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Correlative study on risk factors of depression among acute stroke patients

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Abstract. – BACKGROUND: The causes of post-stroke depression (PSD) were complex, and it is hard to identify the consistent risk factors because the correlation may change along with time.

AIM: To study the prevalence and multiple correlation factors of PSD in acute stroke patients.

PATIENTS AND METHODS: The patients within over 2-6 weeks after stroke were collected and divided into depression group, depressive symptom group, and control group according to the Hamilton Depression Rating Scale for Depression. The NIH (National Institute of Health) Stroke Scale, the Barthel index (BI), the Instrumental Activities of Daily Living (IADL), and the Mini-Mental State Examination (MMSE) were respectively used to evaluate the neurologic impairment, Ability of Daily Life, and cognitive function of patients.

RESULTS: PSD was associated with lower incomes ($p < 0.05$), but not associated with education level, medical insurance, and nature of the acute stroke ($p > 0.05$). The lesion location in the left hemisphere of the brain had a higher morbidity than that in the right hemisphere or both sides. There was a significant difference in the incidence of PSD between multifocal lesions and single lesion ($p < 0.01$).

CONCLUSIONS: Lower income, cognitive dysfunctions, poor activities of daily life, poor social support, and history of hypertension and previous stroke were risk factors for the acute stroke patients to get depression. Stroke survivors with left hemisphere of the brain and more lesions (≥ 2) have more chance to get the PSD.

Key words:

Key words: Post-stroke depression, Vascular risk factors, Lesion location, Activities of daily living, Cognitive dysfunction.

Introduction

It is well known that post-stroke depression (PSD) is common neuropsychiatric consequence of stroke. PSD has a negative impact on social reintegration and quality of life, around one in three patients had PSD, and, however, more than half of all cases are neither diagnosed nor treated[1]. The etiology of PSD includes three aspects: (i) molecular biological changes are the basis of etiology. For example, a recent report investigates the relationship between the brain-derived neurotrophic factor (BDNF) expression and cognitive impairment in PSD rats, and shows that the decrease in BDNF expression in the hippocampus of PSD rats may aggravate cognitive impairment, but the degree of cognitive impairment cannot be reflected by the expression levels of BDNF in the hippocampus[2]. (ii) Aben I et al[3] propose that vascular damage may be related to the PSD. In recent years, scholars have demonstrated that vasoactive drugs such as selective agonist of vasopressin V2 receptors, DDAVP (Desmopressin: 1-desamino-8-D-arginine vasopressin) is effective in correcting anxious depression and the treatment effect could last for 0.5-1 year after the first course of therapy[4]. (iii) PSD is considered as a kind of social psychological reaction after the stroke[5]. A cognitive behavioral therapy (CBT) is carried out to facilitate change of behavior in real life by promoting and encouraging meaningful or pleasurable activities on the PSD patients[6].

In the view of the complex causes of PSD, if we can't prevent the PSD, at least, we should try to limit the process and harm of PSD and take some effective interventions that could reduce depressive symptoms, improve mood and quality of life, and reduce the risk of medical complications including relapse. But it is hard to identify the consistent risk factors because the correlation may change along with time[7]. In our study, we selected patients within average four weeks after a stroke, using case-control design, to investigate the correlation of social-economic factors, vascular factors, brain damage lesions and cognitive impairment with PSD. We aimed to find the early risk factors for acute stroke patients to get depression in order to help physicians quickly take effective measures to stop the occurrence of PSD.

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Patients and Methods

Patients

All persons have given their informed consent prior to their inclusion in the study, and all human studies have been approved by China Ethics Committee and performed in accordance with the ethical standards. Patients who were from the Neurology Department of Shanghai RenJi hospital during June 2006 to June 2008 and suffered a stroke for 2-6 weeks (diagnosed according to the fourth National Conference of the Cerebrovascular Disease Formulated Diagnostic Criteria), without severe mental disorders, cognitive or communication impairment, aphasia, cardiopulmonary function failure or other serious somatic diseases, were initially included in our study. All the participants were above 18 years old, accepted head Magnetic Resonance Imaging (MRI) scans, and cooperated to complete the study after informed content. The local research Ethics Committees approved this study.

Interview: neuro-psychiatric assessment and categorization

Patients were interviewed, using a structured questionnaire, by the trained investigator with the knowledge of instructions and score criteria. Hamilton Depression Scale (HAMD), as a standardized neuro-psychiatric examination for depression rating, was administered. During the interview, the responses required for Montgomery-Asberg Depression Rating Scale (MADRS) were noted, and the Diagnostic and Statistical Manual (DSM-IV) criteria for major depression were applied. The patients were finally divided into three groups. PSD group were stroke survivors who satisfied DSM-IV criteria for major depression and had MADRS scores > 17. Depression symptoms group were stroke survivors who did not satisfied DSM-IV criteria for major depression and had MADRS scores 8-17. Control subjects were stroke survivors who did not satisfied DSM-IV criteria and had scores < 8.

Cognitive function was assessed using the Mini-Mental State Examination (MMSE). According to the different cultural degree, the following patients who: (1) had junior high school or above degree culture and scored ≤ 24; (2) had primary school to enhance their culture and scored ≤ 20; (3) were illiteracy and scored ≤ 17, were considered as cognitive dysfunction.

The Barthel activities of daily living (ADL) Index were used to assess subjects' self-care ability. Their functional status after stroke was divided into four strata: Class 1 (10-20 points, critical defects), Class 2 (25-45 points, major defects), Class 3 (50-70 point, moderate defects), Class 4 (75-90 points, defects), Class 5 (95-100 points, self-care). Instrumental activities of daily living (IADL) were performed to assess subjects' ability to execute. People who scored > 5 points were considered abnormal.

Other assessment: self-reported living status, anamnesis and blood test

Self-reported living and functional status before and after stroke was interviewed with specific questions. Socio-economic factors noted included gender, age, the level of formal education (including four strata, illiteracy, elementary school level, high school and above high school level), economic class (average monthly income <1000 RMB, ≥ 1000 RMB), family care satisfaction (including four levels, poor, moderate, good, very good), medical insurance (social medical care or self supported medical care).

Subjects were asked whether they had been diagnosed with coronary heart disease, diabetes mellitus, hypertension, hyperlipidemia, stroke or other disease. Subjects had an electrocardiogram (ECG) performed.

A blood sample was collected for routine blood count and biochemical tests, triglyceride, total & LDL& HDL cholesterol, blood electrolyte, creatine kinase (CK), glucose. Urine sample was collected for routine urine count, kidney and liver functional examination.

Brain Imaging

MRI brain scans, performed routinely at the time of acute stroke within one month, were assessed for location of brain damage. All the patients accepted MRI scans with cross-sectional T1, T2 and FLAIR weighted imaging. The indexes of spin echo (SE) sequence cross sectional T1 weighted like (T1WI) were as follows: repeat time (TR) / echo time (TE) = 431.5/13.0 ms, layer thickness = 5.0 mm, layer clearance = 1.0 mm. The indexes of SE sequence cross sectional T2 - weighted images (T2WI) : repeat time (TR) / echo time (TE) = 4385.7/120.0 ms, layer thickness = 5.0 mm, layer clearance = 1.0 mm.

According to results of MRI, the likely location of the acute stroke lesion was determined and classified as ischemic and hemorrhagic group, or anterior and posterior circulation, or right/left frontal/temporal/parietal/occipital/lobe,

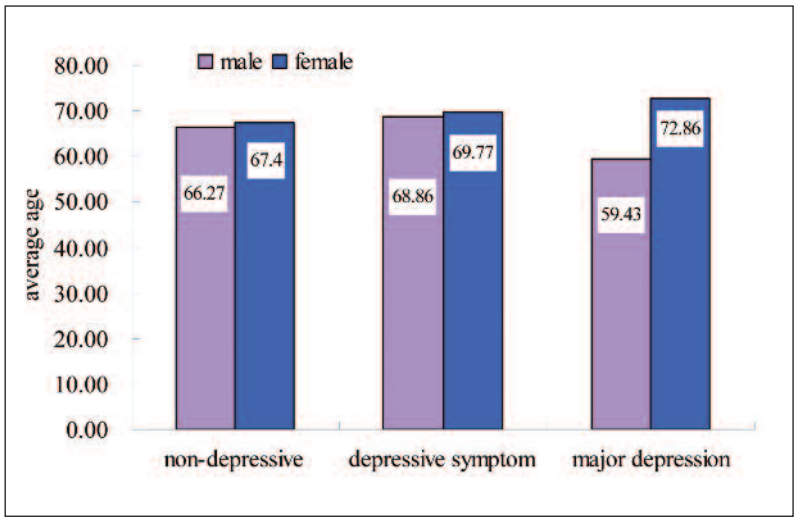

Figure 1. Comparison of age of different gender among three groups. It showed that in the major depression group, female patients were more than ten years older than the male patients. In the depressive symptom group and control group, there was no difference in age between female and male patients.

basal ganglia, cerebella and brainstem, simple left hemisphere stroke or non-simple left hemisphere (including the right hemisphere, bilateral hemisphere and cerebellum). Based on the number of brain lesions, subjects can be divided into single lesion and multiple lesion groups.

Oxford shire community stroke project (OCSP) was assessed for four clinical subtype, total anterior circulation infarct (TACI), partial anterior circulation infarct (PATI), posterior circulation infarct (POCI) and lacunar infarct (LACI).

Statistical analysis

SPSS 16.0 software was used for data record and analysis (SPSS Inc., Chicago, IL, USA). All the continuous variables were expressed as mean ± standard deviation, and counting variables were expressed as rate (%). Continuous variables between cases and controls were compared using one-way analysis of variance or independent *t* test. Counting variables were compared using Chi-squared or Fisher's exact tests. Those variables were considered as significant difference when $p < 0.05$.

Results

Between June 2006 and June 2008, 392 patients including 217 men and 119 women were recruited whose average age was 67.2±11.2 years old (32-88 years old). Fourteen of them were found to fulfill the criteria for major depression, and 84 met criteria of the depressive symptoms. Two hundred and thirty-one patients satisfied the control subject criteria. There was no difference in age and gender proportion among the three groups. Female patients seemed older than male patients among the patients (8.5±11.24 vs. 66.6±11.36 years old), especially significant older than male patients in the depressed group (72.9±12.99 vs. 59.4±10.83, $p = 0.057$; Figure 1).

Socio-economic factors

No significant association was found between depression and education level, medical insurance, life care. There was significantly different in monthly income (Figure 2) and care satisfaction among the three groups (Table I).

Vascular and biochemical factors

Table II showed vascular and biochemical factors among the three groups. There were no significant differences in the prevalence of coronary heart disease, diabetes mellitus and hyperlipidemia among the three groups. The occurrence rate of hypertension in the depressed group, depressive symptoms group and control group were 85.7%, 82.1% and 68.8%, respectively. The occurrence rate of stroke in the depressed group, depressive symptoms group and control group were 85.7%, 48.8% and 10.8%, respectively. It indicated that those with depression were more likely to have a history of hypertension and stroke. The levels of total serum cholesterol, triglyceride, HDL, LDL of cholesterol was similar among the three groups (Table II).

The number of vascular risk factors was 2.24±0.97, 2.23±1.05 and 3.07±0.62 in the control, depressive symptom group and depression group, respectively. It indicated that those with depression were more likely to have the vascular risk factors.

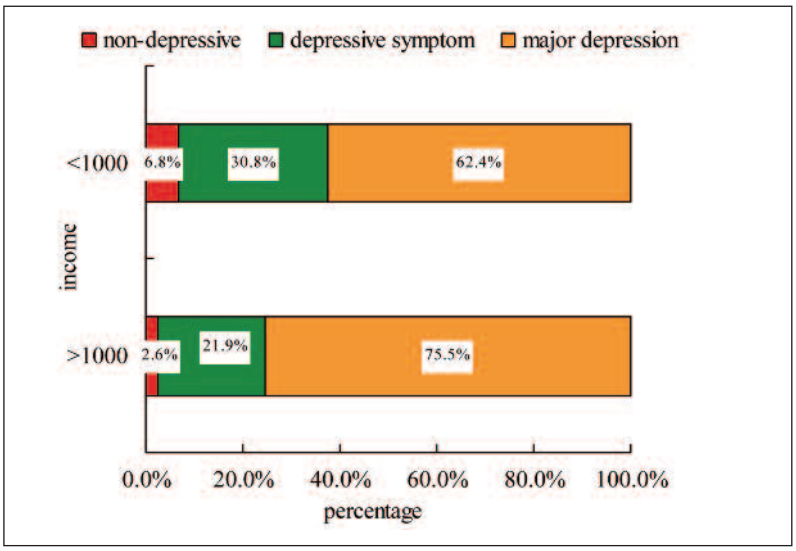

Figure 2. The percentage of the three groups' patients among different income. The result showed that the percentage of PSD patients was much more in the patients who had more than 1000 RMB income of each person per month than that had less than 1000 RMB income of each person per month.

Neuro-imaging findings

Of 329 patients, there were 291 ischemic brain damage cases and 31 hemorrhagic brain damage cases. There was no difference in proportion of the damage characteristic among the three groups ($p = 0.664$).

The distribution of OCSP subtypes (Table III) or the side or location of the acute stroke lesion (Table IV) among the three groups was compared. The distribution of four OCSP subtype were significantly different among the three groups ($p = 0.001$). The occurrence of PSD was much higher in TACI subtype than the other three subtypes (Figure 3). The occurrence of PSD in single left hemisphere was much higher than non single left hemisphere ($p < 0.01$), and it was

Table I. Social-economic characteristics among the three groups.

	Non-depressed	Depressive symptom	Major depression	*p*
n	231	84	14	
Gender				
Male (%)	161 (69.7%)	49 (58.3%)	7 (50.0%)	0.074
Female (%)	70 (30.3%)	35 (41.7%)	7 (50.0%)	
Age (years old)	66.6±11.38	69.2±10.75	66.1±13.44	0.179
Income (RMB)				
< 1000	83 (35.9%)	41 (48.8%)	9 (64.3%)	0.021
> 1000	148 (64.1%)	43 (51.2%)	5 (35.7%)	
Education level				
Illiteracy	78 (33.8%)	38 (45.2%)	5 (35.7%)	
Elementary school	72 (31.2%)	26 (31.0%)	4 (28.6%)	0.310
High school or above	81 (35.1%)	20 (23.8%)	5 (35.7%)	
Medical insurance				
Social medical care	200 (86.6%)	70 (83.3%)	11 (78.6%)	
Self supported	31 (13.4%)	14 (16.7%)	3 (21.4%)	0.603
Care keeper				
Wife/husband	161 (69.7%)	50 (59.5%)	10 (71.4%)	
Children	48 (20.8%)	24 (28.6%)	4 (28.6%)	0.209
Alone	22 (9.5%)	10 (11.9%)	0 (0%)	
Care satisfaction				
Poor	1 (0.4%)	7 (8.3%)	0 (0%)	
Moderate	24 (10.4%)	21 (25.0%)	5 (35.7%)	
Good	103 (44.6%)	32 (38.1%)	4 (28.6%)	0.000
Very good	103 (44.6%)	24 (28.6%)	5 (35.7%)	

Table II. Social-economic characteristics among the three groups.

	Non-depressed	Depressive symptom	Major depression	p
n	231	84	14	
Hypertension	159 (68.8%)	69 (82.1%)	12 (85.7%)	0.028
Diabetes	33 (14.3%)	19 (22.6%)	3 (21.4%)	0.205
Coronary heart Disease	51 (22.1%)	18 (21.4%)	5 (35.7%)	0.513
Stoke	25 (10.8%)	41 (48.8%)	12 (85.7%)	0.000
Hyperlipidemia	69 (29.9%)	24 (28.6%)	4 (28.6)	0.972
TC	5.01±0.96	4.92±0.72	4.88±0.72	0.658
TG	1.86±1.16	1.62±0.91	1.82±1.17	0.238
HDL	1.40±0.47	1.38±0.41	1.26±0.43	0.530
LDL	3.17±0.80	3.09±0.77	3.45±1.43	0.530

much higher in the single lesion than that in multiple lesion ($p < 0.01$). On the other hand, there were no significant differences in the incidence of PSD when all the patients were divided by brain lesion location, such as anterior and posterior circulation, or right/left frontal/temporal/parietal/occipital/lobe, basal ganglia, cerebella and brainstem.

Daily functional and cognitive status

Table V showed that the significant differences in BI score and IADL score among the three groups. PSD patients were likely to get lower BI score and higher IADL scores than the control patients ($p = 0.000$). When all the subjects were divided according the BI grading from class1 to class 5, a positive correlation which was the more serious of daily life damage, the more serious degree of depression was found in Table VI ($p = 0.000$).

The distribution of cognitive impairment or non-cognitive impairment among the three groups was analyzed (Figure 4). We found that subjects with cognitive impairment were more likely to have the symptom of depression or have major depression ($p < 0.01$). The results of MMSE scores further showed that depressed subjects had significantly more cognitive impairment, with mean MMSE scores less than the depressive symptom group and controls (Table VII).

Discussion

Our results clearly indicate that vascular, socio-economic and some biological factors are important in the aetiology of early-phase post-stroke depression. Early studies focused to investigate the occurrence of late-phase PSD over 3 months-3 years after acute stroke[8-10]. Whyte, et al[9] done a system analysis and found that PSD mostly happened over 3-6 months after stroke, and remained at the high level. The prevalence of PSD was different at different stages after stroke[10-14], while 10%-20% was internationally accepted. Our results showed that among 392 patients, only 4.26% had major depression. This was because (1) all the subjects were recruited at average 4 weeks after the stroke, which indicates the occurrence of PSD had not peaked; (2) Patients with severe neurological impairment, cognitive impairment, aphasia, or with a history of depression were excluded in our study. The association of age and gender with depression was always not reached the same conclusion.

Table III. The relationship between OCSP classification and PSD.

OCSP classification	Non-depressed	Depressive symptom	Major depression	p
TACI (%)	9 (33.3%)	14 (51.9%)	4 (14.8%)	
PACI (%)	73 (70.2%)	28 (26.9%)	3 (2.9%)	0.001
POCI (%)	60 (74.1%)	18 (22.2%)	3 (3.7%)	
LACI (%)	69 (80.2%)	14 (16.3%)	3 (3.5%)	

Table IV. The relationship between brain damage and occurrence of PSD.

Property and location of brain damage	Non-depressed	Depressive symptom	Major depression	*p*
Ischemic (%)	211 (70.8%)	74 (24.8%)	13 (4.4%)	
Hemorrhagic (%)	20 (64.5%)	10 (32.3%)	1 (3.2)	0.664
Anterior circulation (%)	164 (69.5%)	62 (26.3%)	10 (4.2%)	
Posterior circulation (%)	67 (72.0%)	22 (23.7%)	4 (4.3%)	0.885
Singer lesion (%)	183 (81.0%)	38 (16.8%)	5 (2.2%)	
Multiple lesion (%)	48 (47.1%)	46 (5.1%)	8 (7.8%)	0.000
Left hemisphere (%)	60 (54.5%)	43 (39.1%)	7 (6.4%)	
Non left hemisphere (%)	171 (78.1%)	41 (18.7%)	7 (3.2%)	0.000
Left frontal lobe (%)	7 (30.4%)	12 (52.2%)	4 (17.4%)	
Non left front lobe (%)	224 (73.2%)	72 (23.5%)	10 (3.3%)	0.000
Left temporal lobe (%)	13 (54.2%)	7 (29.2%)	4 (16.7%)	
Non left temporal lobe (%)	218 (71.5%)	77(25.2%)	10 (3.3%)	0.032
Left parietal lobe (%)	25 (83.3%)	5 (16.7%)	0	
Non left parietal lobe (%)	206 (68.9%)	79 (26.4%)	14 (4.7%)	0.101
Left basal ganglia (%)	42 (42.4%)	50 (50.5%)	7 (7.1%)	
Non left basal ganglia (%)	189 (82.2%)	34 (14.8%)	7 (3.0%)	0.000
Left occipital lobe (%)	16 (84.2%)	3 (15.8%)	0	
Non left occipital lobe (%)	215 (69.4%)	81 (26.1%)	14 (4.5%)	0.217
Right frontal lobe (%)	12 (66.7%)	5 (27.8%)	1 (5.6%)	
Non right frontal lobe (%)	219 (70.4%)	79 (25.4%)	13 (4.2%)	0.932
Right temporal lobe (%)	19 (86.4%)	2 (9.1%)	1 (4.5%)	
Non right temporal lobe (%)	212 (69.1%)	82 (26.7%)	13 (4.2%)	0.129
Right parietal lobe (%)	28 (80.0%)	6 (17.1%)	1 (2.9%)	
Non right parietal lobe (%)	203 (69.0%)	78 (26.5%)	13 (4.4%)	0.383
Right basal ganglia (%)	74 (71.8%)	25 (24.3%)	4 (3.9%)	
Non right basal ganglia (%)	157 (69.5%)	59 (26.1%)	10 (4.4%)	0.905
Right occipital lobe (%)	16 (80.0%)	2 (10.0%)	3 (10.0%)	
Non right occipital lobe (%)	215 (69.6%)	82 (26.5%)	12 (3.9%)	0.130
Brain stem (%)	39 (72.2%)	13 (24.1%)	2 (3.7%)	
Non brain stem (%)	192 (69.8%)	71 (25.8%)	12 (4.4%)	0.933
Cerebellum (%)	13 (86.7%)	2 (13.3%)	0	
Non cerebellum (%)	218 (69.4%)	82 (26.1%)	14 (4.5%)	0.226

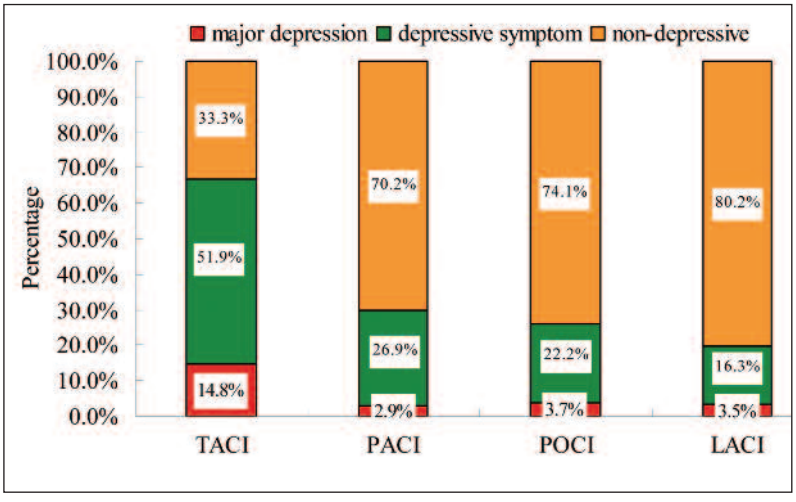

Figure 3. The percentage of PSD patients among different OCSP classification. The occurrence of PSD was much higher in TACI subtype than the other three subtypes ($p < 0.01$).

Table V. Comparison of BI and IADL scores among the three groups.

Group	BI score	IADL score
Non-depressed (n=231)	94.13±13.31	3.50±6.02
Depressive symptom (n=84)	87.80±17.84	6.63±6.72
Major depression (n=14)	76.79±27.29	14.71±8.97
F	12.22	25.43
p	0.000	0.000

Some researchers believed that women were more vulnerable to be affected by physiological and social stress factors and loss psychological balance after stroke[13,15-18]. The other researchers found that men had an equal or even more chance to have PSD[19-21]. Kauhanen M et al[8] mentioned that due to the increase of monoamine oxides, decrease of 5-HT/NE (5-hydroxy-L-tryptamine/norepinephrine) in the old people's brain and bodily function aging, old people (> 60 years old) were more likely to have PSD after stroke. Although influences on the occurrence of depression of age and gender was eliminated in our study, we still found that the female subjects were a little older than the male subjects, and they had the tendency to become depressive. On the other hand, those male subjects of major depression were more than ten years younger than the female subjects in the same group (mean age 59.4 vs. 72.9 years old). We analyzed that because of the economic responsibility in their family and huge life stresses, middle aged-men can't suffer the sudden attack from stroke and become depressive.

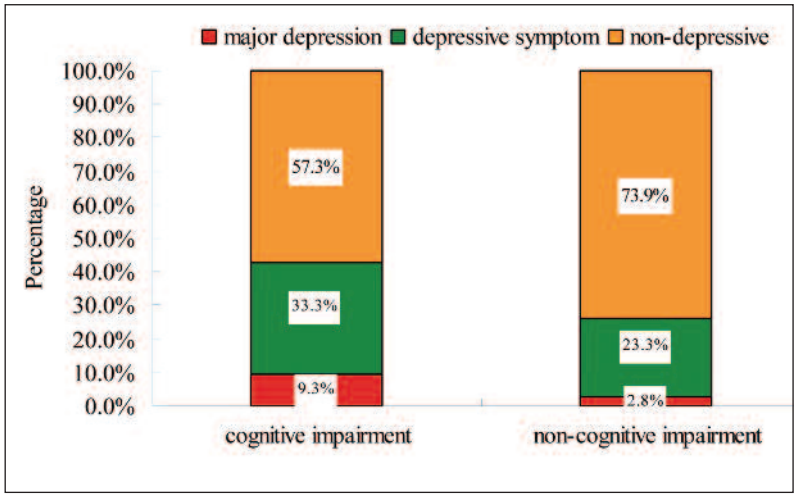

Figure 4. The percentage of the patients in different cognitive level among three groups. Subjects with cognitive impairment were more likely to have the symptom of depression or have major depression ($p < 0.01$).

Table IV. The relationship between BI grading and PSD.

BI grading	Non-depressed (n=231)	Depressive symptom (n=84)	Major depression (n=14)	*p*
Class 1 (0-20 points)	1 (0.4%)	1 (1.2%)	1 (7.1%)	
Class 2 (25-45 points)	5 (2.2%)	2 (2.4%)	2 (14.3%)	
Class 3 (50-70 points)	10 (4.3%)	13 (15.5%)	1 (7.1%)	0.000
Class 4 (75-90 points)	33 (14.3%)	21 (25.0%)	5 (35.7%)	
Class 5 (95-100 points)	182 (78.8%)	47 (56.0%)	5 (35.7%)	

Table VII. Comparison of MMSE scores among the three groups.

Group	n	MMSE scores	F	*p*
Non-depressed	231	25.43±5.11		
Depressive symptom	84	23.69±5.40	5.200	0.006
Major depression	14	22.29±5.70		

Our findings that stroke survivors were not vulnerable to get depression if they got the better care no matter from either the family or the other person, and their economic level was more than 1000 RMB of each one in the family per month. It was easy to understand that stroke made the patients have more medical costs and need more resources of life care. Adequate social support will help stroke survivors easily adapt both physical and psychological changes[13]. Taler-Piliae et al[22] found that depression symptom was prevalent even among the educated and economically advantaged population, which was different from our findings. But our results are similar to their findings that poor quality of life and low social support were major contributors to depressive symptoms.

Our data showed that hypertension and previous stroke history were dependent risk factors for the appearance of PSD, while diabetes mellitus, coronary heart disease, hyperlipoproteinemia, and serum biochemistry index showed no significant effect on the incidence of PSD. The number of vascular risk factors was found to be a significant risk factor for PSD, which was consistent with Mast's research[23]. Mast et al[23] demonstrated that baseline vascular burden was associated with increased odds of positive depression screens at 6- and 18-month follow-up.

Our findings indicated that patients who had lesion in the left hemisphere and multifocal lesions of brain were more likely to have depression than patients who had lesion in non- left hemisphere and single lesion. Our results seemed to support the "vascular depression hypothesis"[18], which proposed that vascular lesions might lead to depression by disrupting the frontal lobe-striatum-globus pallidus-thalamus-cortex fuctional loop which moderated the mood. Kimura et al[24] demonstrated that blood flow of PSD patients in cerebellum especially in the left prefrontal area was much less than those in non PSD patients. It indicated that low perfusion in the left frontal area may induce the depression. Recently, a cross-sectional analysis was conducted and also found that left sided stroke lesion contributed to the early onset post-stroke depression[25]. Considering most of subjects were right-handed, we further analyzed that hemiplegia caused by damage in the left hemisphere made our patients more inconvenient in their daily life and more anxiety than that caused by damage in the right hemisphere. Among the four subtypes of OCSP, only TACI related to the occurrence of PSD. It may be because TACI involved a wide range of body functional damage.

Along with the physical disability and stroke severity, cognitive impairment is also one of factors consistently associated with depression get stroke[26]. We found that PSD patients had severe neurological deficits and cognitive impairments, there was a significant relationship between them ($p < 0.01$). Carota et al[27] reported that BI can be a better predictor of depression than MRI, which was in consistent with our results that the lower BI scores, the more possibility and severe to get the depression. The relationship between cognitive impairment and depression was complex[10,28-30]. It was widely believed that impaired cognition may at least partly a consequence of depression. There were some evidence to explain the relationship between cognition impairment and depression. Murata et al[31] reported that 5-HT/NE insufficiency may induce depression and impair cognition. Furthermore, cortisol levels increased after stroke. High cortisol level was considered to be related with depression, and may cause hippocampus atrophy and impaired cognitive function by inducing neuron death and imbalance of HPA axis.

Conclusions

Our data showed along with serious increase of depression, cognitive impairment also aggravated.

Conflict of interest

The Authors declare that they have no conflict of interests.

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