Depression after Minor Stroke: Prevalence and Predictors

Running title: Depression after minor stroke

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Abstract

Objective: Severity of stroke and disability after stroke are major predictors of post-stroke depression (PSD). The prevalence of PSD in patients with minor stroke is expected to be low because minor stroke is characterized by mild neurological dysfunction. The aim of this study is to investigate the prevalence and predictors of PSD in patients with minor ischemic stroke.

Methods: Patients with first-ever minor ischemic stroke ($n=757$) were followed up at 14 ± 2 days, 3 months, 6 months, and 1 year after stroke. Depression status was assessed at each follow-up. Patients had PSD at follow-ups were classified into two groups according to the time point of the diagnosis of PSD: patients diagnosed at 14 ± 2 days were formed the early-onset PSD group; those who were diagnosed at any subsequent follow-ups constituted the late-onset PSD group.

Results: The 1-year prevalence of PSD in patients with minor stroke was 29.0% (95%CI, 25.2-32.8). Female gender, current smoking at stroke onset, mild global cognitive impairment at 14 ± 2 days and stroke recurrence were independently associated with a high risk of PSD over the 1-year follow-up. Predictors of early-onset PSD included female gender, current smoking and mild global cognitive impairment at 14 ± 2 days, while predictors of late-onset PSD were recurrent smoking and stroke recurrence.

Conclusion: Approximately three in ten patients with first-ever minor ischemic stroke may develop depression during the first year after stroke. Female gender, smoking, mild global cognitive impairment and stroke recurrence predict early-onset or late-onset PSD after minor ischemic stroke.

Key words: Post-stroke depression; ischemic stroke; minor stroke; smoking

Introduction

Post-stroke depression (PSD) is a common complication that occurs in approximately 33% of stroke survivors during the first year after stroke[1] and negatively associated with survival, functional independence and quality of life in stroke patients[2-6]. PSD in patients with minor stroke was usually studied combining with transient ischemic attack (TIA) patients in previous studies and found that the prevalence of PSD after TIA or minor stroke was 18-32%[7]. In these studies, the definition of minor stroke and diagnostic criteria of depression were diverse[7]. Severity of stroke and disability after stroke are major predictors of PSD in stroke in general[8]. Minor stroke is characterized by mild, short-lasting symptoms and relatively low rate of disability[9]. For the distinctly different conditions between minor stroke and TIA, and stroke in general, PSD after minor stroke should be studied separately.

Disability after stroke, cognitive impairment, stroke severity, lesion sites and locations and some vascular risk factors all have been reported to be associated with PSD [1]. The natural courses of PSD is dynamic, that the frequency of PSD was relatively high during the acute stage of stroke and to decrease over time [1, 7]. Due to the dynamic course of PSD, discrepancies in the predictors of PSD reported in previous studies [1] may be related to the time of depression assessment which suggests that PSD has different predictors in the acute and chronic stages of stroke. For this reason, the predictors of PSD should be studied at the acute and chronic stages of stroke separately.

The study investigated the prevalence of PSD during a year follow-up in patients with minor ischemic stroke and explored predictors of PSD in the acute (early-onset PSD) and chronic (late-onset depression) stages of minor stroke.

Methods

Data were retrieved from the database of the PROspective cohort study on Incidence and Outcome of patients with post-stroke Depression in China (PRIOD) (Project No.: ISRCTN62169508). The details of the PRIOD study have been described elsewhere[10]. Briefly, this large scale, multi-center study covering 56 hospitals nationwide was conducted between April 2008 and April 2010 to investigate the prevalence of PSD at different time points within the first year after stroke,

and the association between PSD and stroke outcomes in stroke survivors in mainland China. Consecutively admitted patients with stroke, aged of 18 years and older who could consent to participation entered the study during their hospital stay. Patients with a history of dementia or other known neurological diseases that could affect cognitive functions, history of alcohol or drug abuse, or difficulty in communicating were excluded. Patients enrolled in the PRIOD were followed up at 14±2 days, 3 months, 6 months, and 1 year after the index stroke.

Data collected at baseline included socio-demographic information, medical and family history, stroke severity and neuroimaging information. Stroke severity was measured on admission using the National Institutes of Health Stroke Scale (NIHSS) [11]. Minor stroke was defined as an NIHSS score of ≤ 3 on admission [9].

The locations of the ischemic lesions on MRI or CT scans were identified by qualified radiologists at each study site. The radiologists were blinded to the patients' psychiatric diagnoses. Cognitive impairment was assessed with the Mini Mental State Examination (MMSE) at 14±2 days after stroke [12]. Patients with an MMSE score of < 18 were regarded as moderate to severe cognitive impairment and excluded from the present study [13]. Mild global cognitive impairment was defined as an MMSE score of ≥ 18 and < 27 [14].

Depression (i.e., major depressive disorder, DSM-IV codes 296.30 to 296.36 and 296.20 to 296.26) was diagnosed by neurologists using the Structured Clinical Interview [15] for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [16], at 14±2 days, 3 months, 6 months, and 1-year follow-ups. Patients were categorized into 3 groups according to the diagnosis of PSD and its time point: non-depressed, early-onset and late-onset PSD. Early-onset PSD was defined as depression diagnosed at 14±2 days. Patients diagnosed at any later follow-up and did not withdraw from follow-up before the diagnosis of depression formed late-onset PSD group [17]. Patients who were not diagnosed with depression at any of the four follow-up visits were included in the non-depressed group. The Hamilton Rating Scale for Depression-17 (HRSD-17) [18] was used to assess the severity of depression at the follow-ups. All scales mentioned above were scored by raters who received training and were blinded to the rest of the patients' clinical information.

Other data collected at the follow-ups included antidepressant treatment and recurrence of stroke. The use of antidepressants was defined as administration lasting for 8 weeks or more as reported by the patient or his or her guardian.

The protocol of the PRIOD study was approved by the Medical Ethics Committee of Beijing TianTan Hospital, Capital Medical University. The study was conducted in compliance with the Declaration of Helsinki Guidelines for the Protection of Human Subjects. All participants provided written consent.

Statistical analysis

All analyses were completed using SPSS 19.0 (SPSS, Inc., IBM Company, USA). The χ^2 tests, one-way ANOVA and Wilcoxon rank-sum tests were used to compare socio-demographic data, medical history and clinical characteristics between the two PSD and the non-depressed groups. Multivariate logistic regression analyses and multinomial logistic regression analyses were used to investigate the predictors of different types of PSD. In both multivariate and multinomial regression models, the non-depressed group served as the reference. Gender, smoking, ischemic lesions in periventricular white matter, mild global cognitive impairment at 14±2 days and stroke recurrence at follow-ups were entered in the regression model as independent variables.

For all analyses, a two-tailed probability value of $P < 0.05$ was considered statistically significant.

Results

A total of 1,095 patients with ischemic stroke in PRIOD study met the definition of minor stroke. Patients with a history of stroke ($n=256$), moderate to severe cognitive impairment ($n=27$), psychiatric disease or antidepressant use at stroke onset ($n=16$), alcohol or drug abuse ($n=59$) were excluded. Ultimately, data on 757 patients [mean age, 61.14±11.56 years; 244 females (32.2%)] with first-ever minor ischemic stroke were analyzed.

The frequency of PSD decreased over time from 18.2% to 12.9%, 7.5%, 8.1% at 14±2 days, 3 months, 6 months and 1-year, respectively. Five hundred and forty one patients were assessed for PSD at the 1-year follow-up, 157 (29.0%; 95%CI, 25.2-32.8) patients were diagnosed PSD (Table 1).

Table 1 Frequency and cumulative incidence of PSD at the follow-ups.

Time point	Patients assessed, n	PSD, n	Frequency, %	Of which Newly diagnosed PSD [†] , n	Cumulative diagnosis of PSD, n	Cumulative incidence, % (95% CI)
14±2 days	757	138	18.2	138	138	18.2 (15.5-21.0)
3 months	619	80	12.9	39	154	24.9 (21.5-28.3)
6 months	548	41	7.5	10	147	26.8 (23.1-30.5)
1 year	541	44	8.1	14	157	29.0 (25.2-32.8)

[†]Patients who are diagnosed of PSD for the first time after stroke.

PSD: post-stroke depression; CI: confidence interval.

A total of 201 (26.6%) patients were diagnosed with PSD at follow-ups. One hundred and thirty-eight (18.2%), 63 (8.3%) and 344 (45.4%) patients formed the early-onset PSD, late-onset PSD and the non-depressed groups, respectively. The rest of the 212 (28.0%) patients could not be classified into any of the above-mentioned groups due to missing assessments at some of the follow-up visits. Education level was the only significant different variable between the patients who cannot be classified and those who were classified into above-mentioned groups (Table S1).

Table 2 compares the characteristics among three groups: the early-onset and late-onset PSD groups had higher rates of current smoker on stroke onset, mild global cognitive impairment at 14±2 days and stroke recurrence at follow-ups compared to the non-depressed group. The early-onset PSD group had the highest proportion of periventricular white matter infarctions compared to the other two groups. There was no significant difference between the early-onset and late-onset PSD groups with respect to frequency of antidepressants treatment, 18.1% vs. 12.7%, $P=0.336$. No significant difference was found in the severity of PSD at the time of first-ever diagnosis of depression in patients with early-onset and late-onset PSD, 10.00 (8.00-13.00) vs. 11.00 (9.00-12.00), $P=0.748$.

Table 2 Characteristics of patients according to the categories of PSD.

Variables	Non-depressed (n=344)	Early-onset (n=138)	PSD (n=63)	Late-onset PSD (n=63)	<i>P</i>
Demographic characteristics					
Age, years, mean±SD	61.07±11.76	61.25±11.08		60.21±10.85	0.829
Female, n (%)	110 (32.0)	53 (38.4)		22 (34.9)	0.397
Married, n (%)	322 (93.6)	129 (93.5)		58 (92.1)	0.902
Education level, n (%)					
High school or above	124 (36.3)	58 (42.0)		18 (28.6)	0.174
Vascular risk factors					
Hypertension, n (%)	227 (66.4)	84 (63.6)		46 (75.4)	0.265
Diabetes, n (%)	84 (24.9)	34 (26.2)		15 (24.2)	0.947
Hyperlipidemia, n (%)	70 (22.4)	24 (19.0)		9 (16.1)	0.473
Current smoking, n (%)	98 (28.7)	53 (39.0)		28 (45.2)	0.010
Alcohol consumption, n (%)	33 (9.6)	18 (13.0)		4 (6.3)	0.305
Cardiovascular disease, n (%)	70 (20.8)	35 (25.4)		10 (16.4)	0.324
Atrial fibrillation, n (%)	11 (3.2)	1 (0.7)		1 (1.6)	0.249
Neuroimaging characteristics					
Lesion localization, n (%)					
Frontal lobe	36 (10.5)	18 (13.0)		5 (7.9)	0.524
Temporal lobe	28 (8.1)	9 (6.5)		6 (9.5)	0.735
Parietal-occipital lobe	50 (14.5)	21 (15.2)		13 (20.6)	0.466
Periventricular white matter	8 (2.3)	10 (7.2)		1 (1.6)	0.032
Basal ganglia	196 (57.0)	78 (56.5)		34 (54.0)	0.907
Infra-tentorial region	97 (28.2)	40 (29.0)		14 (22.2)	0.577
Left side lesion, n (%)	115 (34.1)	46 (34.1)		22 (34.9)	0.896
Clinical characteristics					
NIHSS score on admission, median (IQR)	2.00 (1.00-3.00)	2.00 (1.00-3.00)		1.00 (1.00-3.00)	0.114
Mild global cognitive impairment at 14±2 days, n (%)	75 (22.4)	45 (36.3)		17 (30.4)	0.009
HRSD-17 score [†] , median (IQR)	/	10.00 (8.00-13.00)		11.00 (9.00-12.00)	0.748
Taking antidepressants, n (%)	/	25 (18.1)		8 (12.7)	0.336
Stroke recurrence, n (%)	15 (4.4)	12 (8.7)		8 (12.7)	0.021

[†] The HRSD-17 score at the time point of first-ever diagnosis of depression.

IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; HRSD-17, the Hamilton Rating Scale for Depression-17.

The results of logistic regression analyses of the predictors of PSD revealed that female gender, current smoking at stroke onset, mild global cognitive impairment at 14±2 days and stroke recurrence were independent predictors of PSD. Being a current smoker at stroke onset was independently associated with a high risk of both early-onset (OR 2.03, 95% CI 1.22-3.38) and late-onset PSD (OR 2.96, 95% CI 1.47-5.94). Female gender and mild global cognitive impairment were predictors of early-onset PSD, whereas, stroke recurrence was found to be the most powerful predictor of late-onset PSD (OR 3.83, 95% CI 1.51-9.94) (Table 3).

Table 3 Logistic regression analyses of the factors that associated with PSD after minor stroke.

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)
PSD[†]		
Female	1.27 (0.88-1.82)	1.82 (1.17-2.83)
Current smoking	0.93 (0.87-0.99)	2.34 (1.50-3.66)
Mild global cognitive impairment	1.82 (1.22-2.72)	1.75 (1.15-2.65)
Stroke recurrence	2.42 (1.21-4.85)	2.40 (1.15-5.00)
Early-onset PSD[‡]		
Female	1.33 (0.88-2.00)	1.71 (1.04-2.82)
Current smoking	1.59 (1.05-2.41)	2.03 (1.22-3.38)
Mild global cognitive impairment	1.84 (1.08-3.13)	1.83 (1.15-2.90)
Late-onset PSD[‡]		
Current smoking	2.05 (1.18-3.56)	2.96 (1.47-5.94)
Stroke recurrence	3.19 (1.29-7.88)	3.83 (1.51-9.94)

[†] Multivariate logistic regression analysis.

[‡] Multinomial logistic regression analysis.

Gender, current smoking, lesions in periventricular white matter, mild global cognitive impairment at 14±2 days and stroke recurrence were entered in both the multivariate regression and multinomial regression models. The group of non-depressed patients served as the reference.

OR: odds ratio; CI: confidence interval.

Discussion

In this study 29.0% (25.2%-32.8%) of the patients with first-ever minor ischemic stroke developed PSD over the 1-year follow-up, which is in the confidence interval of the prevalence of PSD in stroke survivors in general (33%, 95% CI 23%-43%) [1]. One study reported that over a 30-month follow-up period, 40% of patients with minor ischemic stroke (NIHSS ≤ 5) developed PSD [19]. This higher prevalence could be explained by the longer follow-up period and the differences in the definition of minor stroke. However, the results of our and the previous study [19] suggest that PSD is prevalent even after a minor stroke.

The highest point prevalence of PSD was found at 14 ± 2 days, decreased by approximately 30% at 3 months, and remained stable at a level of 8% since the 6-month follow-up. Approximately 2/3 of PSD were diagnosed in the acute stage of minor stroke. The course of PSD after minor stroke is similar to the natural course of PSD in stroke survivors in general: most patients develop PSD in the acute phase, and a significant proportion would recover in the subsequent assessments while new cases make the overall prevalence of PSD stable [8].

Stroke severity and disability after stroke are the main risk factors for depression after stroke [1, 20]. However, no significant differences were found in stroke severity between the non-depressed, early-onset and late-onset PSD groups, which can be explained by the common characteristics of minor stroke: mild neurological and functional impairment.

Cognitive impairment is another factor that is consistently reported to be associated with PSD [1, 21]. However, data are limited on the relationship between cognitive impairment and PSD after minor stroke. Cognitive impairment is considered to be a manifestation of minor stroke that is more frequent in the first week after stroke [22] with a decreasing frequency over time [7]. The decreasing trends of the frequency of cognitive impairment may help to explain, in part, why cognitive impairment at 2 weeks after stroke was associated with a high risk of early-onset PSD but not with late-onset PSD.

Current smokers had higher NIHSS scores on admission [23] and poorer functional outcome at discharge [24] compared with non-smokers or former smokers. Both higher NIHSS score and disability are considered major predictors of PSD, which might mediate the association between smoking and PSD. However, current smoking was not significantly associated with PSD as being inferred after adjusting for stroke severity and/or disability in general stroke patients [1]. We

analyzed the data of the present study and a significant difference was found neither in NIHSS score on admission [median (interquartile), 2.5 (2.0-3.0) vs. 2.0 (1.0-3.0), $P=0.093$] nor in disability (modified Rankin Score >2) at 14 ± 2 days [14 (5.5%) vs. 26 (5.2%), $P=0.862$] between smokers vs. non-/former smokers. These inconsistencies in the differences in NIHSS score and disability with the results of previous studies [23, 24] are probably due to the mild stroke severity and functional impairment in minor stroke. Smoking has been found to increase the risk of depression both in a longitudinal birth cohort study [25] and a population-based prospective cohort study [26]. As we had excluded the patients with psychiatric disease or antidepressant use at stroke onset, we guess that there might be a higher prevalence of undiagnosed or unreported depression before stroke onset in current smokers and current smokers are more vulnerable to depression after the attack of the minor stroke compared with non-/former smokers. However, depressive mood was not assessed before stroke onset and smoking status was not recorded at follow-ups, which obstructed us from further analyzing and confirming the exact effect of smoking on PSD. The association and possible underlying causes between smoking and PSD should be further studied.

The number of stroke was found to be independently associated with PSD in stroke survivors in a cross-sectional, case-control study [27]. The high incidence of PSD in the acute stage of recurrent stroke and the increased likelihood of disability after recurrent stroke may also contribute to the association between stroke recurrence and late-onset PSD.

Gender was entered into the regression models as an independent variable because of the gender discrepancies in smoking. Although the prevalence of PSD is generally higher among women than men [28], the predictive role of female gender on PSD is still controversial: some studies have reported that female gender was independently associated with a high risk of PSD in the acute phase of stroke [20] and 4 months after stroke [29], but other studies could not confirm this association [1, 19, 30].

The relationship between the location of the stroke lesion and the development of PSD has been thoroughly investigated with controversial results [31-35] and the result of a lately meta-analysis did not support the association between the left hemisphere lesion and an increased risk of PSD (OR 0.99, 95% CI 0.88–1.11) [36]. In this study, no significant correlation was found between the lesion

location or side and PSD after first-ever minor stroke, which is consistent with the results of another study on predictors of PSD after minor stroke [19].

The study has a number of limitations. Cognitive impairment was assessed with the MMSE, which is not the most suitable tool for detecting mild global cognitive impairment. The Montreal Cognitive Assessment (MoCA) is more sensitive than the MMSE for detecting MIC in patients with TIA and stroke [14, 37]. We initially decided to use the MMSE to detect cognitive impairment based on the consideration of the large area discrepancy in education level and local culture nationwide. Another limitation is the high number of dropouts that reduced the generalization of the results. Further, patients who were not grouped had a higher education level. Education level has been reported to be associated with depression after stroke in only a few studies [19, 38] and is not regarded as a major predictor of PSD [1]. Although no difference was found regarding the education level among the non-depressed, early-onset and late-onset PSD groups, the possibility of a bias due to the discrepancy between the education level of study patients and dropouts cannot be ruled out.

Conclusion

In conclusion, approximately three in ten patients with minor ischemic stroke developed PSD over the first year after stroke. Although the incidence of PSD decreased steeply 3 months after stroke, new cases were diagnosed even at the 1-year follow-up. The course of PSD after minor ischemic stroke suggests that the monitoring of patients' moods should begin in the acute stage and be undertaken regularly during the chronic stage after minor ischemic stroke.

Current smoking at stroke onset was a predictor of both early-onset and late-onset PSD after minor stroke. Mild global cognitive impairment independently associated with a high risk of PSD in its acute stage. For that reason, more attention should be paid to the cognitive status at the acute stage of minor stroke. Stroke recurrence was the most important predictor of late-onset PSD. Secondary prevention of stroke may represent an effective way to decrease the risk of PSD at the chronic stage of minor stroke.

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Competing Interest Statement

The authors have no competing interests to report.

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