# Severe Periodontitis Is Associated with Early-Onset Poststroke Depression Status

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*Background:* Poststroke depression (PSD) is one of the most common complications after ischemic stroke, and periodontitis is associated with depression. However, whether severe periodontitis is associated with early-onset PSD status remains unknown. In this study, we aimed to investigate whether there is an association between severe periodontitis and PSD status in acute ischemic stroke patients. *Material and Methods:* We recruited 202 acute ischemic stroke patients within 7 days after stroke onset. Pocket depth and clinical attachment loss were assessed by oral examination to define the severe periodontitis. On the basis of diagnosis of PSD status according to DSM-5 criteria and a 24-item Hamilton Depression Rating Scale score greater than or equal to 8 within 2 weeks after stroke onset, we stratified patients into PSD status or non-PSD status groups and identified the independent predictors for the development of PSD status in multivariate logistic analysis. *Results:* 77 (38.1%) patients were diagnosed as early-onset PSD status. PSD status group showed more severe periodontitis, lower income, lower Barthel Index (BI) score and Montreal Cognitive Assessment score, higher National Institutes of Health Stroke Scale score and modified Rankin scale (mRS) score compared with non-PSD status group. Multivariate logistic regression showed that severe periodontitis (odds ratio 2.401) and NIHSS score (>4, odds ratio 2.130) were independent predictors for early-onset PSD status. *Conclusions:* Severe periodontitis is found to be an important independent predictor of early-onset PSD status in patients with acute ischemic stroke, in addition to the well-known prognostic factors such as nonminor stroke assessed by NIHSS greater than 4.

**Keywords:** Post stroke depression status—acute ischemic stroke—periodontitis—National Institutes of Health Stroke Scale



## Introduction

Poststroke depression (PSD) is one of the most common complications after stroke which approximately affects one third of stroke survivors at any one time,[1] and is associated with poor functional outcomes[2] and higher mortality.[3] Like many other disorders in psychiatry, PSD is a

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multifaceted disorder with diverse causes. However, the pathogenesis of PSD remains unclear. Physical disability, stroke severity, prestroke depression, and cognitive impairment have been recognized as the most consistent predictors of PSD.[4] And PSD status is a transitional state before PSD occurs.

Periodontitis is a chronic inflammatory periodontal disease affecting 46% of adult population in the United States, and its incidence was positively related to increasing age and was higher among males.[5] Some studies have shown that periodontitis is associated with depression.[6-9] However, whether periodontitis is associated with PSD status remains unclear. In some patients with periodontitis, periodontal bacteria, and their products can launch an inflammatory response in the periodontal tissues with systemic consequences, thereby increasing the inflammatory burden of central nervous system.[10] In addition, periodontitis is associated with atherosclerotic vascular disease,[11] which may cause pathologic changes in the perfusion of cerebral atherosclerotic vessels. Thus, it is plausible that all these factors initiated by periodontitis may also contribute to the development of PSD status.

In the current study, we aimed to investigate the association between periodontitis and the development of PSD status in patient with acute ischemic stroke. We hypothesized that periodontitis may play an independent role in the development of PSD status.

## Methods

### *Study Subjects*

From December 2015 to December 2017, we recruited ischemic stroke patients within 7 days of stroke symptom onset in the Department of Neurology, the Affiliated Yuebei People's Hospital of Shantou University Medical College, Shaoguan, China. The inclusion criteria included (1) age greater than or equal to 18 years old; (2) evidence of Ischemic stroke in computed tomography or magnetic resonance imaging; (3) without use of antibiotics in the past 3 months; (4) provision of a written informed consent. The exclusion criteria included (1) patients with a history of depression (clinical diagnosis or previous treatment) or any other psychiatric disorders; (2) patients with inflammatory disorders or any known conditions requiring prophylactic antibiotic treatment before dental examination; (3) patients with serious illness or with disturbance of consciousness. Medical College Ethics Committee, the Affiliated Yuebei People's Hospital of Shantou University Medical College (Shaoguan, Guangdong Province, China) approved the study. All subjects gave informed consent.

### *Oral Examination*

One specially trained dentist performed all periodontal examinations within 7 days after enrollment. The oral health examination included an examination of the oral cavity to make a diagnosis of severe periodontitis. We used the periodontal probe Pcpunc156 (Hu-Friedy, Chicago, IL) to assess pocket depth (distance from free gingival margin to the bottom of the sulcus or periodontal pocket) and clinical attachment loss (distance between probed base of the pocket and cement-enamel junction) for all examined teeth. Measurements were taken at 6 sites per tooth (mesio-, mid-, and distobuccal; mesio-, mid-, and distolingual) for all teeth, excluding third molars. The diagnosis of periodontitis is in accordance with the Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) case definition.[12] Severe periodontitis was defined by presence of 2 or more interproximal sites with greater than or equal to 6 mm attachment loss not only on the same tooth (the number of teeth $\geq$2) and 1 or more interproximal site(s) with greater than or equal to 5 mm pocket depth.

### *Clinical Variables*

After enrollment, trained physicians collected the clinical data via standardized questionnaires, which included demographic characteristics (age, gender, income, education level, etc.), lifestyle characteristics (smoking status, alcohol intake, etc.), and medical history (previous stroke, coronary heart disease, hypertension, diabetes mellitus, hyperlipidemia, etc.) by face-to-face interviews. Stroke severity was evaluated by experienced neurologists using the National Institutes of Health Stroke Scale (NIHSS). The routine laboratory analysis was performed including white blood cell count, high-sensitivity C-Reactive Protein and blood lipid indexes (total cholesterol, triglyceride, high density lipoprotein cholesterol HDL-C, and low density lipoprotein cholesterol LDL-C). The evaluations of cerebral intra- and extracranial artery were performed within 1 week using transcranial and cervical Doppler, computed tomography angiography or magnetic resonance angiography. Electrocardiogram (ECG) and cardiac echography were used to evaluate the thrombus from the heart. The location of the cerebral infarction was confirmed by cranial computed tomography or magnetic resonance imaging. Stroke subtype was classified according to the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST).[13] Functional outcomes were assessed by the Barthel Index (BI) and the modified Rankin scale (mRS) within 2 weeks after stroke. Cognitive functions were assessed by the Montreal Cognitive Assessment (MoCA) within 2 weeks after stroke.

### *Assessment of PSD Status*

We assessed depressive symptoms through the 24-item Hamilton Depression Rating Scale ($HDRS_{24}$)[14] within 2 weeks after stroke. The diagnosis of early-onset PSD status was made according to DSM-5[15] criteria and a $HDRS_{24}$ score greater than or equal to 8. Assessments

were performed by trained physicians who were blinded to the patients' condition. According to the diagnosis of depression, we divided a PSD status group and a non-PSD status group.

DSM-5 criteria (Depressive disorder due to another medical condition): (1) A prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities that predominates in the clinical picture; (2) There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition; (3) The disturbance is not batter explained by another mental disorder; (4) The disturbance does not occur exclusively during the course of a delirium; and (5) The disturbance cause clinical significant distress or impairment in social, occupational, or other important areas of functioning.

### *Statistical Analysis*

We dichotomised all the patients into PSD status and non-PSD status group. We compared the demographic differences (e.g., age, gender, and risk factors) between 2 groups, as well as the medical history, laboratory tests, and the neurological assessment. Continuous data were analysed by independent-sample *t* tests when there was a normal distribution and by the Mann-Whitney test if there was a skewed distribution. Category data were analysed by the $\chi^2$ test. We used multivariate logistic regression to identify the independent predictors for the development of PSD status in ischemic stroke patients. Significance level was defined as $P < .05$ by using SPSS version 20.0 for Windows (SPSS IBM Inc, Chicago, IL).

## Result

We recruited a total of 202 acute ischemic stroke patients (131 males, mean age 61.20 ± 9.99 years, Table 1) within 7 days after stroke onset. Seventy-four (36.6%) patients had a NIHSS greater than 4. Ninety-one (45.0%) patients had a left-side cerebral infarct, 86 (42.6%) patients had a right-side cerebral infarct and the other 25 (12.4%) patients had infarcts on both sides of the brain. Based on the criteria from TOAST study, 106 (52.5%) patients had large artery atherosclerosis and 78 (38.6%) patients had small artery occlusion. Based on the diagnosis criteria of early-onset PSD status, the patients were classified into 2 groups: group 1 had PSD status (77 patients, mean age 62.74 ± 9.73 years), and group 2 had non- PSD status (125 patients, mean age 60.26 ± 10.07 years). The incidence of early onset PSD status was 38.1%.

There was no significant difference between 2 groups in demographic characteristics, lifestyle characteristics, medical history, stroke location, stroke etiology, and laboratory parameters except for the level of income and the prevalence of severe periodontitis ($P = .039$ and .002, respectively, Table 1). Compared with the non-PSD status group, the PSD status group had a higher NIHSS and mRS score and a lower BI and MoCA score (all $P < .001$, Table 1). After analysis of multivariate logistic regression, severe periodontitis, and NIHSS score (>4) were independently associate with early-onset PSD status, with adjusted ORs of 2.401 (95% CI 1.090-5.288; $P = .030$), and 2.130 (95% CI 1.057-4.291; $P = .034$), respectively (Table 2).

## Discussion

This cross-sectional study involving 202 patients with acute ischemic stroke indicated that severe periodontitis is an independent risk factor for the early-onset PSD status after adjusting for other risk factors. The scientific evidence on the association between periodontitis and depression is limited. Several Cross-sectional studies demonstrated a positive correlation of periodontal disease severity with the depression.[7-9] Recently, a large retrospective population-based cohort study observed a positive association between subjects with periodontitis and depression.[6] All these studies only discussed the possible association between periodontitis and depression, without any discussion of potential association between periodontitis and PSD status. In accordance with our hypothesis, our data suggest severe periodontitis may play an independent role in the development of PSD status.

In our study, we found that 38.1% of stroke patients were diagnosed as poststroke depressive state within 2 weeks after stroke onset, which was a little higher than the reported incidence 28%-36% of PSD.[1,16] As we all know, a patient with a diagnosis of PSD must have depressed mood or loss of pleasure or interest lasting more than 2 weeks. And PSD status is a transitional state before PSD occurs. In our study, the baseline assessment was conducted within 14 days of stroke, may be the leading cause of higher incidence. The negative mood and psychological pressure are easily caused by fear that severe neurological deficits would have a terrible effect on the quality of life. Besides, like many other disorders in psychiatry, PSD status is a multifaceted disorder with diverse causes. Aging, poverty and a lack of positive social and family support can also influence the incidence of early-onset PSD status.

Our study found that patients with early-onset PSD status had increased neurological deficits and worse neurological functional recovery, similar to the discovery in previous studies.[2,3] Except the severe periodontitis, there was no association with gender, age, education level, stroke risk factors, past history of diabetes, past history of stroke, TOAST subtype, BI score, mRS score, and MoCA score. Although the level of income is not the independent predictor for early-onset PSD status, low income people are more likely to suffer from early-onset PSD status. This condition may be partly explained by the fact that lower socioeconomic position increases the risk of periodontitis.[17] To some extent, it supports the association between severe periodontitis and early-onset poststroke depressive state. Severe periodontitis may contribute to the depressive symptoms

**Table 1.** *Baseline characteristics in patients with poststroke depression status (Group 1) or non−poststroke depression status (Group 2)*

| Variables | Group 1 (77) | Group 2 (125) | *P* value |
|---|---|---|---|
| Demographic characteristics | | | |
| Age (years) | 62.74 ± 9.73 | 60.26 ± 10.07 | .086 |
| Male, n (%) | 45 (58.4) | 86 (68.8) | .134 |
| BMI | 24.32 ± 3.26 | 24.49 ± 3.54 | .738 |
| Education level, n (%) | | | |
| Low (≤6 years) | 41 (53.2) | 45 (36.0) | .055 |
| Middle (7-9 years) | 23 (29.9) | 51 (40.8) | |
| High (>9 years) | 13 (16.9) | 29 (23.2) | |
| Income (RMB/month), n (%) | | | |
| Low (≤1000) | 31 (40.2) | 31 (24.8) | **.039** |
| Middle (1001-3000) | 35 (45.5) | 63 (50.4) | |
| High (>3000) | 11 (14.3) | 31 (24.8) | |
| Lifestyle characteristics | | | |
| Smoking, n (%) | 36 (46.8) | 68 (54.4) | .291 |
| Drinking, n (%) | 23 (29.9) | 49 (39.2) | .179 |
| Medical history | | | |
| Previous stroke, n (%) | 25 (31.2) | 32 (25.6) | .390 |
| Coronary heart disease, n (%) | 13 (16.9) | 13 (10.4) | .181 |
| Hypertension, n (%) | 62 (80.5) | 91 (72.8) | .214 |
| Diabetes mellitus, n (%) | 20 (26.0) | 22 (17.6) | .154 |
| Hyperlipidemia, n (%) | 23 (29.9) | 29 (23.2) | .292 |
| Severe periodontitis, n (%) | 65 (84.4) | 80 (64.0) | **.002** |
| Lesion location, n (%) | | | |
| Frontal lobe | 3 (3.0) | 4 (3.2) | .800 |
| Parietal lobe | 1 (1.3) | 3 (2.4) | |
| Basal ganglia | 19 (24.7) | 21 (16.8) | |
| Thalamus | 4 (5.2) | 13 (10.4) | |
| Brainstem | 19 (24.7) | 31 (24.8) | |
| Cerebellum | 3 (3.9) | 5 (33.6) | |
| Multiple locations | 26 (33.8) | 42 (33.6) | |
| Subcortical white matter | 2 (2.6) | 6 (4.8) | |
| Lesion location, n (%) | | | |
| Left | 41 (53.2) | 50 (40) | .114 |
| Right | 30 (39) | 56 (44.8) | |
| Both | 6 (7.8) | 19 (15.2) | |
| TOSAT subtype, n (%) | | | |
| LAA | 46 (59.7) | 60 (48.0) | .068 |
| CE | 3 (3.9) | 6 (4.8) | |
| SAO | 28 (36.4) | 50 (40) | |
| Undetermined | 0 (0) | 9 (7.2) | |
| Conventional laboratory tests | | | |
| *Hs-CRP (mg/dL) | .28 (.14-.55) | .24 (.12-.58) | .568 |
| WBC ($\times 10^9$/L) | 7.59 ± 2.20 | 8.00 ± 2.69 | .255 |
| TC (mmol/L) | 4.84 ± 1.12 | 4.876 ± .997 | .791 |
| *TG (mmol/L) | 1.31 (.895-1.63) | 1.43 (1.045-1.94) | .083 |
| LDL-C (mmol/L) | 3.15 ± .97 | 3.17 ± .80 | .900 |
| *HDL-C (mmol/L) | 1.19 (1.02-1.39) | 1.11 (.975-1.265) | .062 |
| Carotid plaque, n (%) | 58 (75.3) | 87 (69.6) | .380 |
| Neurological assessment | | | |
| NIHSS> 4, n (%) | 41 (53.2) | 33 (26.4) | <**.001** |
| NIHSS score | 5 (3-7) | 3 (2-5) | <**.001** |
| *BI score | 70 (50-95) | 95 (75-100) | <**.001** |
| *mRS score | 4 (2-4) | 2 (1-3) | <**.001** |
| *MoCA score | 15 (10-19) | 19 (13-22) | <**.001** |

*Abbreviations:* BI, Barthel Index; BMI, body mass index; CE, cardiac embolism; HDL-C, high density lipoprotein cholesterol; Hs-CRP, High-sensitivity C-Reactive Protein; LAA, large artery atherosclerosis; LDL-C, low density lipoprotein cholesterol; mRS, modified Rankin scale; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; SAO, small artery occlusion; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

All *P* values were 2-sided, and a *P* value less than .05 was considered statistically significant.

*Means non normal distribution measurement data or ordinal data.

**Table 2.** *Multivariate logistic regression analysis for predictive variables*

| Risk variables | OR | 95% CI | *P* value |
|---|---|---|---|
| Age | 0.989 | 0.954-1.026 | 0.560 |
| Male | 0.813 | 0.379-1.748 | 0.597 |
| Income (RMB/month) | | | 0.405 |
| Low (≤1000) | 1.998 | 0.718-5.563 | 0.185 |
| Middle (1001-3000) | 1.404 | 0.569-3.465 | 0.461 |
| High (>3000) | 1 (reference) | | |
| Previous stroke | 0.992 | 0.472-2.084 | 0.983 |
| Diabetes mellitus | 1.500 | 0.628-3.583 | 0.361 |
| Severe periodontitis | 2.729 | 1.173-6.351 | **0.020** |
| NIHSS >4 | 2.243 | 1.102-4.566 | **0.026** |
| BI score | 0.991 | 0.966-1.017 | 0.505 |
| mRS score | 1.188 | 0.770-1.833 | 0.437 |
| MoCA score | 0.968 | 0.907-1.034 | 0.333 |

Note: BI, Barthel Index; mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; 95%CI, 95% confidence interval;

All *P* values less than .05 was considered statistically significant.

through different biological mechanisms. First, previous studies show that periodontitis has an effect on the progression of depression[6-9] before the occurrence of ischemic stroke, which can increase the risk of poststroke depressive state. Further longitudinal studies are needed to determine whether periodontitis plays a role in PSD status. Second, previous studies have provided support for the role of proinflammatory cytokines in the development of poststroke depressive state,[18-20] and these proinflammatory cytokines may lead to PSD status by inducing alterations of the hypothalamus-pituitary-adrenal (HPA) axis and decreasing serotonin synthesis.[21] Periodontitis is also associated with high levels of systemic inflammation via exposure to gram-negative bacteria,[22] and these proinflammatory cytokines initiated by periodontitis[23] may lead to increased susceptibility to poststroke depressive state. However, in our study there is no association between high-sensitivity C-reactive protein and early-onset poststroke depressive state, which is inconsistent with previous study.[18] This discrepancy may be attributed to recruitment of different study cohorts, variation of diagnostic and psychiatric assessment methods and other potential confounders. Further research is needed to determine whether proinflammatory cytokines plays a role in PSD status. Third, periodontitis is associated with atherosclerotic vascular disease,[11] and the brain-oral (dental) axis can cause endothelial dysfunction and blood-brain barrier (BBB) disruption.[24] Therefore, periodontitis may cause pathologic changes in the perfusion of cerebral vessels, which can contribute to the occurrence of PSD status.[25,26] We believe that the aforementioned condition induced by periodontitis may increase the risk of PSD status. In summary, our study demonstrated that severe periodontitis and stroke severity associated with early-onset PSD status.

The current study has some limitations. First, this study only assessed the state of depression within 2 weeks after stroke, and did not follow up to assess the PSD of the patient, such as 3 months, 6 months, and 1 year later. Second, the cross-sectional study has the limitation inherent, which cannot be used to determine causal relationships. Further prospective, randomized, controlled clinical trials with a large sample size should address these critical issues and confirm the current findings. Third, we excluded patients with severe aphasia, cognitive impairment and serious conditions and poor cooperation in oral examination or $HDRS_{24}$ assessment, which may underestimate the actual incidence of early-onset PSD status. Fourth, the prevalence of patients (4.5%) with cardiac embolism was significant lower than previous studies (20%), we think it might be a selection bias for these patients must accomplish the assessment of oral examination and the $HDRS_{24}$, and at the same time, they did not carried out long-term ECG or continuous ECG monitoring. Fifth, the prevalence of patients with severe periodontitis (71.7%) is much higher, it might be associated with the lower socio-economic levels of the patients, most patients (>70%) income were lower 3000 RMB per month in this study. Therefore, these limitations may have an effect to generalize our findings to other patients.

In conclusion, our findings demonstrated that severe periodontitis is independently associated with early-onset PSD status in acute ischemic stroke. The prevention and treatment of periodontitis may offer a new way to improve outcomes of patients with PSD status.

## Conflict of Interest

None.

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