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ORIGINAL RESEARCH

Nomogram for Persistent Post-Stroke Depression and Decision Curve Analysis

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Purpose: Previous studies have shown that persistent post-stroke depression (PSD) was associated with unfavorable prognosis. The aim of this multicenter prospective study was to investigate the predictors associated with persistent PSD, develop a nomogram and validate its clinical usefulness by decision curve analysis (DCA).

Patients and Methods: A total of 875 acute ischemic stroke patients from four hospitals were consecutively recruited and completed 1-year follow-ups. Sociodemographic indicators, vascular risk factors, clinical information, serum biochemical indicators and cytokines were collected on admission. The functional outcome was assessed at 1 year after stroke. Persistent depression was defined as having a presentation of depression at each follow-up points and the depressive symptoms occurring persistently since the diagnosis of depression.

Results: There were 513 patients who experienced PSD during the 1-year follow-up, the cumulative incidence of PSD within 1 year was 58.6%. Persistent PSD was recorded in 289 patients, of which 59 (20.4%) result in unfavorable outcomes. The risk factors of persistent PSD in 1 year after stroke were the Hamilton Depression Scale-17 items (HAMD-17) score at admission, serum direct bilirubin and free serum thyroxine (FT4) level and activated partial thromboplastin time (APTT). Nomogram conducted based on these factors has a C-index (± standard deviation) of 0.655 ± 0.039, and the DCA demonstrated that the nomogram had a favorable clinical utility.

Conclusion: We found that persistent depression after stroke in the first-year time course after stroke was associated with HAMD-17 score at admission, lower serum direct bilirubin and FT4 level, and APTT. A nomogram was developed with advisable clinical usefulness in our study.

Keywords: persistent post-stroke depression, nomogram, decision curve analysis

Introduction

Stroke is a leading disease not only endangering physical health outcome but also causing emotional disturbance. Post-stroke depression (PSD) is a common complication after stroke, which contributes to an increasing disability and lower quality of life.[1–4] The incidence of PSD at different time course after stroke was reported to be as high as 18.8–41.8%,[5–8] early onset PSD could happen in 1 month after stroke, while later onset PSD occurs in the subsequent follow-up visits after stroke.[9,10] PRIOD study had indicated that the PSD can be transient, persistent, or maybe recurrent.[5,11] Among the patients with depression after stroke, those who developed persistent depression were reported to be more disabled and have more severe depressive symptoms. Previous studies have shown that persistent PSD was associated with unfavorable prognosis measured by modified Rankin Scale (mRS) and quality of life (QoL).[5,12,13] A multicenter study including 56 hospitals in mainland China showed that patients with persistent depression after stroke were 7.6 times higher than others in the risk of poor 1-year prognosis.[5] However, there are few studies researching on the risk factors related to persistent depression after stroke.

The aim of this multicenter prospective study was to investigate the predictors associated with persistent PSD, develop a nomogram that contributes to risk prediction for patients, and validate its clinical usefulness by decision curve analysis (DCA).

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Methods

Study Design and Participants

This is a multicenter prospective cohort study conducted in four large 3A hospitals: Wuhan Tongji Hospital, Wuhan First Hospital, Wuhan Central Hospital and Fujian Provincial Hospital (Registration number: ChiCTR-ROC-17013993). A total of 1027 stroke patients treated in the above hospitals were recruited into the study from May 2018 to October 2019. Written informed consent was given from all the participants in accordance with the Declaration of Helsinki. And the research was approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (ID:TJ-IRB20171108).

Inclusion criteria for this study were as follows: 1) age ≥18 years; 2) admitted to hospital within 7 days of first stroke onset; 3) acute ischemic stroke diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) scans, with clinical presentations according to the World Health Organization (WHO) criteria for stroke.[14] And patients with any of the following conditions were excluded from the study: 1) brain dysfunction was caused by non-vascular causes such as traumatic brain injury, brain tumor or metastatic brain tumor; 2) history of depression or antidepressant use, dementia, or other mental illness; 3) unable to cooperate to the assessment as aphasia, dysarthria, blindness, deafness, or cognitive dysfunction (Mini-mental State Examination (MMSE) score <19 points, and illiterate patients <17 points); 4) diagnosed as transient ischemic attack (TIA) or hemorrhagic stroke; 5) unable to conduct the follow-up. At last, 857 patients were included in the final study.

Information Acquisition

The standard case report forms (CRF) were used to collect sociodemographic indicators, vascular risk factors and clinical information of patients during the first 24 hours of admission. Sociodemographic indicators included gender, age, body mass index (BMI), educational level and marital status. Vascular risk factors covered smoking, drinking, coronary heart disease (CHD), hypertension, diabetes and hyperlipidemia. Clinical information such as National Institutes of Health Stroke Scale (NIHSS) score, Mini-Mental State Examination (MMSE), Center for Epidemiologic Studies Depression Scale (CES-D), neuroticism assessed by Eysenck Personality Questionnaire (EPQ), mental resilience assessed by Connor–Davidson resilience scale (CD-RISC), Social Support Rating Scale (SSRS) and the Hamilton Depression Scale-17 items (HAMD-17) were also obtained at admission by trained neurologists. Moreover, serum samples for assay of biochemical indicators and cytokines were sampled at 6 a.m. the day after admission.

The PSD diagnosis was established according to the DSM-V at the follow-up. At the same time, HAMD-17 was assessed for depression severity at 2 weeks, 3 and 6 months, and 1 year (day 14±2, day 84±7, day 182±7, day 360±7, respectively) after stroke onset. The mRS score was obtained to determine functional outcome at 1 year. The follow-up at each center was conducted by systematically trained neurologists by outpatient visit or video telephone. None of these physicians knew the baseline information of patients. All raters were blinded to the baseline information of patients.

Persistent depression was defined as having a presentation of depression at each follow-up points and the depressive symptoms occurring persistently since the diagnosis of depression. Recurrent depression was defined as depression at non-consecutive follow-up time points. Transient depression was defined as depressive symptoms showed only at one time point or at 2–3 consecutive follow-up points without recurrence.[5,6,12] The unfavorable prognosis of 1 year after stroke was considered mRS score ≥2.[15]

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences version 22.0 (SPSS, Chicago, IL) and R version 3.5.2 (http://www.r-project.org). Categorical data were presented as frequencies and proportions, and the variables were compared using chi-square test and Fisher's exact test in univariate analysis. Continuous data were expressed as medians and interquartile ranges, and Mann–Whitney *U*-test was used for comparing these variables. To get the best possible result, variables with $P < 0.10$ in univariate analysis results should be subjected to stepwise backward multivariable logistic regression analysis. A two-tailed P value less than 0.05 ($P<0.05$) was identified as statistical

significance. The adjusted odds ratio (aOR) and 95% confidence intervals (CIs) for the risk factors were obtained by multivariate-adjusted binary logistic regression.

On this basis, a nomogram of persistent PSD during 1 year was formulated by predictors in multivariable logistic regression analysis by using the package "rms". Internal validation of the nomogram was conducted by a resampling method, reflected in the concordance index and the calibration curves. Moreover, the clinical usefulness of the nomogram was evaluated by decision curve analysis (DCA), which was conducted by calculating the net benefit at different threshold risk of the model using the package "rmda". DCA was founded in 2006 by Dr Andrew J Vickers,[16,17] the method was based on a probability threshold to express the relative harms of false positives and false negatives, it was a rising method for evaluating clinical predictive models these years.

Results

Baseline Characteristics of Patients

The study included a total of 875 acute ischemic stroke patients after evaluation (mean age, 59.06±10.48) (Figure 1), with 513 patients experienced PSD during the 1-year follow-up. The cumulative incidence of PSD within 1 year was 58.6% (Table 1). Of those 513 patients, there were 119 females and 394 males. There were 338 patients (65.8%) from Tongji Hospital, 130 patients (25.3%) from Wuhan First Hospital, 32 patients (6.2%) from Wuhan Central Hospital and 13 patients (2.5%) from Fujian provincial hospital. Among those patients who experienced PSD, there were 289 patients with persistent PSD, 181 patients with transient PSD, and 43 patients with recurrent PSD, the cumulative incidence of persistent PSD in the first year after stroke was 33.0%. For patients with persistent PSD, unfavorable outcomes were recorded in 59 (20.4%) patient. Neither transient PSD nor recurrent PSD has significant association with 1-year prognosis after stroke (P = 0.302, 0.950). In the multivariable logistic regression analysis adjusting for confounding factors, we found that persistent PSD was an independent risk factor for unfavorable prognosis (adjusted odds ratio [aOR] = 3.389; 95% confidence interval [CI], 2.171–5.291; P < 0.001).

Compared with others, patients with persistent depression after stroke were more likely to be married, had significantly higher NIHSS scores at admission, tended to get higher scores in CES-D scale and HAMD-17 scale,

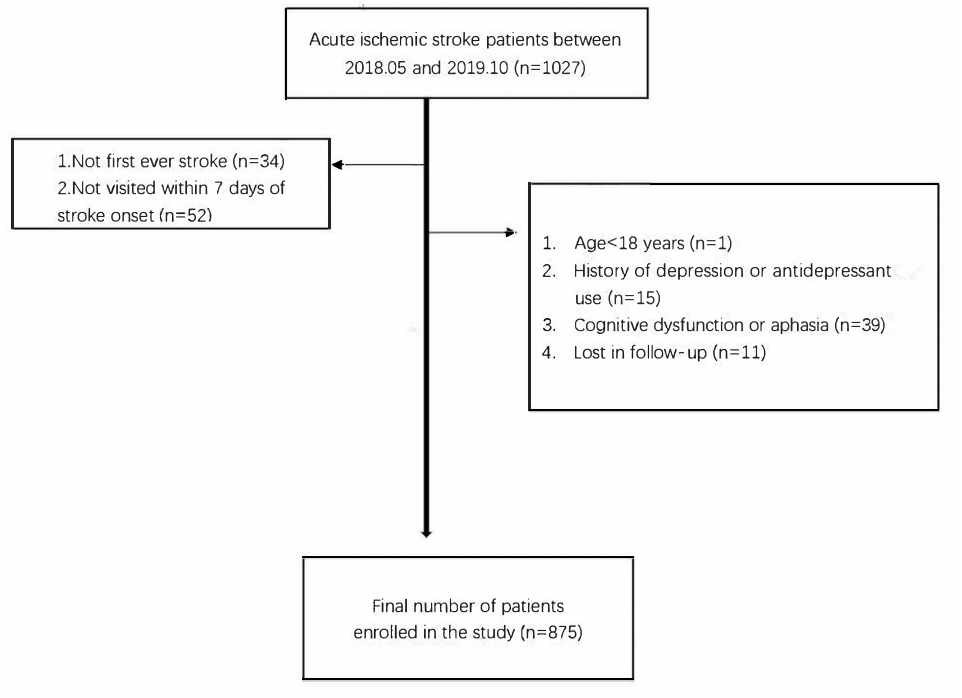

Figure 1 Flow chart of the research.

Table 1 Incidence of Depression in Stroke Patients

Time Point	No. of Patients	Patients of Newly Occurring PSD	PSD Cumulative Incidence (%)	PSD Newly Occurring Incidence (%)	Transient PSD	Persistent PSD	Recurrent PSD
14d	875	301	34.4	34.4	70	193	38
84d	574	113	47.3	19.7	52	56	5
182d	461	59	54.1	12.8	19	40	/
360d	402	40	58.6	10.0	40	/	/

were more likely to be neurotic and get less score in MMSE scale. Moreover, patients with persistent PSD were more likely to have lower serum direct bilirubin level, free serum thyroxine level (FT4), IL-18 level, BDNF level, longer activated partial thromboplastin time (APTT), and higher serum fibrinogen level (Table 2).

Risk Factors of Persistent PSD

As showed in Table 2, the risk factors of persistent PSD in 1 year after stroke were HAMD-17 score at admission ([aOR], 1.031; [CI], 1.007–1.056, P=0.011), serum direct bilirubin ([aOR], 0.924; [CI], 0.855–0.998, P=0.046) and FT4 level ([aOR], 0.946; [CI], 0.916–0.977, P<0.001) and APTT ([aOR],1.048; [CI], 1.020–1.076, P<0.001). These variables were independently associated with persistent PSD even after adjusting for confounding factors like age, gender, marriage, education level, BMI, vascular risk factors and NIHSS score on admission.

Predictive Model of Persistent PSD and Model Evaluation

All the variables identified in the multivariate logistic regression analysis of persistent PSD were involved in constructing the nomogram (Figure 2). A risk of persistent PSD could be obtained by calculating the total points of each predictors. Calibration curves were plotted to measure the calibration of the nomogram, accompanied with the Hosmer–Lemeshow test and 1000 bootstrap resamples.[18] The Harrell's C-index (±standard deviation) was 0.655±0.039 and the calibration curves for this model demonstrated a moderate agreement between the predicted risk and actual observations (Figure 3).

The DCA for persistent PSD nomogram is presented in Figure 4. It showed that if the risk threshold of a patient is between 12% and 70%, there will be more net benefit than either treating all patients or treating none by using the nomogram to decide whether or not to conduct treatment. The decision curve demonstrated that the nomogram had a favorable clinical utility.

Discussion

This is a multicentric prospective cohort study on PSD with 1-year follow-up in first-ever acute ischemic stroke patients. The cumulative incidence of PSD was 58.6%, more than half of these patients with PSD were diagnosed in the first month after stroke onset, the incidence of newly occurring PSD was continuously declining in the first-year time course of stroke. In 56.3% of PSD patients depression was persistent during 1-year time course after stroke. The study demonstrated that persistent depression after stroke was an independent predictor of unfavorable functional outcome at 1 year, which was consistent with previous studies.[5,12,13,19]

PSD is a critical complication after stroke, which can occur in different phases in the course of stroke. Previous studies indicated that persistent PSD was linked with poor prognosis and the relief of PSD could be associated with the improvement of quality of life.[20–22] In view of the cumulative incidence of PSD and persistent depression reported in this study was higher than previous studies, determining predictors of persistent depression after stroke is of essence. We have identified HAMD-17 score, APTT, serum direct bilirubin and FT4 at admission, related to the occurrence of persistent PSD in the first-year time course, and developed a nomogram to facilitate the individualized risk prediction of persistent PSD. To the best of our knowledge, it is the first research to construct a nomogram for the prediction of persistent PSD.

HAMD-17 score at admission may represent the depression condition of patients in the baseline. We found that high HAMD-17 scores were associated with persistent PSD. A patient would be more likely to develop persistent depression in the first-year course after stroke if he/she was diagnosed with depression at the admission just after the stroke onset.

Table 2 Comparison of Baseline Characteristics Between Persistent PSD and Others

	Persistent PSD (n=289)	Others (n=586)	Univariate Analysis	Multivariate Analysis		
			P value	*P* value	OR	95% CI
Sociodemographic indicators						
Gender, female (n,%)	71(24.6%)	117(20.0%)	0.125			
Age, years, median (IQR)	59(55–65)	59(53–66)	0.683			
Education, high school or above (n,%)	105(68.1%)	230(39.2%)	0.330			
Married (n,%)	279(96.5%)	543(92.7%)	0.047*			
BMI, median (IQR)	24.56(22.49–26.44)	24.51(22.68–26.42)	0.907			
Vascular risk factors						
Diabetes (n,%)	76(26.3%)	161(27.5%)	0.713			
Hypertension (n,%)	179(61.9%)	358(61.1%)	0.809			
Smoking (n,%)	129(44.6%)	269(45.9%)	0.723			
Drinking (n,%)	153(52.9%)	327(55.8%)	0.424			
Hyperlipemia (n,%)	62(21.5%)	140(23.9%)	0.421			
CHD (n,%)	29(10%)	50(8.5%)	0.466			
Clinical information						
NIHSS score, median (IQR)	3(2–6)	3(1–5)	0.030*			
CES-D score, median (IQR)	13(8–20)	12(6–17)	0.008*			
N dimension, median (IQR)	9(5–12)	8(4–11)	0.003*			
MMSE score, median (IQR)	25(22–28)	26(23–29)	0.007*			
HAMD-17 score, median (IQR)	8(4–14)	6(3–11)	<0.001*	0.011*	1.031	1.007–1.056
CD-RISC score, median (IQR)	64(52–76)	64(55–75)	0.441			
SSRS score, median (IQR)	39(32–44)	37(31–43)	0.053			
Biochemical indicators						
Albumin, median (IQR)	40.61(38.60–42.80)	40.61(38.60–42.80)	0.787			
Globulin, median (IQR)	28.03(25.70–29.90)	28.03(25.30–30.10)	0.763			
Direct bilirubin, median (IQR)	3.80(2.70–4.65)	3.77(2.70–4.70)	0.039*	0.046*	0.924	0.855–0.998
Indirect bilirubin, median (IQR)	8.20(5.40–9.90)	8.48(5.80–10.20)	0.398			
LDH, median (IQR)	187.00(159.50–208.50)	182.00(156.75–198.95)	0.092			
HCY, median (IQR)	14.00(11.95–16.60)	14.65(11.60–16.60)	0.949			
CRP, median (IQR)	3.60(1.10–7.41)	5.96(1.40–7.41)	0.061			
TSH, median (IQR)	2.22(1.23–2.35)	2.05(1.22–2.48)	0.706			
FT4, median (IQR)	1.09(0.96–4.39)	4.39(1.00–8.39)	<0.001*	0.001*	0.946	0.916–0.977
APTT, median (IQR)	34.50(32.65–37.35)	33.38(27.90–36.72)	<0.001*	0.001*	1.048	1.020–1.076
Fibrinogen, median (IQR)	3.34(2.89–3.74)	3.30(2.71–3.61)	0.029*			
Cytokines						
TNF-alpha, median (IQR)	45.00(24.87–58.54)	43.63(23.69–52.95)	0.591			
IL-10, median (IQR)	10.05(3.99–42.23)	11.36(3.93–43.60)	0.083			
IL-6, median (IQR)	5.75(2.12–12.73)	5.93(2.43–16.04)	0.162			
IL-1β, median (IQR)	76.03(32.97–176.37)	107.62(35.51–181.92)	0.190			
IL18, median (IQR)	2012.57(993.32–4522.39)	2642.48(1095.28–3914.49)	0.014*			
BDNF, median (IQR)	3.60(2.17–7.10)	5.04(2.37–7.10)	0.029*			

Note: *$p<0.05$.

Abbreviations: OR, odds ratio; CI, confidence interval; IQR, interquartile range; BMI, body mass index; CHD, coronary heart disease; NIHSS, National Institutes of Health Stroke Scale; CES-D, Center for Epidemiologic Studies Depression Scale; N, neuroticism; MMSE, Mini-Mental State Examination; HAMD-17, Hamilton Depression Scale-17 items; CD-RISC, Connor–Davidson resilience scale; SSRS, Social Support Rating Scale; LDH, lactate dehydrogenase; HCY, homocysteine; CRP, C-reactive protein; TSH, thyroid-stimulating hormone; FT4, free serum thyroxine level; APTT, activated partial thromboplastin time; TNF, tumor necrosis factor; IL, interleukin; BDNF, brain-derived neurotrophic factor.

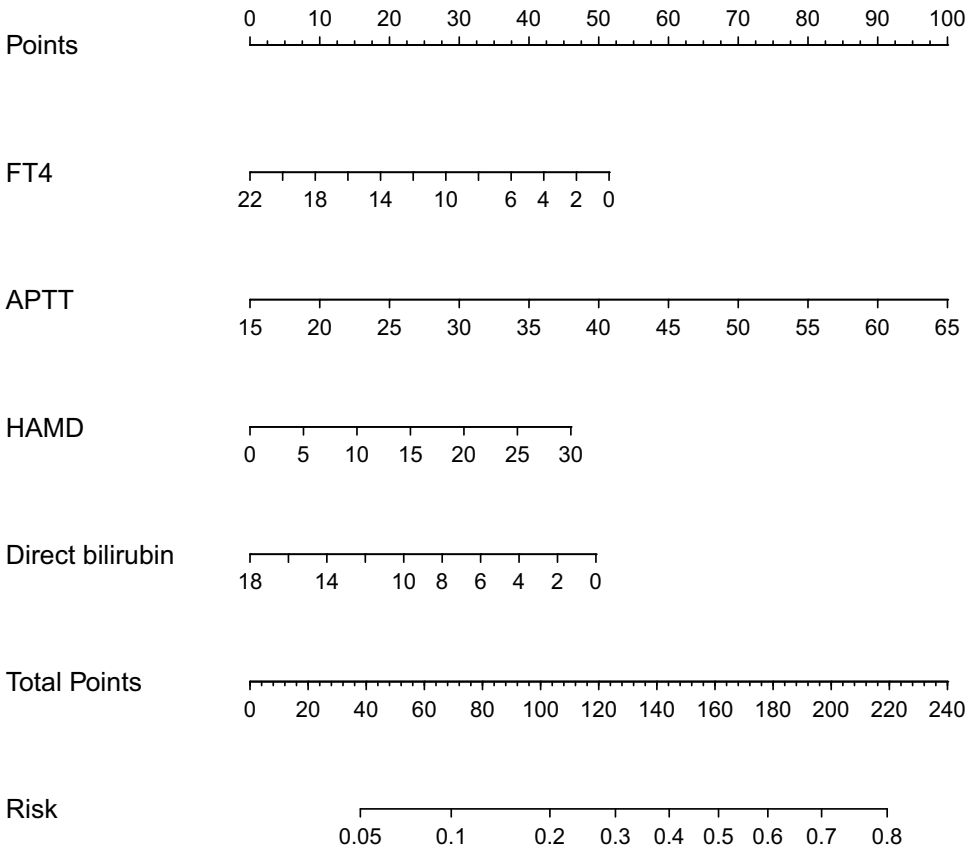

Figure 2 Nomogram predicting persistent depression in 1-year time course after stroke.
Abbreviations: FT4, free serum thyroxine level; APTT, activated partial thromboplastin time; HAMD, Hamilton Depression Scale-17 items.

Patients who had experienced more severe stroke tended to have higher psychological stress, which always manifests as depressive symptoms and scores in scale assessing.[23–26] On univariate analysis in our study, stroke severity represented by NIHSS score was associated with persistent depression. Hence, the link between HAMD-17 score at admission and persistent depression might be explained by stroke severity.

There were hardly any researches going into the link between serum FT4 and persistent PSD. FT4 is a sensitive indicator of thyroid function, which can reflect thyroid function directly even in the circumstances of concentration and binding force of plasma thyroid binding protein changing under physiological and pathological conditions. Interaction of the thyroid and serotonin system was suggested to be a potential underlying mechanism of the association between FT4 and PSD. Thyroxine has modulatory effects on the brain serotonin system, and previous studies have demonstrated that reduced levels of thyroxine could slow serotonergic transmission and decrease 5-HT responsiveness in the brains nervous system, which contributed to depression and suicidal behaviors.[27–29] In addition, thyroid hormones are used as an effective adjunct antidepressant treatment over the decades, and exogenous thyroid hormones may increase 5-HT2 receptor sensitivity, desensitize 5-HT1A raphe autoreceptors, and increase 5-HT release in cortical and hippocampal.[27,30,31] Patients with lower serum FT4 level tend to develop more depressive symptoms and respond slower to antidepressant treatment compared with others.[32–35] Besides, lower FT4 may perform weakly in neuroprotective effect when removing glutamate in the reperfusion phase after ischemic stroke.[36] However, in a research with small sample size, FT4 was found to have no significant association with PSD.[33] It is indispensable to make further research to the relationship between FT4 and persistent PSD.

Bilirubin is a useful antioxidant in our body, and the relationship of a low serum direct bilirubin level with persistent PSD was observed in the study. Very few of previous studies had researched the relationship between serum direct bilirubin level and PSD, and the evidence is controversial. A prospective cohort of 635 participants conducted in

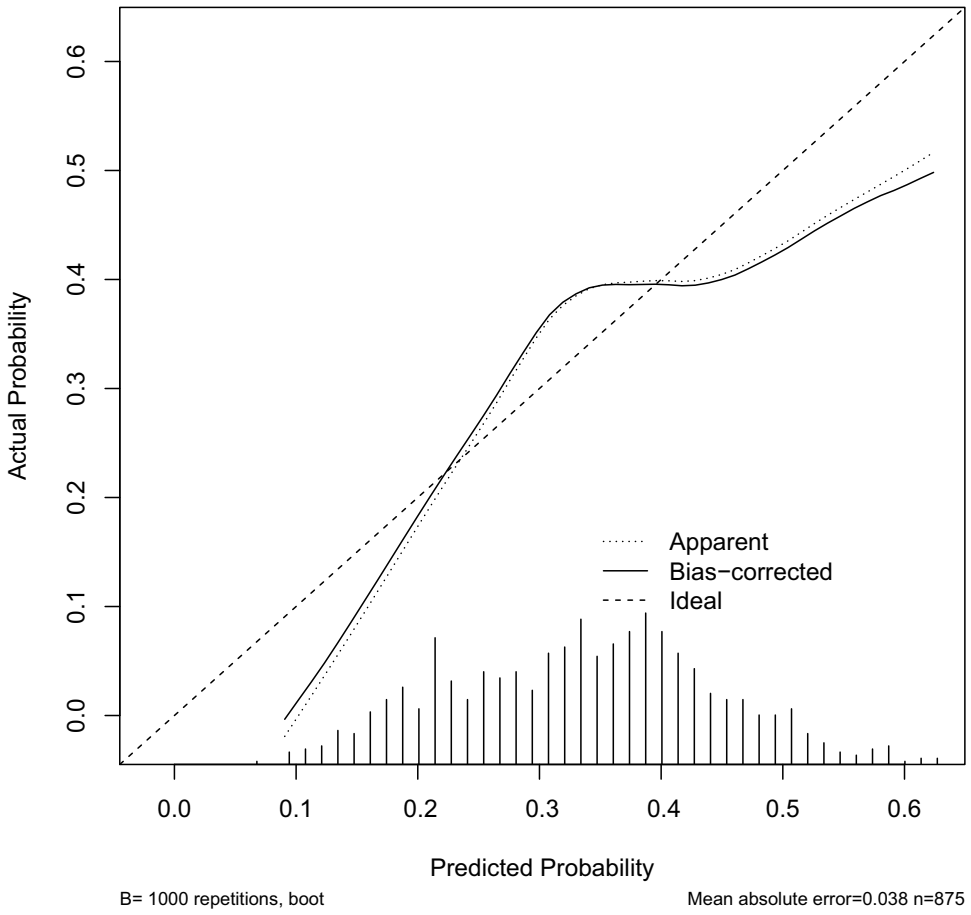

Figure 3 Calibration plots of the nomogram.

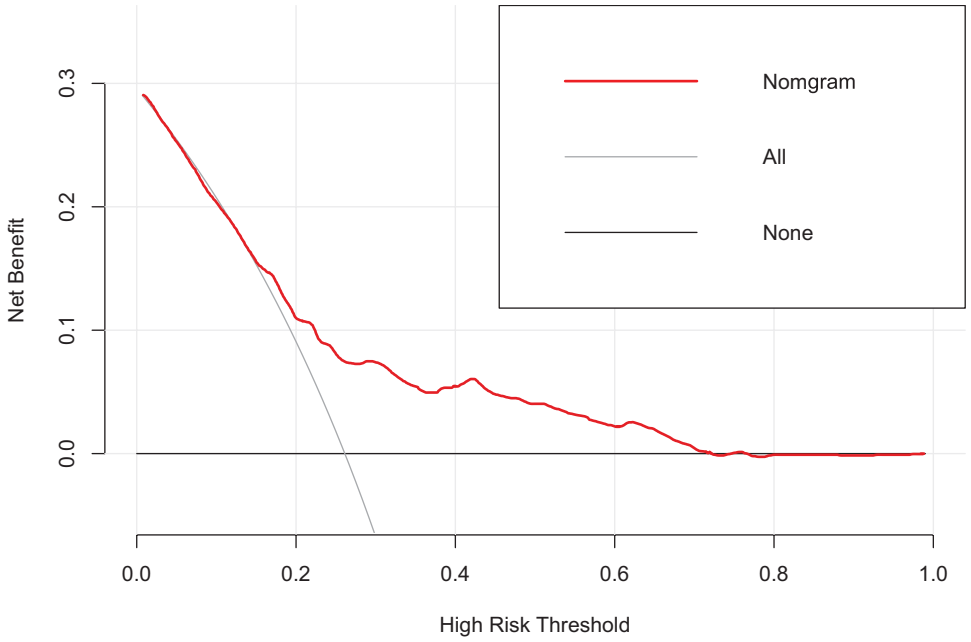

Figure 4 Decision curve analysis of the model.

Hong Kong demonstrated that high serum bilirubin could predict PSD at 3 months after stroke.[37] Another study found that lower levels of serum bilirubin on admission was associated with PSD between 3 and 6 months post-stroke.[38] The potential explanations of the relation we could infer were as follows. Numerous studies have found that acute ischemic stroke could generate strong oxidative stress and free radicals, which is an important pathogenesis of post-stroke depression.[39–42] There is now growing evidence that serum bilirubin plays a beneficial role in antioxidant, anti-inflammatory and cellular protection in the body, especially the human brain.[43–46] Serum direct bilirubin, as an important antioxidant in central nervous system, has a powerful antioxidant protective effect against free radical damage after acute stroke.[38,44,45] The imbalance between antioxidants and oxidant activity in patients with low serum direct bilirubin would be not conductive to the antioxidant capacity that protect body from ischemic injury. Moreover, Gao et al believe that lower levels of serum bilirubin were related to greater stroke severity, which induces stronger oxidative stress.[38] Further studies about the relationship between serum bilirubin and PSD will be required.

The APTT represents the time of intrinsic coagulation. The APTT test reflects the activities of coagulation factors like factor XII, XI, IX, and VIII in the intrinsic procoagulant pathway.[47] Different from previous studies, we had found that prolonged APTT played a role in persistent depression after stroke. However, APTT was considered having no significant relationship with depression in a research of blood coagulation and major depression.[48] Another research about the patients with CHD found that shorter APTT represented higher perception of stress, which could worsen the cardiovascular prognosis.[49] Similarly, researchers had demonstrated that shortened APTT was associated with stroke severity and functional outcome,[50] while in the group of persistent depression after stroke in our study, patients were found to have prolonged APTT, more severe stroke and unfavorable prognosis. Despite this, we speculated that the correlation between prolonged APTT and persistent PSD observed in our study may be explained by increasing hemorrhagic transformation. Prolongation of APTT was reported to be associated with the risk of hemorrhagic transformation in ischemic stroke patients after thrombolysis, which could aggravate the stroke severity and worsen functional outcome.[51] While on the contrary, in the research of stroke patients who did not receive thrombolysis, APTT was not significant in relation to hemorrhagic transformation.[52] Thus, the mechanisms are still not well understood and need further study.

To the best of our knowledge, this is the first multicenter prospective cohort study to research the predictors of persistent depression in the first-year time course after stroke with a relatively large sample size. We discovered several predictive factors associated with persistent PSD, and developed a nomogram for the prediction realization. Moreover, we demonstrated the clinical applicability of the nomogram by decision curve analysis. However, several limitations of this study need to be addressed. First, several patients were excluded from our study for the reason of dementia or aphasia at admission, and yet these patients may had experienced more severe strokes. Thus, patients included in our study may have a relatively mild stroke attack with a mean NIHSS score of 4, and the NIHSS score was 0–21. This might explain why there was no significant association between NIHSS score and persistent PSD in the multivariate analysis in our study to some extent. Second, no comparison of the baseline characteristics was made between the patients lost at follow-up and those be included in the analysis. Third, the study failed to record and analyze the relationship between antidepressant therapy and the type of depression or functional prognosis after stroke. Last, though the C-index of nomogram was not that desirable which only reached 0.655±0.039, the decision curve analysis demonstrated that the model was of satisfactory clinical use.

Conclusions

We found that persistent depression after stroke in the first-year time course after stroke was associated with HAMD-17 score at admission, lower serum direct bilirubin and FT4 level, and APTT. A nomogram was developed with advisable clinical usefulness in our study. However, further investigations either in basic science or in clinical research are required to confirm these findings.

Data Sharing Statement

The data and R codes that was used to generate the results can be made available upon request from corresponding authors.

Ethics Approval and Informed Consent

The research was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (ID: TJ-IRB20171108). Written informed consent was obtained from all subjects or their caregivers.

Author Contributions

All authors met the following conditions:

1. Made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas.
2. Drafted or wrote, or substantially revised or critically reviewed, the article.
3. Agreed on the journal to which the article will be submitted.
4. Reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage.
5. Agree to take responsibility and be accountable for the contents of the article.

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Disclosure

All authors declare no competing interests in the work.

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