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Original Article

Predictive value of systemic immune-inflammatory markers for lung cancer-associated cerebral infarction: a retrospective cohort study

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Abstract: To clarify the prognostic role of immune inflammatory biomarkers in lung cancer-related cerebral infarction (CI). This retrospective cohort study enrolled 152 lung cancer patients, and they were divided into a lung cancer with CI group (n=48) and a lung cancer without CI group (n=104); an additional 52 patients without lung cancer were included as the simple CI group. Observed endpoints included neutrophil (NEUT), lymphocyte (LYMPH), platelet (PLT), red cell distribution width (RDW), C-reactive protein (CRP), procalcitonin (PCT), systemic inflammatory index (SII), neutrophil/lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and Essen stroke risk score (ESRS). Cox regression model was used to screen independent risk factors for lung cancer-associated CI, and receiver operating characteristic (ROC) curves with area under the curve (AUC) were used to assess the predictive value of biomarkers. The incidence of CI in 152 lung cancer patients was 31.6%. Compared with lung cancer patients without CI, those with CI were older, had a higher proportion of stage IV disease, and showed elevated levels of ESRS, NEUT, PLT, RDW, CRP, PCT, SII, NLR, and PLR, while LYMPH levels were decreased (all $P<0.001$). Age ≥65 years, stage IV disease, SII≥1250×10^9/L, NLR≥7, and CRP≥10 mg/L were independent risk factors (all $P<0.001$). The SII-NLR-CRP combined model had the highest AUC (0.918), with 89.4% sensitivity and 90.4% specificity in predicting lung cancer-related CI. Systemic immune inflammatory markers have significant predictive value for lung cancer-related CI. The SII-NLR-CRP combined model exhibits excellent predictive efficacy for this condition, which is superior to individual biomarkers and provides a reliable reference for clinical evaluation.

Keywords: Lung cancer, cerebral infarction, systemic immune-inflammatory biomarkers, predictive value

Introduction

Malignant tumors are a leading cause of death globally, and their disease burden is increasing against the backdrop of a rapidly aging global population. According to data from the National Cancer Center of China, lung cancer ranks first in both incidence and mortality among malignant tumors. In 2023, China saw over 830,000 new cases and over 700,000 deaths from lung cancer, accounting for 23.9% of all cancer-related deaths [1]. Cerebral infarction (CI) is a common complication of lung cancer, significantly impacting patient prognosis. It not only leads to neurological deficits and reduced quality of life but also significantly increases treatment difficulty and medical costs [2, 3]. Therefore, identifying the relevant risk factors for CI in lung cancer patients and constructing an effective prediction system is of significant clinical value for early intervention and improving patient survival outcomes.

Tumor-associated thrombosis is a complex process. Lung cancer cells can directly invade the blood vessel wall or indirectly damage the vascular endothelial tissue by releasing cytokines, thereby disrupting the integrity of the blood vessel wall [4]. Tumor cells can also release tissue factors, carcinogens, and other mediators, activating the coagulation system while inhibiting the fibrinolytic system, leading to a hypercoagulable state [5]. In addition to the two mechanisms mentioned above, common

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accompanying factors in lung cancer, such as anemia, decreased activity levels, and malnutrition, can further exacerbate slow blood flow and coagulation abnormalities, thereby promoting thrombosis [6].

At present, the relationship between systemic immune inflammatory responses and tumor progression has received widespread attention. In the tumor microenvironment, the interaction between immune cells and inflammatory mediators can promote tumor proliferation, invasion, and metastasis, and is also associated with thrombosis [7]. Immune inflammatory cells are an essential component of the human immune inflammatory response, and changes in their number and function play a crucial role in tumor-associated thrombosis. Neutrophils (NEUTs) can activate platelets (PLT) and coagulation factors by releasing NEUT extracellular traps, thereby promoting thrombosis [8]. Lymphocytes (LYMPH) are the primary effector cells in anti-tumor immunity, and their functional suppression facilitates tumor immune escape, while also regulating coagulation function through cytokine networks. PLTs possess dual characteristics of immune regulation and coagulation, and can participate in the thrombosis process through interactions with tumor cells and immune cells [9]. Comprehensive indicators derived from immune inflammatory cells, such as systemic inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), have been proven to be closely related to the prognosis of various malignancies and the risk of thromboembolism [10].

In addition to the aforementioned cellular immune inflammatory biomarkers, soluble inflammatory mediators and hematological indicators such as C-reactive protein (CRP), procalcitonin (PCT), and red blood cell distribution width (RDW) also play important roles in tumor-associated immune inflammatory responses [11]. CRP, a classic acute-phase reactant, indicates the presence of inflammation when elevated, and can accelerate thrombus formation by activating the complement system and PLT aggregation [12]. PCT is a sensitive marker of bacterial infection and sepsis, and its levels are usually elevated in cancer patients with infectious complications; infection itself is also an important trigger for thrombosis [13]. RDW is closely associated with the body's inflammatory status, nutritional status, and oxidative stress levels; abnormally elevated RDW can indirectly promote thrombus formation by reducing erythrocyte deformability and affecting hemodynamics [14, 15]. Currently, these immune-inflammatory biomarkers have been applied to the prognostic assessment and complication prediction of various malignant tumors, but systematic clinical evidence regarding their prediction of lung cancer-related CI remains scarce.

The innovation of this study lies in its systematic exploration of the association between multiple systemic immune-inflammatory biomarkers and the risk of lung cancer-related CI, providing clinical evidence from the perspective of immune-inflammatory activity to explain the high incidence of CI in lung cancer patients. This study screened systemic immune-inflammatory biomarkers with high predictive efficacy and constructed a comprehensive predictive model, providing a simple, economical, and easily accessible tool for assessing the risk of lung cancer-related CI. This helps in the early identification of CI risk in lung cancer patients, facilitating timely preventive interventions for high-risk groups by clinicians.

In conclusion, systematic research on the prediction of lung cancer-related CI using immune-inflammatory biomarkers is of practical significance and an urgent need in clinical practice. This study aims to fill the existing research gap through a retrospective cohort study design, providing a new perspective for the risk prediction and clinical prevention and treatment of lung cancer-related CI.

Materials and methods

Patient screening

Study design and participants: This retrospective cohort study included patients admitted to the First Affiliated Hospital of Henan Medical University from January 2022 to December 2024. A total of 222 lung cancer patients were initially screened. After applying the inclusion and exclusion criteria, 206 patients were identified. Among these, 54 patients with CI unrelated to lung cancer were excluded based on the diagnostic criteria for lung cancer-associated CI. Ultimately, 152 lung cancer patients

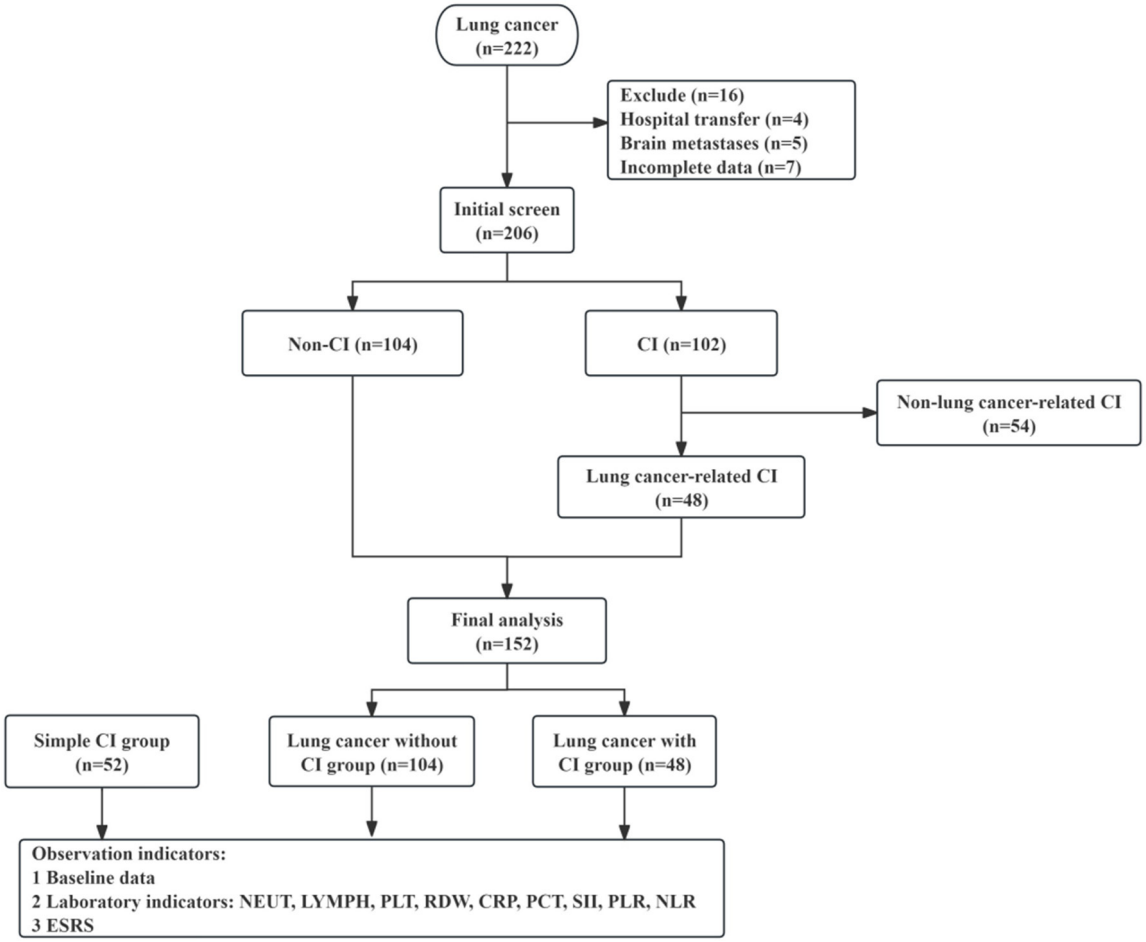

Figure 1. Study flow chart. NEUT: Neutrophil; LYMPH: Lymphocyte; PLT: Platelet; RDW: Red Cell Distribution Width; CRP: C-reactive Protein; PCT: Procalcitonin; SII: Systemic Inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; ESRS: Essen Stroke Risk Score; CI: Cerebral Infarction.

were enrolled and divided into two groups according to the occurrence of CI during the treatment period: the lung cancer with CI group (n=48) and the lung cancer without CI group (n=104). In addition, 52 patients with non-lung cancer CI admitted during the same period were selected as the simple CI group (**Figure 1**).

Inclusion criteria: (1) Definitive diagnosis of lung cancer confirmed by pathological examination, in accordance with the diagnostic criteria specified in the Clinical Practice Guidelines for Lung Cancer (2023 Edition) [16]; (2) Age ≥18 years; (3) Received standardized treatment in the First Affiliated Hospital of Henan Medical University for at least 1 month; (4) Complete clinical data available.

Exclusion criteria: (1) History of other malignant tumors or presence of brain metastasis from lung cancer; (2) History of thromboembolic diseases (such as CI, myocardial infarction, deep vein thrombosis) within 6 months prior to admission, or receiving long-term anticoagulant therapy; (3) Complicated with severe infectious diseases or autoimmune diseases; (4) Complicated with severe liver or kidney dysfunction, hematological diseases, or other severe underlying conditions [17]; (5) Incomplete clinical data; (6) Patients who were transferred to another hospital or abandoned treatment midway.

Diagnostic criteria for lung cancer-associated CI: (1) Acute onset with symptoms of neurological deficit; (2) Newly identified CI lesions on cranial CT or MRI, in accordance with the imaging diagnostic criteria stated in the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2023 [18]; (3) CI occur-

ring after the diagnosis of lung cancer and during the course of treatment; (4) Exclusion of other definite etiologies by neurologists based on imaging features (multiple bilateral lesions in different vascular territories or findings consistent with the imaging characteristics of Trousseau syndrome) and laboratory results (markedly elevated D-dimer, abnormal fibrinogen levels, etc.), including large-artery atherosclerotic CI (≥50% stenosis of the carotid or intracranial large arteries or presence of unstable plaques), cardioembolism (atrial fibrillation, valvular heart disease, recent myocardial infarction, and other cardiac disorders), small-vessel occlusive disease (arteriolar hyalinosis caused by hypertension, diabetes mellitus, etc.), and other definite causes (vasculitis, non-neoplastic hypercoagulable states, trauma, etc.).

All cases of lung cancer-associated CI were confirmed by two independent neurologists (associate chief physician or higher) who reached a consensus after separate evaluations [18].

Data collection: For all lung cancer patients enrolled in the study, fasting peripheral venous blood samples were collected within 7 days after pathological confirmation of lung cancer (baseline) and before the clinical diagnosis of CI. For patients who developed CI, a second blood sample was collected within 24 hours after CI diagnosis. For patients in the lung cancer without CI group, blood test data at corresponding time points matched for disease course and hospitalization period were selected to ensure comparability of baseline blood sampling timing. For patients in the simple CI group, peripheral venous blood samples were collected within 7 days before and within 24 hours after CI diagnosis. All collected data were used for baseline and comparative analyses.

Observation indicators

Routine blood test indicators: The test indicators included NEUT, LYMPH, PLT, and RDW. All were measured using a fully automated blood analyzer (Sysmex XN-9000, Sysmex Medical Electronics (Shanghai) Co., Ltd., China).

Inflammatory factor indicators: CRP was measured using an immunoturbidimetric assay on a fully automated biochemical analyzer (Beckman Coulter AU5800, Beckman Coulter Trading (China) Co., Ltd., USA).

PCT was measured using an electrochemiluminescence immunoassay on a fully automated analyzer (Roche Cobas e601, Roche Diagnostics Products (Shanghai) Co., Ltd., Switzerland).

Composite immune-inflammatory biomarkers: Composite biomarkers, including SII, NLR, and PLR, were calculated using the complete blood count data from Section 2.3.1. The specific formulas and reference standards are as follows:

SII = PLT ($\times10^9$/L) × NEUT ($\times10^9$/L)/LYMPH ($\times10^9$/L). A value <330.0×10^9/L indicates a low inflammatory state, while ≥330.0×10^9/L indicates a high inflammatory state.

NLR = NEUT ($\times10^9$/L)/LYMPH ($\times10^9$/L). This is a dimensionless ratio; <2.5 is normal, 2.5-5.0 is slightly elevated, and >5.0 is significantly elevated.

PLR = PLT ($\times10^9$/L)/LYMPH ($\times10^9$/L). This is also a dimensionless ratio; <150 is normal, and ≥150 is elevated [19, 20].

ESRS: ESRS was used to assess the risk of recurrent ischemic stroke. The scoring system is based on 9 clinical risk factors: age ≥65 years, hypertension, diabetes, history of myocardial infarction, other cardiovascular diseases (including angina and valvular heart disease, excluding atrial fibrillation), peripheral artery disease, smoking history (current smoking or cessation <1 year), history of ischemic stroke/transient ischemic attack (TIA), and atrial fibrillation. Each risk factor scores 1 point, with a total score ranging from 0 to 9. Higher scores indicate a higher risk of ischemic stroke.

Clinical outcome indicator: The primary outcome indicator was the occurrence of CI, diagnosed using a head CT scanner (GE Revolution EVO, GE Healthcare (China) Co., Ltd., China) or a cranial MRI scanner (Siemens Prisma 3.0T, Siemens Healthcare Systems Co., Ltd., Germany).

Ethical statement

This study strictly adhered to the Declaration of Helsinki [21], and the study protocol was approved by the Medical Ethics Committee of

the First Affiliated Hospital of Henan Medical University (Ethics Approval No.: EC-2025-744). Because this study did not interfere with the patient's diagnosis or treatment process, did not increase additional medical risks, and all data were routinely collected clinical information, the Ethics Committee approved a waiver of informed consent.

Sample size calculation

The sample size was calculated using the standard formula for cohort studies:

$n = (Z\alpha/2\sqrt{[P(1-P)]} + Z\beta\sqrt{[P0(1-P0) + P1(1-P1)]})^2/(P1-P0)^2$.

Referring to reported incidence rates of 30%-35% in similar studies [22, 23] and our team's previous clinical data, the expected overall incidence of the outcome event was set at 32%. With a Type I error α of 0.05 (two-sided, Zα/2=1.96), a power of 90% (Zβ=1.28), a moderate effect size (Cohen's d=0.5), and a case-control ratio of 1:2, the minimum required total sample size was calculated to be 138 cases (46 in the lung cancer with CI group and 92 in the lung cancer without CI group). Considering the potential for missing data in retrospective studies, the sample size was increased by 10%-15%.

The final enrolled sample of 152 patients (48 with CI, 104 without CI) met the minimum requirements for Cox regression and ROC curve analysis, and the observed incidence of 31.6% was consistent with the pre-specified value.

Statistical analysis

SPSS 27.0 software was applied for data analysis. Normality tests (Kolmogorov-Smirnov test) and homogeneity of variance tests (Lvene test) were performed on the continuous data. Normally distributed and homogeneous variance-compliant continuous data are expressed as mean ± standard deviation (mean ± SD), and one-way ANOVA was used for comparisons between groups. Non-normally distributed continuous data were expressed as median (interquartile range) [M (Q1, Q3)], and Kruskal-Wallis test is used for comparisons between groups. Count data were expressed as number of cases (percentage) [n (%)], and chi-square test was used.

Cox proportional hazards used to exclude confounding factors and screen for independent risk factors for lung cancer-related CI. Receiver operating characteristic (ROC) curve analysis was used to determine the predictive value of each immune inflammatory marker and the combined model, and the area under the curve (AUC) was calculated. All statistical tests were two-tailed, and P<0.05 was considered statistically significant.

Results

Comparison of baseline characteristics and multivariate analysis

As shown in **Table 1**, the average age of patients in the lung cancer with CI group and the simple CI group was significantly higher than that in the lung cancer without CI group (P<0.001), while no significant differences were observed in BMI or sex distribution among the three groups (all P>0.05). Pathological type distribution was comparable between the two lung cancer groups (P=0.781), but the proportion of patients with stage IV tumors was significantly higher in the lung cancer with CI group than in the lung cancer without CI group (P<0.001). The proportions of patients with hypertension, diabetes, and coronary heart disease (CHD) were significantly higher in both the lung cancer with CI group and the simple CI group compared with the lung cancer without CI group (all P<0.05), whereas smoking history showed no difference among the three groups (P=0.839). Treatment regimens did not differ significantly between the two lung cancer groups (P=0.330).

Multivariate logistic regression analysis (**Table 2**) showed that age (OR=1.094, 95% CI: 1.004-1.147, P<0.001), tumor stage (OR=1.882, 95% CI: 1.574-2.251, P<0.001), ESRS (OR=1.102, 95% CI: 1.062-1.142, P<0.001), hypertension (OR=1.126, 95% CI: 0.875-1.449, P=0.036), and CHD (OR=1.183, 95% CI: 0.924-1.512, P=0.033) were independently associated with an increased risk of lung cancer-associated CI. BMI, sex, pathological type, smoking history, diabetes, and treatment regimen showed no significant associations (all P>0.05).

Comparison of individual biomarkers

As shown in **Table 3**, levels of NEUT, PLT, RDW, CRP, and PCT were significantly higher in both

Table 1. Comparison of baseline data [mean ± SD, n (%)]

Indicators	Lung cancer with CI group (n=48)	Simple CI group (n=52)	Lung cancer without CI group (n=104)	*P*	Effect size
Age (years)	68.25±4.08	66.92±6.33	62.33±4.47	<0.001	η^2=0.228
BMI (kg/m^2)	24.83±1.10	24.76±1.09	24.79±0.88	0.938	η^2=0.001
Gender (n%)				0.932	Cramer's V=0.026
Male	29 (60.4)	31 (59.6)	65 (62.5)		
Female	19 (39.6)	21 (40.4)	39 (37.5)		
Pathological Type (n%)				0.781	Cramer's V=0.057
Adenocarcinoma	27 (56.2)	0 (0.0)	56 (53.8)		
Squamous Carcinoma	14 (29.2)	0 (0.0)	28 (26.9)		
SCLC	7 (14.6)	0 (0.0)	20 (19.2)		
Tumor Staging (n%)				<0.001	Cramer's V=0.300
I-III	17 (35.4)	0 (0.0)	70 (67.3)		
IV	31 (64.6)	0 (0.0)	34 (32.7)		
Smoking History (n%)	25 (52.1)	26 (50.0)	49 (47.1)	0.839	Cramer's V=0.041
Hypertension (n%)	30 (62.5)	31 (59.6)	40 (38.5)	0.005	Cramer's V=0.226
Diabetes (n%)	18 (37.5)	20 (38.5)	23 (22.1)	0.046	Cramer's V=0.174
CHD (n%)	15 (31.2)	16 (30.8)	17 (16.3)	0.031	Cramer's V=0.184
Therapeutic Regimen (n%)				0.330	Cramer's V=0.150
Surgery	11 (22.9)	0 (0.0)	30 (28.8)		
Chemotherapy	15 (31.2)	0 (0.0)	42 (40.4)		
Chemotherapy + Immunotherapy	20 (41.7)	0 (0.0)	28 (26.9)		
Others	2 (4.2)	0 (0.0)	4 (3.8)		

Note: BMI: Body Mass Index; SCLC: Small Cell Lung Cancer; CHD: Coronary Heart Disease; SD: Standard Deviation; 95% CI: 95% Confidence Interval; CI: Cerebral Infarction.

Table 2. Results of multivariate linear regression analysis (effects of confounding factors)

Indicators	β	P	HR	95% CI for HR
Age (years)	-0.24	<0.001	1.094	1.004, 1.147
BMI (kg/m^2)	0.06	0.634	1.062	0.827, 1.365
Gender (n%)	-0.38	0.352	0.683	0.306, 1.525
Pathological Type (n%)	-0.42	0.412	0.657	0.277, 1.556
Tumor Staging (n%)	-1.25	<0.001	1.882	1.574, 2.251
Smoking History (n%)	-0.34	0.391	0.711	0.326, 1.550
Hypertension (n%)	-0.89	0.036	1.126	0.875, 1.449
Diabetes (n%)	-0.72	0.102	1.085	0.812, 1.452
CHD (n%)	-0.95	0.033	1.183	0.924, 1.512
Therapeutic Regimen (n%)	-0.62	0.156	1.075	0.798, 1.447
ESRS	-0.68	<0.001	1.102	1.062, 1.142

Note: ESRS: Essen Stroke Risk Score; HR: Hazard Ratio; BMI: Body Mass Index; CHD: Coronary Heart Disease; 95% CI: 95% Confidence Interval.

the lung cancer with CI group and the simple CI group than in the lung cancer without CI group (all P<0.05), while LYMPH levels were significantly lower (P<0.05). These findings indicate more pronounced inflammatory responses and abnormal hematopoietic indicators in patients with CI.

Comparison of composite inflammatory index

As shown in **Table 4**, the composite inflammatory indices (SII, NLR, and PLR) were significantly higher in both the lung cancer with CI group and the simple CI group than in the lung cancer without CI group (all P<0.05), indicating a robust systemic inflammatory response consistent with ischemic injury.

Comparison of ESRS

As shown in **Table 5**, ESRS was significantly higher in both the lung cancer with CI group and the simple CI group than in the lung cancer without CI group (all P<0.05).

Table 3. Comparison of individual biomarker (mean ± SD)

Indicators	Lung cancer with CI group (n=48)	Simple CI group (n=52)	Lung cancer without CI group (n=104)	*P*	*Effect size* (η^2)
NEUT ($\times10^9$/L)	7.95±1.09[a,b]	7.21±1.74[a]	5.18±0.71	<0.001	0.537
LYMPH ($\times10^9$/L)	0.82±0.31[a,b]	0.97±0.39[a]	1.34±0.24	<0.001	0.367
PLT ($\times10^9$/L)	325.54±29.35[a,b]	310.25±44.92[a]	245.37±17.16	<0.001	0.610
RDW (%)	15.23±0.98[a,b]	14.27±2.36[a]	13.13±0.64	<0.001	0.292
CRP (mg/L)	19.89±10.92[a,b]	16.09±9.39[a]	6.94±3.60	<0.001	0.363
PCT (ng/mL)	0.67±0.37[a,b]	0.54±0.32[a]	0.22±0.10	<0.001	0.383

Note: [a]*P*<0.05 vs. Lung cancer without CI group; [b]*P*<0.05 vs. Simple CI group; NEUT: Neutrophil; LYMPH: Lymphocyte; PLT: Platelet; RDW: Red Cell Distribution Width; CRP: C-reactive Protein; PCT: Procalcitonin; CI: Cerebral Infarction; SD: Standard Deviation.

Table 4. Comparison of composite inflammatory index (mean ± SD)

Indicators	Lung cancer with CI group (n=48)	Simple CI group (n=52)	Lung cancer without CI group (n=104)	*P*	*Effect size* (η^2)
SII ($\times10^9$/L)	1831.04±551.97[a,b]	1608.46±595.67[a]	818.94±211.54	<0.001	0.533
NLR	10.62±2.71[a,b]	9.10±3.58[a]	3.94±0.21	<0.001	0.643
PLR	442±133.96[a,b]	392.46±124.60[a]	188.74±20.63	<0.001	0.617

Note: [a]*P*<0.05 vs. Lung cancer without CI group; [b]*P*<0.05 vs. Simple CI group; SII: Systemic Inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; CI: Cerebral Infarction; SD: Standard Deviation.

Table 5. Comparison of ESRS (mean ± SD)

Indicators	Lung cancer with CI group (n=48)	Simple CI group (n=52)	Lung cancer without CI group (n=104)	*P*	*Effect size* (η^2)
ESRS (scores)	5.17±1.26[a,b]	4.04±1.10[a]	1.21±0.75	<0.001	0.759

Note: [a]*P*<0.05 vs. Lung cancer without CI group; [b]*P*<0.05 vs. Simple CI group; CI: Cerebral Infarction; SD: Standard Deviation; ESRS: Essen Stroke Risk Score.

Independent risk factors for CI in lung cancer patients

Univariate Cox proportional hazards regression analysis was performed for all candidate variables. Variables with P<0.10 were included in the multivariate model. The Schoenfeld residual test confirmed that the proportional hazards assumption was met (all P>0.05).

After adjusting for confounding factors (demographic characteristics, tumor-related indicators, underlying diseases, and lifestyle history) (**Table 6**), the results showed that age ≥65 years, stage IV lung cancer, SII≥1250×10^9/L, NLR≥7, and CRP≥10 mg/L were independent risk factors for CI in patients with lung cancer.

Age ≥65 years (HR=1.094, 95% CI: 1.004-1.147, P<0.001) and stage IV lung cancer (HR=1.882, 95% CI: 1.574-2.251, P<0.001) were associated with a modest increase in risk. Elevated inflammatory markers, including CRP≥10 mg/L (HR=2.989, 95% CI: 2.156-4.144, P<0.001), NLR≥7 (HR=2.009, 95% CI: 1.637-2.465, P<0.001), and SII≥1250×10^9/L (HR=1.023, 95% CI: 1.017-1.030, P<0.001) were all significant independent predictors.

Notably, the combined model incorporating all three inflammatory markers (CRP+SII+NLR) demonstrated the strongest predictive power. Patients meeting all three criteria had a 6.26-fold increased risk of cerebral infarction compared with those meeting none (HR=6.26, 95% CI: 3.359-11.666, P<0.001).

Conversely, RDW≥14%, PCT≥0.35 ng/mL, PLR ≥300, hypertension, diabetes, and coronary heart disease were not identified as independent risk factors in this adjusted model (all P>0.05).

Based on the Cox regression results, a combined prediction model incorporating CRP, SII, and NLR was constructed with the following

Table 6. Analysis of independent risk factors

Indicators	*B*	*P*	HR	95% CI for HR
Age (≥65 years)	0.090	<0.001	1.094	1.004, 1.147
Stage IV Lung Cancer	0.632	<0.001	1.882	1.574, 2.251
RDW (≥14%)	-0.246	0.159	0.782	0.555, 1.101
CRP≥10 mg/L	1.095	<0.001	2.989	2.156, 4.144
PCT≥0.35 ng/mL	0.278	0.555	1.321	0.459, 2.727
SII≥1250×10^9/L	0.023	<0.001	1.023	1.017, 1.030
NLR≥7	0.698	<0.001	2.009	1.637, 2.465
PLR≥300	0.422	0.174	1.524	0.565, 2.136
Hypertension	0.586	0.285	1.796	1.002, 3.656
Diabetes	0.219	0.265	1.245	0.745, 2.589
CHD	0.437	0.857	1.547	0.845, 3.121
CRP+SII+NLR	1.834	<0.001	6.26	3.359, 11.666

Note: HR: Hazard Ratio; 95% CI: 95% Confidence Interval; RDW: Red Cell Distribution Width; CRP: C-reactive Protein; PCT: Procalcitonin; SII: Systemic Inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio.

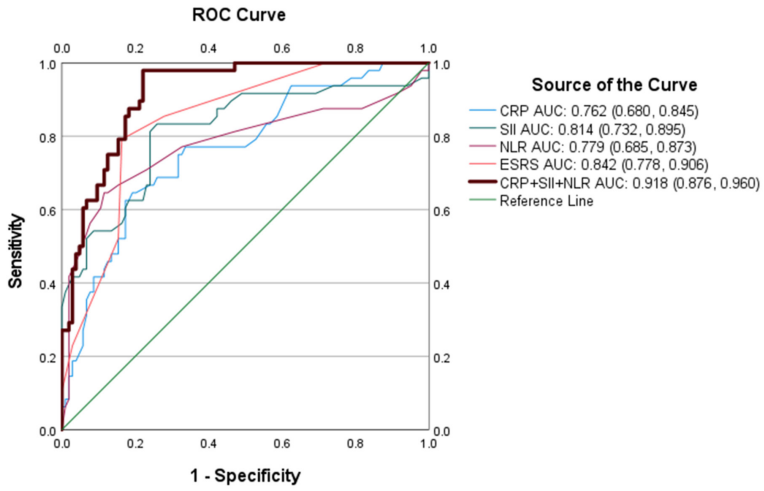

Figure 2. Predictive efficacy of indicators for cerebral infarction in patients with lung cancer. Note: The ROC curve of SII, CRP, NLR, ESRS and combined model (CRP+SII+NLR) was plotted, and the results demonstrated the predictive efficacy of SII, CRP, NLR, ESRS and combined model (CRP+SII+NLR). ROC: Receiver Operating Characteristic; AUC: Area under the Curve; CRP: C-reactive Protein; SII: Systemic Inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; ESRS: Essen Stroke Risk Score.

prediction formula: Logit(P) = 1.834 + 1.095 × CRP + 0.023 × SII + 0.698 × NLR.

Predictive efficacy for CI in lung cancer patients

ROC curve analysis was performed to evaluate the predictive efficacy of individual indicators and the combined model for CI in lung cancer patients. Among single inflammatory indicators, SII exhibited the highest AUC (0.814, 95% CI: 0.732-0.895), followed by NLR (AUC=0.779, 95% CI: 0.685-0.873), CRP (AUC=0.762, 95% CI: 0.680-0.845) and ESRS (AUC=0.842, 95% CI: 0.778-0.906) (**Figure 2**). All four indicators demonstrated moderate predictive value.

Notably, the combined model incorporating CRP, SII, and PLR showed optimal predictive efficacy, with an AUC of 0.918 (95% CI: 0.876-0.960) (**Figure 2**), which was significantly higher than that of any single indicator (all *P*<0.05) (**Table 7**). The combined model showed a sensitivity of 88.6%, a specificity of 85.4%, and a negative predictive value of 91.3%, which can effectively rule out low-risk patients.

These findings suggest that combined detection of inflammation-related indicators improves the accuracy of predicting CI risk in lung cancer patients, providing a more reliable assessment tool for early clinical identification of high-risk populations.

Comparison of indicators after CI

After the onset of CI, the lung cancer with CI group had significantly higher levels of NEUT (P<0.001), PLT (P=0.021), RDW (P=0.002), CRP (P<0.001), PCT (P=0.009), SII (P<0.001), NLR (P<0.001) and PLR (P<0.001) than those with simple CI. In contrast, LYMPH levels were significantly lower in the lung cancer with CI group than in the simple CI group (P=0.012) (**Table 8**). These results indicate that patients with lung cancer complicated by CI exhibit more severe systemic inflammatory responses and immune disorders than those with simple CI.

Table 7. Predictive efficacy of CI in patients with lung cancer

Indicators	Area	95% CI for area	*Z*	*Delong (P)*	*Cut-off Value*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
CRP	0.762	0.68, 0.845	-3.994	<0.001	>10 mg/L	68.5	74.2	62.3	79.1
SII	0.814	0.732, 0.895	-2.40	0.016	≥1250×10^9/L	75.3	78.6	68.9	83.4
NLR	0.779	0.685, 0.873	-2.925	0.003	≥7	71.2	76.8	65.4	81.2
CRP+SII+NLR	0.918	0.876, 0.960	-	-	≥2 points	88.6	85.4	82.1	91.3
ESRS	0.842	0.778, 0.906	2.128	0.033	≥3	79.4	80.2	72.6	85.8

Note: *P* and *Z*: vs. CRP+SII+NLR; PPV: Positive Predictive Value; NPV: Negative Predictive Value; CRP: C-reactive Protein; SII: Systemic Inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; ESRS: Essen Stroke Risk Score.

Table 8. Comparison of indicators after CI (mean ± SD)

Indicators	Lung cancer with CI group (n=48)	Simple CI group (n=52)	*P*	*Effect size (Cohen'S D)*
NEUT (×10^9/L)	10.97±1.46	8.87±1.12	<0.001	1.622
LYMPH (×10^9/L)	0.61±0.21	0.79±0.46	0.012	0.502
PLT (×10^9/L)	336.67±8.46	320.17±31.77	0.021	0.469
RDW (%)	17.12±1.48	16.16±1.45	0.002	0.652
CRP (mg/L)	28.92±4.39	21.48±3.49	<0.001	1.884
PCT (ng/mL)	0.95±0.24	0.74±0.51	0.009	0.532
SII (×10^9/L)	2079.04±265.09	1840.31±185.73	<0.001	1.05
NLR	12.04±2.11	10.43±1.25	<0.001	0.938
PLR	469.23±60.45	413.10±29.35	<0.001	1.197

Note: CI: Cerebral Infarction; NEUT: Neutrophil; LYMPH: Lymphocyte; PLT: Platelet; RDW: Red Cell Distribution Width; CRP: C-reactive Protein; PCT: Procalcitonin; SII: Systemic Inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; SD: Standard Deviation.

Table 9. Comparison of specificity of the combined prediction models

Indicators	Area	95% CI for area	Sensitivity	Specificity
Lung cancer CI group	0.824	0.76, 0.888	89.4%	90.4%
Simple CI group	0.609	0.515, 0.703	71.2%	58.7%

Note: CI: Cerebral Infarction.

Comparison of specificity of the combined prediction models

Table 9 presents a comparison of the predictive performance of the combined model between the lung cancer complicated by CI group and the simple CI group. In the lung cancer complicated by CI group, the combined model achieved a relatively high AUC of 0.824, with a sensitivity of 89.4% and a specificity of 90.4%. In contrast, in the simple CI group, the combined model had a much lower AUC of 0.609, with a sensitivity of 71.2% and a specificity of 58.7%. Overall, the combined prediction model demonstrated superior diagnostic value in the lung cancer complicated by CI group compared with the simple CI group.

Discussion

CI is a severe cerebrovascular complication that can occur during the clinical course of lung cancer [24]. Systemic immune-inflammatory biomarkers have been identified as being strongly correlated with prognosis, distant metastasis, and thrombotic events in various malignant tumors. However, systematic studies on the value of systemic immune-inflammatory biomarkers in predicting lung cancer-associated CI remain scarce [25]. Therefore, this retrospective cohort study explored the predictive value of systemic immune-inflammatory biomarkers for lung cancer-associated CI, aiming to provide evidence-based support for early clinical identification of high-risk patients and the formulation of individualized intervention strategies.

A cohort of 204 lung cancer patients was enrolled in the current study, with a CI incidence of 31.6%. This incidence was higher than the

thromboembolic event rate in the general lung cancer population, indicating a significantly elevated risk of CI in lung cancer patients. Baseline data analysis showed that the average age and percentage of stage IV lung cancer patients in the lung cancer CI group and simple CI group were notably higher than those in the lung cancer without CI group, which is consistent with previous findings that advanced age and late-stage tumors are risk factors for malignancy-associated thrombosis [26, 27]. In terms of laboratory indicators, the lung cancer with CI group exhibited elevated levels of inflammatory and hematopoietic indicators (NEUT, PLT, RDW, CRP, PCT), significantly reduced LYMPH, and higher levels of composite immune-inflammatory biomarkers (SII, NLR, PLR). These results reflect a marked immune imbalance and inflammatory activation in lung cancer patients with CI [28]. Cox proportional hazards model further confirmed that age ≥65 years, stage IV lung cancer, SII≥1250×10^9/L, NLR≥7, and CRP≥10 mg/L might represent independent risk factors for CI in patients diagnosed with lung cancer.

After the onset of CI, the levels of NEUT, PLT, RDW, CRP, PCT, SII, NLR, and PLR in the lung cancer by CI group were significantly higher than those in the simple CI group, while the level of LYMPH was significantly lower in the former group than in the latter. The combined prediction model for the lung cancer with CI group achieved a sensitivity of 89.4% and a specificity of 90.4%. In contrast, the combined prediction model for the simple CI group showed a sensitivity of 71.2% and a specificity of 58.7%. Collectively, the combined prediction model may exhibit superior diagnostic value in the lung cancer with CI group compared with that in the simple CI group.

Lung cancer cells can activate the immune system by releasing pro-inflammatory cytokines, promoting NEUT proliferation, and inducing lymphocyte apoptosis, potentially leading to an increase in NLR [29]. Inflammatory factors can damage vascular endothelial cells and activate the coagulation system, thereby increasing the risk of thrombosis. As a classic inflammatory marker, elevated CRP levels can, to some extent, reflect the severity of systemic inflammation. CRP can also induce the expression of vascular endothelial adhesion molecules, further promoting PLT aggregation and increasing the likelihood of thrombosis [30].

SII integrates changes in the levels of NEUT, LYMPH, and PLT, comprehensively reflecting the body's immunosuppressive status and tendency for thrombosis. Elevated levels of these markers often indicate that lung cancer patients may simultaneously exhibit abnormal immune function and coagulation disorders, thus potentially providing a more comprehensive reference for predicting the risk of CI [31]. Advanced age and late-stage lung cancer themselves are high-risk factors for thrombotic events. Elderly patients exhibit decreased vascular elasticity and impaired coagulation regulation, while stage IV lung cancer patients have a high tumor burden and a high rate of distant metastasis, which can induce a tumor-associated hypercoagulable state [32]. These factors act in concert with immune-inflammatory biomarkers, further increasing the risk of CI. ROC curve analysis demonstrated that SII possessed the highest predictive efficacy among single biomarkers, and the combined model constructed with SII, NLR, and CRP exhibited significantly superior predictive efficacy compared with single biomarkers.

Elevated systemic immune-inflammatory markers, including SII, NLR, and CRP, play a pivotal, multi-faceted role in the pathogenesis of lung cancer-associated CI by orchestrating a pathological cascade linking chronic systemic inflammation, immune dysregulation, endothelial dysfunction, and hypercoagulability.

Mechanistically, lung cancer cells secrete abundant pro-inflammatory cytokines (IL-6, TNF-α, G-CSF) that drive neutrophilic leukocytosis, promote the formation of pro-thrombotic tumor-associated neutrophils, and induce the release of neutrophil extracellular traps (NETs). NETs directly capture platelets and erythrocytes to form thrombotic nuclei while activating the intrinsic coagulation pathway [33]. Concurrently, these cytokines suppress adaptive immunity via PD-L1/PD-1 and TGF-β signaling, causing lymphopenia that impairs endothelial repair and immune clearance of microthrombi, thereby elevating NLR as a surrogate marker of this pro-inflammatory/immunosuppressive imbalance [29].

As an integrated biomarker, SII amplifies this pathogenic axis by incorporating thrombocytosis: cancer-derived thrombopoietin and mucins stimulate megakaryopoiesis and platelet hyperactivation, with activated platelets releasing P-selectin, vWF, and CD40L to enhance endothelial adhesion, aggregate formation, and tissue factor expression - initiating the extrinsic coagulation cascade. CRP, synthesized hepatically in response to IL-6, further potentiates thrombosis by activating endothelial VCAM-1/ICAM-1 expression, inhibiting fibrinolysis via PAI-1 upregulation, and triggering the NLRP3 inflammasome to release IL-1β, forming a self-sustaining inflammatory loop.

At the molecular level, these markers converge on NF-κB, STAT3, and MAPK signaling pathways, which upregulate TF, pro-adhesive molecules, and pro-coagulant factors while disrupting endothelial tight junctions (ZO-1, occludin) to increase blood-brain barrier permeability [26]. A recent five-year study [33] confirmed that NLR drives hypercoagulability via the NF-κB-TF axis. Another study [12] delineated CRP's role in amplifying inflammation and coagulation via IL-1β release. In conclusion, SII, NLR, and CRP are not merely passive indicators but also active mediators that synergistically drive a vicious cycle of inflammation-immune dysregulation-coagulation activation, ultimately leading to endothelial injury, arterial thrombosis, and cerebral infarction in patients with lung cancer.

In studies on NSCLC prognosis prediction [34], the AUC of SII was 0.853 (95% CI: 0.802-0.908) and that of NLR was 0.727 (95% CI: 0.664-0.808), which are close to the predictive efficacy of SII and NLR in this study. A prospective cohort study [35] investigating the relationship between CRP and lung cancer showed that CRP was correlated with lung cancer risk, with an AUC of 0.79 (95% CI: 0.76-0.81), which is consistent with the predictive efficacy of CRP in this study. These studies collectively support the close association between systemic immune-inflammatory biomarkers and lung cancer-associated CI, with the core mechanism pointing to inflammation-mediated vascular endothelial injury and hypercoagulable state.

Nevertheless, the outcomes of the present study are inconsistent with those of certain prior investigations. In a study on peripheral blood inflammatory biomarkers predicting outcomes in NSCLC [34], PLR emerged as a valid predictor of both patients' response to neoadjuvant immunotherapy and their prognostic outlook. However, in this study, PLR had relatively low predictive efficacy and failed to qualify as an independent predictive risk factor. Another related investigation indicated that elevated RDW was an independent prognostic factor for overall survival in NSCLC patients who underwent surgical intervention.

The main reasons for the above differences include heterogeneity of the study population, definition of endpoint events, and differences in sample characteristics. First, variations in pathological type distribution may lead to divergent results: adenocarcinoma accounted for more than 50% of patients in this study, whereas most similar studies focused primarily on squamous cell carcinoma [7]. Different pathological types of lung cancer secrete distinct inflammatory and procoagulant profiles, which may affect the predictive performance of each biomarker [36]. Second, the setting of endpoint events significantly influences research outcomes. Existing studies mostly use overall survival or all-cause death as endpoints [24], whereas this study specifically focused on cancer-associated cerebral infarction, a specific thrombotic complication, targeting a completely distinct clinical outcome. Third, differences exist in sample size and statistical methodologies. Recent large-sample studies mainly adopted nomogram construction to validate the prognostic value of indicators such as NLR and CAR [3]. In contrast, this study employed propensity score matching combined with Cox regression analysis, which effectively reduced selection bias and confounding bias, enabling more rigorous and reliable risk stratification for lung cancer-associated cerebral infarction. This analytical framework better aligns with the clinical characteristics of acute cerebrovascular events in patients with lung cancer, thereby yielding results with greater clinical applicability and robustness.

The innovations of this study are mainly reflected in three aspects. First, it focuses on lung cancer-associated CI as a specific complication, which differs from previous studies that conducted general analyses of all thrombotic

events, and more specifically reveals the association between immune-inflammatory biomarkers and cerebrovascular thrombosis. Second, a combined prediction model of SII, NLR, and CRP was constructed, and its superior predictive efficacy over single biomarkers was verified, providing a more reliable risk assessment tool for clinical practice. Third, the independent predictive value and cut-off values of each biomarker were clarified through multivariate regression, offering data support for the formulation of quantitative risk stratification criteria.

Study limitations

As a retrospective cohort study, this research inevitably has certain limitations. First, the study used single-center data with a relatively limited sample size. All participants were recruited from a single hospital, which may introduce selection bias. The external validity of the results requires further verification by multi-center, large-sample studies. Second, long-term follow-up of patients was not conducted, so it was impossible to analyze the association between dynamic changes of immune-inflammatory biomarkers and the onset time of CI, nor to explore the relationship between biomarker levels and the severity or prognosis of CI. Additionally, other confounding factors that may affect the results - such as patients' medication history and specific details of tumor treatment regimens - were not included in the study, which might have caused some interference in the analysis of risk factors.

This study did not include a lung cancer without CI group, and thus it is impossible to directly compare and rule out the possibility that the elevation of inflammatory markers is a common characteristic of CI itself. Formal internal and external validations were not conducted in this study, thus failing to yield stable and reliable validation outcomes and compromising the generalizability of the results. The predictive model has not undergone external data validation, and thus its stability in predictive performance across different populations and clinical centers cannot be guaranteed.

Future studies could carry out multi-center, prospective cohort studies to expand the sample size and improve the follow-up system, exploring the dynamic changes of immune-inflammatory biomarkers and their relationships with lung cancer treatment and CI prognosis.

Conclusion

Systemic immune-inflammatory responses play an important role in the occurrence of lung cancer-related CI. In clinical practice, dynamic monitoring of these inflammatory markers helps in the early identification of high-risk patients.

Disclosure of conflict of interest

None.

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