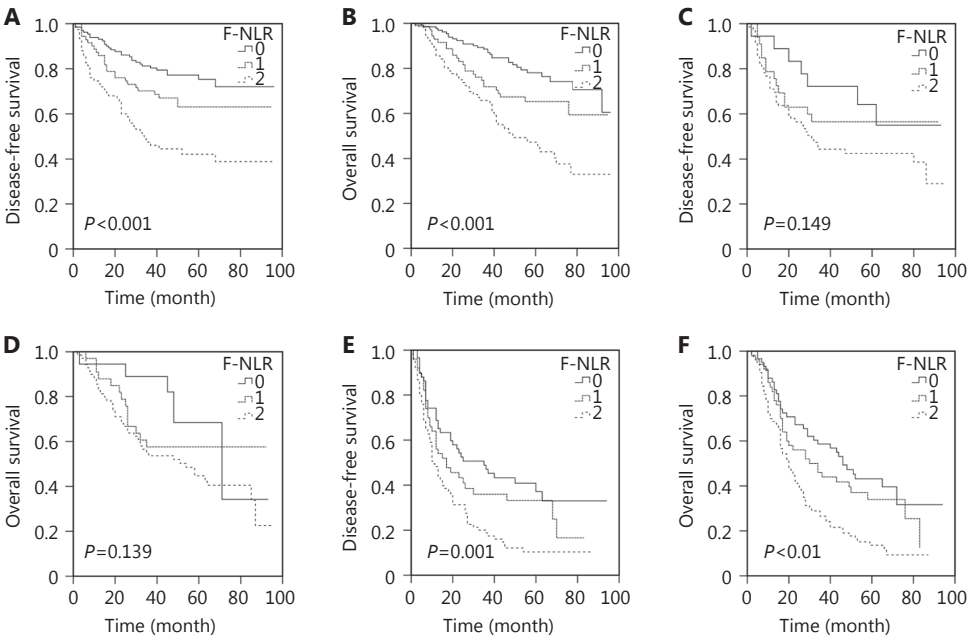

Figure 2 Survival curves of patients with NSCLC (stage I-IIIA) in F-NLR. (A) DFS curve of patients with stage I NSCLC with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P > 0.001$). (B) OS curve of patients with stage I NSCLC with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P > 0.001$). (C) DFS curve of patients with stage II NSCLC with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P = 0.149$). (D) OS curve of patients with stage II NSCLC with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P = 0.139$). (E) DFS curve of patients with stage IIIA NSCLC with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P = 0.001$). (F) OS curve of patients with stage IIIA NSCLC with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P > 0.001$).

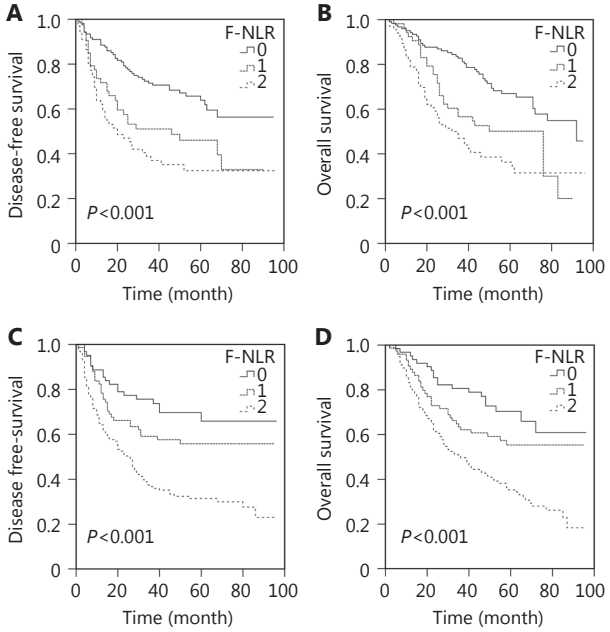

Figure 3 Survival curves of patients with adenocarcinoma or squamous carcinoma in F-NLR. (A) DFS curve of patients with adenocarcinoma with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P > 0.001$). (B) OS curve of patients with adenocarcinoma with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P > 0.001$). (C) DFS curve of patients with squamous carcinoma with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P > 0.001$). (D) OS curve of patients with squamous carcinoma with F-NLR=0, F-NLR=1, and F-NLR=2 (log-rank test, $P > 0.001$).

mentioned above, was performed. As shown in **Table 4**, multivariate analysis revealed that F-NLR was significantly related to DFS and OS [hazard ratio (HR), 1.466; 95% confidence interval (CI), 1.243–1.730; $P < 0.001$ for DFS and HR, 1.512; 95% CI, 1.283–1.783; $P < 0.001$ for OS, respectively] along with pathological stage and D-dimer. Therefore, multivariate analysis demonstrated that F-NLR was considered an independent prognostic indicator for DFS and OS.

Discussion

Although substantial developments have been made in the treatment and diagnosis of lung cancer, the median survival of NSCLC remains unsatisfactory. An appropriate prognostic factor may enable the suitable risk classification of patients with tumors and allow the assignment of appropriate prospective treatment. Cancer progression and survival are not determined solely by the tumor characteristics. Patient-related factors also play a crucial role in survival. Based on the preoperative blood specimens collected from 589 patients, we investigated the prognostic significance of F-NLR. We also analyzed the association between F-NLR and clinicopathologic or clinical laboratory characteristics.

In the last few decades, inflammation has been increasingly accepted as a hallmark of cancer[3]. Inflammation can increase the risk of cancer by producing bioactive molecules from the cells infiltrating the tumor microenvironment. Inflammation-related cells introduce crucial cytokines to the tumor microenvironment, thereby promoting the growth, angiogenesis, invasion, metastasis, and survival of cancer cells[18-20]. Increasing evidence has revealed that systemic inflammation responses are crucial prognostic indicators[21]. NLR is a systemic inflammation index, which is calculated by dividing the neutrophil count by the lymphocyte count. Lymphocytes, as key components of the host's anticancer immunity, perform important functions in immunosurveillance and immunoediting and contribute to the inhibition of tumor cell proliferation and migration[21]. T lymphocytes exert a killing effect on target cells and help induce tumor cell apoptosis in cancer patients[22]. Increased amounts of circulating blood lymphocytes are an advantageous prognostic index in resected NSCLC[23,24]. Similar to lymphocytes, neutrophils are recognized as important components of tumor inflammation and immunology. Circulating neutrophils can produce a variety of cytokines, including tumor necrosis factor-α, vascular endothelial growth factor (VEGF), and interleukin, which can promote tumor progression[25,26]. Neutrophil extracellular traps, which are secreted by neutrophils, can contribute to tumor metastasis by sequestering the tumor cell[27]. Donskov[28] reported that increased neutrophil levels infiltrating the tumor tissue and circulating in the blood are insufficient prognostic indexes in several cancers, including colorectal cancer, lung cancer, and head and neck cancer. With the combination of neutrophil and lymphocyte counts, NLR can be used as a representative index to indicate a systemic inflammatory response in patients with various cancers[6-8].

Hyperfibrinogenemia is involved in tumor aggressiveness in various malignancies[10-12]. Although many studies have investigated the causes of hyperfibrinogenemia in malignant tumors, the underlying mechanism remains unclear. Liver-produced fibrinogen is a major acute-phase protein. When a malignant neoplasm or systemic inflammation is present, the fibrinogen level in the plasma is increased; this fibrinogen can be transformed into fibrin by activated thrombin. Yamaguchi et al.[29] indicated that cancer cells can produce interleukin-6, which accelerates the secretion of fibrinogen in patients with lung cancer. Similarly, Sahni et al.[30] found that tumor cells

Table 3 Univariate analysis for DFS and OS

Item	DFS			OS		
	P	HR	95% CI	*P*	HR	95% CI
Age, years (≤ 60, >60)	0.478	1.085	0.866–1.360	0.391	1.104	0.881–1.384
Gender (male, female)	0.714	0.956	0.751–1.217	0.355	0.892	0.701–1.136
Smoking (yes, no)	0.783	0.967	0.761–1.229	0.375	0.897	0.705–1.141
Histology (adenocarcinoma, SqCC, others)	0.109	1.146	0.970–1.353	0.111	1.144	0.970–1.350
Tumor location (left, right)	0.604	0.941	0.749–1.183	0.562	0.935	0.744–1.175
Lesion (peripheral, central)	0.023	1.324	1.040–1.686	0.014	1.355	1.064–1.726
Resection type (pneumonectomy, lobectomy)	0.041	1.400	1.013–1.933	0.038	1.407	1.019–1.943
Pathological stage (I, II, IIIA)	<0.001	1.788	1.569–2.038	<0.001	1.783	1.564–2.031
Tumor size, cm (< 4, ≥4)	<0.001	1.796	1.415–2.281	<0.001	1.755	1.382–2.228
Adjuvant chemotherapy (yes, no)	0.138	1.187	0.946–1.488	0.217	1.153	0.920–1.445
Adjuvant radiotherapy (yes, no)	0.001	1.685	1.235–2.300	0.004	1.571	1.151–2.143
F-NLR (0, 1, 2)	<0.001	1.644	1.431–1.888	<0.001	1.647	1.434–1.891
NLR (≥2.30, <2.30)	<0.001	2.196	1.751–2.754	<0.001	2.199	1.753–2.757
Fibrinogen (<3.48 g/L，≥ 3.48 g/L)	<0.001	1.707	1.352–2.155	<0.001	1.733	1.373–2.188
LDH (≥195.5, <195.5 U/L)	0.003	1.443	1.134–1.835	0.005	1.415	1.112–1.799
D-dimer (≥0.15, <0.15 mg/L)	<0.001	1.546	1.232–1.939	0.002	1.437	1.144–1.803
Neutrophil ratio (≥62.35, <62.35%)	<0.001	2.015	1.607–2.526	<0.001	2.007	1.601–2.517
Monocyte ratio (≥8.97, <8.97%)	0.008	1.399	1.093–1.791	0.006	1.412	1.103–1.807
Lymphocyte ratio (≤ 26.55, >26.55%)	<0.001	0.450	0.359–0.565	<0.001	0.451	0.359–0.565
WBC count (≥7.805, <7.805×10^3/μL)	0.007	1.386	1.092–1.760	0.008	1.379	1.087–1.751
Platelet count (≥202, <202×10^9/L)	0.140	1.216	0.938–1.577	0.160	1.205	0.929–1.563
ALP (≥66.5, <66.5 U/L)	0.002	1.465	1.152–1.862	0.003	1.430	1.126–1.818
Hb (≤137.5, >137.5 g/L)	0.022	0.769	0.613–0.964	0.040	0.789	0.630–0.989

DFS: disease-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; SqCC: squamous cell carcinoma; F-NLR: combination of fibrinogen concentration and neutrophil to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; LDH: lactate dehydrogenase; WBC: white blood cell; ALP: alkaline phosphatase; Hb: hemoglobin.

can synthesize fibrinogen. Fibrinogen eventually stimulates tumor proliferation and angiogenesis by its interaction with VEGF and fibroblast growth factor-2[30,31]. When fibrinogen is converted, fibrin is involved in metastasis and new vessel formation[32,33]. Palumbo et al.[34] demonstrated that the fibrin formed around circulating tumor cells can prevent natural killer cells from killing tumor cells.

Hence, F-NLR presents a good prognostic indicator for patients with cancer. Fibrinogen or NLR alone may exert a limited effect on tumor progression. F-NLR increases the unfavorable effect of fibrinogen and NLR, which eventually increases the predicted significance for patients with cancer. Recently, Wang et al.[16] reported that patients with a low F-NLR score may exhibit a better prognosis than those with a high F-NLR score and that the preoperative F-NLR score can be considered a useful independent prognostic marker, consistent with the results of our study. In the present study, multivariate analysis using the characteristics selected in univariate analysis revealed that preoperative F-NLR was significantly correlated with DFS and OS, as well as pathological stage and D-dimer. According to the results of the Kaplan-Meier analysis and log-rank test, our study revealed that the preoperative F-NLR level can stratify the patients into different risk categories. Moreover, when the patients with different pathological stages were analyzed separately, the DFS and OS in the patients with F-NLR = 0 were higher than those with F-NLR = 1 or F-NLR = 2 in stage I and IIIA. However, in patients with stage II NSCLC, the

Table 4 Multivariate analysis for DFS and OS

Item	DFS			OS		
	P	HR	95% CI	*P*	HR	95% CI
Lesion (peripheral, central)	0.642	0.931	0.687–1.260	0.603	0.923	0.682–1.249
Resection type (pneumonectomy, lobectomy)	0.265	1.246	0.846–1.836	0.246	1.257	0.854–1.851
Pathological stage (I, II, IIIA)	<0.001	1.602	1.379–1.862	<0.001	1.648	1.419–1.914
Tumor size (< 4 cm, ≥4 cm)	0.951	0.991	0.751–1.309	0.878	0.978	0.741–1.292
Adjuvant radiotherapy (yes, no)	0.195	1.239	0.896–1.714	0.377	1.157	0.837–1.601
F-NLR (0, 1, 2)	<0.001	1.466	1.243–1.730	<0.001	1.512	1.283–1.783
LDH (≥195.5, <195.5 U/L)	0.186	1.196	0.917–1.560	0.294	1.152	0.885–1.500
D-dimer (≥0.15, <0.15 mg/L)	0.007	1.403	1.096–1.796	0.012	1.371	1.071–1.756
Monocyte ratio (≥8.97, <8.97%)	0.079	1.279	0.972–1.684	0.057	1.304	0.992–1.714
WBC count (≥7.805, <7.805×10^3/μL)	0.564	1.080	0.832–1.402	0.687	1.055	0.812–1.370
ALP (≥66.5, <66.5 U/L)	0.071	1.283	0.979–1.683	0.093	1.260	0.962–1.650
Hb (≤137.5, >137.5 g/L)	0.337	0.887	0.695–1.133	0.302	0.879	0.688–1.123

DFS: disease-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; F-NLR: combination of fibrinogen concentration and neutrophil to lymphocyte ratio; LDH: lactate dehydrogenase; WBC: white blood cell; ALP: alkaline phosphatase; Hb: hemoglobin.

correlation between F-NLR and prognosis was insignificant, which indicates that F-NLR may be more predictive in stage I or IIIA cancers than in stage II. Our study also found that the preoperative F-NLR level was significantly correlated with both DFS and OS in patients with adenocarcinoma or squamous carcinoma. Furthermore, a close relationship was observed between F-NLR and pathological stage, lesion, lymph node metastasis, and tumor size. To reveal the pathological status of tumor progression, preoperative F-NLR levels calculated from blood specimens should be evaluated. The advantage of the F-NLR score was based on the fibrinogen concentration and NLR, which were obtained from the routine blood sample analysis. Therefore, F-NLR may serve as a more inexpensive and widespread hematologic marker than other tumor markers.

This study had some limitations. First, this study was a retrospective analysis and all data were obtained from a single institute. Second, although we restricted the influence of other factors, blood cell counts can be influenced by a variety of factors.

Conclusions

The preoperative F-NLR score can be considered a valuable prognostic indicator in patients with NSCLC after surgery. A close relationship between F-NLR and cancer progression was also observed in patients with NSCLC who underwent surgery. Thus, F-NLR may be considered for routine clinical use as a reliable and low-cost biomarker.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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