Thoracic Cancer

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ORIGINAL ARTICLE OPEN ACCESS

Association of Baseline Serum Uric Acid With Venous Thromboembolism and Clinical Outcomes in Patients With Non-Small Cell Lung Cancer

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Received: 13 January 2025 | **Revised:** 14 April 2025 | **Accepted:** 16 April 2025

Funding: This work was supported by the National Natural Science Foundation of China (grant no. 82370058), Clinical Research Incubation Project, Beijing Chao-Yang Hospital, Capital Medical University (grant no. CYFH202212) and the Reform and Development Program of Being Institute of Respiratory Medicine (grant no. Ggyfz202513).

Keywords: non-small cell lung cancer | prognosis | serum uric acid | venous thromboembolism

ABSTRACT

Objective: This study aimed to analyze the association between baseline serum uric acid (SUA) level and venous thromboembolism (VTE) and clinical outcomes in patients with non-small cell lung cancer (NSCLC).

Materials and Methods: We conducted a prospective analysis of 626 patients with newly diagnosed or recurrent/progressive NSCLC between September 2021 and August 2024. Receiver operating characteristic (ROC) curve was used to determine the optimal cutoff values for risk factors related to VTE, and clinical characteristics and treatment outcomes were collected and compared according to these values. Fine–Gray regression analyses were used to identify the risk factors of VTE, and survival was analyzed using log-rank test and Cox regression analysis.

Results: In the study, 72 patients (11.50%) experienced VTE. Patients with VTE had a higher baseline SUA level than those without VTE ($p = 0.000$). The optimal threshold of baseline SUA to predict VTE was 310 μmol/L. The incidence of VTE was higher in the high SUA group than that of the low SUA group (19.1% vs. 7.9%, $p < 0.001$). In multivariable analysis, the baseline SUA level was associated with the risk of VTE (sub-distribution hazard ratio (SHR) = 2.830, 95% CI 1.689–4.742, $p = 0.000$). Additionally, the higher SUA level was associated with a worse disease-free survival (DFS) in newly diagnosed patients with NSCLC staged I–IIIA (adjusted HR = 1.948, 95% CI 1.121–3.384, $p = 0.018$).

Conclusions: Among NSCLC patients, a baseline feature of high SUA (≥ 310 μmol/L) was associated with an increased risk of VTE and a worse clinical outcome.

1 | Introduction

Venous thromboembolism (VTE) is a common occurrence among individuals diagnosed with non-small cell lung cancer (NSCLC), impacting approximately 10%–15% of this patient demographic [1–3]. Significant evidence suggests that thrombotic complications correlate with a poorer prognosis and represent the second leading cause of mortality among patients

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with cancer [4–7]. The processes underlying the development of cancer-related thrombosis are probably intricate and involve multiple factors. These mechanisms emphasize the tightly interconnected and highly dynamic relationships that exist among the tumor, its microenvironment, and the hemostatic system [8]. A recent comprehensive meta-analysis has confirmed multiple genetic loci linked to VTE, which are integral components of metabolic pathways [9].

Uric acid serves as the final metabolite of purine catabolism, primarily originating from dietary intake of foods high in purines and glutamate, in addition to the degradation of nucleic acids within the organism. Prior research has demonstrated that increased serum uric acid (SUA) levels are associated with an elevated risk of cardiovascular diseases. Only few studies have reported a positive association between SUA levels and VTE risk [10–14]. For example, an observational investigation utilizing a substantial Taiwanese dataset revealed that gout is an independent risk factor for both deep vein thromboembolism (DVT) and pulmonary embolism (PE) [10]. A separate single-center prospective cohort investigation indicated that individuals exhibiting elevated SUA levels experienced a 3-fold heightened risk of VTE recurrence among those with a history of VTE who had successfully undergone oral anticoagulation therapy [13]. Meanwhile, in a recent cohort study conducted in China, along with a Mendelian randomization (MR) analysis, it was discovered that increased levels of SUA are linked to the onset of VTE within the Asian demographic [14].

Notwithstanding these observations, the aforementioned investigations did not concentrate explicitly on individuals diagnosed with cancer. Considering the likelihood that SUA may affect coagulation processes, the objective of the present study was to explore the relationship between baseline SUA levels and VTE, along with its implications for the clinical outcomes of patients with NSCLC.

2 | Material and Methods

2.1 | Patients

Consecutive patients with NSCLC between September 2021 and August 2024 at Beijing Chao-Yang Hospital who met the following inclusion criteria were included in the prospective observational study: histologically confirmed NSCLC diagnosis, biopsy performed as part of their clinical management either at initial diagnosis or upon disease recurrence/progression, willingness to participate, and completion of written informed consent. The exclusion criteria were VTE diagnosed >3 months prior to biopsy, ongoing anticoagulation therapy, or insufficient data The patients were followed up prospectively for a maximum 4.2 years' observation period until the occurrence of death, loss of follow-up, withdrawal of consent, or the censure date (October 1, 2024), with the median follow-up period being 13 months (7.13–25.01 months). The study was approved by the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China (no. 2024-KE-407), in accordance with the Declaration of Helsinki.

2.2 | Data Collection

Patient-related data, comorbidity-related factors, and tumor-related factors were collected from patients' electronic medical records at the time of initial diagnosis or upon disease progression. Patient-related factors included age, sex, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG), performance status (PS), and smoking history. Comorbidity-related factors included hypertension (defined as SBP ≥ 140 and/or DBP ≥ 90 or ongoing antihypertensive medications), cerebrovascular disease (including ischemic stroke, transient ischemic attack, coronary heart disease, and peripheral arterial occlusion), diabetes mellitus, and gout. Tumor-related factors such as histological subtype, mutation type, cancer stage [15], metastatic sites, and treatment details were also documented.

Laboratory variables were measured within 1 month of blood collection for biopsy. These variables included complete blood counts, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), fibrinogen degradation products (FDPs), SUA, and D-dimer. White blood cell count and lymphocyte count were determined using the KX-21 automatic blood cell analyzer (Nishimikang, Japan). CRP levels were measured by the turbidimetric method; FDPs and D-dimer levels were assessed by immunoturbidimetry. SUA (μmol/L), creatinine level (μmol/L) and lactic dehydrogenase (LDH)(U/L) were measured by Dimension RxL auto analyzer (Dade Behring Diagnostics, Deer-field, IL, USA) following standard operating procedures. Glomerular filtration rate (GFR) was estimated through the 2021 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation. All biochemical tests were completed in the Laboratory Department of Beijing Chao-Yang Hospital.

2.3 | Outcome Measurement

The primary outcome of this study was the occurrence of VTE, including superficial vein thrombosis (SVT), DVT, and PE [16]. The VTE was assessed within 3 months before and 6 months after biopsy. SVT and DVT were diagnosed using venous ultrasound or CT angiography, whereas PE was confirmed via CT pulmonary angiography or ventilation-perfusion scans.

Secondary outcome included overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS). OS is defined as the time from diagnosis to death from any cause. PFS includes local or distant progression or death. DFS is defined as the time from surgery to disease recurrence in patients staged I–IIIA who underwent R0 resection. Response to treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

2.4 | Statistical Analysis

Mean ± SD or median (interquartile range) were used to describe continuous variables as appropriate. Categorical variables were described as frequencies and percentages. The

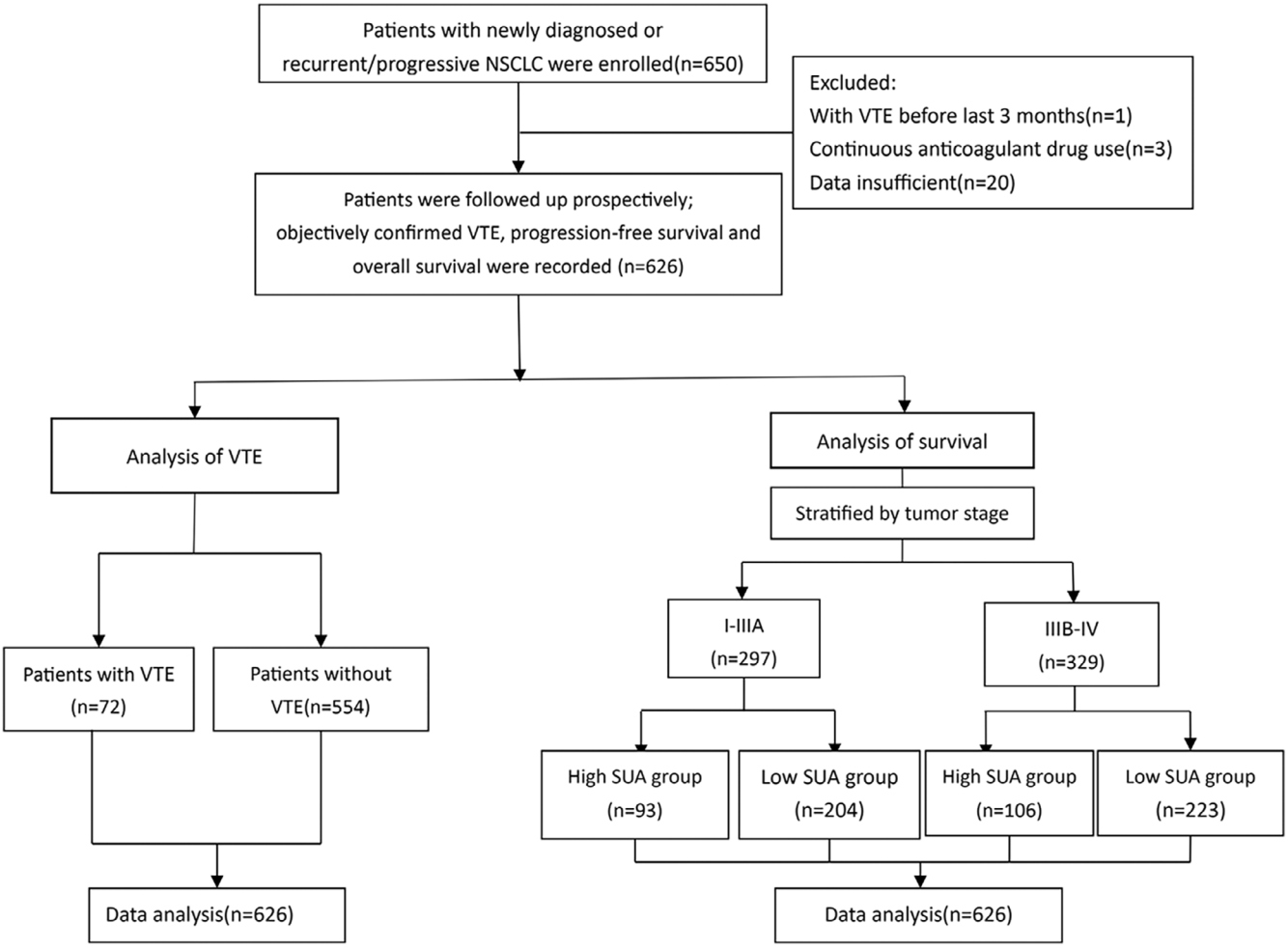

FIGURE 1 | Study flow diagram (NSCLC, non-small cell lung cancer; SUA, serum uric acid; VTE, venous thromboembolism).

receiver operating characteristic (ROC) curve was performed to determine the best cutoff value of baseline SUA for the prediction of VTE. Medians between two groups were compared with a Mann–Whitney *U* test. Correlations were analyzed with a Spearman correlation coefficient. As death was considered a competing event during follow-up time, VTE outcomes were studied in a competing risk framework [17]. In order to compare the cumulative VTE incidence between groups, a proportional sub-hazard regression model according to Fine and Gray was conducted. Furthermore, a model adjusting for FDP or CRP levels was used for competing risk and Cox regression analysis. A ROC curve analysis with area under the curve (AUC) computing was performed for the different VTE multivariable models to obtain the AUC values.

The association of SUA level with DFS/PFS and OS was assessed in Cox regression analysis. A multivariable model including age, sex, tumor histology, smoking history, and ECOG PS was conducted as well. Restricted mean survival time (RMST) as a sensitivity analysis using STATA 16.0 (StataCorp), with τ set at 25, 36, 48 months, respectively, to provide more comparable prognostic estimates. Time-dependent AUC and the calibration plot as evaluation of SUA's discriminative ability for prognosis were displayed by R.

Statistical significance was defined as a two-tailed p value of < 0.05 for all tests. Statistical analyses were performed with SPSS version 26.0, STATA 16.0 (StataCorp) and R version 4.1.0 R package: timeROC [0.4], ggplot2 [3.4.4], survival [3.3.1], and rms [6.3–0].

3 | Results

3.1 | Patient Characteristics

A total of 650 patients with NSCLC were initially enrolled in this study. Twenty-four participants were excluded: (1) history of VTE within 3 months preceding enrollment ($n = 1$); (2) active therapeutic anticoagulation at baseline (defined as uninterrupted use for > 7 consecutive days prior to screening, $n = 3$); and (3) incomplete baseline data ($n = 20$) (Figure 1). Thus, 626 eligible patients were included in this study. Finally, 40 patients were lost to follow-up, predominantly owing to an inability to contact patients by phone for assessment. Of these, 445 patients were alive and censored at last follow-up.

The clinicopathological characteristics of the study participants are summarized in Table 1. The median age of all patients was 65 years, and 69.3% of the patients were older than 60 years.

TABLE 1 | Baseline demographic and clinical characteristics of the study population ($N = 626$).

Characteristics	All patients ($n = 626$) (%)	Patients with VTE ($n = 72$) (%)	Patients without VTE ($n = 554$) (%)	p
Age (years)				
Median (range)	65 (58–71)	65 (58–71)	69 (63–74)	0.001[†]
< 60	192 (30.7)	13 (18.1)	179 (32.3)	
≥ 60	434 (69.3)	59 (81.9)	375 (67.7)	
Sex				
Male	302 (48.2)	29 (40.3)	273 (49.3)	0.151
Female	324 (51.8)	43 (59.7)	281 (50.7)	
BMI (kg/m^2)	24.04 (21.54–26.22)	24.16 (21.62–26.62)	24.01 (21.51–26.13)	0.926[†]
Smoking history				
Never	387 (61.8)	45 (62.5)	342 (61.7)	0.900
Current and former	239 (38.2)	27 (37.5)	212 (38.3)	
Comorbidity types				
Hypertension	243 (38.8)	33 (45.8)	210 (37.9)	0.194
Diabetes mellitus	100 (16.0)	13 (18.1)	87 (15.7)	0.608
Cerebrovascular disease	109 (17.4)	13 (18.1)	96 (17.5)	0.878
Gout	7 (1.1)	2 (2.8)	5 (0.9)	0.408[†]
ECOG PS				
0–1	483 (77.2)	43 (59.7)	440 (79.4)	0.000
2–4	143 (22.8)	29 (40.3)	114 (20.6)	
Stage at enrollment				
I–IIIA	297 (47.4)	27 (37.5)	270 (48.7)	0.072
IIIB–IV	329 (52.6)	45 (62.5)	284 (51.3)	
Tumor histology				
LUAD	537 (85.8)	69 (95.8)	468 (84.5)	0.009[†]
Non-LUAD	89 (14.2)	3 (4.2)	86 (15.5)	
LUSC	63 (10.1)	2 (2.8)	61 (11.0)	
PSC	9 (1.4)	0 (0)	9 (1.6)	
ASC	5 (0.8)	1 (1.4)	4 (0.7)	
LCNEC	3 (0.5)	0 (0)	3 (0.5)	
others	9 (1.4)	0 (0)	9 (1.6)	
Patient Status				
Newly diagnosed	450 (71.9)	47 (65.3)	403 (72.7)	0.185
Recurrent/progressive	176 (28.1)	25 (34.7)	151 (27.3)	
EGFR gene				
Wild	325 (51.9)	24 (33.3)	301 (54.3)	0.001
Mutated	301 (48.1)	48 (66.7)	253 (45.7)	
KRAS gene				

(Continues)

TABLE 1 | (Continued)

Characteristics	All patients ($n=626$) (%)	Patients with VTE ($n=72$) (%)	Patients without VTE ($n=554$) (%)	p
Wild	548 (87.5)	65 (90.3)	483 (87.2)	0.510
Mutated	78 (12.5)	7 (9.7)	71 (12.8)	
ALK gene				
Wild	597 (95.4)	71 (98.6)	526 (94.9)	0.110[†]
Mutated	29 (4.6)	1 (1.4)	28 (5.1)	
PD-L1 status				
No tested	529 (84.5)	465 (83.9)	64 (88.9)	0.603[†]
TPS < 1%	20 (3.2)	19 (3.4)	1 (1.4)	
TPS 1%–50%	53 (8.5)	49 (8.8)	4 (5.6)	
TPS > 50%	24 (3.8)	21 (3.8)	3 (4.2)	
All lines therapy[§]				
TKIs	263 (42.4)	39 (54.9)	224 (40.7)	0.023
Chemotherapy	230 (37.0)	31 (43.7)	199 (36.2)	0.219
Antiangiogenic therapy	71 (11.4)	16 (22.5)	55 (10.0)	0.002
Immunotherapy	55 (8.9)	7 (9.9)	48 (8.7)	0.752
Radiotherapy	34 (5.5)	8 (11.3)	26 (4.7)	0.023
Surgery	323 (52.0)	24 (33.8)	299 (54.4)	0.001
Baseline laboratory values				
Median (range)				
WBC ($\times 10^9$ cells/L)	6.9 (5.58–8.75)	7.71 (5.92–9.36)	6.89 (5.65–8.75)	0.067[†]
NLR	2.52 (1.76–4.08)	2.69 (1.96–5.38)	2.50 (1.73–3.86)	0.025[‡]
CEA (ng/ml)	3.17 (1.49–4.53)	4.72 (1.74–16.29)	2.77 (1.39–13.26)	0.150[‡]
LDH (U/L)	188 (164–220)	207 (159.25–236)	187 (163–217)	0.030[‡]
CRP (mg/L)	0.50 (0.40–2.34)	1.34 (0.40–4.12)	0.50 (0.36–1.35)	0.005[†]
D-dimer (mg/L)	0.46 (0.245–1.17)	0.95 (0.40–4.57)	0.44 (0.22–1.08)	0.000[‡]
FDPs (ng/ml)	320 (265–401)	355 (273.65–442.13)	312.4 (261.00–374.35)	0.001[‡]
SUA (μmol/L)	261 (201–344)	315 (224–352)	252 (199–332)	0.000[‡]
eGFR (mL/min/1.73 m^2)	99.3 (93.0–106.2)	95.99 (93.3–106.4)	99.6 (93.3–106.4)	0.044[‡]

Note: [†]Continuity correction, [‡]Wilcoxon rank–sum test, others by Pearson $\chi 2$ test. [§]Data available for 621 patients; 5 patients were unable to accurately describe their treatment.

Abbreviations: ALK, anaplastic lymphoma kinase; ASC, adenosquamous carcinoma; CEA, carcinoembryonic antigen; CI, confidence interval; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; eGFR, estimated glomerular filtration rate; FDP, fibrinogen degradation products; KRAS, Kirsten ratsarcoma viral oncogene homolog; LCNEC, large cell neuroendocrine carcinoma; LDH, lactate dehydrogenase; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; PSC, pulmonary sarcomatoid carcinoma; SUA, serum uric acid; TKIs, tyrosine kinase inhibitors; TPS, tumor proportion score; VTE, venous thromboembolism; WBC, white blood cell.

Female patients (51.8%) and people who never smoke (61.8%) were predominant in this study. Regarding the patient status, newly diagnosed and recurrent patients were 71.9% and 29.1%, respectively.

Seventy-two have developed VTE, consisted of 39 DVT events, 17 PE events, 13 combined PE and DVT events, and 3 SVT events (Table S1). Among these, 63 patients received anticoagulation therapy. Twenty-five cases were treated with low-molecular weight heparin (LMWH), 17 received novel oral anticoagulants (NOACs), 21 cases received LMWH followed by NOACs, and 1 patient was treated with unfractionated heparin followed by warfarin. Nine patients did not receive anticoagulant therapy.

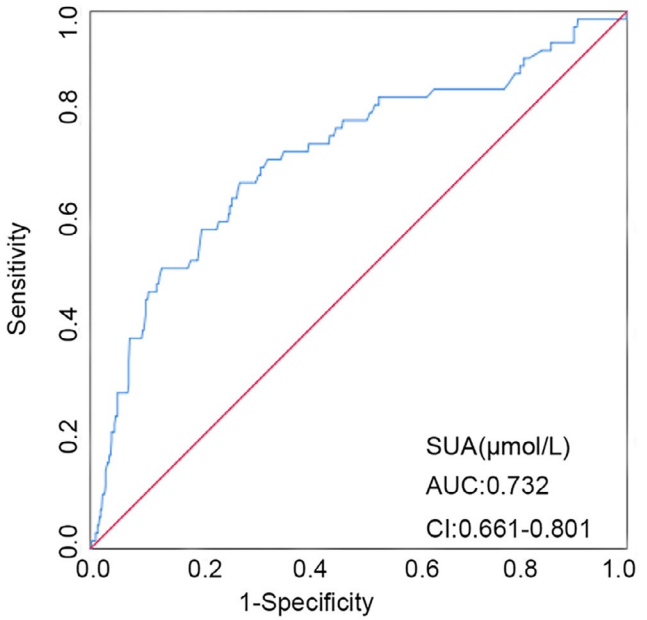

FIGURE 2 | Association between baseline SUA levels and VTE ($n = 626$). ROC curve analysis: AUC = 0.732, sensitivity = 69.6%, specificity = 68.7%, cutoff value 310 μmol/L (AUC, area under the curve; CI, confidence interval; NSCLC, non-small cell lung cancer; ROC curve, receiver operating characteristic curve; SUA, serum uric acid; VTE, venous thromboembolism.).

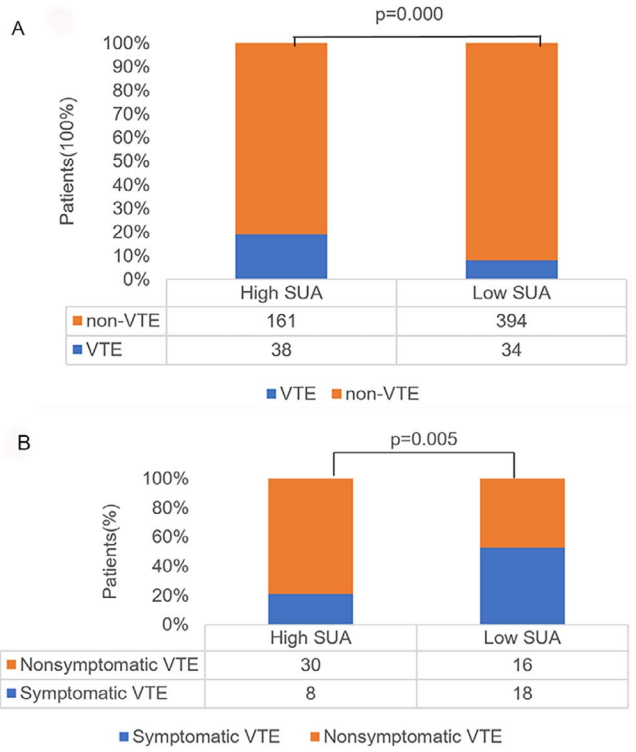

FIGURE 3 | The clinical characteristics of VTE. (A) The clinical characteristics of VTE in patients with high SUA and low SUA, respectively. High group: ≥ 310 μmol/L; low group: SUA < 310 μmol/L. (B) The clinical characteristics of symptomatic and non-symptomatic VTE in patients with high SUA and low SUA, respectively (SUA, serum uric acid; VTE, venous thromboembolism).

TABLE 2 | Correlation between SUA levels and markers of hemostasis and inflammation.

	r	95% CI	*p*
CRP	0.139	0.013–0.260	0.022
D-dimer	0.104	−0.008-0.223	0.072
FDPs	0.098	0.021–0.234	0.025
WBC	0.016	−0.125-0.124	0.704
Platelet counts	0.047	−0.073-0.167	0.443

Note: Statistical analysis was performed with a Spearman correlation coefficient. Abbreviations: CRP, C-reactive protein; FDPs, fibrinogen degradation products; SUA, serum uric acid; WBC, white blood cell counts.

3.2 | Association Between Baseline SUA Level and VTE

Among patients with VTE, the median age was 65 years, and 51.8% were female. Notably, patients with VTE had significantly higher baseline SUA level than those without VTE (315 versus 252 μmol/L, $p = 0.000$) (Table 1). We further performed ROC curve analysis to determine the optimal cutoff value of SUA for the prediction of VTE (Figure 2) (AUC = 0.732, 95% CI 0.661–0.801, sensibility = 69.6%, specificity = 68.7%, $p = 0.000$). The positive predictive value (PPV) was 19.10% (95% confidence interval (CI) 16.02%–22.17%), and the negative predictive value (NPV) was 92.06% (95% CI 89.94%–94.17%). The optimal cutoff value for SUA was 310 μmol/L, determined using the maximal Youden index. These results indicated that the level of SUA was highly effective in identifying patients at risk for VTE.

Therefore, patients with baseline peripheral-blood SUA ≥ 310 μmol/L were defined as the high SUA group, and the others were defined as the low SUA group. The baseline demographic and clinical characteristics of patients grouped by SUA level are listed in Table S2. As is shown, patients with a high SUA level had a higher proportion of older patients (81.9%) and a higher BMI (24.41 vs. 23.85, $p = 0.015$) than those with a low SUA level. The chi-squared test confirmed comparable EGFR mutation rates between the high-SUA (49.2%) and low-SUA (47.5%) groups ($\chi^2 = 0.158$, df = 1, $p = 0.691$), with an odds ratio of 1.071 (95% CI 0.765–1.499). Moreover, SUA levels showed a weak positive correlation with CRP and FDPs, but not with D-Dimer, platelet counts, and white blood counts (Table 2).

In the high SUA group, 19.1% (38/199) patients developed VTE, whereas in the low SUA group, 7.9% (34/428) patients developed VTE (Figure 3A). Additionally, in the high-SUA group, the incidence of non-symptomatic VTE was higher than that of symptomatic VTE ($p = 0.005$) (Figure 3B).

The cumulative incidence of VTE at 6 months was 18.26% in the high-SUA group and 7.30% in the low-SUA group, respectively ($p = 0.014$) (Figure 4). Subsequently, Fine–Gray competing risks regression with death as a competing risk regression analysis revealed that baseline peripheral-blood SUA level was associated with VTE (sub-distribution hazard ratio (SHR) = 2.830, 95% CI 1.689–4.742, $p = 0.000$) (Table 3). Moreover, when a patient status was stratified, the baseline-SUA level remained a risk

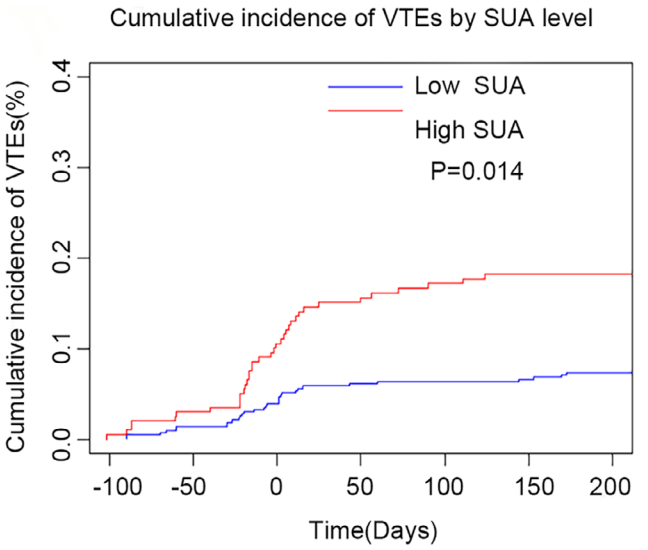

FIGURE 4 | Cumulative incidence of VTE among NSCLC stratified by SUA level. The cumulative incidence of VTE was higher in the high SUA group than in the low SUA group (NSCLC, non-small cell lung cancer; SUA, serum uric acid; VTE, venous thromboembolism).

factor for VTE in both newly diagnosed and recurrent/progressive patients with NSCLC (SHR = 2.696, 95% CI 1.422–5.112, $p < 0.001$; SHR = 3.491, 95% CI 1.464–8.325, $p < 0.001$, respectively) (Table S3A,B).

In a separate analysis adjusting for CRP or FDPs levels, the association remained significant (CRP adjusted SHR of SUA = 2.204, 95% CI 1.071–3.718; FDPs adjusted SHR of SUA = 2.758, 95% CI 1.613–4.717). When CRP (adjusted SHR of SUA = 1.998, 95% CI 1.002–4.072) or FDPs (adjusted SHR of SUA = 2.71, 95% CI 1.554–4.754) levels were added to the clinical covariates model, the association was weakened significantly (Table 3).

3.3 | SUA and Clinical Outcomes

The survival curves for DFS and OS were numerically more favorable in patients staged I–IIIA with low SUA level (1-year DFS and OS rate of 90.3% and 94.5%, respectively) than those with high-SUA level (1-year DFS and OS rate of 75.1% and 89.5%, respectively). The Kaplan–Meier curves showed patients staged I–IIIA with low-SUA level had a better DFS than those with high SUA level (HR = 2.201, 95% CI 1.275–3.799, $p = 0.0037$) (Figure 5A).

In patients staged IIIB–IV with low-SUA level, 1-year PFS and OS rates were 58.4% and 68.3%, respectively. In those with high-SUA level, 1-year PFS and OS rates were 52.2% and 69.6%, respectively (Figure 6A,B). The median DFS/PFS and OS of patients were not totally reached. Kaplan–Meier curves showed there was no difference between the low SUA and high-SUA groups for PFS of patients staged IIIB–IV (HR = 1.151, 95% CI 0.819–1.616, $p = 0.418$) (Figure 5B).

Similarly, patient status was further stratified; in newly diagnosed patients with NSCLC staged I–IIIA, survival analysis revealed that those with low SUA level seemed to have a better OS

TABLE 3 | Association between SUA levels and VTE risk in different multivariable models.

	SHR (95% CI)	*p*	AUC
Model 1, *N* = 611			
SUA	2.801 (1.688–2.464)	0.000	0.624 (0.553–0.696)
Age	2.124 (1.09–4.138)	0.020	
Sex	0.49 (0.281–0.854)	0.048	
Model 2, *N* = 605			
SUA	2.830 (1.689–4.742)	0.000	0.660 (0.591–0.728)
Age	1.747 (0.904–3.376)	0.097	
Sex	0.568 (0.335–1.044)	0.119	
Tumor histology	3.478 (1.026–11.848)	0.045	
ECOG PS	2.223 (1.289–3.835)	0.004	
Smoking history	1.445 (0.680–3.073)	0.281	
Model 3, *N* = 318			
SUA	1.998 (1.002–4.072)	0.049	0.748 (0.669–0.827)
Age	2.455 (0.959–6.284)	0.061	
Sex	0.472 (0.215–1.037)	0.062	
Tumor histology	7.938 (1.031–61.113)	0.047	
ECOG PS	3.286 (1.554–6.993)	0.002	
Smoking history	0.785 (0.254–2.429)	0.675	
CRP	1.011 (0.994–1.029)	0.212	
Model 4, *N* = 520			
SUA	2.717 (1.554–4.754)	0.002	0.693 (0.624–0.763)
Age	2.010 (0.974–4.146)	0.059	
Sex	0.453 (0.241–0.851)	0.014	
Tumor histology	4.583 (1.292–16.261)	0.018	
ECOG PS	2.069 (1.099–3.897)	0.016	
Smoking history	1.071 (0.435–2.643)	0.882	
FDPs	1.004 (1.002–1.006)	0.001	
Model 5, *N* = 318			
SUA	2.204 (1.071–3.718)	0.022	0.574 (0.474–0.674)
CRP	1.013 (0.997–1.029)	0.120	
Model 6, *N* = 520			
SUA	2.758 (1.613–4.717)	0.000	0.643 (0.566–0.720)
FDPs	1.003 (1.001–1.005)	0.005	

Abbreviations: AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; FDPs, fibrinogen degradation products; HR, hazard ratio; SUA, serum uric acid; VTE, venous thromboembolism; WBC, white blood cell counts.

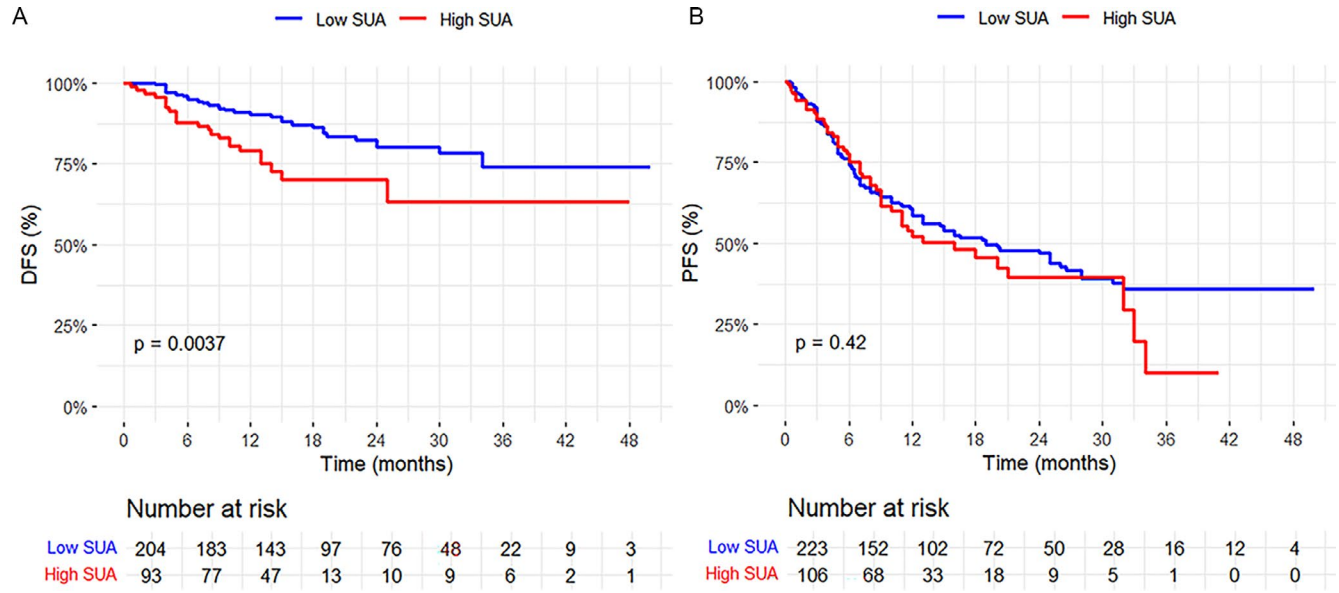

FIGURE 5 | (A) In patients staged I–IIIA, Kaplan–Meier curves showing patients with low-SUA level had better DFS compared with those with high-SUA level. (B) In patients staged IIIB–IV, Kaplan–Meier curves showing no difference between patients with low-SUA level and those with high-SUA level (DFS, disease-free survival; NSCLC, non-small cell lung cancer; PFS, progression-free survival; SUA, serum uric acid).

than others (log-rank $p = 0.021$) (Figure 6C). In patients staged IIIB–IV, no significance of OS was revealed in four subgroups (log-rank $p = 0.093$) (Figure 6D).

RMST-based sensitivity analyses demonstrated consistent prognostic effects of SUA for DFS in patients staged at I–IIIA (all $p < 0.05$). Although nonsignificant restricted mean survival differences of survival outcomes across SUA strata were revealed with RMST-based sensitivity analyses for neither PFS for patients staged at IIIB–IV (all $p > 0.05$) nor OS (all $p > 0.05$) at the prespecified clinical time horizon of 24, 36, 48 months, respectively.

Baseline high-SUA level remained a significant predictor of poorer DFS when controlled for age, sex, smoking history, tumor histology, and ECOG PS in patients staged I–IIIA (adjusted HR 1.948; 95% CI 1.121–3.384, $p = 0.018$) (Table 4). Univariate and multivariate Cox analysis of DFS for patients staged I–IIIA and PFS for patients staged IIIB–IV were shown in Table 4A,B, respectively, whereas the analysis of OS did not lead to the anticipated conclusions (Tables S5 and 6A,B).

The predictive value of baseline SUA in patients staged in I–IIIA was evaluated. Time-dependent AUCs were 0.74 (95% CI 0.57–0.93), 0.61 (95% CI 0.50–0.72), 0.63 (95% CI 0.54–0.72) at 3, 6, 12 months, respectively. The calibration plot revealed close alignment between predicted and observed probabilities, and the prognostic model demonstrated moderate discriminative ability (C-index = 0.602, 95% CI 0.567–0.637, $p = 0.005$) with satisfactory calibration.

4 | Discussion

To our knowledge, this is the first study to investigate the predictive value of baseline peripheral-blood SUA level for both VTE and clinical outcomes of patients with NSCLC. Our results indicated that high SUA level is significantly associated with the occurrence of VTE in patients with NSCLC, with an optimal threshold of 310 μmol/L for assessing VTE risk. In the high-SUA group, the incidence of non-symptomatic VTE was higher than that of symptomatic VTE. In addition, the higher baseline SUA level was correlated with shorter DFS in newly diagnosed patients with NSCLC in the I–IIIA stage.

As mentioned earlier, several high-quality studies indicated that advanced age [18], ECOG PS, VTE history, histology, stage, antiangiogenic therapy, and TKIs may be correlated with the occurrence of cancer-associated VTE [1–3, 5, 8, 18, 19]. A substantial population-based cohort analysis involving half a million patients with Danish cancer has provided current estimates regarding the frequency of cancer-associated VTE, identifying significant risk factors including a history of prior VTE (SHR 7.6, 95% CI 7.2–8.0), distant metastasis (SHR 3.2, 95% CI 2.9–3.4), and use of antiangiogenic therapy (SHR 4.4, 95% CI 3.8–5.2) and so on [19]. A retrospective analysis involving 1998 consecutive Asian patients diagnosed with NSCLC identified several independent risk factors associated with VTE. In the context of locally advanced NSCLC, advanced age, the occurrence of pneumonectomy, and the use of palliative radiotherapy emerged as noteworthy predictors. Conversely, in patients with metastatic NSCLC, the histological subtype of adenocarcinoma, when compared with squamous cell carcinoma, along with a history of smoking—either former or current—were found to be significant predictors of VTE [18]. Comparably, similarly, our research arrived at an analogous conclusion.

Although uric acid is mainly recognized as a metabolic byproduct resulting from purine degradation, its physiological roles remain incompletely elucidated. Current clinical studies indicate a positive correlation between SUA levels and both the occurrence and recurrence of VTE, suggesting that increased SUA may function as a potential risk factor for VTE,

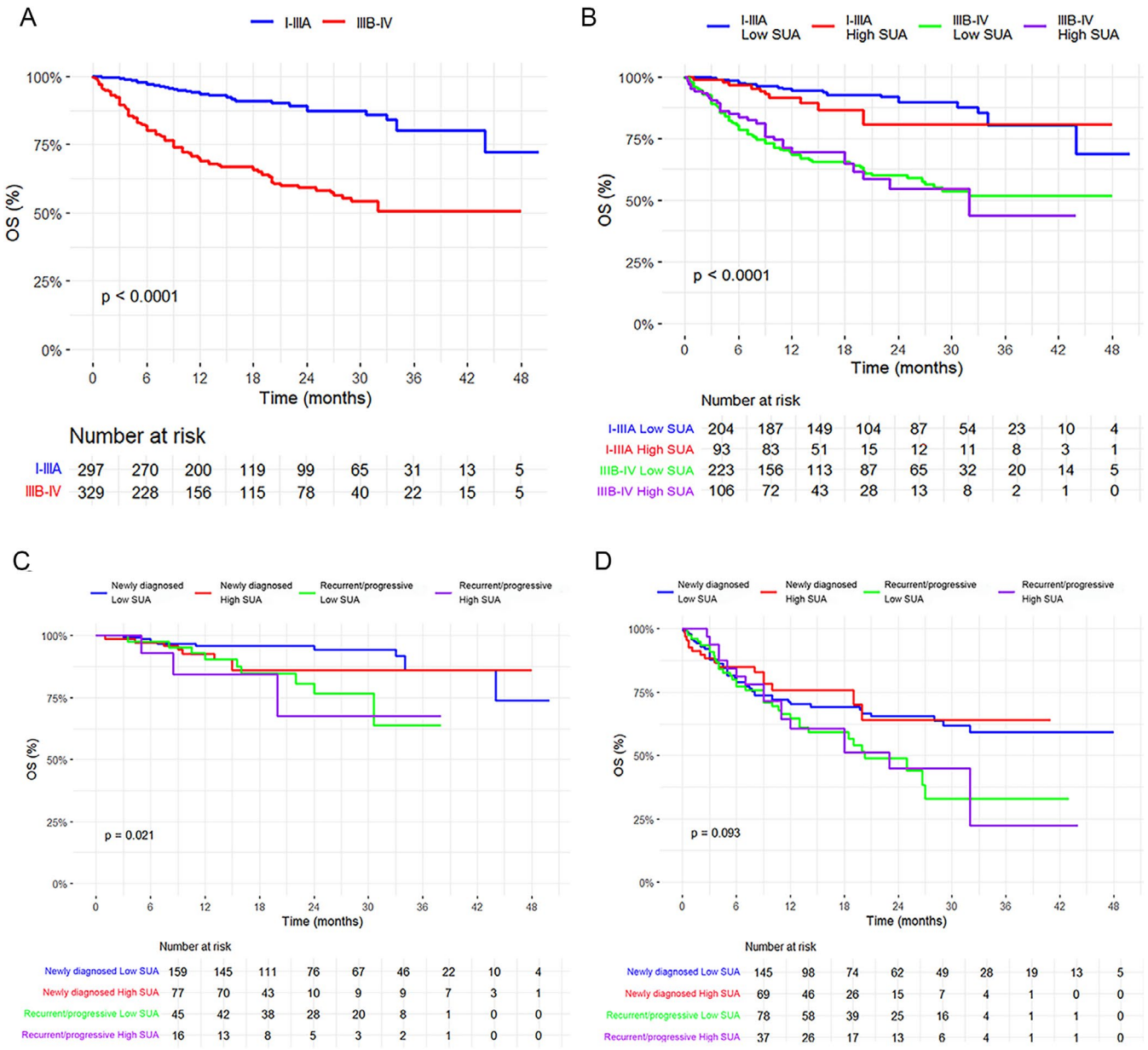

FIGURE 6 | (A) Kaplan–Meier curve showing patients staged IIIB–IV had worse OS than patients staged I–IIIA. (B) Kaplan–Meier curves showing OS rate among the tumor stage groups with different SUA levels differed significantly (log-rank $p < 0.001$). Stratified by patient status: (C) In patients staged I–IIIA, Kaplan–Meier curves showing newly diagnosed patients with low-SUA levels had better OS than other patients (log-rank $p < 0.001$). (D) In patients staged IIIB–IV, Kaplan–Meier curves showing no difference in OS in four subgroups (log-rank $p = 0.093$) (NSCLC, non-small cell lung cancer; OS, overall survival; SUA, serum uric acid).

as illustrated in Table 5. An illustration of this can be found in the Atherosclerosis Risk in Communities (ARIC) Study, which included 14126 participants aged 45–64 years. This study initially identified a correlation between elevated SUA levels and a heightened risk of VTE [11]. Additional researchers have highlighted the significance of SUA as an independent predictor of short-term mortality in cases of PE [20], as well as its association as a risk factor for VTE among individuals diagnosed with gout [21].

Nonetheless, the fundamental pathophysiological mechanisms are not yet fully understood, and the direct correlation between SUA levels and cancer-related VTE has yet to be substantiated. Preliminary investigations have suggested that SUA could serve as a crucial connection between endothelial dysfunction, inflammatory processes, and a pro-thrombotic environment. Recently, a study has illustrated the thrombotic function of endothelial cells (ECs) in hyperuricemia, highlighting the role of TMEM16F in facilitating the exposure of phosphatidylserine (PS) and the release of microparticles (MPs) [23].

Moreover, elevated SUA concentrations have been demonstrated to enhance the expression of lethal-7c (let-7c), a microRNA associated with impaired platelet function. In a hyperuricemia animal model, increased SUA levels were observed to stimulate the MEF2C-dependent and NF-κB signaling pathways through let-7c, ultimately leading to the

TABLE 4 | Multivariable Cox regression analyses of baseline-SUA level with DFS/PFS in NSCLC patients stratified by stage.

	HR	95% CI	Adjusted *p*
I–IIIA			
High SUA versus low SUA	1.948	1.121–3.384	0.018
IIIB-IV			
High SUA versus low SUA	1.128	0.801–1.587	0.490

Note: DFS was analyzed for patients in the I–IIIA stage, and PFS was analyzed for those in the IIIB–IV stage. The multivariate Cox regression analysis is adjusted for age, sex, smoking history, tumor histology, and ECOG PS (HR, hazard ratio; DFS, disease-free survival; PFS, progress-free survival; SUA, serum uric acid).

development of thrombosis [24]. Furthermore, research conducted both in vitro and in vivo has demonstrated that elevated levels of SUA are associated with inflammatory cytokines and contribute to the process of systemic sterile inflammation [25–27]. A population-based cross-sectional study identified a significant positive correlation between SUA levels and the plasma concentrations of CRP, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [28]. Additionally, prior research has shown that inflammatory mediators are capable of increasing the expression of tissue factors on the surfaces of circulating monocytes and neutrophils, thereby triggering the activation of the coagulation cascade [29, 30]. Potential biological links between hyperuricemia and VTE risk in NSCLC may involve: (1) SUA-mediated activation of the NLRP3 inflammasome, promoting prothrombotic states [31]; (2) uric acid crystal-induced endothelial dysfunction by reducing eNOS (endothelial nitric oxide synthase) activity and increasing ROS (reactive oxygen species) [32]; (3) comorbid metabolic disorders (e.g., insulin resistance) associated with elevated SUA [33]. Tumor hypoxia could exacerbate these pathways by increasing xanthine oxidase activity, warranting further exploration.

As is shown in Table 1, the VTE group contains a higher number of EGFR mutation cases. Although no studies have directly investigated the association between SUA and EGFR gene expressions, emerging preclinical and clinical evidence suggests potential mechanistic links through shared signaling pathways. In vascular smooth muscle cells, uric acid modulates MAPK signaling by inhibiting phosphatase activity, thereby sustaining MAPK phosphorylation [34]. Notably, in pancreatic β-cells, uric acid triggers ERK activation [35]. Intriguingly, URAT1 inhibitor treatment has been shown to suppress ERK pathway activation, ameliorating uric acid-induced cellular damage—a finding that underscores the critical role of intracellular urate in MAPK regulation [36]. Given that the MAPK/ERK cascade serves as a key downstream effector of EGFR receptor tyrosine kinase activity, it is plausible to hypothesize crosstalk between EGFR signaling and uric acid metabolism. Furthermore, an observational study revealed that elevation in SUA levels predicts favorable response to erlotinib treatment in patients with metastatic NSCLC [37]. Notably, In the real world, the high-dose furmonertinib-based treatment may potentially increase SUA level in patients with EGFR-mutated NSCLC with leptomeningeal metastasis [38]. These pharmacodynamic interactions suggest a potential bidirectional relationship between EGFR signaling and uric acid metabolism. Mechanistic studies are warranted to elucidate whether: (1) EGFR activation directly modulates urate transporters (e.g., URAT1, GLUT9), or (2) intracellular urate accumulation feedback-regulates EGFR downstream effectors (e.g., MAPK/ERK). Prospective validation in multiethnic cohorts with standardized SUA monitoring protocols is crucial to determine its clinical significance as a predictive biomarker.

Our findings extend the role of ECOG PS and SUA in VTE. They are independent risk factors for VTE, which have been confirmed by multiple linear tests, stratified analysis, and interaction tests (not listed in the text). Although ECOG PS reflects systemic consequences of cancer-related debilitation (reduced ambulation, muscle wasting), elevated SUA may promote thrombosis through xanthine oxidase-mediated endothelial dysfunction [35] and NLRP3 inflammasome activation [26].

Our prospective study was the first to identify a negative correlation between SUA levels and clinical outcomes in patients with newly diagnosed NSCLC staged I–IIIA. Specifically, elevated SUA levels were associated with decreased DFS in this patient cohort. Conversely, no significant differences in SUA levels were observed in patients with stages IIIB–IV. This discrepancy may be attributed to the influence of confounding variables associated with the various lines of treatment, which could affect both the production and metabolism of uric acid.

Indeed, one retrospective research study suggested that SUA level was an independent predictor of 30-day PE-related mortality (odds ratio = 1.20, $p = 0.002$) [20]. Furthermore, a separate retrospective clinical investigation conducted in South Korea developed a biomarker model which demonstrated that SUA serves as a prognostic marker for blood biomarkers in individuals diagnosed with unprovoked acute PE [22]. Additionally, our study indicates that lower SUA levels are probably linked to better OS in newly diagnosed patients staged I–IIIA. This observation could be attributed to the fact that individuals exhibiting elevated SUA levels encounter an increased likelihood of VTE, a condition that negatively impacts their OS across different therapeutic approaches.

The evaluation of SUA's prognostic performance was confirmed in patients staged in I–IIIA by time-dependent ROC curves (3/6/12-month intervals) and calibration plots, clarifying SUA's predictive role in clinical outcomes.

In summary, our findings suggest that baseline SUA levels are correlated with VTE, indicating that baseline SUA could serve as a predictive biomarker for the clinical outcomes in patients with NSCLC.

This study has several limitations: First, our single-center design predominantly included Han Chinese patients. Future multiethnic validations are required before broader clinical application. Second, this study was restricted to patients with NSCLC, which precludes extrapolation of findings to other major histological types (e.g., small cell lung cancer) or broader clinical contexts. Future multicentric studies incorporating heterogeneous

TABLE 5 | Characteristics of studies that assessed SUA and VTE.

Study	Country	Year	Study type	Population	Race	Assessment method	Type of VTE	Cutoff value	Predictor of survival
Kubota et al. [11]	America	2016	Prospective	15 792 general population containing pan-cancer	Caucasian, African American	An uricase method (enzymatic-colorimetric assay)	PE and/or DVT of the lower extremity, iliac vein, or inferior vena cava, intracranial or intracardiac thrombus[a]	No	No
Ozsu et al. [20]	Turkey	2017	Retrospective	337 patients diagnosed acute PE	Caucasian	An enzymatic spectrophotometric method	Acute PE	No	30-day mortality
Lee et al. [22]	Korea	2019	Retrospective	265 patients with unprovoked acute PE	Asian	An automatic biochemistry analyzer	Unprovoked acute PE	No	No
De Lucchiet al. [13]	Italy	2020	Prospective	486 patients with a previous diagnosed episode of DVT and/or PE	Caucasian	An uricase method (enzymatic-colorimetric assay)	VTE (DVT and/or PE) recurrence	No	No
Weng et al. [14]	China	2023	Prospective	3754 patients with VTE from CURES (containing pan-cancer) and 10477 controls from CHARLS	East Asian	Automated chemistry analyzer	DVT and/or PE, recurrence of VTE	No	No
Current study	China	2024	Prospective	NSCLC	East Asian	Automated chemistry analyzer	SVT, DVT and/or PE	Yes	DFS/PFS, OS

Abbreviations: ARIC, the Atherosclerosis Risk in Communities Study; CHARLS, the China Health and Retirement Longitudinal Survey; CURES, the China Pulmonary Thromboembolism Registry Study; DFS, disease-free survival; DVT, deep vein thrombosis; NHIRD, the National Health Insurance Research Database; NSCLC, non-small cell lung cancer; OS, overall survival; PE, pulmonary embolism; PFS, progression-free survival; SUA, serum uric acid; SVT, superficial vein thrombosis; VTE, venous thromboembolism.

[a]ICD-9-CM codes: 415.1x, 451, 451.1x, 451.2, 451.8x, 451.9, 453.0, 453.1, 453.2, 453.8, 453.9, 996.7x, and 999.2, as well as procedure code 38.7.

populations across disease stages (e.g., limited vs. extensive SCLC) are warranted to validate the potential generalizability of SUA thresholds in comprehensive lung cancer management. Third, the limited duration of follow-up hindered the attainment of a median time estimate; therefore, prolonged follow-up is crucial for subsequent research. At last, although we adjusted for key covariates, residual confounding (e.g., dietary purine intake, genetic polymorphisms and metabolic parameters) might persist. Prospective studies incorporating granular lifestyle, genomic data, metabolic parameters, and treatment-related variables are needed to address this.

5 | Conclusions

Our findings demonstrate a significant correlation between the baseline peripheral-blood SUA levels and the occurrence of VTE, as well as clinical outcomes in patients newly diagnosed with stage I–IIIA NSCLC. A threshold SUA of 310 μmol/L may serve as a useful indicator for assessing the risk of VTE, with elevated SUA levels potentially signifying a poor prognosis for patients with NSCLC in I–IIIA stage. These results imply that patients exhibiting high baseline SUA levels warrant meticulous monitoring. Additionally, further prospective studies are essential to substantiate our conclusions.

Author Contributions

Xue-Li Zhang, Chen Zhang, and Lu Lang collected the relevant data. Xue-Li Zhang and Chen Zhang drafted the manuscript text. Xue-Li Zhang and Chen Zhang performed statistical analyses. Yu-Hui Zhang designed this study and revised the paper. Jia-Wen Yi gave critical comments. Min Zhu gave critical comments and revised the paper. All authors approved the final version of the manuscript.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its Supporting Information.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.