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Longitudinal assessment of anxiety/depression rates and their related predictive factors in acute ischemic stroke patients

A 36-month follow-up study

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Abstract

This study aimed at investigating the longitudinal changes of poststroke anxiety/depression rates, and their potential risk factors in acute ischemic stroke (AIS) patients.

A total of 250 first diagnosis of AIS patients were enrolled and followed for 36 months. Anxiety/depression of patients were assessed using hospital anxiety and depression scale (HADS) at month (M) 0 (M0) and then every 3 months till M36.

During 36-month follow-up, both HADS-anxiety score (from 6.9 ± 3.1 at M0 to 8.0 ± 3.5 at M36) and anxiety rate (from 41.2% at M0 to 54.0% at M36) (both $P < .01$) were increased with time longitudinally. Meanwhile, HADS-depression score (from 6.2 ± 3.0 at M0 to 6.9 ± 3.1 at M36) and depression rate (from 32.4% at M0 to 40.4% at M36) (both $P > .05$) displayed an upward trend with time longitudinally but without statistical significance. By forward multivariate logistic regression analysis, female, diabetes and higher National Institute of Health Stroke Scale (NIHSS) score independently predicted elevated anxiety risk at M0, M12, M24, and M36 (all $P < .05$); while longer education duration and hypertension independently predicted raised anxiety risk at M0 and M12 (all $P < .05$), respectively. Regarding depression, diabetes independently predicted increased depression risk at M0, M12, M24, and M36 (all $P < .01$); longer education duration independently predicted higher depression risk at M0 and M12 (both $P < .05$); female independently predicted increased depression risk at M24 and M36 (both $P < .01$); higher NIHSS score independently predicted raised depression risk at M24 and M36 (both $P < .01$).

Poststroke anxiety and depression are frequent, which deteriorate with time; besides, female, diabetes, NIHSS score, hypertension and education duration independently predicted increased poststroke anxiety or depression risk in AIS patients.

Abbreviations: AIS = acute ischemic stroke, CKD = chronic kidney disease, HADS = hospital anxiety and depression scale, HADS-A = HADS-anxiety, HADS-D = HADS-depression, M = month, NIHSS = National Institute of Health Stroke Scale.

Keywords: acute ischemic stroke, anxiety, depression, occurrence, risk factors

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1. Introduction

Acute ischemic stroke (AIS), as the major cause of permanent disability and mortality worldwide is initiated by the sudden loss of cerebral blood flow due to large or small artery occlusions both intracranially and extracranially, which leads to neuron death and necrosis in brain.[1,2] AIS mortality has been declined and the proportion of survivors has been increased over the last 20 years with the implementation of stroke units and the use of thrombolysis/thrombectomy.[3] However, poststroke survivors frequently experience a variety of physiological distress, especially anxiety and depression.[4] Anxiety is marked by persistent and excessive feeling of worry or fear that is difficult to control, plus 3 or more of the following physical symptoms: restlessness, fatigue, diminished concentration, irritability, muscle tension and/or insomnia.[5] Depression is characterized by loss of interest or pleasure in activities that are used to be enjoyable, loss of energy, decreased concentration, psychic retardation, appetite disturbance and insomnia.[4] Anxiety and depression may be associated with less rehabilitation service comply, worse functional outcomes, decreased quality of life and raised mortality.[6] Therefore, effective management of poststroke anxiety and depression is necessary for improving prognosis in AIS patients.

From previous studies, sociodemographic variables, clinical variables, magnetic resonance imaging variables, and laboratory indexes are reported as potential predictive factors for anxiety and depression AIS patients.[7–14] For example, gender and acute infarcts in cerebral hemispheric white matter correlates with higher poststroke anxiety in AIS patients at 3 months post-stroke.[7] Another study unravels that increased serum high-sensitivity C-reactive protein and homocysteine at admission are independent predictive factors of poststroke depression in AIS patients at 6 months after stroke.[8] However, majority of the previous studies are conducted with a relatively short follow-up duration (ranging from 1 month–1 year), furthermore, they only explore the anxiety and/or depression related predictive factors at 1 or 2 time points. Thereby, further study with extended follow-up period to analyze the potential predictive factors for anxiety and depression in AIS patients is necessary. In the present study, we followed up 250 first diagnosis of AIS patients for 36 months, and aimed at investigating the longitude changes of poststroke anxiety/depression rates, as well as their potential predictive factors in these patients.

2. Methods

2.1. Patients

From July 2014 to June 2016, 250 AIS patients admitted in The Second Affiliated Hospital of Harbin Medical University were consecutively enrolled in this study. The inclusion criteria were: first diagnosis of AIS; aged 50 to 85 years old; able to understand the items in hospital anxiety and depression scale (HADS) exactly and complete the HADS assessment independently; and could be followed up regularly. The exclusion criteria were: had documented history of anxiety, depression or other mental health disorders; had evidence of cerebral hemorrhage or subarachnoid hemorrhage; had moderate or severe cognition impairment (defined as mini-mental state examination score $\leq$ 20); had severe disorders in kidney or liver; and complicated with hematological malignancies or solid tumors. This study was approved by the Institutional Review Board of The Second Affiliated Hospital of Harbin Medical University, and all patients or their guardians provided written informed consents. Notably, if patients presented with severe symptoms (only a small number of patients), their guardians had the legal abilities to get the information, make the decisions and sign the consent forms.

2.2. Data collection

After enrollment, the baseline characteristics of AIS patients were recorded, which included demographic characteristics, comorbidities, education duration, marital status, employment status before stroke, lesion location, severity of stroke, and severity of cognition impairment. The severity of stroke was assessed using National Institute of Health Stroke Scale (NIHSS), and the severity of cognition impairment was assessed using mini-mental state examination scale.

2.3. Treatment, follow-up, and assessment

At baseline and during the follow-up period, AIS patients with severe anxiety or severe depression received antianxiety treatment or antidepressant treatment, respectively. As for AIS patients with moderate anxiety or depression, they received antianxiety or ant-depressant treatment according to their clinical status. During the follow-up, 47 (18.8%) AIS patients received antianxiety treatments and 35 (14.0%) AIS patients received antidepressants. While the numbers were underestimated since the information about antianxiety and antidepressant treatments in some patients was not recorded. All patients were followed up every 3 months until the completion of scheduled 36-month follow-up or death. During follow-up, anxiety, and depression of the patients were assessed using HADS at baseline (M0), month 3 (M3), month 6 (M6), month 9 (M9), month 12 (M12), month 15 (M15), month 18 (M18), month 21 (M21), month 24 (M24), month 27 (M27), month 30 (M30), month 33 (M33), and month 36 (M36).[15–17] The HADS has 14 items: 7 items were designed for anxiety measuring HADS-anxiety (HADS-A) and other 7 items were designed for depression measuring HADS-depression (HADS-D). The total score of HADS-A was ranging from 0 to 21, and the total score $\geq$8 was defined as anxiety.[18] The total score of HADS-D was ranging from 0 to 21, and the total score $\geq$8 was defined as depression.[18] Of note, the severity of anxiety and depression were not categorized (0–7, no anxiety/depression; 8–10, mild anxiety/depression; 11–14, moderate anxiety/depression; 15–21, severe anxiety/depression) since multivariate logistic regression analyses for independent predictive factors for anxiety or depression with different severity would be unable to perform. For the patients who lost follow-up, they were analyzed using the last visit data.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 22.0 software (IBM, Chicago, IL), and figures were plotted using GraphPad Prism 7.01 software (GraphPad Software, San Diego, CA). Comparison between independent 2 groups was determined by Student *t* test or Chi-square test. Comparison among multiple groups was determined by one-way analysis of variance or linear-by-linear association test. Independent predictive factors for anxiety or depression were analyzed by forward multivariate logistic regression model. P value $< .05$ was considered significant.

3. Results

3.1. Demographic and clinical characteristics

The mean age of AIS patients was 67.5 ± 8.6 years, and there were 91 (36.4%) females/159 (63.6%) males (Table 1). The number (percentage) of AIS patients who were current smoker was 64 (25.6%). As for comorbidities, 213 (85.2%), 132 (52.8%), 89 (35.6%), and 34 (13.6%) patients had hypertension, hyperlipemia, diabetes and chronic kidney disease (CKD), respectively. The detailed information regarding other characteristics were displayed in Table 1.

3.2. HADS-A score and anxiety rate at different time points

HADS-A score was 6.9 ± 3.1, 7.3 ± 3.1, 7.7 ± 3.3, and 8.0 ± 3.5 at M0, M12, M24, and M36, respectively, which exhibited an increasing trend ($P = .002$) (Table S1, Supplemental Digital Content, http://links.lww.com/MD/G520) (Fig. 1A). As for anxiety rate, 103 (41.2%), 109 (43.6%), 122 (48.8%), and 135 (54.0%) AIS patients presented with anxiety at M0, M12, M24, and M36, respectively, and the anxiety rate displayed an

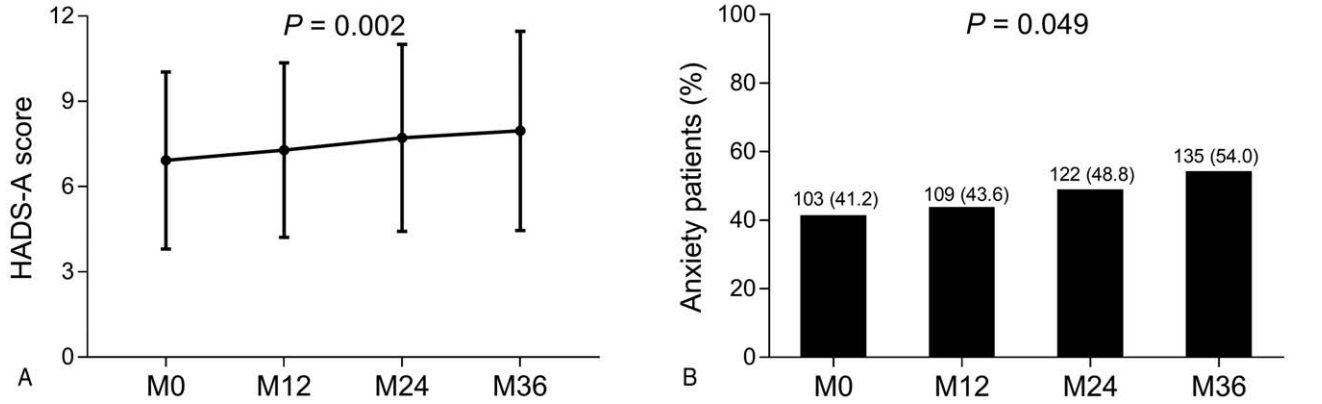

Figure 1. HADS-A score and anxiety rate within 36-month follow-up period. HADS-A score in AIS patients at M0, M12, M24, and M36 (A). Anxiety rate in AIS patients at M0, M12, M24 and M36 (B). AIS = acute ischemic stroke, HADS-A = hospital anxiety and depression scale-anxiety, M = month.

upward trend throughout 36 months as well ($P = .049$) (Fig. 1B). Taken together, these findings indicated that anxiety was increased gradually over time in AIS patients.

Table 1

Baseline characteristics of AIS patients.

Items	AIS patients (N = 250)
Age (yr), mean ± SD	67.5 ± 8.6
Gender, No. (%)	
Female	91 (36.4)
Male	159 (63.6)
Current smoker, No. (%)	64 (25.6)
Hypertension, No. (%)	213 (85.2)
Hyperlipidemia, No. (%)	132 (52.8)
Diabetes, No. (%)	89 (35.6)
CKD, No. (%)	34 (13.6)
Education duration (yr), mean ± SD	7.5 ± 3.7
Marital status, No. (%)	
Single	39 (15.6)
Married	122 (48.8)
Divorced/widowed	89 (35.6)
Employment status before stroke, No. (%)	
Unemployed	223 (89.2)
Employed	27 (10.8)
Lesion location, No. (%)	
Left	107 (42.8)
Right	88 (35.2)
Bilateral/brainstem/unknown	55 (22.0)
NIHSS score	
Mean ± SD	7.2 ± 3.0
Range	1.0-18.0
MMSE score	
Mean ± SD	26.4 ± 1.8
Range	22.0–30.0
HADS-A score	
Mean ± SD	6.9 ± 3.1
Range	2.0–16.0
Anxiety, No. (%)	103 (41.2)
HADS-D score	
Mean ± SD	6.2 ± 3.0
Range	2.0–14.0
Depression, No. (%)	81 (32.4)

AIS = acute ischemic stroke, CKD = chronic kidney disease, HADS-A = hospital anxiety and depression scale-anxiety, HADS-D = hospital anxiety and depression scale-depression, MMSE = mini-mental state examination, NIHSS = National Institute of Health Stroke Scale, SD = standard deviation.

3.3. HADS-D score and depression rate at different time points

HADS-D score was 6.2 ± 3.0, 6.5 ± 3.2, 6.7 ± 2.8, and 6.9 ± 3.1 at M0, M12, M24, and M36, respectively, and further comparison analysis showed that HADS-A score was with an upward trend but without statistical significance ($P = .084$) (Table S1, Supplemental Digital Content, http://links.lww.com/MD/G520) (Fig. 2A). As for depression rate, 81 (32.4%), 89 (35.6%), 94 (37.6%), and 101 (40.4%) AIS patients presented with depression at M0, M12, M24, and M36, respectively, and further comparison analysis displayed that depression rate also exhibited an upward trend but without statistical significance ($P = .227$) (Fig. 2B). Taken together, these findings indicated that depression elevated gradually over time in AIS patients.

3.4. Correlation of baseline characteristics with anxiety rate at M0/M12/M24/M36

In AIS patients, gender (female) ($P = .023$), hypertension ($P = .024$), diabetes ($P = .006$), CKD ($P = .025$), longer education duration ($P = .029$), employment status before stroke (unemployed vs employed) ($P = .034$), and higher NIHSS score ($P = .009$) were correlated with increased anxiety rate at M0 (Table 2). Gender (female) ($P = .013$), hypertension ($P = .010$), diabetes ($P = .003$), and higher NIHSS score ($P = .020$) were correlated with raised anxiety rate at M12. Gender (female) ($P < .001$), diabetes ($P < .001$), CKD ($P = .046$), employment status before stroke (unemployed vs employed) ($P = .035$), and higher NIHSS score ($P = .001$) were correlated with higher anxiety rate at M24. Gender (female) ($P = .009$), diabetes ($P < .001$), CKD ($P = .014$), employment status before stroke (unemployed vs employed) ($P = .023$), and higher NIHSS score ($P = .025$) were correlated with elevated anxiety rate at M36.

3.5. Correlation of baseline characteristics with depression at M0/ M12/M24/M36

In AIS patients, hypertension ($P = .023$), diabetes ($P = .010$), CKD ($P = .018$), longer education duration ($P = .012$), and marital status (single/divorced/widowed vs married) ($P = .003$) were correlated with increased depression rate at M0 (Table 3). Diabetes ($P < .001$), CKD ($P = .023$), and longer education duration ($P = .003$) were correlated with raised depression rate at M12. Older age ($P = .023$), gender (female) ($P = .008$), diabetes

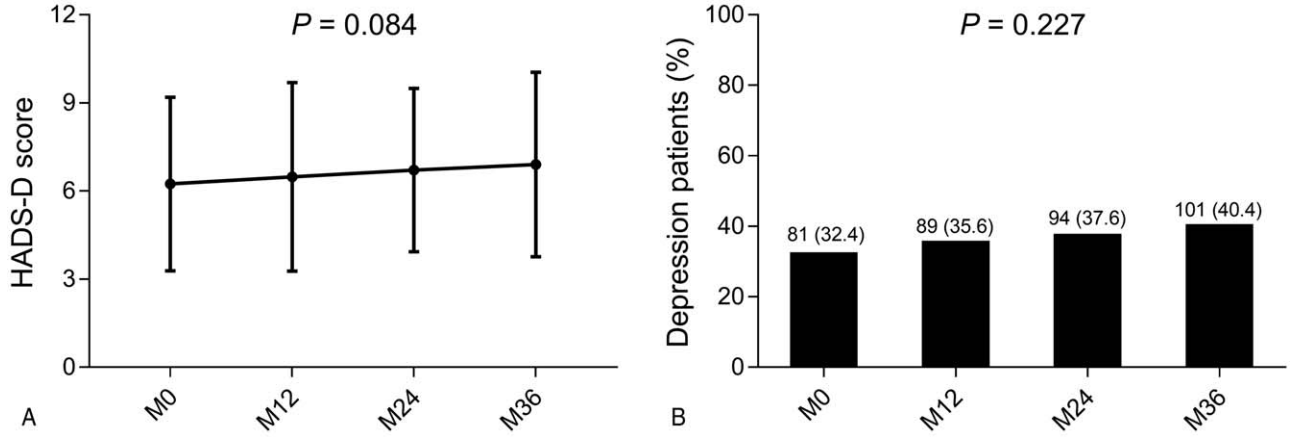

Figure 2. HADS-D score and depression rate within 36-month follow-up period. HADS-D score in AIS patients at M0, M12, M24, and M36 (A). Depression rate in AIS patients at M0, M12, M24, and M36 (B). AIS = acute ischemic stroke, HADS-D = hospital anxiety and depression scale-depression, M = month.

($P=.002$), marital status (single/divorced/widowed vs married) ($P=.005$), employment status before stroke (unemployed vs employed) ($P=.030$), and higher NIHSS score ($P=.007$) were correlated with higher depression rate at M24. Gender (female) ($P=.013$), diabetes ($P<.001$), marital status (single/divorced/widowed vs married) ($P=.034$), and higher NIHSS score ($P<.001$) were correlated with elevated depression rate at M36.

3.6. Independent predictive factors for anxiety at M0/M12/M24/M36

Forward multivariate logistic regression analysis revealed that female ($P=.007$, OR = 2.181), diabetes ($P=.011$, OR = 2.048), longer education duration ($P=.013$, OR = 1.101), and higher NIHSS score ($P=.005$, OR = 1.139) were independent predictive factors for elevated anxiety at M0 (Table 4). Female ($P=.011$, OR = 2.029), hypertension ($P=.037$, OR = 2.410), diabetes ($P=.011$, OR = 2.033), and higher NIHSS score ($P=.015$, OR = 1.118) were independent predictive factors for raised anxiety at M12. Female ($P<.001$, OR = 3.234), diabetes ($P<.001$, OR = 2.968), and higher NIHSS score ($P<.001$, OR = 1.195) were independent predictive factors for increased anxiety at M24. Female ($P=.008$, OR = 2.111), diabetes ($P<.001$, OR = 2.767), and higher NIHSS score ($P=.014$, OR = 1.121) were independent predictive factors for increased anxiety at M36. These data indicated that female, diabetes and

Table 2

Comparison of clinical characteristics between anxiety patients and nonanxiety patients at M0/M12/M24/M36.

	M0			M12			M24			M36		
Items	**Nonanxiety (n = 147)**	**Anxiety (n = 103)**	***P* value**	**Nonanxiety (n = 141)**	**Anxiety (n = 109)**	***P* value**	**Nonanxiety (n = 128)**	**Anxiety (n = 122)**	***P* value**	**Nonanxiety (n = 115)**	**Anxiety (n = 135)**	***P* value**
Age (yr), mean ± SD	66.8 ± 8.6	68.4 ± 8.4	.139	66.8 ± 8.6	68.4 ± 8.5	.141	67.0 ± 9.0	68.0 ± 8.1	.349	66.6 ± 8.6	68.2 ± 8.5	.137
Gender, No. (%)			**.023**			**.013**			**<.001**			**.009**
Female	45 (30.6)	46 (44.7)		42 (29.8)	49 (45.0)		32 (25.0)	59 (48.4)		32 (27.8)	59 (43.7)	
Male	102 (69.4)	57 (55.3)		99 (70.2)	60 (55.0)		96 (75.0)	63 (51.6)		83 (72.2)	76 (56.3)	
Current smoke, No. (%)	41 (27.9)	23 (22.3)	.321	38 (27.0)	26 (23.9)	.578	39 (30.5)	25 (20.5)	.071	32 (27.8)	32 (23.7)	.457
Hypertension, No. (%)	119 (81.0)	94 (91.3)	**.024**	113 (80.1)	100 (91.7)	**.010**	104 (81.3)	109 (89.3)	.072	94 (81.7)	119 (88.1)	.155
Hyperlipidemia, No. (%)	73 (49.7)	59 (57.3)	.235	70 (49.6)	62 (56.9)	.256	65 (50.8)	67 (54.9)	.513	60 (52.2)	72 (53.3)	.855
Diabetes, No. (%)	42 (28.6)	47 (45.6)	**.006**	39 (27.7)	50 (45.9)	**.003**	31 (24.2)	58 (47.5)	**<.001**	27 (23.5)	62 (45.9)	**<.001**
CKD, No. (%)	14 (9.5)	20 (19.4)	**.025**	15 (10.6)	19 (17.4)	.120	12 (9.4)	22 (18.0)	**.046**	9 (7.8)	25 (18.5)	**.014**
Education duration (yr), mean ± SD	7.1 ± 3.8	8.1 ± 3.4	**.029**	7.2 ± 3.9	8.0 ± 3.3	.089	7.5 ± 4.0	7.6 ± 3.4	.834	7.7 ± 4.0	7.4 ± 3.4	.586
Marry status, No. (%)			.103			.061			.301			.254
Single	20 (13.6)	19 (18.4)		20 (14.2)	19 (17.4)		20 (15.6)	19 (15.6)		18 (15.7)	21 (15.6)	
Married	80 (54.4)	42 (40.8)		78 (55.3)	44 (40.4)		68 (53.1)	54 (44.3)		62 (53.9)	60 (44.4)	
Divorced/widowed	47 (32.0)	42 (40.8)		43 (30.5)	46 (42.2)		40 (31.3)	49 (40.2)		35 (30.4)	54 (40.0)	
Employment status before stroke, No. (%)			**.034**			.121			**.035**			**.023**
Unemployed	126 (85.7)	97 (94.2)		122 (86.5)	101 (92.7)		109 (85.2)	114 (93.4)		97 (84.3)	126 (93.3)	
Employed	21 (14.3)	6 (5.8)		19 (13.5)	8 (7.3)		19 (14.8)	8 (6.6)		18 (15.7)	9 (6.7)	
Lesion location, No. (%)			.741			.817			.802			.773
Left	60 (40.8)	47 (45.6)		61 (43.3)	46 (42.2)		55 (43.0)	52 (42.6)		52 (45.2)	55 (40.7)	
Right	54 (36.7)	34 (33.0)		51 (36.2)	37 (33.9)		43 (33.6)	45 (36.9)		39 (33.9)	49 (36.3)	
Bilateral/brainstem/unknown	33 (22.5)	22 (21.4)		29 (20.5)	26 (23.9)		30 (23.4)	25 (20.5)		24 (20.9)	31 (23.0)	
NIHSS score, mean ± SD	6.8 ± 2.7	7.8 ± 3.3	**.009**	6.8 ± 2.8	7.7 ± 3.2	**.020**	6.6 ± 2.7	7.8 ± 3.2	**.001**	6.7 ± 2.9	7.6 ± 3.1	**.025**
MMSE score, mean ± SD	26.5 ± 2.0	26.3 ± 1.6	.281	26.5 ± 2.0	26.4 ± 1.6	.682	26.5 ± 1.9	26.3 ± 1.8	.570	26.5 ± 2.0	26.3 ± 1.7	.552

Comparison was determined by Student *t* test or Chi-square test. Boldface represented as *P* value < .05.

CKD = chronic kidney disease, MMSE = mini-mental state examination, NIHSS = National Institute of Health Stroke Scale, SD = standard deviation.

Table 3

Comparison of clinical characteristics between depression patients and nondepression patients at M0/M12/M24/M36.

Items	M0			M12			M24			M36		
	Nondepression (n = 169)	Depression (n = 81)	*P* value	Nondepression (n = 161)	Depression (n = 89)	*P* value	Nondepression (n = 156)	Depression (n = 94)	*P* value	Nondepression (n = 149)	Depression (n = 101)	*P* value
Age (yr), mean ± SD	66.9 ± 8.6	68.7 ± 8.3	.125	67.4 ± 8.7	67.7 ± 8.2	.766	66.6 ± 8.9	69.0 ± 7.8	**.023**	66.8 ± 8.8	68.5 ± 8.2	.134
Gender, No. (%)			.205			.124			**.008**			**.013**
Female	57 (33.7)	34 (42.0)		53 (32.9)	38 (42.7)		47 (30.1)	44 (46.8)		45 (30.2)	46 (45.5)	
Male	112 (66.3)	47 (58.0)		108 (67.1)	51 (57.3)		109 (69.9)	50 (53.2)		104 (69.8)	55 (54.5)	
Current smoke, No. (%)	45 (26.6)	19 (23.5)	.591	44 (27.3)	20 (22.5)	.399	42 (26.9)	22 (23.4)	.537	42 (28.2)	22 (21.8)	.255
Hypertension, No. (%)	138 (81.7)	75 (92.6)	**.023**	134 (83.2)	79 (88.8)	.238	128 (82.1)	85 (90.4)	.071	124 (83.2)	89 (88.1)	.285
Hyperlipidemia, No. (%)	86 (50.9)	46 (56.8)	.382	81 (50.3)	51 (57.3)	.289	77 (49.4)	55 (58.5)	.160	74 (49.7)	58 (57.4)	.228
Diabetes, No. (%)	51 (30.2)	38 (46.9)	**.010**	44 (27.3)	45 (50.6)	**<.001**	44 (28.2)	45 (47.9)	**.002**	40 (26.8)	49 (48.5)	**<.001**
CKD, No. (%)	17 (10.1)	17 (21.0)	**.018**	16 (9.9)	18 (20.2)	**.023**	18 (11.5)	16 (17.0)	.221	17 (11.4)	17 (16.8)	.220
Education duration (yr), mean ± SD	7.1 ± 3.6	8.4 ± 3.8	**.012**	7.0 ± 3.5	8.5 ± 3.8	**.003**	7.3 ± 3.7	8.0 ± 3.6	.156	7.3 ± 3.7	7.8 ± 3.6	.290
Marry status, No. (%)			**.003**			1.000			**.005**			**.034**
Single	24 (14.2)	15 (18.5)		25 (15.5)	14 (15.7)		23 (14.7)	16 (17.0)		23 (15.4)	16 (15.8)	
Married	95 (56.2)	27 (33.3)		86 (53.4)	36 (40.5)		88 (56.5)	34 (36.2)		82 (55.1)	40 (39.6)	
Divorced/widowed	50 (29.6)	39 (48.2)		50 (31.1)	39 (43.8)		45 (28.8)	44 (46.8)		44 (29.5)	45 (44.6)	
Employment status before stroke, No. (%)			.103			.266			**.030**			.105
Unemployed	147 (87.0)	76 (93.8)		141 (87.6)	82 (92.1)		134 (85.9)	89 (94.7)		129 (86.6)	94 (93.1)	
Employed	22 (13.0)	5 (6.2)		20 (12.4)	7 (7.9)		22 (14.1)	5 (5.3)		20 (13.4)	7 (6.9)	
Lesion location, No. (%)			.780			.177			.530			.802
Left	74 (43.8)	33 (40.7)		74 (46.0)	33 (37.1)		70 (44.9)	37 (39.4)		66 (44.3)	41 (40.6)	
Right	57 (33.7)	31 (38.3)		50 (31.0)	38 (42.7)		55 (35.2)	33 (35.1)		52 (34.9)	36 (35.6)	
Bilateral/brainstem/unknown	38 (22.5)	17 (21.0)		37 (23.0)	18 (20.2)		31 (19.9)	24 (25.5)		31 (20.8)	24 (23.8)	
NIHSS score, mean ± SD	6.9 ± 3.0	7.7 ± 2.9	.074	7.0 ± 3.1	7.6 ± 2.9	.111	6.8 ± 3.0	7.8 ± 3.0	**.007**	6.6 ± 2.7	8.1 ± 3.2	**<.001**
MMSE score, mean ± SD	26.5 ± 1.8	26.2 ± 1.9	.291	26.5 ± 1.8	26.3 ± 1.9	.534	26.6 ± 1.8	26.1 ± 1.9	.057	26.5 ± 1.8	26.2 ± 1.9	.169

Comparison was determined by Student *t* test or Chi-square test. Boldface represented as *P* value < .05.

CKD = chronic kidney disease, MMSE = mini-mental state examination, NIHSS = National Institute of Health Stroke Scale, SD = standard deviation.

NIHSS score were convincing independent predictive factors for raised anxiety at each time point, while hypertension and education duration were potential independent predictive factors for elevated anxiety at certain time points in AIS patients.

3.7. Independent predictive factors for depression at M0/M12/M24/M36

Forward multivariate logistic regression analysis disclosed that diabetes ($P = .012$, OR = 2.027) and longer education duration ($P = .016$, OR = 1.096) were independent predictive factors for raised depression at M0 (Table 5). Diabetes ($P < .001$, OR = 2.731) and longer education duration ($P = .004$, OR = 1.116) were independent predictive factors for elevated depression at M12. Female ($P = .006$, OR = 2.171), diabetes ($P = .003$, OR = 2.328), and higher NIHSS score ($P = .004$, OR = 1.142) were independent predictive factors for increased depression at M24. Female ($P = .008$, OR = 2.149), diabetes ($P = .001$, OR = 2.655), and higher NIHSS score ($P < .001$, OR = 1.212) were independent predictive factors for increased depression at M36 in AIS patients. These data suggested that diabetes was a convincing independent predictive factor for higher depression at each time

Table 4

Analyses of factors predicting anxiety at M0/M12/M24/M36.

Items	Forward multivariate logistic regression model			
	P value	OR	95%CI	
			Lower	Higher
M0 anxiety				
Female	.007	2.181	1.241	3.832
Diabetes	.011	2.048	1.182	3.548
Longer education duration	.013	1.101	1.021	1.188
Higher NIHSS score	.005	1.139	1.041	1.246
M12 anxiety				
Female	.011	2.029	1.173	3.510
Hypertension	.037	2.410	1.052	5.519
Diabetes	.011	2.033	1.175	3.517
Higher NIHSS score	.015	1.118	1.022	1.222
M24 anxiety				
Female	<.001	3.234	1.817	5.755
Diabetes	<.001	2.968	1.672	5.267
Higher NIHSS score	<.001	1.195	1.086	1.315
M36 anxiety				
Female	.008	2.111	1.211	3.681
Diabetes	<.001	2.767	1.577	4.856
Higher NIHSS score	.014	1.121	1.024	1.227

Factors predicting anxiety were analyzed by forward multivariate logistic regression model.

OR = odds ratio, CI = confidence interval, NIHSS = National Institute of Health Stroke Scale.

Table 5

Analyses of factors predicting depression at M0/M12/M24/M36.

Items	Forward multivariate logistic regression model			
	P value	OR	95%CI	
			Lower	Higher
M0 depression				
Diabetes	.012	2.027	1.166	3.524
Longer education duration	.016	1.096	1.017	1.180
M12 depression				
Diabetes	<.001	2.731	1.573	4.741
Longer education duration	.004	1.116	1.035	1.202
M24 depression				
Female	.006	2.171	1.246	3.782
Diabetes	.003	2.328	1.340	4.045
Higher NIHSS score	.004	1.142	1.043	1.250
M36 depression				
Female	.008	2.149	1.224	3.775
Diabetes	.001	2.655	1.515	4.652
Higher NIHSS score	<.001	1.212	1.102	1.333

Factors predicting depression were analyzed by forward multivariate logistic regression model.
OR = odds ratio, CI = confidence interval, NIHSS = National Institute of Health Stroke Scale.

point, whilst female, education duration and NIHSS score were potential independent predictive factors for increased depression at certain time points in AIS patients.

4. Discussion

Anxiety (occurrence rate ranging from 15%–40.0%) and depression (occurrence rate ranging from 27.3%–55%) are common in AIS patients.[7–14] However, most of the prior studies assess anxiety or depression rate at 1 or 2 time points with relatively short follow-up duration (1 month–1 year).[7–14] The present study assessed anxiety/depression rates at various time points in AIS patients within 36-month follow-up duration, which found that anxiety and depression were highly prevalent and with an upward trend in occurrence during the 36-month follow-up after stroke in AIS patients. These findings could be explained by that: AIS might trigger brain injury, impact multiple cognitive domains and compromise patients' daily functions, thus, leading to higher anxiety and depression rate in AIS patients[19]; AIS patients might experience stroke recurrence during the follow-up period, which exacerbated cognitive function, elevated medical complication rates and adversely impacted the recovery speed, thus, resulting in more severe anxiety and depression[20]; and along with the slow and difficult process of stroke recovery, especially when the recovery outcomes were not satisfactory after a large amount of hard work and dedications, AIS patients might experience feelings of abandonment, emotional outbursts and ultimately anxiety/depression in later stages of stroke.[21] Therefore, anxiety and depression rates increased with time. Notably, the anxiety (from 41.2%–54.0%) and depression (from 32.4%–40.4%) rates of AIS patients were higher than those in most previous studies, which might result from different assessment criteria used to evaluate anxiety/depression (eg, Hamilton rating scale/Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision vs HADS) and variations in study cohort population (eg, different severity of stroke).

A few studies with short follow-up duration disclose some potential predictive factors for higher poststroke anxiety risk in AIS patients.[7–14] For instance, serum glutathione peroxidase, catalase, superoxide dismutase and malondialdehyde are increased in AIS patients with anxiety compared to patients without anxiety at 1 month after stroke.[22] Another study reveals that age, living with offspring, widowhood, NIHSS score, body mass index, homocysteine, and high-sensitivity C-reactive protein are independent predictive factors for increased depression risk in AIS patients at 1 month after stroke.[12] However, data regarding the predictive factors for anxiety and depression at multiple time points in AIS with relatively long follow-up duration (36 months) is rare. In the present study, we assessed the predictive factors for anxiety and depression at M0, M12, M24, and M36 in AIS patients. It was observed that female, diabetes and NIHSS score were convincing independent predictive factors for increased anxiety at each time point, while hypertension and education duration were potential independent predictive factors for elevated anxiety at specific time points, which were different from the findings of previous studies due to varying inclusion criteria (eg, different severity of stroke).[7] As for depression, diabetes was a convincing independent predictive factor for raised depression risk at each time point, whilst female, education duration and NIHSS score were potential independent predictive factors for increased depression risk at specific time points, which were partially consistent with a previous study conducted by Tsai et al[13] that female and NIHSS score independently predicted higher depression risk in AIS patients. The findings were in line with the previous studies. Herein, the explanations of our findings were proposed: Females experienced major fluctuations of ovarian hormones (particularly estrogen/progesterone) across their lifespan, and estrogen/progesterone were well known gonadal steroids that affected brain regions involved in the modulation of mood and behaviors, which might influence neurochemical pathways linked to anxiety and depression.[23] Thereby, female AIS patients were more prone to anxiety and depression. Diabetes associated hyperglycemia/hyperinsulinemia might intensify the activity of the hypothalamic–pituitary–adrenal axis and subsequently trigger the arousal of nervous system, which in turn enhanced anxiety and depression; in addition, diabetes might impose elevated psychological burden due to perceived disabilities and awareness of having a chronic

illness, which enhanced anxiety and depression in AIS patients.[24] NIHSS score reflected the level of stroke severity, and AIS patients with higher NIHSS score exhibited elevated stroke severity as well as significant cognition decline along with exacerbated memory problems, deficit of attention and impaired executive function, which further decreased patients' quality of life and daily living activities, thereby, leading to higher anxiety and depression risk.[25] AIS patients with hypertension might have a greater symptom burden, treatment-related side effects, lower quality of life and additional financial difficulties, which resulted in a raised anxiety and depression occurrence. AIS patients with longer education duration might face dramatical transitions in person's role in the family and society, which increased their psychological burden, thereby, leading to higher anxiety and depression occurrence.

The present study was the first study that explored the longitudinal change of anxiety and depression, as well as their predictive factor in AIS patients with a longer follow-up (more than 3 years). Nonetheless, the present study was subject to several limitations. First, only 1 screening tool (HADS score) was used to evaluate the anxiety and depression of AIS patients, which might cause assessment bias. Thereby, more anxiety and depression measurement methods were needed for further validation. Second, the sample size was relatively small, which might reduce the statistic power of the analysis, thereby further studies with large sample size should be adopted for validation. Finally, the patients who lost follow-up were analyzed using the last visit data, which might cause potential bias.

To conclude, poststroke anxiety and depression are highly frequent, which increase with time; besides, female, diabetes, higher NIHSS score, hypertension and longer education duration independently predict increased poststroke anxiety or depression risk in AIS patients. The clinical implication of the findings is that close observation of AIS patients and routine screening for anxiety or depression are needed for facilitating functional recovery and improving quality of life in AIS patients, especially in those with factors for anxiety or depression. Meanwhile, further studies with more screening tools for anxiety and depression are warranted to validate our findings.

Author contributions

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