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RESEARCH ARTICLE

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The correlation of lncRNA SNHG16 with inflammatory cytokines, adhesion molecules, disease severity, and prognosis in acute ischemic stroke patients

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Abstract

Background: Long non-coding RNA small nucleolar RNA host gene 16 (lncRNA SNHG16) is involved in the pathogenesis of acute ischemic stroke (AIS) through the regulation of brain endothelial cell viability, inflammation, atherosclerotic plaque formation, and neural apoptosis. This study aimed to evaluate the prognostic value of lncRNA SNHG16 in AIS patients.

Methods: Newly diagnosed AIS patients (N = 120) were serially recruited. Their lncRNA SNHG16 expressions in peripheral blood mononuclear cells (PBMCs) were detected by reverse transcription-quantitative polymerase chain reaction (RT-qPCR); serum inflammatory cytokines and adhesion molecules were determined using enzyme-linked immunosorbent assay (ELISA). The accumulating recurrence-free survival (RFS) and overall survival (OS) were analyzed. Moreover, controls (N = 60) were recruited and their lncRNA SNHG16 expressions in PBMCs were detected.

Results: LncRNA SNHG16 was declined in AIS patients compared to controls ($p < 0.001$). Moreover, lncRNA SNHG16 was not related to any comorbidities in AIS patients (all $p > 0.05$). Interestingly, lncRNA SNHG16 was negatively related to tumor necrosis factor alpha (TNF-α) ($p < 0.001$), interleukin 6 (IL-6) ($p = 0.013$), and intracellular cell adhesion molecule-1 (ICAM-1) ($p = 0.024$), while positively correlated with interleukin 10 (IL-10) ($p = 0.022$) in AIS patients. Besides, lncRNA SNHG16 was inversely associated with the National Institutes of Health Stroke Scale (NIHSS) score in AIS patients ($p = 0.003$). During the follow-up period, in 14 (11.7%) patients occurred recurrence and 5 (4.2%) patients died. Unexpectedly, lncRNA SNHG16 was not associated with accumulating RFS ($p = 0.103$) or OS ($p = 0.150$) in AIS patients.

Conclusion: LncRNA SNHG16 relates to lower inflammatory cytokines, adhesion molecules, and milder disease severity, but fails to predict prognosis in AIS patients.

KEYWORDS
acute ischemic stroke, disease severity, inflammatory cytokines, long non-coding RNA small nucleolar RNA host gene 16, prognosis

1 | INTRODUCTION

Acute ischemic stroke (AIS), as one of the critical cerebro-cardiovascular diseases, accounts for 7.63 million newly diagnosed cases and 3.29 million mortality cases in 2019 globally.[1] Despite the recent advances in AIS management (such as intravenous thrombolysis, mechanical thrombectomy, anticoagulation therapy, etc.), the narrowing therapeutic window for AIS patients remains a huge challenge in the clinical practice.[2–4] Even for those AIS patients with successful reperfusion, the recurrence and mortality rates remain high.[5,6] Hence, it is necessary to identify novel biomarkers to monitor disease progression and improve AIS management.

Long non-coding RNA small nucleolar RNA host gene 16 (lncRNA SNHG16) is first reported in carcinomas.[7–9] Meanwhile, several recent studies report that lncRNA SNHG16 also participates in AIS pathogenesis via the regulation of brain endothelial cell proliferation, inflammatory cytokine production, and atherosclerotic plaque formation.[10–12] For instance, lncRNA SNHG16 promotes human brain endothelial cell proliferation, while suppressing cell apoptosis through regulation of the microRNA-15a-5p/bcl-2 axis.[10] Besides, lncRNA SNHG16 regulates the expression of inflammatory cytokines (including tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin 6 (IL-6)) in vitro.[11] Furthermore, lncRNA SNHG16 regulates the nuclear factor-kappa B (NF-κB) pathway in macrophages and further mediates progression of atherosclerosis.[12] In the clinical field, only two recent studies have reported that lncRNA SNHG16 is dysregulated in atherosclerotic patients.[12,13] However, the clinical role of lncRNA SNHG16 in AIS patients remains unclear and requires exploration.

Hence, this study was intended to explore the association of lncRNA SNHG16 with inflammatory cytokines, adhesion molecules, disease severity, recurrence, and death in AIS patients.

2 | METHODS

2.1 | Participants

This study serially recruited 120 newly diagnosed AIS patients treated in the hospital within 24 h after symptoms onset from July 2016 to December 2020. The recruitment criteria were set as: (a) newly diagnosed as AIS according to the American Stroke Association Guideline[14]; (b) aged over 18 years; (c) had no intracranial hemorrhage which was confirmed by the images of computed tomography (CT) scan or magnetic resonance angiography (MRA); (d) willing to provide peripheral blood (PB) samples; and (e) able to understand the study and willing to be followed up regularly. The patients who presented with severe infection, or had a prior history of malignant disease, were excluded from the study. Additionally, the study also enrolled 60 subjects who had at least two high-risk factors of stroke (including history of smoke, hypertension, hyperlipidemia, hyperuricemia, diabetes mellitus (DM), and chronic kidney disease (CKD)) as controls. To eliminate the potential bias, age and gender of the controls were matched to those of the AIS patients: the age limitation was 50–80 years; the gender ratio was 4:1 (male vs. female). The controls who had a history of stroke, or had met the exclusion criteria for AIS patients, were also ineligible for the study. The written informed consents were collected from all participants or the guardians. The study was permitted by the Ethics Committee of The First Affiliated Hospital of Xingtai Medical College.

2.2 | Data documentation

Clinical characteristics of AIS patients were obtained for study analysis, including age, gender, body mass index (BMI), history of smoke, comorbidities, and National Institutes of Health Stroke Scale (NIHSS) score. NIHSS score was collected within 24 h after hospitalization to evaluate the disease severity.

2.3 | Peripheral blood (PB) collection and detection

Peripheral blood (PB) was sampled from AIS patients immediately after hospitalization and from controls after recruitment, respectively. After PB collection, peripheral blood mononuclear cells (PBMCs) were separated from PB of all participants, then RNA was extracted using QIAamp RNA Blood Mini Kit (Qiagen, Germany) to evaluate lncRNA SNHG16 expression. The lncRNA SNHG16 expression was assessed by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). In brief, the reverse transcription was performed using iScript™ cDNA Synthesis Kit (Bio-Rad) and the qPCR was conducted using KOD SYBR® qPCR Mix (Toyobo). The relative expression of lncRNA SNHG16 was calculated by the $2^{-\Delta\Delta Ct}$ method where glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as an internal reference. The detailed sequences of primers were in line with those of a previous study and displayed as follows: lncRNA SNHG16, forward, 5′-TGTTCGTCATGGGTGTGAAC-3′, reverse, 5′-ATGGCATGGACTGTGGTCAT-3′; GAPDH, forward, 5′-AAGGTGAAGGTCGGAGTCAA-3′, reverse, 5′-AATGAAGGGGTCA TTGATGG-3′.[15] Besides, serum was isolated from PB of AIS patients to detect the levels of inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-10), and adhesion molecules (intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)) by enzyme-linked immunosorbent assay (ELISA) using commercial Human ELISA Kits (Bio-Techne China Co., Ltd.). The experimental process was in stringent accordance with the instructions from the manufacturer.

2.4 | Follow-up

Clinical follow-up for AIS patients was carried out by clinic visit or telephone according to the AIS Guideline.[14] The continuous

follow-up was performed until April 30, 2021. The median follow-up duration was 18 months, with the range of 3–52 months. Based on the follow-up information, recurrence-free survival (RFS) and overall survival (OS) were imputed. Patients who did not experience a RFS or OS event at the time of final analysis were censored at the last date of disease assessment.

2.5 | Statistics

Statistical analysis was completed by SPSS V.24.0 (IBM Corp.), and graphs were constructed by GraphPad Prism V.6.01 (GraphPad Software Inc.) and R V.4.0.5 (ggplot2 package, available at www.r-project.org). Mann–Whitney U test was used for the comparison of lncRNA SNHG16 expression between two groups. Spearman's rank correlation test or Mann–Whitney U test was applied for correlation between two variables. Kaplan-Meier curve was plotted for the display of RFS and OS, and log-rank test was used for the determination of RFS and OS differences between groups. Cox's proportional hazard regression was carried out for prognostic factor analysis. A value of $p < 0.05$ was considered as statistically significant.

3 | RESULTS

3.1 | Clinical features

Among recruited AIS patients, the mean age was 64.4 ± 9.4 years (Table 1). Meanwhile, there were 35 (29.2%) females and 85 (70.8%) males. Moreover, in 97 (80.8%), 59 (49.2%), 60 (50.0%), 26 (21.7%), and 27 (22.5%) patients occurred the comorbidities of hypertension, hyperlipidemia, hyperuricemia, DM, and CKD, respectively. Furthermore, the median NIHSS score was 6.0 with the interquartile range (IQR) of 4.0–11.0. The detailed clinical features of AIS patients are exhibited in Table 1.

TABLE 1 Characteristics of AIS patients

Items	AIS patients ($N = 120$)
Demographics	
Age (years), mean ± SD	64.4 ± 9.4
Gender, *n* (%)	
Female	35 (29.2)
Male	85 (70.8)
BMI (kg/m^2), mean ± SD	23.9 ± 2.9
History of smoke, *n* (%)	59 (49.2)
Comorbidities	
Hypertension, *n* (%)	97 (80.8)
Hyperlipidemia, *n* (%)	59 (49.2)
Hyperuricemia, *n* (%)	60 (50.0)
DM, *n* (%)	26 (21.7)
CKD, *n* (%)	27 (22.5)
Disease features	
NIHSS score, median (IQR)	6.0 (4.0–11.0)
Cytokines	
TNF-α (pg/ml), median (IQR)	100.4 (75.3–143.6)
IL-1β (pg/ml), median (IQR)	2.0 (1.3–2.8)
IL-6 (pg/ml), median (IQR)	15.2 (10.9–22.0)
IL-10 (pg/ml), median (IQR)	60.2 (42.1–92.7)
ICAM-1 (ng/ml), median (IQR)	84.9 (56.6–125.6)
VCAM-1 (ng/ml), median (IQR)	554.4 (447.4–752.8)

Abbreviations: AIS, acute ischemic stroke; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; ICAM-1, intercellular cell adhesion molecule-1; IL-10, interleukin 10; IL-1β, interleukin-1 beta; IL-6, interleukin 6; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale;SD, standard deviation; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1.

3.2 | LncRNA SNHG16 expression and its relationship with comorbidity

LncRNA SNHG16 was decreased in AIS patients compared to controls [median (IQR): 0.503 (0.327–0.770) vs. 1.003 (0.844–1.564), $p < 0.001$] (Figure 1). Then, further correlation analyses displayed that lncRNA SNHG16 was not related to any comorbidities in AIS patients (all $p > 0.05$) (Table 2).

3.3 | Correlation of lncRNA SNHG16 with inflammatory cytokines, adhesion molecules, and disease severity

LncRNA SNHG16 was negatively related to TNF-α ($rs = -0.327$, $p < 0.001$), IL-6 ($rs = -0.227$, $p = 0.013$), ICAM-1 ($r_s = -0.206$, $p = 0.024$), while positively correlated with IL-10 ($r_s = 0.209$, $p = 0.022$); there was no correlation of lncRNA SNHG16 with IL-1β ($r_s = -0.158$, $p = 0.086$) or VCAM-1 ($r_s = -0.164$, $p = 0.074$) (Figure 2A–F).

Moreover, lncRNA SNHG16 was inversely associated with NIHSS score ($r_s = -0.269$, $p = 0.003$) (Figure 3). Also, lncRNA SNHG16 was negatively related to stroke severity based on NIHSS scores in AIS patients ($r_s = -0.219$, $p = 0.016$) (Figure S1).

3.4 | Association of lncRNA SNHG16 with recurrence and death

The median follow-up was 18 months ranging from 3 to 52 months. At the last follow-up date, in 14 (11.7%) patients occurred recurrence, and 5 (4.2%) patients died. K-M curves and log-rank test analyses displayed that there was no association of lncRNA SNHG16 with accumulating RFS ($p = 0.103$) (Figure 4) or accumulating OS ($p = 0.150$) (Figure 5).

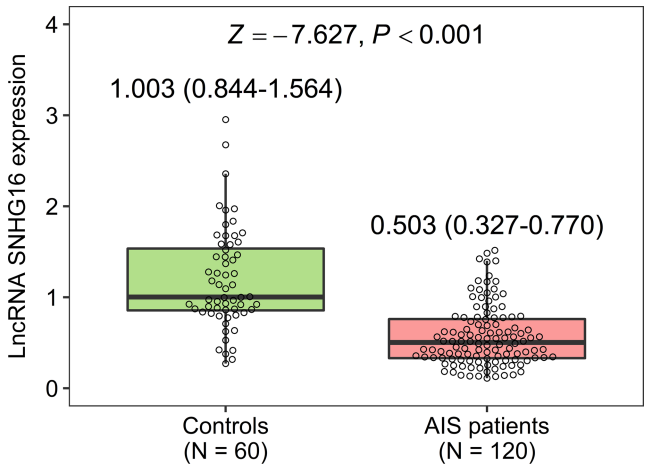

FIGURE 1 Long non-coding RNA small nucleolar RNA host gene 16 (LncRNA SNHG16) was reduced in acute ischemic stroke (AIS) patients

TABLE 2 Correlation of lncRNA SNHG16 expression with comorbidities in AIS patients

Items	LncRNA SNHG16, median (IQR)	Statistic (Z)	*p* Value
Hypertension			
No	0.490 (0.377–0.897)	−1.237	0.216
Yes	0.514 (0.317–0.681)		
Hyperlipidemia			
No	0.517 (0.332–0.784)	−0.711	0.477
Yes	0.428 (0.320–0.756)		
Hyperuricemia			
No	0.531 (0.347–0.698)	−0.640	0.522
Yes	0.439 (0.304–0.789)		
DM			
No	0.516 (0.305–0.777)	−0.296	0.767
Yes	0.459 (0.356–0.710)		
CKD			
No	0.490 (0.317–0.756)	−0.437	0.662
Yes	0.514 (0.344–0.775)		

Abbreviations: AIS, acute ischemic stroke; CKD, chronic kidney disease; DM, diabetes mellitus; IQR, interquartile range; LncRNA SNHG16, long non-coding RNA small nuclear RNA host gene 16.

3.5 | Factors relating to RFS and OS

Univariate Cox's regression analyses were conducted to determine the factors correlating with RFS and OS in AIS patients, and it was observed that lncRNA SNHG16 ((hazard ratio (HR): 0.071, $p = 0.042$) was related to prolonged RFS (Table S1), while it did not relate to OS (HR = 0.054, $p = 0.104$) (Table S2) in AIS patients. Moreover, NIHSS score (HR = 1.211, $p < 0.001$) and TNF-α (HR = 1.009, $p = 0.005$) were linked with shorter RFS, also NIHSS score (HR = 1.179, $p = 0.011$) was correlated with shorter OS in AIS patients.

4 | DISCUSSION

LncRNA SNHG16 has been observed to be dysregulated in atherosclerotic diseases. For example, lncRNA SNHG16 is overexpressed in oxidized low-density lipoprotein (ox-LDL) treated THP-1 macrophages and vascular smooth muscle cells (VSMCs), while its downregulation is reported in endothelial cells and neural cells following oxygen-glucose deprivation.[10,12,16,17] Clinically, aberrant expression of lncRNA SNHG16 has been reported in atherosclerosis patients.[12,13] While no relevant study has detected the expression of lncRNA SNHG16 in AIS patients. In the current study, it was discovered that lncRNA SNHG16 was downregulated in AIS patients compared to controls. The possible reason to explain this finding was that lncRNA SNHG16 promoted microvascular endothelial cell proliferation, suppressed the migration of VSMCs, and inhibited the production of inflammatory cytokines, which further slowed the progression of atherosclerosis in AIS patients.[10–13] Thus, lncRNA SNHG16 was negatively associated with AIS risk.

Moreover, it was also observed that lncRNA SNHG16 was negatively linked with TNF-α, IL-6, ICAM-1, and NIHSS score, while positively related to IL-10 in AIS patients, which could be explained as that: (a) lncRNA SNHG16 regulated multiple microRNAs (such as microRNA-146a-5p, microRNA-370-3p, microRNA-105-5p, etc.) and signaling pathways (such as NF-κB and janus kinase 1/signal transducer and activator of transcription 3 (JAK1/STAT-3) pathways) to suppress inflammatory cytokines and adhesion molecules in AIS patients.[11,18,19] (b) Less vascular inflammation was related to a lower risk of rupture of the atherosclerotic plaque in the cranial blood vessels and further led to a preserved neurological function and milder disease severity (reflected by the NIHSS score) in AIS patients.[20–22] (c) LncRNA SNHG16 was negatively related to adhesion molecules as discussed earlier, which might further inhibit the migration and proliferation of VSMCs, thereby suppressing the formation of foam cell in subendothelial space and preventing the progression of atherosclerosis, thus leading to lower disease severity in AIS patients.[23]

In order to determine the prognostic value of lncRNA SNHG16 in AIS management, the recurrence and mortality events were recorded during the follow-up period, then RFS and OS were analyzed by K-M curve and log-rank tests. Subsequently, it was observed that lncRNA SNHG16 high was not correlated with accumulating RFS or OS in AIS patients, although a tendency between lncRNA SNHG16 and the favorable prognosis was discovered. The possible reasons of these findings were: (a) lncRNA SNHG16 might prevent the occurrence and development of atherosclerotic plaques in the cranial vasculature, therefore reducing the risk of vascular occlusion, oxidative stress, and neural apoptosis, which was further related to a longer RFS and OS in AIS patients to some degree.[24–27] (b) The relatively small sample size of the current study might contribute to the low statistical power, also multiple factors might affect the AIS prognosis, thus only a tendency (but without statistical significance) of lncRNA SNHG16 correlating with accumulating RFS and OS in AIS patients was observed.

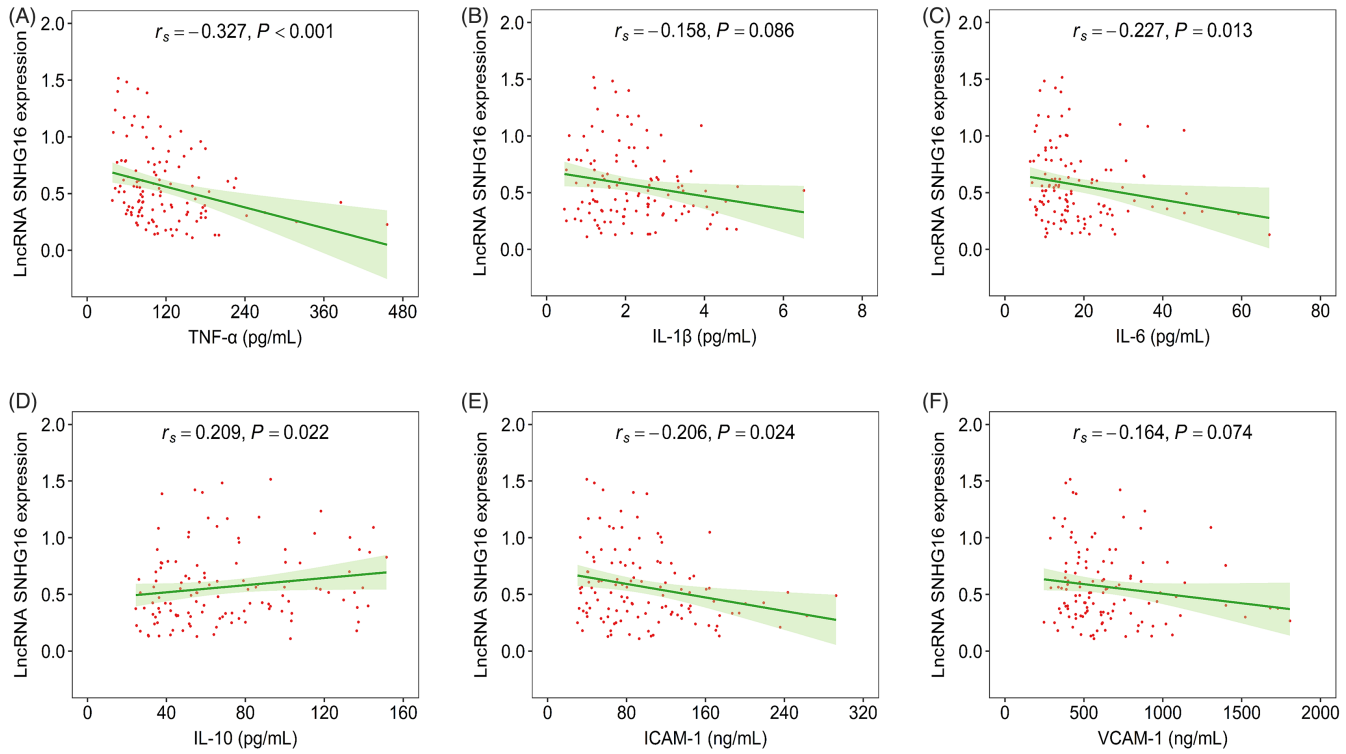

FIGURE 2 Long non-coding RNA small nucleolar RNA host gene 16 (LncRNA SNHG16) was linked to inflammatory cytokines and adhesion molecules in acute ischemic stroke (AIS) patients. Association of lncRNA SNHG16 with tumor necrosis factor alpha (TNF-α) (A), interleukin-1 beta (IL-1β) (B), interleukin 6 (IL-6) (C), interleukin 10 (IL-10) (D), intracellular cell adhesion molecule-1 (ICAM-1) (E), and vascular cell adhesion molecule-1 (VCAM-1) (F)

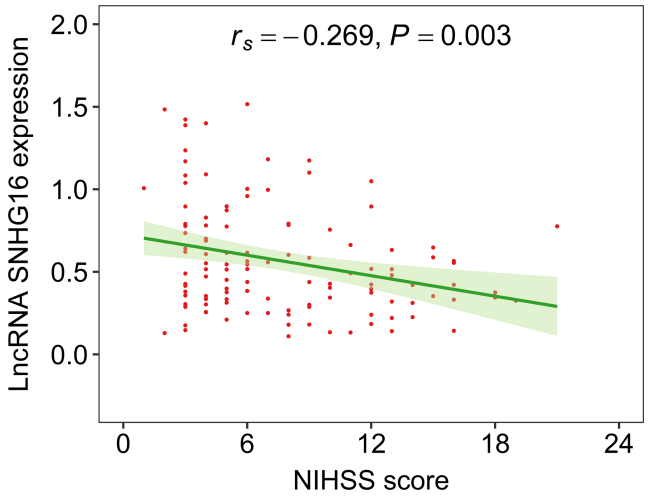

FIGURE 3 Long non-coding RNA small nucleolar RNA host gene 16 (LncRNA SNHG16) was negatively related to disease severity in acute ischemic stroke (AIS) patients

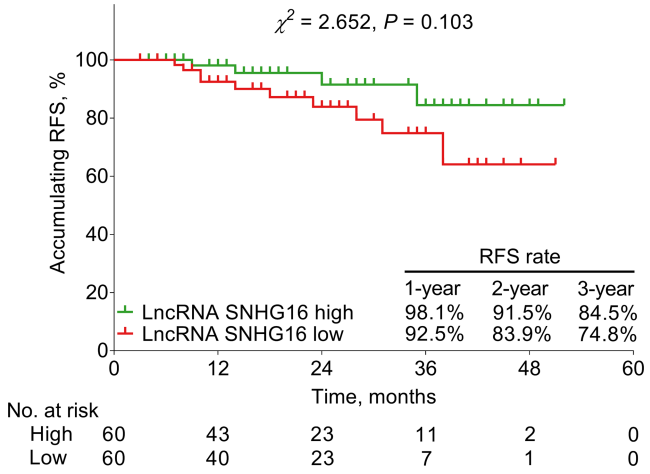

FIGURE 4 Long non-coding RNA small nucleolar RNA host gene 16 (LncRNA SNHG16) high was not associated with accumulating recurrence-free survival (RFS) in acute ischemic stroke (AIS) patients

The present study exhibits several clinical implications. The measurement of lncRNA SNHG16 could provide certain evidence for assessing disease severity and progression in AIS patients. Moreover, our study suggested that lncRNA SNHG16 might participate in AIS pathogenesis, while further molecular experiments were warranted. However, several limitations occurred in the current study. For instance, healthy subjects were not recruited in the current study to comprehensively analyze the expression of lncRNA SNHG16 among them. Moreover, the correlation of lncRNA SNHG16 with atherosclerotic plaques in AIS patients required further investigation. Furthermore, the modified Rankin scale (mRS) at 3 months after the first stroke in AIS patients was not recorded in the current study, which might be improved in the forthcoming studies.

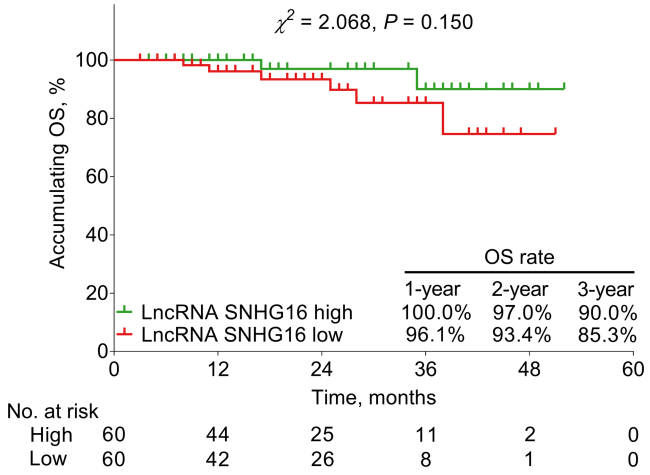

FIGURE 5 Long non-coding RNA small nucleolar RNA host gene 16 (LncRNA SNHG16) high was not correlated with accumulating overall survival (OS) in acute ischemic stroke (AIS) patients

In conclusion, lncRNA SNHG16 relates to lower inflammatory cytokines, adhesion molecules, and milder disease severity, but fails to predict prognosis in AIS patients.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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