Postprint: Predictive Value of Serum Uric Acid for Perioperative Ischemic Stroke in Non-Small Cell Lung Cancer Patients

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Abstract

Background Perioperative acute ischemic stroke (POAIS) is a serious complication of surgical procedures that can increase surgical mortality and reduce patients' quality of life. Its pathogenesis is complex, and relevant research is particularly lacking in patients with non-small cell lung cancer (NSCLC).

Objective To investigate the influencing factors of POAIS occurrence in NSCLC patients and the predictive value of serum uric acid (SUA) for POAIS in NSCLC patients.

Methods We collected 25 NSCLC patients who underwent pulmonary resection and developed POAIS at the Fourth Hospital of Hebei Medical University from July 2014 to April 2022 as the case group, and randomly selected 126 NSCLC patients without POAIS as the control group after matching by age and sex. Preoperative baseline data, intraoperative data, and postoperative pathology-related data were collected for all patients. Multivariate Logistic regression was used to explore the influencing factors of POAIS in NSCLC patients, and receiver operating characteristic (ROC) curve was employed to evaluate the predictive value of preoperative SUA for POAIS in NSCLC patients.

Results The 151 patients had a mean age of (64$±$7) years, with males accounting for 57.62% (87/151). Multivariate Logistic regression analysis showed that SUA was an influencing factor for POAIS in NSCLC patients [OR=0.990, 95%CI (0.982, 0.998), P=0.019]. ROC curve analysis revealed that the area under the curve of SUA for predicting POAIS in NSCLC patients was 64%, with an optimal cutoff value of 307.4 mol/L, sensitivity of 58.7%, and specificity of 76.0%.

Conclusion Preoperative SUA level is an independent predictor of POAIS in NSCLC patients. Higher baseline SUA levels may indicate a lower risk of POAIS

occurrence.

Full Text

Predictive Value of Serum Uric Acid in Perioperative Ischemic Stroke in Patients with Non-small Cell Lung Cancer

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Abstract

Background: Perioperative acute ischemic stroke (POAIS) is a severe complication of surgery that increases surgical mortality and reduces patients' quality of life. Its pathogenesis is complex and remains poorly explored, particularly in patients with non-small cell lung cancer (NSCLC). **Objective:** To investigate the influencing factors of POAIS in NSCLC patients and evaluate the predictive value of serum uric acid (SUA) for POAIS occurrence. **Methods:** Clinical data were retrospectively collected from 25 NSCLC patients who developed POAIS after lung resection at the Fourth Hospital of Hebei Medical University between July 2014 and April 2022 (case group). A control group of 126 NSCLC patients without POAIS was randomly selected after matching by age and sex. Preoperative baseline data, intraoperative parameters, and postoperative pathology-related data were collected for all patients. Multivariate logistic regression was used to explore influencing factors of POAIS, and receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of preoperative SUA. **Results:** The mean age of the 151 patients was (64$±$7) years, with 57.62% (87/151) being male. Multivariate logistic regression analysis showed that SUA was an independent influencing factor for POAIS in NSCLC patients [OR=0.990, 95%CI (0.982, 0.998), P=0.019]. ROC curve analysis revealed that the area under the curve (AUC) for SUA predicting POAIS was 0.64, with an optimal cutoff value of 307.4 mol/L, sensitivity of 58.7%, and specificity of 76.0%. **Conclusion:** Preoperative SUA level

is an independent predictor of POAIS in NSCLC patients. Higher baseline SUA levels may indicate a lower risk of POAIS occurrence.

Keywords: Carcinoma, Non-small-cell lung; Ischemic stroke; Uric acid; Perioperative period; Root cause analysis; Forecasting

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) being the most common type [1-4]. Surgical resection remains the preferred treatment for early-stage NSCLC, yet ischemic stroke represents a serious perioperative complication that significantly reduces quality of life and increases economic burden. The incidence of POAIS in lung cancer surgery ranges from 0.2% to 0.8% according to various studies [5-7].

Perioperative acute ischemic stroke (POAIS) is defined as acute ischemic stroke occurring intraoperatively or within 30 days postoperatively [8]. Its etiology is complex, involving surgery-related tissue injury and subsequent acute systemic inflammatory responses [9-10]. Additional risk factors include advanced age, discontinuation of antithrombotic therapy, diabetes mellitus, history of stroke, hypertension, atrial fibrillation, and acute thrombotic intracranial arterial occlusion [11-15].

The hypercoagulation state (HCS) induced by cancer is a common cause of cancer-related ischemic stroke (CRIS) [16]. Trousseau syndrome (TS), a paraneoplastic hypercoagulable state causing venous or arterial thrombosis, frequently manifests as cerebral infarction due to arterial thrombosis, with lung cancer being the most common malignancy associated with TS [17]. Studies have identified left upper lobectomy (LUL) as an independent risk factor for POAIS in lung cancer patients [18-19], potentially related to thrombus formation in the left superior pulmonary vein (LSPV) stump [5,20-22]. HATTORI et al. [5] found that heightened thrombotic status may be associated with the LSPV. The unique hypercoagulable characteristics of cancer combined with the distinct pulmonary anatomy may augment POAIS risk beyond traditional risk factors, particularly under surgical stress.

Serum uric acid (SUA), a natural antioxidant in humans, may exert protective effects in POAIS pathogenesis and progression. This study investigates the predictive value of preoperative SUA levels for POAIS in NSCLC patients, aiming to provide novel theoretical and clinical insights for POAIS prevention.

Methods

Study Population

We retrospectively collected clinical data from NSCLC patients who underwent lung resection at the Fourth Hospital of Hebei Medical University between July 2014 and April 2022.

Inclusion criteria: (1) Age >18 years; (2) Postoperative pathology confirming primary NSCLC; (3) Lung resection performed under general anesthesia via thoracoscopy or thoracotomy; (4) Confirmed POAIS: acute onset during or after surgery with focal neurological deficits (unilateral facial or limb weakness/numbness, etc.), with symptoms lasting either any duration when imaging shows responsible ischemic lesions, or >24 hours when lacking imaging evidence, and neuroimaging [diffusion-weighted MRI showing high signal intensity explaining neurological symptoms, or CT excluding hemorrhage/space-occupying lesions] confirming new cerebral infarction in a vascular territory.

Exclusion criteria: (1) Other systemic malignancies; (2) Any prior lung surgery; (3) Brain metastasis; (4) Suspected intracranial venous system disease; (5) No cranial imaging available.

Grouping: Twenty-five POAIS patients meeting the criteria were enrolled as the case group. A control group of 126 NSCLC patients without POAIS was randomly selected from the same hospital period, matched by age and sex. Since all 25 case group patients had adenocarcinoma or squamous carcinoma pathology, control group subjects were limited to these pathological types. Three patients with incomplete intraoperative blood pressure data and one breast cancer patient were excluded, resulting in 126 control group patients.

Data Collection

Clinical data: Baseline data included demographics (age, sex, BMI), cardiovascular/cerebrovascular disease history [coronary atherosclerotic heart disease (CAHD), cerebral infarction], cardiovascular risk factors [hypertension, hyperlipidemia, type 2 diabetes, atrial fibrillation, active smoking ($ 10*cigarettes/week*), *alcoholconsumption*($20ml daily, $ $1 time/week)], medication history (antiplatelet agents, statins), preoperative chemotherapy, and laboratory findings [white blood cell count, fibrinogen, red blood cell count, hemoglobin, platelet count, D-dimer, estimated glomerular filtration rate (eGFR), SUA, serum creatinine, total cholesterol, intracranial/extracranial large artery stenosis (one or more lesions with 50%-99% stenosis)].

Surgical and pathology data: Intraoperative parameters included surgical approach, resection site, operation duration, anesthesia duration, and intraoperative blood pressure. Postoperative pathology data included pathological type, disease stage, vascular invasion, and visceral pleural invasion.

Blood pressure measurement: Intraoperative blood pressure was monitored

via invasive arterial pressure, recorded every 5 minutes. Systolic blood pressure (SBP) and its coefficient of variation (CV) were primary indicators. Maximum, minimum, and mean SBP were recorded. Standard deviation (SD) and CV were calculated as follows:

$$CV = \frac{\sqrt{\frac{\sum(BP_i - BP_{mean})^2}{n-1}}}{BP_{mean}}$$

Definitions: Intraoperative hypotension was defined as SBP <80 mmHg [8] or mean arterial pressure <55 mmHg [23]. Early-stage NSCLC referred to Stage I and II patients [24].

Statistical Analysis

Data were analyzed using SPSS 22.0 software. Normally distributed continuous variables were expressed as ($\bar{x}\pm s$) and compared using independent samples t-test. Non-normally distributed variables were expressed as M(QR) and compared using Wilcoxon rank-sum test. Categorical variables were expressed as frequencies or percentages (%) and compared using ^{2} test or Fisher' s exact test. Univariate and multivariate logistic regression analyses were performed to identify influencing factors for POAIS. Multicollinearity analysis was conducted for confounders in multivariate logistic regression. ROC curve analysis determined the optimal cutoff value, sensitivity, and specificity of SUA for predicting POAIS. Bivariate Pearson correlation analysis examined relationships between preoperative SUA and hypertension, type 2 diabetes, and large artery stenosis (r>0.3 considered correlated). P<0.05 indicated statistical significance.

Results

Comparison of Baseline Demographics and Clinical Characteristics

The 151 patients had a mean age of (64$±$7) years (range 44-80), with 87 males (57.62%). The case group had higher proportions of preoperative chemotherapy, higher white blood cell counts and fibrinogen levels, and lower SUA levels compared to the control group (P<0.05). No significant differences were observed between groups in age, sex, BMI, history of hypertension, CAHD, type 2 diabetes, cerebral infarction, atrial fibrillation, hyperlipidemia, smoking, alcohol consumption, medication history, red blood cell count, hemoglobin, platelet count, D-dimer, eGFR, serum creatinine, total cholesterol, or proportion of large artery stenosis (P>0.05) .

Comparison of Surgical and Pathology-Related Indicators

The case group showed higher proportions of thoracotomy, longer operation and anesthesia durations, more advanced disease stages, higher rates of

visceral pleural invasion, and lower intraoperative SBP CV compared to controls (P<0.05). No significant differences were found in resection site, maximum/minimum/mean SBP, pathological type, or vascular invasion rates (P>0.05) .

Logistic Regression Analysis of POAIS Influencing Factors

Univariate logistic regression analysis identified preoperative chemotherapy, white blood cell count, fibrinogen, SUA, surgical approach, operation duration, anesthesia duration, visceral pleural invasion, and disease stage as influencing factors for POAIS (P<0.05) .

Multivariate logistic regression analysis, incorporating significant univariate variables plus potential SUA-influencing factors (sex, BMI), revealed that SUA [β=-0.010, SE=0.004, Wald ^{2}=5.525; OR=0.990, 95%CI (0.982, 0.998); P=0.019] was an independent influencing factor for POAIS. No multicollinearity was detected among confounders.

ROC Curve Analysis of SUA for Predicting POAIS

ROC curve analysis showed that SUA predicted POAIS with an AUC of 0.64. The optimal cutoff value was 307.40 mol/L, with sensitivity of 58.7% and specificity of 76.0% [Figure 1: see original paper].

Correlation Analysis Between Preoperative SUA and Vascular Risk Factors

Bivariate Pearson correlation analysis showed no significant correlation between preoperative SUA levels and hypertension (r=0.204, P<0.05), type 2 diabetes (r=-0.064, P>0.05), or large artery stenosis (r=-0.022, P>0.05) .

Discussion

POAIS is a severe complication of lung cancer surgery [25]. Although increasingly recognized, its pathological mechanisms remain unclear. This study demonstrates that SUA is a predictive factor for POAIS in NSCLC patients, with elevated SUA serving as a protective factor.

Previous studies suggest POAIS mechanisms include hypotension, previously unknown large artery stenosis, anemia-related tissue hypoxia, systemic inflammation, endothelial dysfunction, and HCS from discontinued antithrombotic therapy [8]. Surgery triggers both systemic and brain-specific inflammatory responses, with neuroinflammation now recognized as a key component of ischemic stroke [26]. Inflammatory responses activate the coagulation system, which in turn amplifies inflammation. Preoperative chronic inflammation characterized

by abnormal accumulation of inflammatory cells and cytokines increases post-operative cardiovascular complications and mortality [27]. Our study found that higher preoperative SUA levels reduced POAIS risk in NSCLC patients (P=0.019). The ROC-derived optimal cutoff of 307.4 mol/L indicates that NSCLC patients with preoperative SUA above this threshold have reduced POAIS risk, suggesting that relatively high SUA concentrations may mitigate oxidative and inflammatory stress from surgery through antioxidant [28] and anti-inflammatory [29] properties.

Oxidative damage plays an important role in cancer development [30]. Uric acid provides antioxidant defense against oxidant- and free radical-induced aging in cancer patients. Tumor cell breakdown may increase SUA levels, stimulating immune-mediated cytotoxic death while inhibiting tumor cell proliferation and migration [31]. Cancer patients face increased acute ischemic stroke risk in the first months after diagnosis, particularly in advanced disease and adenocarcinoma [32]. Cancer-related cerebral infarction is typically attributed to TS, likely mediated by cancer-induced HCS that damages vascular endothelium through various pathological factors and hemostatic, coagulation, fibrinolytic, and anticoagulant system dysfunction [17]. Inflammation and pro-angiogenesis are key processes through which cancer cells promote HCS [33]. As a potent natural antioxidant and free radical scavenger [28], uric acid' s protective effects in acute ischemic stroke have been studied extensively [34-38], with additional findings of anti-inflammatory [29] and vascular endothelial growth factor down-regulation [39] functions under specific conditions. Our results suggest SUA may reduce POAIS risk by inhibiting cancer progression and alleviating cancer-induced HCS.

Elevated serum D-dimer levels are more common in acute stroke with cancer [40]. TS thrombi are white, fibrin- and platelet-rich solid thrombi, unlike the red, fragile, erythrocyte- and leukocyte-rich thrombi of atherosclerosis [41]. Active cancer patients with acute cerebral infarction have lower rates of traditional cerebrovascular risk factors (e.g., type 2 diabetes) [40], but higher rates of multiple infarcts [42] and cryptogenic stroke [40]. Adenocarcinoma is common in TS due to its thromboembolic nature [40], collectively confirming HCS' s role in CRIS.

Many cancer patients share demographic and vascular risk factors with stroke patients (e.g., advanced age, hypertension) and may develop stroke from atherosclerosis and small vessel disease. Higher POAIS rates in elderly patients and those with comorbidities (e.g., hypertension, type 2 diabetes) may relate to perioperative stress-induced atherosclerotic plaque destabilization [43-44]. Our study matched groups by age and found no association between POAIS and hypertension, diabetes history, or large artery stenosis. Furthermore, SUA showed no correlation with these three factors, excluding their confounding effects on our results.

Studies have identified LUL and left pneumonectomy (LP) as independent POAIS predictors [18-21], potentially due to longer LSPV stumps and reduced

blood flow causing pulmonary vein thrombosis after LUL [19,21]. Our study found no correlation between resection site and POAIS, and lacked postoperative chest CT data to verify pulmonary vein remnant length differences or thrombosis evidence. While some research suggests intraoperative hypotension or blood pressure fluctuations cause POAIS [8], we found higher SBP CV in the control group, possibly related to more hypertensive patients, higher maximum SBP, and lower minimum SBP. This contrary finding likely lacks clinical significance, possibly because no patients experienced intraoperative hypotension.

This study has several limitations. First, it is a single-institution retrospective study with a small case group sample size. Second, asymptomatic ischemic strokes without MRI or strokes occurring post-discharge at other hospitals may have led to underreporting, preventing calculation of true POAIS incidence. Third, dietary differences and their potential impact on SUA were not considered, limiting generalizability. Fourth, SUA may play different roles across cancer types and stages. Given the relatively low POAIS incidence and complex pathogenesis in NSCLC, larger prospective multicenter studies are warranted.

In conclusion, SUA level is an influencing factor and predictor of POAIS in NSCLC patients. SUA' s predictive value deserves further investigation to provide comprehensive strategies for minimizing POAIS risk in NSCLC patients.

Author Contributions

BAI Haiwei, LIU Junyan, and HAN Ying conceptualized the study. BAI Haiwei performed data analysis and drafted the manuscript. MI Xiaokun conducted feasibility analysis. LIU Qingrui revised the manuscript. BAI Haiwei, ZHU Lin, and WANG Yingnan collected data. LIU Junyan provided quality control. HAN Ying provided quality control, review, and overall supervision.

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Note: Figure translations are in progress. See original paper for figures.