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The expression changes endothelial and fibrinolytic biomarkers in acute ischemic stroke patients with OSA

Zhencan Huang[1], Yanan Zhang[1], Qingqing Sun[1] and Zan Wang[1*]

Abstract

Objective To assess the expression changes of serum fibrinogen, E-selectin, and tissue-type plasminogen activator (t-PA) in acute ischemic stroke (AIS) patients with varying degrees of obstructive sleep apnea syndrome (OSA), and evaluate their value in diagnosing AIS with OSA.

Methods Data were gathered from 80 patients with AIS who were admitted to the First Hospital of Jilin University between January 2023 and December 2023. Out of these, 60 patients completed the NIHSS Scale, ESS Scale, STOP-Bang Scale, and underwent polysomnography within a week of symptom onset. Based on the apnea-hypopnea index (AHI) score, patients were categorized into three groups: 15 in the non-exposed group (AHI < 5), 15 in the mildly exposed group (5 ≤ AHI ≤ 15), and 30 in the moderately to severely exposed group (AHI > 15). Serum levels of fibrinogen, E-selectin, and t-PA were determined using enzyme-linked immunosorbent assay.

Results Polysomnography results indicated AIS with OSA had an increased arousal index and oxygen desaturation index ($P < 0.001$). Additionally, serum levels of fibrinogen, E-selectin, and t-PA were markedly elevated in the moderately-severely exposed group compared to the non-exposed group ($P < 0.001$), and these levels positively correlated with the severity of OSA. ROC curves showed the sensitivities of serum of fibrinogen, E-selection, and t-PA was 84.4%, 80%, and 82.2%, respectively, and the specificities of 60%, 66.7%, and 66.7%, compared with that of PSG respectively.

Conclusion The expression of serum fibrinogen, E-selectin, and t-PA is elevated in AIS with OSA and correlates with the severity of OSA.

Keywords Obstructive sleep apnea syndrome, Acute ischemic stroke, Fibrinogen, E-selectin, Tissue-type plasminogen activator

*Correspondence:
Zan Wang
wangzan@jlu.edu.cn
[1]Sleep Centre, Department of Neurology, The First Hospital of Jilin University, Changchun, People's Republic of China

Introduction

Acute ischemic stroke (AIS) is an acute focal neurological impairment caused by cerebrovascular ischemia. Globally, it is one of the major causes of disability and death, with approximately 3.29 million deaths annually [1]. Patients with AIS face a high risk of recurrence within five years, highlighting the critical need for research and intervention in modifiable risk factors. Sleep-disordered breathing (SDB) is a prevalent chronic condition affecting nearly 936 million people globally, with 425 million experiencing moderate to severe obstructive sleep apnea (OSA) [2]. OSA is marked by repeated episodes of partial (hypopnea) or complete (apnea) blockage of airflow during sleep, causing intermittent hypoxia and fragmented sleep. These disruptions result in daytime drowsiness, fatigue, irritability, lack of concentration, and even cognitive impairment [3]. The severity of OSA is determined using the apnea-hypopnea index (AHI). This classification is broken down into three categories: mild (AHI between 5 and 15), moderate (AHI between 15 and 30), and severe (AHI 30 or higher) [4].

Seiler et al. discovered that the incidence of sleep apnea in patients with AIS is 71%, nearly four times that of the masses [5]. As an independent risk factor for patients with ischemic stroke [6], OSA directly increases the risk of stroke mainly through intermittent hypoxemia and sympathetic hyperactivity. During the process of OSA, the autonomic nervous system exhibits an excessive compensatory response, with sympathetic hyperactivity and a weakening of the activity of the parasympathetic nervous system on blood vessels [7]. This change leads to systemic inflammation and increased platelet activity, subsequently causing vascular endothelial dysfunction, which is closely related to the occurrence of cerebrovascular diseases. In addition, intermittent hypoxemia triggers oxidative stress and a hypercoagulable state of the blood, resulting in dysfunction of the fibrinolytic system and promoting the occurrence of stroke [8]. Moreover, it also worsens other cardiovascular risk factors, such as high blood pressure and arrhythmias, significantly impacting stroke prognosis [9]. Although polysomnography is the definitive test for the diagnosis of OSA, its complexity, requirement for extensive medical personnel, and high cost can delay diagnosis and treatment [10].

Advancements in biomarker research have shown that specific biomarkers in OSA patients could be crucial for predicting diagnosis, disease severity, and response to therapy [11–13]. However, studies on endothelial function and the fibrinolytic system in AIS patients with OSA are relatively scarce. E-selectin, a type of cell adhesion molecule, is mainly expressed on the surface of endothelial cells [14]. During the systemic inflammatory response, it can mediate the adhesion between leukocytes and endothelial cells, enabling leukocytes to migrate to the site of inflammation. In patients with OSA, repeated hypoxia during sleep can trigger an inflammatory response, leading to an increase in the expression of E-selectin, promoting the adhesion and migration of inflammatory cells, and participating in the pathophysiological process of acute ischemic stroke [15]. Together with the abnormal fibrinolytic system, it promotes pathological changes such as thrombus formation. t - PA, a serine protease, mainly functions to activate plasminogen into plasmin, thereby dissolving fibrinogen and exerting an anticoagulant effect. In AIS patients with OSA, the level of fibrinogen will increase, promoting platelet aggregation and thrombus formation [16]. This study aims to investigate the expression of serum t-PA, E-selectin, and fibrinogen in AIS with OSA and assess their diagnostic value for AIS combined with OSA.

Methods

The study was approved by the ethics committee of the First Hospital of Jilin University and was conducted in accordance with the Declaration of Helsinki (Approval No. 24K042-001). All participants and their guardians gave informed consent.

Participants

We recruited 80 acute ischemic stroke (AIS) patients who were enrolled in the Department of Neurology of the First Hospital of Jilin University between January 2023 to December 2023. Finally, 60 patients underwent polysomnography within a week of symptom onset. Given the frequency of OSA in AIS patients (71%) [5], the patients were collected in a 1:3 ratio and categorized into two groups: 15 patients in the non-exposed group (AIS without OSA) and 45 patients in the exposed group (AIS with OSA). The exposed group was further divided into mildly exposed ($5 \le AHI \le 15$; $n = 15$) and moderately-severely exposed ($AHI > 15$; $n = 30$) according to the apnea-hypopnea index (AHI) score.

Inclusion and exclusion criteria

The inclusion criteria included: **1. Non-exposed group**: age, gender, cerebral infarction site matched with exposed group, and no sleep disorder in PSG. **2. Exposed group**: (1) Diagnosed with OSA according to the International Classification of Sleep Disorders, 3rd edition; (2) aged between 18 and 65 years; (3) and having a cerebral infarction located in the region dominated by the internal carotid artery system with a maximum infarct lesion diameter greater than 20 mm.

The exclusion criteria included: (1) Patients with transient ischemic attack or acute ischemic stroke undergoing endovascular therapy or intravenous thrombolysis; (2) Patients with sleep disorders excluding OSA; (3) Patients with comorbid respiratory conditions, including acute

respiratory infections, chronic obstructive pulmonary disease, interstitial lung disease, lung infections, bronchiectasis, and bronchial asthma; (4) recent use of medications affecting sleep breathing (benzodiazepines, sedative antidepressants, opioids, etc.); (5) Generalized Anxiety Disorder-7 (GAD-7) score ≥ 9 or Patient Health Questionnaire-9 (PHQ-9) score ≥ 5.

Clinical data

All patients underwent comprehensive clinical data collection on admission, including age, sex, height, weight calculated body mass index (BMI), Epworth Sleepiness Scale (ESS) assessment, National Institutes of Health Stroke Scale (NIHSS) assessment, STOP-Bang questionnaire, past medical history, neurologic examination, and head imaging of stroke site and maximum infarct lesion diameter.

Polysomnography

Polysomnography (PSG) was used to monitor all patients for at least 8 h at our hospital's sleep center (Compumedics, Australia). Results of the PSG have been scored by certified PSG technologists., following the American Academy of Sleep Medicine's revised interpretation criteria for sleep stages and related events, version 2.6.

Apnea was diagnosed as a fall in peak temperature sensor excursion of ≥ 90% of baseline, lasting for at least two respiratory cycles. Hypopnea was considered as ≥ 30% decline in nasal pressure signal excursion from pre-event baseline, lasting at least two breathing cycles, with ≥ 3% desaturation in blood oxygen saturation or associated arousal. The apnea-hypopnea index (AHI) was computed as the mean number of apnea and/or hypopnea events per hour of sleep. Oximetric measures derived from PSG channels included the oxygen desaturation index (ODI), minimum oxygen saturation of arterial blood (Min SaO_2), and mean oxygen saturation of arterial blood (Mean SaO_2). ODI was calculated as the number of events per hour in which the decrease in oxygen saturation was ≥ 3% from baseline.

Table 1 Clinical characteristics of acute ischemic stroke among different groups

	Control group (15)	Mildly exposed group (15)	Moderately-Severely exposed group (30)	*P*-value
Age, years	61.67 ± 9.28	58.40 ± 9.57	57.49 ± 9.09	0.344
Male, n (%)	10(66.7)	7(70.0)	27(77.1)	0.720
BMI, kg/m^2	22.79 ± 2.25	25.43 ± 4.06	27.26 ± 4.06	0.001
Smoke, n (%)	5(33.3)	7(70.0)	17(48.6)	0.200
Drink, n (%)	2(13.3)	5(50.0)	13(37.1)	0.124
Hypertension, n (%)	13(86.7)	5(50.0)	26(74.3)	0.158
Hyperlipidemia, n (%)	3(20.0)	3(30.0)	14(40.0)	0.377
Diabetes, n (%)	4(26.7)	2(20.0)	16(45.7)	0.215

Abbreviation: BMI, body mass index

Fibrinogen, E-selection, and t-PA serum level detection

Blood samples were taken from all patients the following morning after an 8-hour fast on enrolment and processed by centrifugation at 3000 rpm for 10 min. Serum was kept at -80 °C until the time of testing. Serum levels of fibrinogen, E-selectin, and tissue-type plasminogen activator (t-PA) were detected using enzyme-linked immunosorbent assay (ELISA) kits (Jianglai Biotechnology Co., Ltd., Shanghai, China).

Statistical analysis

IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Shapiro-Wilk test was used to examine the normal distribution of continuous variables. Data with a normal distribution were expressed as mean ± standard deviation, while data with a skewed distribution were expressed as median with interquartile range. Categorical data were presented as absolute values and percentages. Differences between multiple groups of independent samples were compared using one-way analysis of variance (ANOVA) or the Kruskal-Wallis H test, for data distribution. The Pearson correlation test was employed to examine the relationship between the apnea-hypopnea index and serum levels of fibrinogen, E-selectin, and t-PA. Receiver operating characteristic (ROC) curves were generated to calculate the sensitivity, specificity, and cut-off points for fibrinogen, E-selectin, and t-PA serum levels in predicting OSA, based on the Youden index.

Results

Baseline characteristics

Sixty patients were included in this study, divided into three groups: 15 in the non-exposed group, 15 in the mildly exposed group and 30 in the moderately-severely exposed group. There were no significant differences among the groups in terms of age, gender, NIHSS score, smoking history, drinking history, hypertension, diabetes mellitus, and hyperlipidemia. However, BMI ($P = 0.001$), ESS scores ($P = 0.003$), and STOP-Bang scores ($P < 0.001$) were significantly higher in the moderately-severely exposed group compared to the non-exposed group (Tables 1 and 2).

Polysomnography parameters

Polysomnography (PSG) parameters showed that AIS patients with OSA had a higher proportion of stage N1 sleep ($P = 0.002$) and a lower proportion of stage N3 sleep ($P < 0.001$). Additionally, these patients exhibited an increased arousal index and oxygen desaturation index

Table 2 The scale of NIHSS, ESS, STOP-Bang in different groups

	Non-exposed group (15)	Mildly exposed group (15)	Moderately-Severely exposed group (30)	*P*-value
NIHSS	3.67 ± 2.41	4.30 ± 3.02	4.49 ± 2.59	0.601
ESS	6.13 ± 2.53	5.20 ± 3.39	9.69 ± 4.87	0.003
STOP-Bang	3.20 ± 0.78	3.30 ± 1.64	5.11 ± 1.57	<0.001

Abbreviation: NIHSS, National Institute of Health stroke scale, ESS, Epworth Sleepiness Scale

Table 3 The PSG parameters of acute ischemic stroke in different groups

	Non-exposed group (15)	Mildly exposed group (15)	Moderately-Severely exposed group (30)	*P*-value
TST, min	400.07 ± 45.39	399.05 ± 42.33	395.19 ± 69.31	0.978
Sleep Efficiency (%)	75.99 ± 11.11	70.22 ± 20.84	71.51 ± 10.22	0.439
Stage N1, %	29.30 ± 8.93	31.98 ± 10.13	46.31 ± 19.46	0.002
Stage N2, %	39.14 ± 11.94	42.66 ± 9.20	34.92 ± 16.58	0.291
Stage N3, %	13.13 ± 4.26	5.43 ± 4.95	2.71 ± 2.78	<0.001
REM, %	17.95 ± 4.57	19.94 ± 7.22	16.09 ± 6.24	0.186
AHI, episodes/h	4.04 ± 0.78	11.95 ± 2.88	44.77 ± 22.08	<0.001
ODI, episodes/h	0.58 ± 0.50	2.78 ± 2.47	22.58 ± 19.45	<0.001
Min SaO_2, %	91.73 ± 2.84	85.10 ± 7.20	80.29 ± 10.52	<0.001
Mean SaO_2, %	96.53 ± 0.74	95.60 ± 1.65	94.03 ± 2.35	<0.001
Arousal index, episodes/h	1.81 ± 1.04	2.27 ± 0.49	17.21 ± 17.56	<0.001

Abbreviation: TST, total sleep time; REM, rapid eye movement; N, non-rapid eye movement; Min SaO_2, minimum oxygen saturation of arterial blood; Mean SaO_2, mean oxygen saturation of arterial blood; ODI, oxygen desaturation index. AHI, apnea-hypopnea index

Table 4 Comparison of fibrinogen, E-selectin, and t-PA in different groups

	Non-exposed group (15)	Mildly exposed group (15)	Moderately-Severely exposed group (30)	*P*-value
Fibrinogen, g/L	2.39 ± 0.75	2.96 ± 0.88	3.50 ± 0.83	0.001
E-selectin, ng/ml	8.30 ± 1.52	9.71 ± 1.57	10.99 ± 2.22	0.001
t-PA, ng/ml	8.14 ± 2.12	9.46 ± 1.51	10.67 ± 1.86	0.001

Abbreviation: tissue-type plasminogen activator

(ODI) ($P < 0.001$), and decreased minimum and mean oxygen saturation levels ($P < 0.001$) (Table 3)

Serum levels of fibrinogen, E-selectin, and t-PA

The serum levels of fibrinogen, E-selectin, and t-PA were markedly increased in the moderately-severely exposed group in comparison to the non-exposed group ($P < 0.001$), while there were no significant differences between the mildly exposed and non-exposed groups. These biomarkers' levels increased with the severity of OSA (Table 4; Fig. 1)

Correlation analysis

Pearson correlation analysis revealed that AHI values in stroke patients were positively correlated with serum levels of fibrinogen ($r = 0.409$, $P = 0.001$), E-selectin ($r = 0.591$, $P < 0.001$), and t-PA ($r = 0.622$, $P < 0.001$) (Fig. 2).

Diagnostic performance of biomarkers

Receiver operating characteristic (ROC) curve analysis demonstrated that the areas under the curve (AUC) for fibrinogen, E-selectin, and t-PA were 0.792 (95% CI: 0.67 to 0.92, $P = 0.001$), 0.813 (95% CI: 0.70 to 0.93, $P = 0.001$), and 0.796 (95% CI: 0.70 to 0.92, $P = 0.001$), respectively. The cutoff values for fibrinogen, E-selectin, and t-PA were 2.475 g/L, 8.7 ng/mL, and 8.65 ng/mL, with sensitivities of 84.4%, 80%, and 82.2%, and specificities of 60%, 66.7%, and 66.7%, respectively (Fig. 3).

Discussion

In our study, we found that AIS patients with OSA exhibited increased light sleep (percentage of stage N1), decreased deep sleep (percentage of stage N3), higher arousal index, and higher ODI, along with reduced minimum and mean oxygen saturation levels. OSA, a sleep-related breathing disorder, is associated with intermittent hypoxemia and sleep fragmentation, with intermittent hypoxemia thought to be a contributing factor in the development of OSA-related complications [17, 18]. Therefore, the increase in light sleep and decrease in deep sleep observed in these patients may be attributed to OSA-induced sleep fragmentation and frequent awakenings, which lead to decreased sleep quality and further impact stroke recovery. This increase in ODI, accompanied by a reduction in minimum oxygen saturation and mean oxygen saturation, is indicative of intermittent hypoxemia during sleep. Sustained low blood oxygen levels can promote thrombosis by increasing blood viscosity, further contributing to hypoxia and impairing neurological recovery [19, 20].

Gottlieb et al. observed a decline in the proportion of deep sleep and a compensatory increase in non-rapid eye movement (NREM) sleep stages 1–2 in patients with chronic-phase ischemic stroke combined with moderate-to-severe OSA, in comparison to healthy controls [21]. Additionally, Xu et al. found that the ODI, the proportion of time with oxygen saturation below 90%, and the respiration-related arousal index were significantly higher, while the lowest oxygen saturation ($LSaO_2$) was considerably lower in the stroke with OSA group than in the stroke alone group [22]. Consequently, continuous positive airway pressure (CPAP) therapy for OSA has been

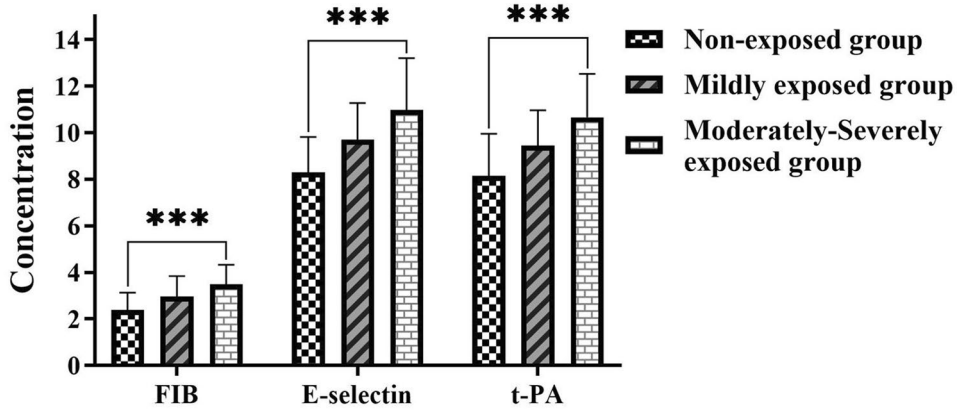

Fig. 1 Comparison of fibrinogen (FIB), E-selectin, and t-PA serum levels in mildly exposed group, moderately-severely exposed group, and non-exposed group

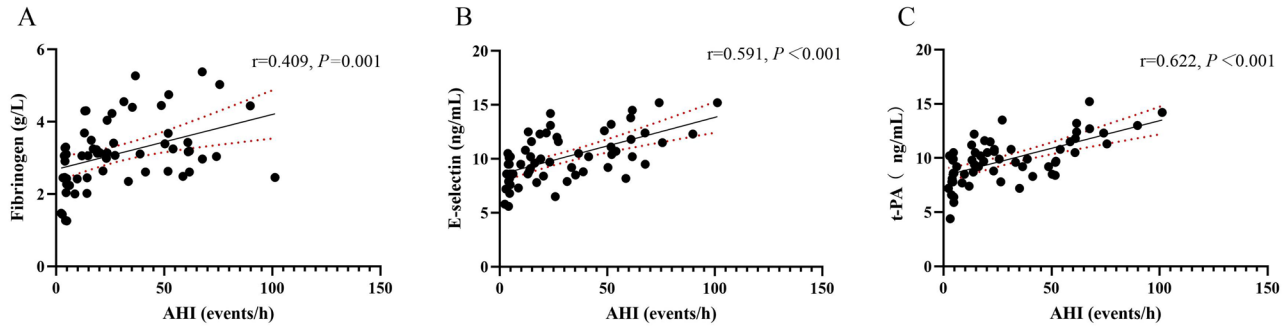

Fig. 2 Relations between apnea-hypopnea index (AHI) and the serum levels of fibrinogen (**A**), E-selectin (**B**), and t-PA (**C**)

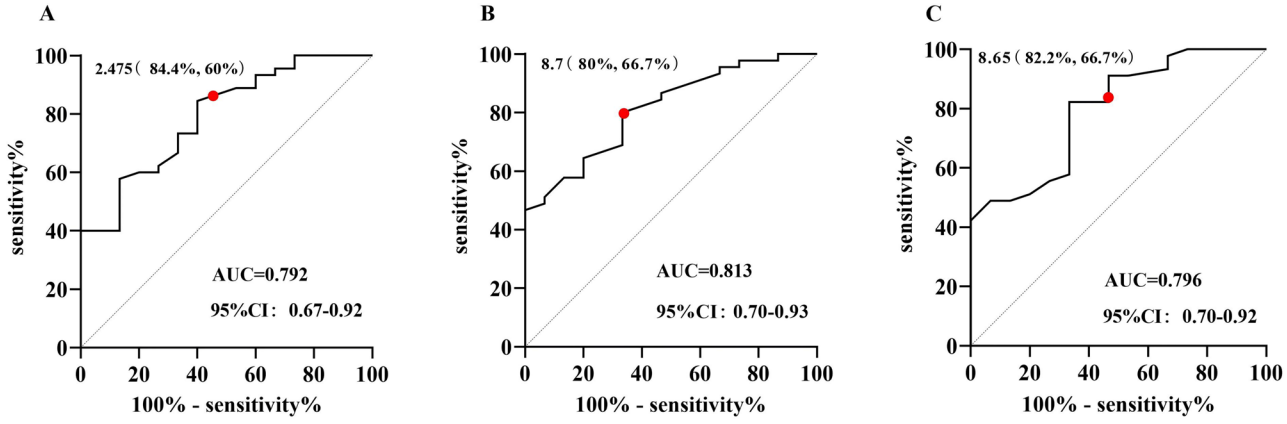

Fig. 3 Receiver operating characteristic (ROC) curve for fibrinogen (**A**), E-selectin(**B**), and t-PA(**C**) of stroke with OSA. Each panel shows the area under the curve (AUC), cutoff value, sensitivity, and specificity values

proved to improve the prognosis of AIS patients in specific circumstances [23]. Early diagnosis and intervention of OSA in AIS patients suspected of having comorbid OSA is crucial for improving clinical outcomes [24].

Our study also found that BMI, ESS scores, and STOP-Bang scores were significantly higher in acute ischemic stroke patients with moderate -severe OSA than in patients without OSA. BMI is a critical measure of obesity, which increases fat deposition in the upper airways, leading to airway narrowing and the development of OSA [25]. Given that overweight is a common risk factor for both AIS and OSA, AIS patients with OSA typically have a higher BMI. Frequent nocturnal apneas and arousals in OSA patients result in sleep fragmentation and reduced sleep efficiency, causing significant daytime somnolence and affecting daytime cognitive functions in AIS patients [26]. Consequently, AIS patients with OSA exhibited higher degrees of sleepiness as reflected

by the ESS score. The STOP-Bang questionnaire, which assesses the risk of OSA by evaluating eight indicators (snoring, fatigue, witnessed apnea, hypertension, BMI, age, neck circumference, and gender) [27], indicated that AIS patients with OSA had substantially elevated STOP-Bang scores compared to those without OSA due to the accumulation of these risk factors. Reuter et al. discovered that stroke patients often lack the typical signs and symptoms of OSA, thereby limiting the effectiveness of common screening tools (e.g., ESS, STOP-Bang, and Berlin Questionnaire) in stroke patients, resulting in the underdiagnosis and undertreatment of severe OSA [28].

Blood biomarkers are key to detection of patients at high risk of OSA, primarily due to the pathophysiologic mechanisms underlying the condition [29]. Our study found that serum levels of fibrinogen, E-selectin and t-PA were markedly higher in acute ischemic stroke patients with moderate-severe OSA versus those without OSA. Moreover, these biomarkers gradually raised with the severity of OSA.

E-selectin, specifically expressed on endothelial cells, mediates the rolling of leukocytes on endothelial cells, facilitating the recruitment of neutrophils, monocytes, and T cells to sites of inflammation. This process can lead to endothelial dysfunction and inflammatory responses [14]. Sun et al. reported that various cellular adhesion molecules, including E-selectin, were markedly increased in OSA patients versus healthy controls. Furthermore, multivariate linear regression analysis indicated a significant correlation between elevated E-selectin levels and OSA severity [30]. Richard et al. found that E-selectin levels within 6 h of acute stroke onset independently predicted the 3-month prognostic outcome [15]. Additionally, in a mouse model of ischemic stroke, the expression of E-selectin was upregulated in cerebral blood vessels damaged by reperfusion ischemia. Increased E-selectin levels may induce the migration of leukocytes or neutrophils into brain tissue, further contributing to cytokine release and free radical-mediated injury [31]. Our team's preliminary research discovered that ApoB-100 levels were raised in the serum of OSA patients in comparison to healthy controls [32]. Consequently, OSA can also impact endothelial function through lipid metabolism abnormalities. ApoB-100 has a powerful stimulatory influence on cholesterol esterification in macrophages, promoting foam cell formation and affecting endothelial function [33]. These findings underscore the complex interplay between OSA, endothelial dysfunction, and stroke pathophysiology.

Fibrinogen is primarily synthesized and secreted by hepatocytes, playing a crucial role in the coagulation process and platelet aggregation by forming fibrin monomers under the action of thrombin. T-PA is a serine protease, and is secreted primarily by the endothelial cells of blood vessels and converts plasminogen to plasmin, which degrades fibrinogen and various coagulation factors. Bikov et al. found that OSA induces a hypercoagulable state, activating the fibrinolytic system, and Overactivation of this system can lead to thrombus formation and vascular occlusion, one of the mechanisms by which OSA raises risk of cerebrovascular disease [34]. Qiu et al. observed increased levels of fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and D-dimer in OSA patients, suggesting a reduced capacity of the fibrinolytic system to degrade fibrinogen [35]. Our study demonstrated that AIS patients with moderate-to-severe OSA have elevated levels of fibrinogen and t-PA. The increase in t-PA may represent a compensatory response to the hypercoagulable state induced by OSA, aiming to mitigate the impact of elevated fibrinogen on blood hypercoagulability. Steffanina et al. reported significant elevations in both PAI-1 and t-PA in OSA patients in comparison to healthy controls [36], indicating an imbalance in the fibrinolytic system. This imbalance is further evidenced by the fact that elevated PAI-1 counteracts the effects of t-PA. Consequently, the suppressive role of elevated PAI-1 on t-PA exceeds the ability of t-PA to degrade fibrinogen, resulting in elevated levels of both fibrinogen and t-PA (Fig. 4).

The major diagnostic criteria for acute ischemic stroke (AIS) with OSA are currently based on polysomnography (PSG). However, PSG is complex and expensive to perform. Studies by Fiedorczuk et al. suggest that CRP, IL − 6, TNF - α, and IL − 8 hold promise as biological markers for the diagnosis of OSA in the healthy population. Receiver - operating characteristic (ROC) curve analysis shows that the areas under the curve (AUC) of CRP, IL − 8, TNF - α in plasma and IL − 6, CRP in serum are all less than 0.75 [37]. Compared with the above - mentioned inflammation - related biological markers, the AUC of the three indicators in this study is greater than 0.75. The sensitivity at the cut - off value is over 80%, and the positive rate for diagnosing AIS patients with OSA is relatively high. However, the specificity of the three indicators is between 60 and 70%, resulting in a mediocre screening effect for AIS patients without OSA. This is mainly because most patients with ischemic stroke have metabolic syndrome (such as hypertension, diabetes, hyperlipidemia, etc.), and metabolic syndrome can also affect endothelial cell function and the fibrinolytic system [38–40]. Therefore, diagnosing AIS patients with OSA without metabolic syndrome may have better specificity. Patients with a history of habitual snoring or witnessed apnea should be suspected of having OSA. Although bedside questionnaires can be used to screen for sleep apnea, a systematic review concludes that most obstructive sleep apnea screening questionnaires have high sensitivity but low specificity in stroke patients. Due to their

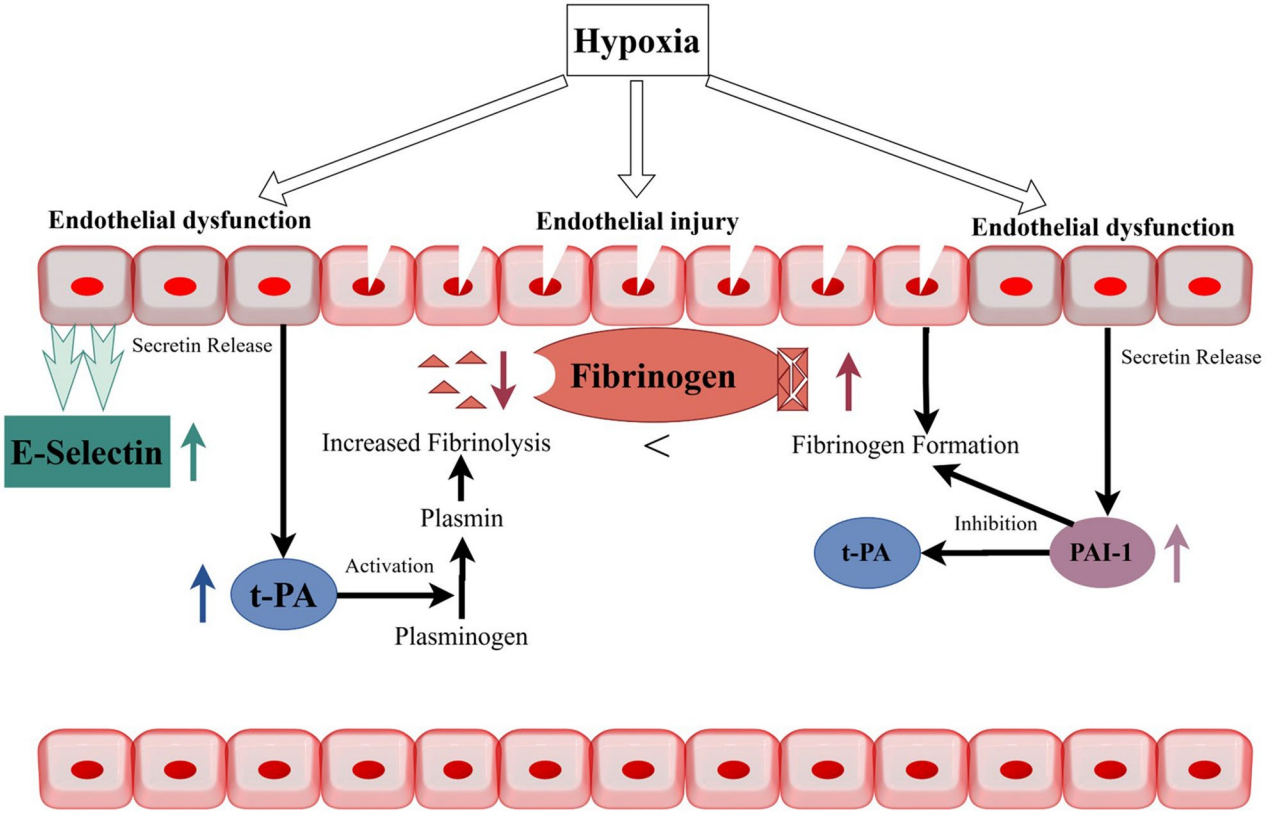

Fig. 4 Diagram of the mechanism by which hypoxia leads to elevated secretion of E-selectin, fibrinogen, and t-PA by vascular endothelial cells. Abbreviation: t-PA: tissue-type plasminogen activator; PAI-1: plasminogen activator inhibitor-1

poor overall predictive value, current questionnaires cannot be recommended as sufficiently accurate screening tools for stroke - related sleep apnea [41]. Biomarkers, being objective and quantifiable indicators, offer a promising alternative. In addition, subsequent studies could also combine the above - mentioned biomarkers、simple questionnaires and magnetic resonance imaging (MRI) techniques for the diagnosis and the assessment of prognosis of AIS patients with OSA [42, 43].

Continuous positive airway pressure (CPAP) treatment is regarded as the first - line treatment for OSA [44]. CPAP treatment for OSA reduces the risk of ischemic stroke by improving endothelial cell dysfunction, abnormal blood coagulation, and excessive activation of fibrinolysis [45–47]. Therefore, if long - term CPAP - treated AIS patients with OSA are continuously followed up, the above three biological markers may show improvement. AIS can also damage endothelial cells and activate the fibrinolytic system [48, 49]. Thus, as ischemic stroke progresses from the acute phase to the chronic phase, the above three biological indicators may be partially restored. In addition, in AIS patients with OSA, CPAP treatment can also indirectly improve risk factors for AIS such as hypertension, diabetes, and hyperlipidemia, thereby restoring the above three biological markers. Considering that 91% of AIS patients with OSA still have persistent OSA three months later [50], the biological markers in this study can guide the efficacy of CPAP treatment in chronic - phase ischemic stroke patients with OSA. By comprehensively assessing fibrinogen, E-selectin, and t-PA levels, we can effectively screen and manage this high-risk population, ultimately improving their quality of life and long-term health conditions for AIS patients.

Nevertheless, our study has limitations. Firstly, relatively small samples and single-center studies are susceptible to factors such as hospital location, patient origin, and medical technology level, leading to random errors in the study results. Second, the study did not conduct long-term follow-up of patients. The condition of patients with acute ischemic stroke complicated by OSA may change over time, and the dynamic changes of serum fibrinogen, E-selectin, and t-PA during disease development and their impact on long-term prognosis are not yet clear. Long-term follow-up can help to understand the relationship between these indicators and disease recurrence, patient quality of life, and provide more comprehensive information for clinical treatment and prognosis evaluation. In addition, CPAP treatment is considered to be the first-line treatment plan for OSA, and we did

not follow up whether the levels of these biomarkers decreased after CPAP treatment. If the above indicators recover after CPAP treatment, it may be possible to guide the efficacy of CPAP treatment by following up these indicators, eliminating the cumbersome process and high price of PSG [10]. Finally, it should be emphasized that our blood samples were stored at -80℃ for some time. As indicated by previous relevant research [51], this storage condition might cause changes in the concentration of the detected substances.

Conclusions

Acute ischemic stroke (AIS) patients with OSA exhibit disrupted sleep architecture, characterized by a prolonged light sleep (N1), a shortened deep sleep (N3), and an increased arousal index. In these patients, serum levels of fibrinogen, E-selectin, and t-PA are elevated, showing a linear correlation with the severity of OSA. These serological markers may thus be valuable in diagnosing OSA in AIS patients, and may have strong correlation as a monitoring form of OSA treatment and prognosis evaluation in the future, which has theoretical value. Further studies are needed to confirm the practical application.

Abbreviations

AIS	Acute Ischemic Stroke
AHI	Apnea-Hypopnea Index
ApoB-100	Apolipoprotein B-100
AUC	Under the Curve
BMI	Body Mass Index
CPAP	Continuous Positive Airway Pressure
ELISA	Enzyme Linked Immunosorbent Assay
ESS	Epworth Sleeping Scale
GAD-7	Generalized Anxiety Disorder-7
$LSaO_2$	Lowest Oxygen Saturation
Mean SaO_2	Mean Oxygen Saturation of Arterial Blood
Min SaO_2	Minimum Oxygen Saturation of Arterial Blood
N	Non-Rapid Eye Movement
NIHSS	National Institutes of Health Stroke Scale
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea Syndrome
PAI-1	Tissue Plasminogen Activator Inhibitor-1
PHQ-9	Patient Health Questionnaire-9
PSG	Polysomnography
REM	Rapid Eye Movement
ROC	Receiver Operating Characteristic
SDB	Sleep-Disordered Breathing
t-PA	type-Plasminogen Activator
TST	Total Sleep Time

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Not applicable.

Author contributions

Z H: drafting the original manuscript. Y Z: data collection and analysis. Q S: conception and design of the study. Z H and Y Z: material preparation. Z H and Z W: critical revision of the manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the First Hospital of Jilin University and was conducted in accordance with the Declaration of Helsinki (Approval No. 24K042-001). All participants and their guardians gave informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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