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Anxiety faintly and depression remarkably correlate with recurrence in acute ischemic stroke patients

A study with 3-year longitude evaluation and follow-up

Shaoqun Luan, MM[a], Xin Wu, MB[b], Shaohua Yin, MB[a,*]

Abstract

Clinical value of anxiety and depression in acute ischemic stroke (AIS) is rarely studied. Thus, the aim of this study was to explore longitudinal changes of anxiety and depression, as well as their correlation with recurrence in AIS.

A total of 120 AIS patients and 120 controls were enrolled in the study. Furthermore, comparison of the hospital anxiety and depression scale (HADS) score or rate between AIS and controls was determined by Mann–Whitney *U* test or Chi-square test. In AIS patients, change of HADS scores or linear trend of anxiety and depression rate over time were determined by Friedman test or Mantel-Haenszel Chi-square test. Moreover, correlation of anxiety and depression with the recurrence rate was analyzed by log-rank test.

HADS for anxiety score, anxiety rate, HADS for depression score and depression rate were all elevated in AIS patients compared with controls (all $P < .001$). In AIS patients, HADS for anxiety score was elevated from discharged from hospital (M0) to month (M) 36 ($P = .027$), while anxiety rate was not ($P = .107$). Besides, HADS-D score and rate were both increased from M0 to M36 (both $P < .001$). Moreover, accumulating recurrence rate was 6.7%, 11.7%, and 17.5% at 1 year, 2 years, and 3 years, respectively. Additionally, anxiety at M24 ($P = .033$), depression at M0, M12, M24, and M36 (all $P < .05$) were all correlated with increased accumulating recurrence rate.

Continuous monitoring of anxiety and depression might be beneficial for the management of AIS prognosis.

Abbreviations: AIS = acute ischemic stroke, HADS = hospital anxiety and depression scale, HADS-A = hospital anxiety and depression scale for anxiety, HADS-D = hospital anxiety and depression scale for depression.

Keywords: acute ischemic stroke, anxiety, depression, longitude assessment, recurrence rate

1. Introduction

Acute ischemic stroke (AIS) is a cerebrovascular disease with cerebral ischemic induced by arterial stenosis or occlusion, which mainly results from the accumulation of lipids and complex carbohydrates, as well as the formation of thrombosis.[1–3] The cardinal symptoms of AIS patients are hemiplegia, sensory disturbance, and numbness, which even can menace the life.[3] In recent years, despite great progress in the AIS treatment therapies (including intravenous thrombolysis, revascularization therapy, and mechanical thrombectomy), it still remains increasing recurrence, mortality, and disability (including motive and cognitive disabilities).[2,4–8] Considering that AIS is still a disease with poor outcomes and cause a huge burden in China, the exploration of prognosis-related factors to improve AIS management is crucial.[7,8]

Anxiety and depression, as common mental complications, usually occur after stroke.[9–11] It has been reported that depression and anxiety deteriorate post-stroke neurological disorders, consequently leads to unsatisfactory prognosis.[12,13] For instance, an interesting study presents that anxiety is related to unfavorable functional outcomes of transient ischemic attack and stroke.[9] Furthermore, depression is correlated with high risk of recurrence of stroke[14]; meanwhile, depression also has been reported to be associated with elevated mortality in stroke survivors.[15] However, these studies only illustrate a single-time point assessment of anxiety and depression in stroke, the longitude changes of anxiety and depression along with the progress of AIS are not fully uncovered. In addition, it has been reported that the change of depression in long-term period is correlated with progression of neurological disease.[16] Hence, we deduced that anxiety and depression might be variated along with time and correlated with prognosis in stroke.

Editor: Wen-Jun Tu.

SL and XW contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

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

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How to cite this article: Luan S, Wu X, Yin S. Anxiety faintly and depression remarkably correlate with recurrence in acute ischemic stroke patients: a study with 3-year longitude evaluation and follow-up. Medicine 2022;101:3(e28521).

Received: 28 June 2021 / Received in final form: 15 December 2021 / Accepted: 16 December 2021

http://dx.doi.org/10.1097/MD.0000000000028521

Therefore, the aim of this study was to investigate 3-year longitude variation in severity and rate of anxiety and depression in AIS, as well as their correlation with recurrence of AIS, consequently improve the management of AIS.

2. Methods

In this study, 120 newly-diagnosed AIS patients treated in our hospital from April 2016 to February 2018 were included consecutively. All enrolled patients were identified by meeting the following enrollment criteria: first-ever diagnosis of AIS without evidence of intracranial hemorrhage; age ≥18 years; able to fulfill the evaluation of Hospital Anxiety and Depression Scale (HADS) on discharge from the hospital; willing to be followed up regularly. The exclusion criteria were: had a history of stroke; known documented psychiatric disorders before AIS onset; severe cognitive impairment resulted in an inability to understand the research; had uncontrolled comorbidities that seriously affect mental health; had a history of drug abuse; had history of cancer; lactating or pregnant patients. In addition, 100 controls were screened out from high-risk population of stroke, who were concomitant with at least 2 of the following risk factors: current smoke, hypertension, hyperlipidemia, hypeluricemia, diabetes mellitus, and chronic kidney disease. The eligible criteria for those controls were: had age and gender matched to the enrolled AIS patients; able to complete the HADS assessment; had no documented history of psychiatric disorders, cognitive impairment, uncontrolled comorbidities, drug abuse, or cancer; not in lactating or pregnancy. This study had acquired the approval from the Institutional Review Board. The signed informed consents were collected from all participants. Meanwhile; the current research and data processing involved Ethics Committee, the approval number of Ethics Committee was 2015-SJNK-001 and the time was January 13, 2015.

2.1. Data collection

Basic demographics and the stroke risk factors of all participants were recorded after recruitment. For AIS patients, the National Institutes of Health Stroke Scale (NIHSS) score that evaluated on the day of hospitalization was also collected.

2.2. Anxiety and depression evaluation

For the AIS patients, the anxiety and depression were initially evaluated on the day when they were discharged from hospital (M0), which were then repeatedly measured at 1 year (month 12, M12), 2 years (month 24, M24), and 3 years (month 36, M36) after discharge form the hospital. The evaluation of anxiety and depression for controls was completed after they signed the informed consents. The HADS for anxiety (HADS-A) subscale and the HADS for depression (HADS-D) subscale were respectively applied to assess the anxiety status and depression status of participants. Both the HADS-A subscale and the HADS-D subscale had a maximum score of 21, and the HADS-A score >7 was considered as anxiety; similarly, the HADS-D score >7 was considered as depression.[17]

2.3. Recurrence assessment

During the 36-month study follow-up for AIS patients, recurrence of stroke was documented to assess the accumulating recurrence rate. The last follow-up date was February 28, 2021.

2.4. Statistical analysis

Comparison of clinical features between 2 groups was examined by *t* test or Chi-square test. Comparison of HADS score between 2 groups was determined by Mann–Whitney *U* test. Comparison of anxiety rate and depression rate between 2 groups was determined by Chi-square test. Change of HADS scores over time was determined by Friedman test. Linear trend of anxiety rate and depression rate over time was determined by Mantel-Haenszel Chi-square test. Kaplan–Meier curve was plotted to elucidate the accumulating recurrence rate. Correlation of anxiety and depression with the accumulating recurrence rate was analyzed by log-rank test. Statistical description and statistical inference were fulfilled using SPSS 22.0 (IBM Corp., Armonk, NY), and figures were generated using GraphPad Prism 7.02 software (GraphPad Software Inc., San Diego, CA). Statistical significance was concluded if there was a P value $<.05$ in the analysis.

3. Results

3.1. Study flow

In our study, 140 AIS patients and 110 controls with at least 2 stroke risk factors were enrolled. Among AIS patients, 20 patients were excluded (including 9 patients who declined to participate in study, 8 patients who did not meet the inclusion criteria, 3 patients who met the exclusion criteria). Among controls, 10 controls were excluded (including 6 controls who declined to participate in study, 2 controls who did not meet the inclusion criteria, 1 control who met the exclusion criteria). Subsequently, 120 AIS patients and 100 controls were recruited. Furthermore, HADS-A and HADS-D at M0, M12, M24, M36, as well as accumulating recurrence rate were assessed in AIS patients. Meanwhile, HADS-A and HADS-D were also assessed in controls at enrollment. Moreover, follow-up was performed in AIS patients. During the follow-up period, there were 4 (3.3%) AIS patients who lost follow-up between M0 and M12, 9 (7.5%) AIS patients who lost follow-up between M12 and M24, as well as 9 (7.5%) AIS patients who lost follow-up between M24 and M36. Finally, all patients were included in the analysis, during which missing measured data were processed by last observation carried forward method, and recurrence data for patients lost to follow-up were censored at their last visit dates (Fig. 1).

3.2. Characteristics

In 120 AIS patients, the mean age was 66.0 ± 9.5 years, meanwhile, there were 82 (68.3%) men and 38 (31.7%) women. Besides, in controls, the mean age was 65.3 ± 8.4 years, there were 66 (66.0%) men and 34 (34.0%) women. Further analysis showed that there were more AIS patients with hyperuricemia (52 [43.3%]) compared with controls with hyperuricemia (26 [26.0%]) ($P = .008$). However, no difference was found in age, gender distribution, BMI, current smoke, hypertension, hyperlipidemia, education status, marry status or location between AIS patients and controls (all $P > .05$). In addition, the median of National Institutes of Health Stroke Scale score was 10.0 (6.3–12.8) in AIS patients. Additionally, regarding the use of selective serotonin reuptake inhibitor, there were 5 (4.2%) patients administrated with citalopram and 3 (2.5%) patients administrated with sertraline (Table 1).

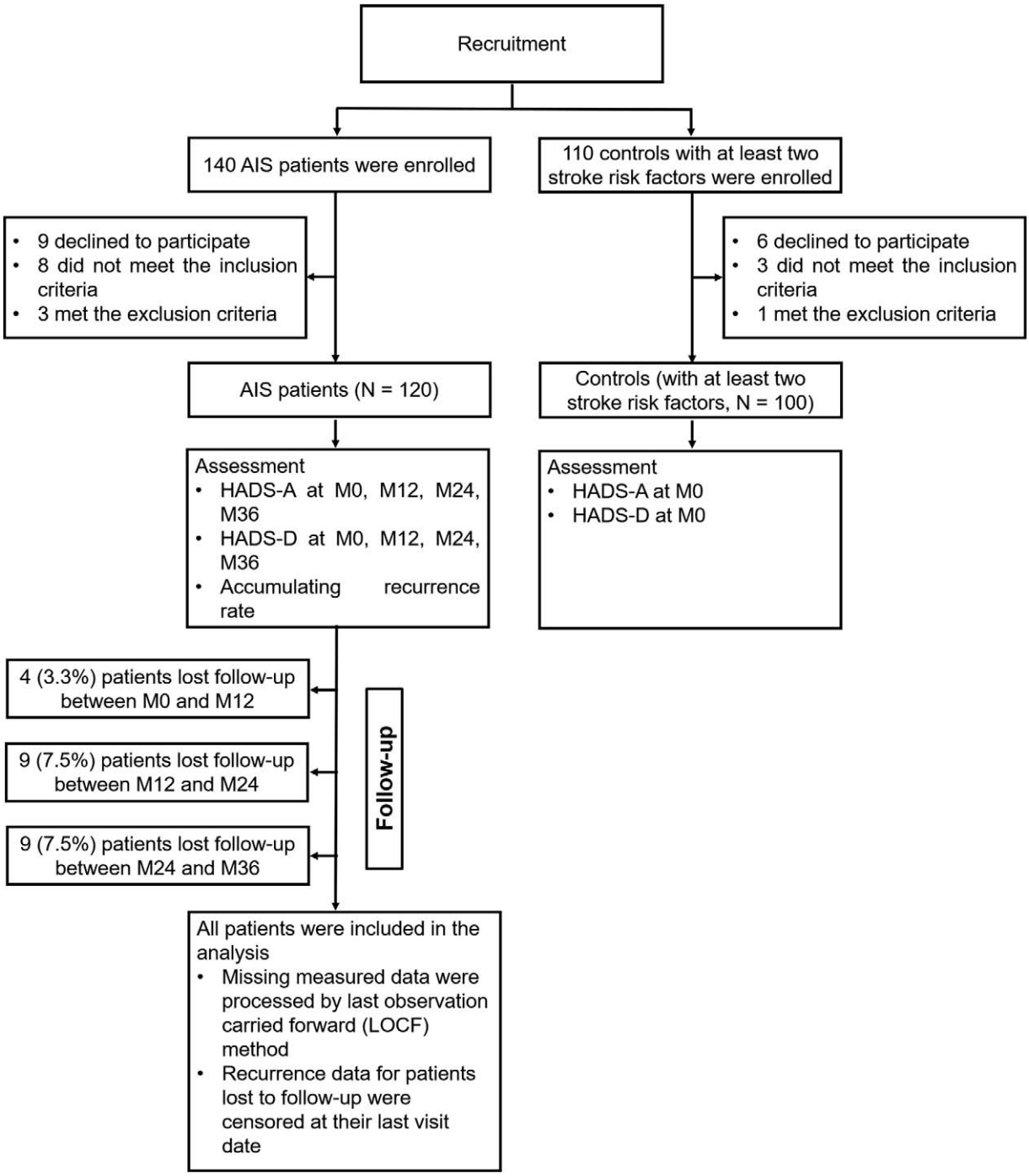

Figure 1. Flow chart. AIS = acute ischemic stroke, HADS-A = the hospital anxiety and depression scale for anxiety, HADS-D = the hospital anxiety and depression scale for depression, M = month.

3.3. Comparison of HADS-A score, HADS-D score, anxiety rate, and depression rate between AIS patients and controls

HADS-A score was elevated in AIS patients (median value: 7.0 [5.3–9.0]) compared with controls (median value: 4.0 [3.0–6.0]) ($P < .001$) (Fig. 2A). Besides, HADS-D score was also enhanced in AIS patients (median value: 6.0 [5.0–8.0]) compared with controls (median value: 4.0 [2.0–6.0]) ($P < .001$) (Fig. 2B). Furthermore, both anxiety rate (30.0% vs 9.0%) and depression rates (29.2% vs 8.0%) were increased in AIS patients compared with controls (both $P < .001$) (Fig. 2C and D).

3.4. Comparison of HADS-A score, HADS-D score, anxiety rate, and depression rate at different time points in AIS patients

HADS-A score was increased with time in AIS patients ($P = .027$) (Fig. 3A). However, no difference was found in anxiety rate at different time points ($P = .107$) (Fig. 3B). Besides, both HADS-D

Table 1

Characteristics.

Characteristics	Controls (N = 100)	AIS patients N = 120)	*P* value
Age (yrs), mean ± SD	65.3 ± 8.4	66.0 ± 9.5	.552
Gender, No. (%)			.714
Male	66 (66.0)	82 (68.3)	
Female	34 (34.0)	38 (31.7)	
BMI (kg/m^2), mean ± SD	24.2 ± 2.9	23.8 ± 2.3	.176
Current smoke, No. (%)	45 (45.0)	53 (44.2)	.902
Hypertension, No. (%)	79 (79.0)	102 (85.0)	.247
Hyperlipidemia, No. (%)	49 (49.0)	60 (50.0)	.883
Hyperuricemia, No. (%)	26 (26.0)	52 (43.3)	.008
DM, No. (%)	16 (16.0)	26 (21.7)	.288
CKD, No. (%)	11 (11.0)	19 (15.8)	.299
Education, No. (%)			.559
Primary school or below	22 (22.0)	31 (25.8)	
Junior high school	26 (26.0)	38 (31.7)	
High school	36 (36.0)	34 (28.3)	
University or above	16 (16.0)	17 (14.2)	
Marry status, No. (%)			.526
Married	40 (40.0)	43 (35.8)	
Single/Divorced/Widowed	60 (60.0)	77 (64.2)	
Location, No. (%)			.196
Urban	12 (12.0)	22 (18.3)	
Rural	88 (88.0)	98 (81.7)	
NIHSS score, median (IQR)	–	10.0 (6.3–12.8)	–
SSRI use, No. (%)			
Citalopram	–	5 (4.2)	–
Sertraline	–	3 (2.5)	–

AIS = acute ischemic stroke, BMI = body mass indexes, CKD = chronic kidney disease, DM = diabetes mellitus, IQR = interquartile range, NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor.

score and depression rate were elevated with time in AIS patients (both $P < .001$) (Fig. 4A and B).

3.5. Accumulating recurrence rate in AIS patients

Recurrence rate was 6.7% at 1 year, 11.7% at 2 year, and 17.5% at 3 year among AIS patients (Fig. 5A). Moreover, the accumulating recurrence rate of AIS patients was shown in Fig. 5B.

3.6. Comparison of accumulating recurrence rate between AIS patients with or without anxiety

Accumulating recurrence rate was elevated in AIS patients with anxiety at M24 compared with those without anxiety at M24 ($P = .033$) (Fig. 6C). However, no difference was found in accumulating recurrence rate between AIS patients with anxiety at M0/M12/M36 and those without anxiety at M0/M12/M36 accordingly (all $P > .05$) (Fig. 6A, B, and D).

3.7. Comparison of accumulating recurrence rate between AIS patients with or without depression

Accumulating recurrence rate was respectively increased in AIS patients with depression at M0 ($P = .027$), M12 ($P = .003$), M24 ($P = .034$), or M36 ($P = .010$) compared with those without depression at M0, M12, M24, or M36 accordingly (Fig. 7A–D).

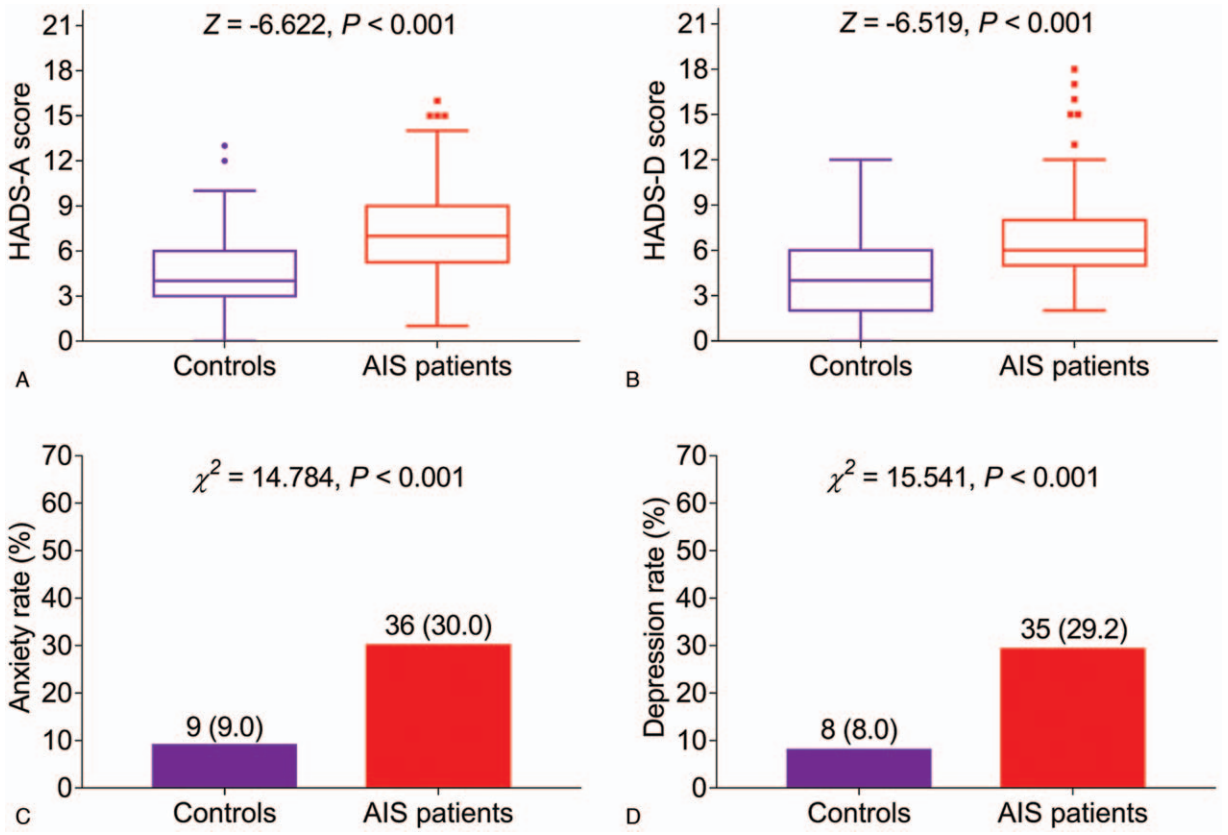

Figure 2. Anxiety and depression in AIS patients and controls. Comparison of HADS-A score (A), HADS-D score (B), anxiety rate (C), and depression rate (D) between AIS patients and controls. AIS = acute ischemic stroke, HADS-A = the hospital anxiety and depression scale for anxiety, HADS-D = the hospital anxiety and depression scale for depression.

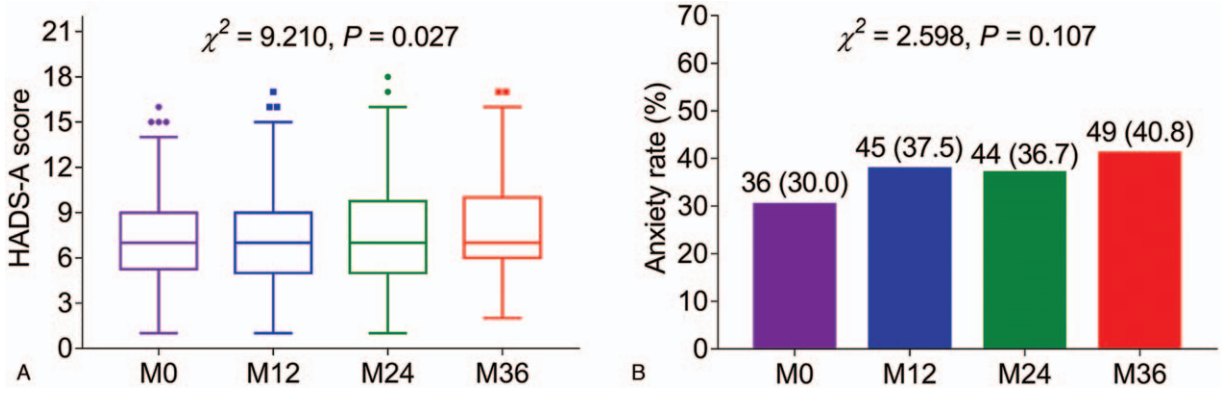

Figure 3. Longitude anxiety change. Comparison of HADS-A score (A) and anxiety rate (B) at different time points. HADS-A = the hospital anxiety and depression scale for anxiety, M = month.

4. Discussion

In this study, we found several interesting results: compared with non-stroke controls, the anxiety and depression status deteriorated, meanwhile, anxiety and depression rates were elevated in AIS patients; anxiety status was worsened to a certain extent with time, furthermore, depression status was aggravated obviously with time among AIS patients; anxiety was weakly associated with AIS recurrence, while depression was strongly associated with AIS recurrence.

Regarding prevalence of depression in patients with cardiac-cerebral vascular disease and health people, it has been illustrated that the prevalence of depression is elevated among patients with myocardial infarction compared with non-myocardial infarction populations.[18] Another study also shows that the prevalence

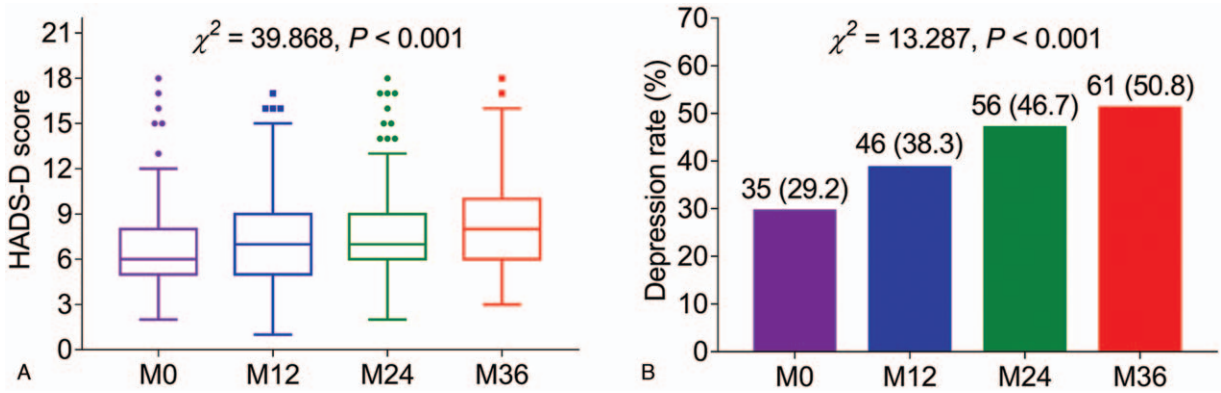

Figure 4. Longitude depression change. Comparison of HADS-D score (A) and depression rate (B) at different time points. HADS-D = the hospital anxiety and depression scale for depression, M = month.

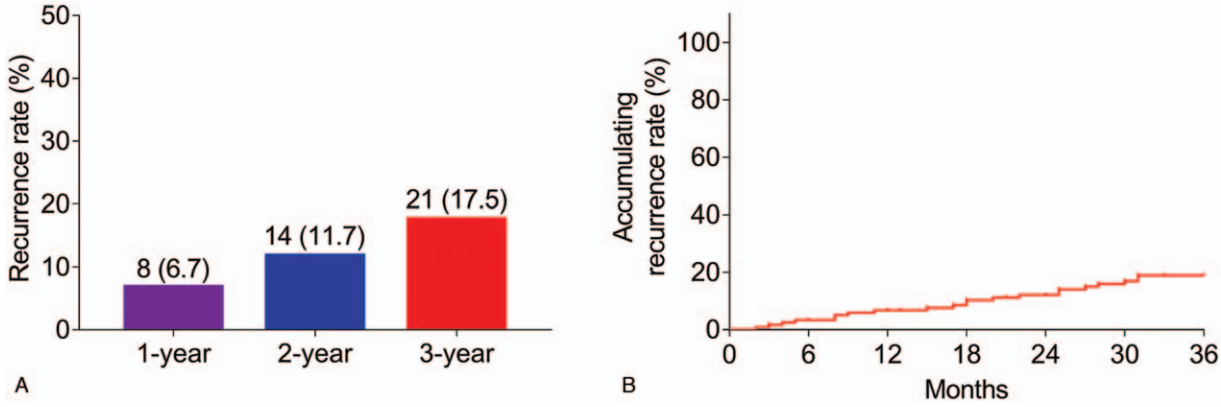

Figure 5. Disease recurrence in AIS patients. Recurrence rate (A) and accumulating recurrence rate (B) at different time points. AIS = acute ischemic stroke.

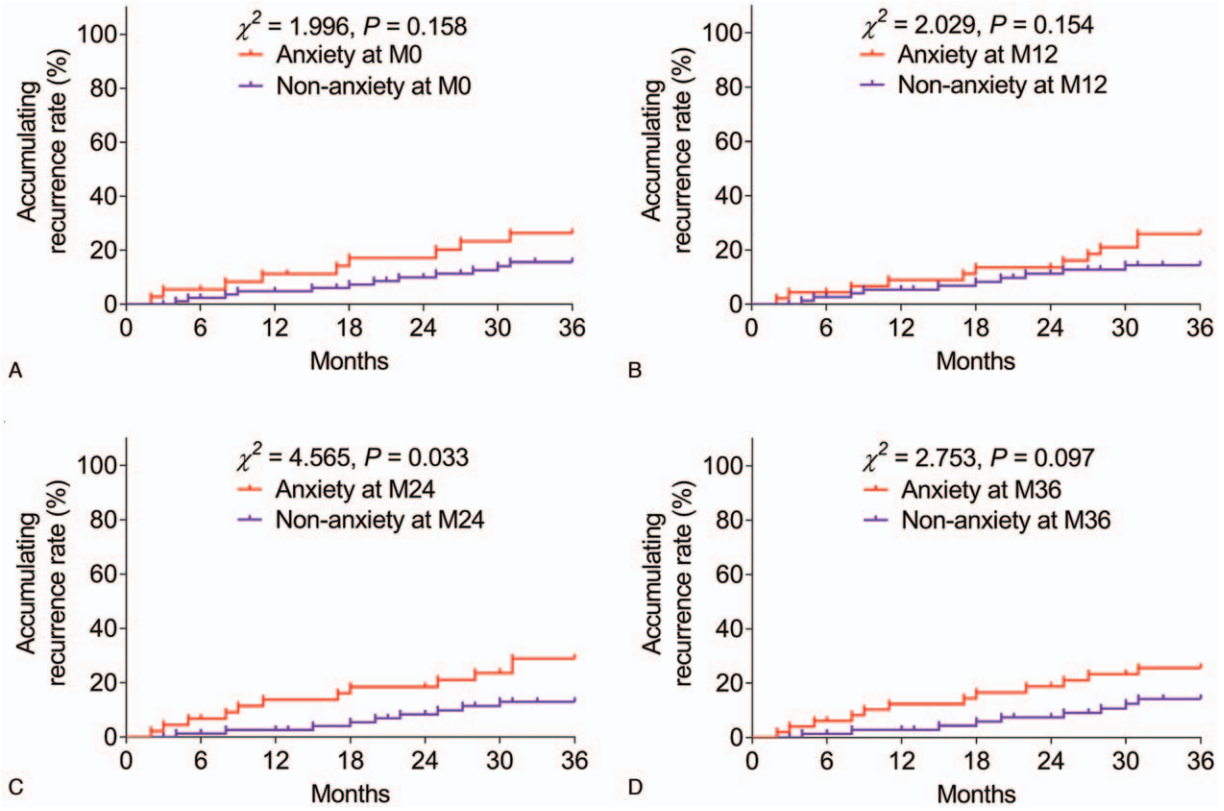

Figure 6. Correlation of anxiety with AIS accumulating recurrence rate. Comparison of accumulating recurrence rate between anxiety patients and non-anxiety patients at M0 (A), M12 (B), M24 (C), and M36 (D). AIS = acute ischemic stroke, M = month.

rate of anxiety is increased in coronary heart disease patients compared with general populations.[19] In our study, we found that AIS patients had worse status and higher incidence of depression or anxiety compared with populations without stroke. Possible reasons could be that: depression or anxiety was correlated with high-risk lifestyles, including smoking, excessive drinking, lack of exercises, and unhealthy diet, which might result in AIS[20,21]; depression or anxiety would have a strong relationship with diabetes, furthermore, diabetes could lead to vascular aging, which might be associated with the development of AIS.[22,23] Depression affected the pathophysiological of several organ systems, including blood pressure and vascular tone, which maybe lead to AIS.[24,25] Therefore, AIS patients had unfavorable status and high prevalence of depression or anxiety compared with non-stroke populations.

In terms of the variation of anxiety and depression in AIS, few studies assess longitude changes of anxiety and depression in AIS. Thus, in order to explore this issue, we conducted this study and found that the anxiety deteriorated to some extent with time, while depression was worsened obviously with time in AIS. Possible explanations could be that: with increasing age and the progress of disease, the mental state of the patients might continue to deteriorate, thus, anxiety and depression were both worsened with time in AIS[2,26]; anxiety could be alleviated to a certain extent through rehabilitation training and cognitive behavioral therapy, thus, anxiety was aggravated to some extent with time, while depression was worsened markedly with time in AIS.[27] AIS was a disease correlated with inflammation, furthermore, inflammatory process might increase depression symptoms with time,[28–30] therefore, depression status was aggravated notably, as well as its rate was elevated with time.

As for the correlation of anxiety and depression with prognosis of cardiac-cerebral vascular diseases, previous studies have exhibited that depression is linked to worse outcomes of coronary heart disease.[31,32] Depression has also been illustrated to be associated with poor prognosis in patients with transient ischemic attack.[9] Furthermore, another study presents that anxiety is linked to unfavorable outcomes of stroke.[33] In our study, we found that anxiety was weakly correlated with the recurrence of AIS, while depression was strongly associated with the recurrence of AIS. Possible explanations might be that: depression might be correlated with behavioral mechanism in AIS, such as the incoordination to secondary prevention (including smoking and lack of exercises), which could result in the recurrence of AIS[34,35]; depression might be associated with biological mechanism in AIS, such as inflammatory processes, which could affect the recurrence of AIS.[28,36] Therefore, accumulating recurrence rate of AIS was elevated markedly in AIS patients with depression compared with those without depression.

In the current study, HADS subscales were applied rather than other common depression scales like Hamilton depression scale to assess the anxiety status and depression status of participants, which might be explained by that: Hamilton depression scale only could be used by psychiatrist who had received systematic training, while in the current study anxiety and depression were evaluated by nurses who were not qualified to apply Hamilton depression scale; the current study aimed to evaluate longitudinal change with multiple evaluations of anxiety and depression in the

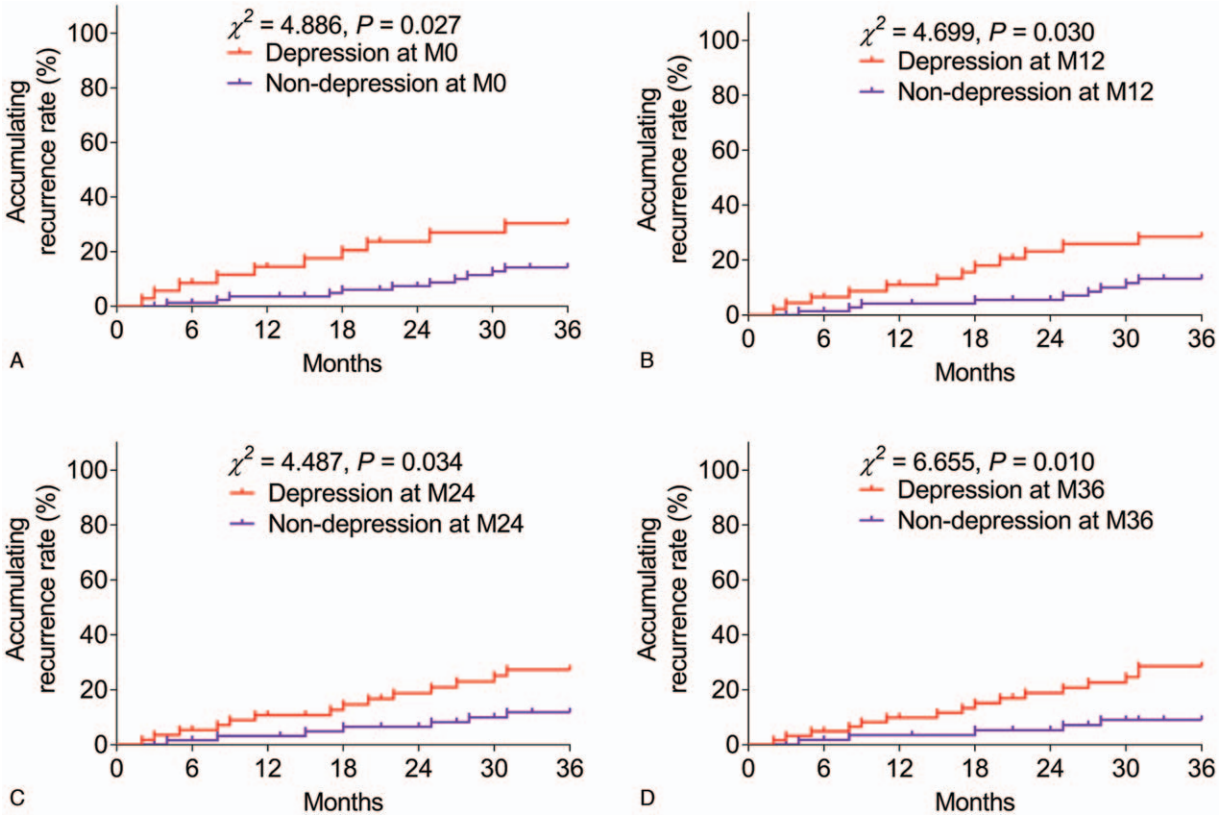

Figure 7. Correlation of anxiety with AIS accumulating recurrence rate. Comparison of accumulating recurrence rate between depression patients and non-depression patients at M0 (A), M12 (B), M24 (C), and M36 (D). AIS = acute ischemic stroke, M = month.

36-month follow-up among AIS patients; meanwhile, HADS subscale was relatively convenient with high feasibility (only 14 questions), which would not take much time.

Our study existed several limitations: the sample size was limited, which might result in less statistical power in analyses; anxiety and depression were evaluated by AIS patients themselves according to HADS questionnaire, which might exist subjective bias; the follow-up period was not long enough, hence the correlation of anxiety and depression with longer-term prognosis in AIS patients could be investigated in the future; more comprehensive and in-depth understanding of mechanisms of depression and anxiety in the development and progression of AIS needed to be explored in the future, which could facilitate the depression/anxiety-based management in AIS; poor functional recovery and reduced quality of life might have impact on depression and anxiety disorder in AIS patients, hence modified rankin scale scores among patients at admission and discharge could be explored in the further study; the relationship between stroke and depression among AIS patients with scoring neurological disability could be explored in the further study.

To be conclusive, anxiety faintly and depression obviously deteriorate along with time in AIS; moreover, anxiety weakly and depression strongly associate with AIS recurrence. These data suggest that continuous monitoring of anxiety and depression maybe beneficial for the management of AIS recurrence.

Author contributions

Conceptualization: Shaoqun Luan, Shaohua Yin.
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Formal analysis: Shaoqun Luan, Xin Wu, Shaohua Yin.
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Supervision: Shaoqun Luan, Shaohua Yin.
Writing – original draft: Shaoqun Luan, Xin Wu.
Writing – review & editing: Shaoqun Luan, Shaohua Yin.

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