High serum levels of 8-OHdG are an independent predictor of post-stroke depression in Chinese stroke survivors

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Purpose: Although previous studies have investigated oxidative stress biomarkers in association with depression in non-stroke subjects, the association between oxidative deoxyribonucleic acid damage and post-stroke depression (PSD) remains unelucidated.

Patients and methods: Two hundred forty-one first-ever ischemic stroke patients were consecutively recruited within the first 24 h of stroke onset and were followed up at 1 month. Serum 8-hydroxy-2′-deoxyguanosine (8-OHdG) and catalase (CAT) levels were measured within 24 h of admission using a commercially available enzyme-linked immunosorbent assay. The 17-item Hamilton Depression Scale was used to evaluate depressive symptoms. Diagnosis of PSD was made in line with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria for depression.

Results: Serum levels of 8-OHdG ($p<0.001$) and CAT ($p=0.025$) increased in depressed patients at admission. A positive correlation was found between the 8-OHdG and CAT levels in both the total stroke patients ($r=0.320, P<0.001$) and the depressed patients ($r=0.300, P=0.012$). The 8-OHdG levels were positively correlated with the 17-item Hamilton Depression Scale scores ($r=0.129, P=0.046$) in depressed patients. Multivariate analyses found that 8-OHdG levels $\geq$200.0 ng/L were independently associated with PSD (odds ratio, 7.477; 95% CI, 3.342–16.289, $P<0.001$) after adjusting for possible relevant confounders.

Conclusion: Higher serum 8-OHdG levels at admission were found to be correlated with PSD 1 month after stroke.

Keywords: oxidative stress, 8-hydroxy-2′-deoxyguanosine, catalase, depression, stroke

Introduction

Post-stroke depression (PSD) is a highly prevalent neuropsychiatric sequela of stroke that acts as an important index of both functional and treatment outcomes in patients. PSD can interfere with stroke recovery and is associated with the severity of stroke, cognitive impairment, and increased mortality. Therefore, early diagnosis and intervention in PSD are beneficial to the functional recovery of stroke patients. However, research into the etiological mechanisms of PSD in clinical populations is limited.

Accumulating evidence has suggested that ischemic stroke is intimately linked to acute bursts of reactive oxygen species (ROS) or reactive nitrogen species (RONS), and oxidative deoxyribonucleic acid (DNA) damage appears to be involved in the pathogenesis of brain ischemia. Antioxidants can remove ROS and RON through scavenging radicals and suppressing the oxidative stress pathway, further preventing oxidative damage to neurons. An imbalance between the generation of ROS by pro-oxidants and the defense mechanisms against ROS by antioxidants can elic...
pathological changes such as lipid peroxidation, DNA damage, autoimmune responses, and protein carbonylation.\textsuperscript{6,7} Catalase (CAT) serves as an intracellular antioxidant enzyme that metabolizes ROS into less toxic molecules and catalyzes hydrogen peroxide into water and oxygen.\textsuperscript{8} Previous studies have reported that serum or plasma CAT levels were significantly lower in acute ischemic stroke (AIS) patients than in controls.\textsuperscript{9,10} A recent longitudinal observational study of stroke patients demonstrated decreased serum CAT levels in stroke patients compared with controls within 24 h of the onset of ischemia, and its levels did not change during the subsequent 21 days.\textsuperscript{9}

Oxidative DNA damage has been proposed to be a causative factor in blood–brain barrier dysfunction and is known to induce neuronal degeneration and apoptosis.\textsuperscript{11,12} Damage to DNA is indicated by increased levels of 8-hydroxy-2’-deoxyguanosine (8-OHdG), a repair product of the oxidation of guanine in DNA.\textsuperscript{13} 8-OHdG can be detected in human tissue, blood samples, or urine and is considered a reliable and pivotal biomarker of generalized and cellular oxidative stress.\textsuperscript{14,15} Previous studies have reported that peripheral 8-OHdG is a valuable indicator of the severity of oxidative brain damage in acute cerebral infarction.\textsuperscript{16} The role of 8-OHdG as a potential and predictive biomarker of atherosclerosis, cardiovascular disease, neurodegenerative disorders, such as Alzheimer’s disease and Parkinson’s disease, and psychiatric disorders, such as schizophrenia, has been well recognized.\textsuperscript{17–19} Elevated levels of 8-OHdG have been reported to be correlated with clinical outcomes of stroke and have a close relationship with atherosclerotic plaque types and vascular recurrence in non-cardioembolic stroke patients.\textsuperscript{13,20,21} Recently, Myoren et al found that increased 8-OHdG might be able to powerfully predict cardiovascular-related death.\textsuperscript{22}

Previous studies have assessed the role of CAT or 8-OHdG in patients with depression, but these studies were controversial. While some authors have reported increased CAT activity in depressed patients, several studies have revealed no significant changes compared with healthy controls.\textsuperscript{3,23} Additionally, lower gene expression of CAT was noted in patients with major depression.\textsuperscript{24} Although the majority of studies have identified that levels of 8-OHdG increased in depressed patients, a recent study of a large adult cohort found no increased levels of 8-OHdG.\textsuperscript{25–27}

Thus, it is reasonable that oxidative stress biomarkers and levels of antioxidant enzymes may have a predictive role in PSD. The findings of a recent study suggested that the activity of CAT in erythrocytes is negatively correlated with Geriatric Depression Scale scores during a brain stroke.\textsuperscript{6} However, no study to date has investigated the relationship between levels of oxidative DNA damage and PSD. Furthermore, the results of a study of a multiracial–ethnic stroke cohort suggested that racial–ethnic differences might have a role in the prevalence of depression among stroke survivors.\textsuperscript{28} The main aim of our study was to explore if high levels of 8-OHdG contribute to the development of PSD in Chinese subjects who suffered an AIS.

**Patients and methods**

**Patients and study design**

Two hundred forty-one patients who were consecutively admitted to the Stroke Unit of the First Affiliated Hospital of Wenzhou Medical University within the first 24 h of first-ever ischemic stroke onset between October 2013 and September 2014 were enrolled in this study.

Participants were excluded if the following criteria were identified: a history of depression (clinical diagnosis or previous treatment) or other psychiatric disorders; a history of psychiatric treatment; use of antioxidants drugs or vitamin supplementation within the prior 30 days; an application of thrombolytic therapy; implant of a carotid or coronary stent or other major surgical interventions; a medical history of pre-stroke dementia; significant acute or chronic inflammatory factors or neurological illnesses other than stroke; severe aphasia or dysarthria; major medical illness; and age <18 years. A flow chart of the study design is shown in Figure S1.

The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University with the following reference number: 201340. All participants provided written informed consent prior to participation in accordance with the Declaration of Helsinki of 1975.

**Neuropsychiatric assessment**

The severity of depressive symptoms at admission (baseline) was measured with the 17-item Hamilton Depression Scale (HAMD-17) within 24 h of admission.\textsuperscript{29} The HAMD-17 has been the gold standard in depression trials since its introduction in 1960 by Hamilton.\textsuperscript{30} Numerous studies have examined the high validity and utility of the HAMD-17 as a useful screening tool for depressive symptoms, and the optimal cutoff point has been found to be 7 in the general population or in patients with neurological diseases such as stroke, epilepsy, and severe traumatic brain injury.\textsuperscript{31–34}

Patients with possible depressive symptoms at 1 month after onset of the neurological symptoms of the acute stroke were further interviewed with the Structured Clinical
Interview of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), for the diagnosis of PSD. One of the trained psychologist researchers administered the DSM-IV, and 2 neuropsychologists conducted the psychiatric rating scales.

Functional and neurological assessment
Acute stroke was confirmed by cranial CT or diffusion-weighted MRI in all enrolled patients. Upon admission to the Stroke Unit, an expert neurologist performed a full neurological evaluation of the patients and recorded the type and location of the index stroke. The quantitative evaluation of stroke-induced neurological deficits during the acute phase was conducted using the National Institutes of Health Stroke Scale (NIHSS) at admission. An NIHSS score ≤3 is defined as minor stroke, and >3 as moderate-to-severe stroke. The Barthel index (BI) and the Mini-Mental State Exam (MMSE) were used to assess functional and cognitive impairment, respectively, at discharge.

Serum 8-OHdG and CAT measurement
Blood was collected from the antecubital vein within 24 h of admission. Blood samples were centrifuged at 3,000 rpm for 10 min, and the plasma was separated and aliquots of the samples were immediately stored at −80°C before the assays. The samples were thawed only once before the analyses. The serum 8-OHdG and CAT antibody concentrations were measured by a commercially available enzyme-linked immunosorbent assay (Xinfan Biotechnology Co., Ltd, Shanghai, China). All procedures used in the present study followed the instructions strictly. The optical density value was measured with a microplate reader at a wavelength of 450 nm. Then, we calculated the concentration of 8-OHdG and CAT according to the standard curve. All standards and samples were tested in duplicate wells. The inter-assay and intra-assay coefficients of variation for 8-OHdG were 11% and 9%, respectively. The mean minimum detectable dose of human 8-OHdG was 10 ng/L, and the line range was 10–300 ng/L. The inter-assay and intra-assay coefficients of variation for human CAT were 11% and 9%, respectively, and the mean minimum detectable dose was 3 U/L. The measurement range of the human CAT kit was 3–90 U/L.

Statistical analysis
Categorical data were recorded as relative and absolute frequencies. Continuous variables were tested for distribution using the Kolmogorov–Smirnov test. The normally distributed continuous variables were analyzed with Student’s t-test or analysis of variance and are described as the mean ± SD, whereas the asymmetrically distributed variables were analyzed with the Mann–Whitney U test or the Kruskal–Wallis test and are expressed as the median interquartile range. Correlations between 8-OHdG and the variables were assessed using Spearman’s correlation coefficient.

A receiver-operating characteristic (ROC) curve analysis was used to determine the diagnostic accuracy and optimal cutoff values of 8-OHdG in the diagnosis of PSD. The area under the curve (AUC) was provided with a 95% CI, which was obtained by using MedCalc 12.5 (MedCalc Software, Ostend, Belgium). We treated the serum 8-OHdG level as a dichotomized variable (by the optimal cutoff) in the statistical analyses. The influence of the serum 8-OHdG levels on PSD was estimated by binary logistic regression analysis, after adjusting for potential confounders regarded as being clinically relevant. A 2-sided P-value <0.05 was regarded as statistically significant. All data analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA).

Results
The study cohort consisted of 552 patients at baseline. By the time of the follow-up at 1 month, 241 patients remained in our study. However, these 241 patients were similar in terms of their baseline characteristics such as age, sex, and NIHSS scores (all P>0.05) compared with the overall cohort. The baseline clinical characteristics of enrolled patients with AIS are shown in Tables 1, 2, and S1.

The occurrence of PSD was 29.0%. Patients with PSD had more severe strokes (P<0.001), and poorer functional outcomes (P=0.013) and cognitive functioning (P=0.018) than those without PSD.

The serum 8-OHdG levels of all stroke patients and patients with PSD and without PSD at admission were 183.0±59.8, 218.0 (170.6–246.7), and 164.8 (121.1–208.0) ng/L (Figure 1), respectively. The serum 8-OHdG levels at baseline were significantly higher in patients with PSD than in patients without PSD at 1 month (P<0.001, Tables 1 and S2). A positive correlation was found between the 8-OHdG and CAT levels in both the total stroke patients (r=0.320, P<0.001, Figure 2) and the depressed patients (r=0.300, P=0.012). 8-OHdG was positively correlated with the HAMD scores (r=0.129, P=0.046) in depressed patients. No significant differences in serum CAT or 8-OHdG levels were identified between the minor stroke and the moderate-to-severe stroke groups (Table S3). Statistical analysis revealed no influence of age, NIHSS scores (Table S4), or BI scores on 8-OHdG levels in stroke patients (all P>0.05).
In the logistic regression analysis, 8-OHdG, taken as a continuous variable, was independently associated with PSD (OR, 1.019; 95% CI, 1.012–1.027, *P* < 0.001, Table 2) after being adjusted for age, sex, NHISS scores, MMSE scores, BI scores, current smoking status, current drinking status, and fasting blood glucose and CAT levels.

Based on the ROC curve, the optimal cutoff is of serum 8-OHdG levels as an indicator for the prediction of PSD.
was projected to be 200.0 ng/L, which yielded a sensitivity of 65.7% and a specificity of 71.0%, with an AUC of 0.723.

### Discussion

To the best of our knowledge, this is the first study that explored the relationship between serum 8-OHdG levels and depression in stroke patients at 1 month post-stroke.

In the present study, we found that the prevalence of PSD was 29.0% 1 month after stroke, which was in agreement with the results of recent studies. A prior meta-analysis of 50 studies, which included 20,293 patients, reported that the pooled prevalence of PSD was 29% at any time point within 5 years. We also found that the disability severity was related to PSD. Impairment in activities of daily living has been consistently identified as a risk factor for PSD. Similarly, Matsuzaki et al found that depression occurred independently after stroke and could individually influence functional recovery.

Our main findings indicated that elevated serum 8-OHdG is an independent predictor for the development of PSD at 1 month. Similarly, 1 previous study indicated strong evidence that serum 8-OHdG increased significantly in participants with major depression, and participants with recurrent episodes of depression had more DNA damage than those with single episodes. Increased levels of oxidative stress biomarkers have been demonstrated in subjects with a history of suicide attempts. A recent clinical study demonstrated that the association between the presence of depressive symptoms and 8-OHdG levels is independent of the menstrual cycle. While some studies have reported increased 8-OHdG levels in depression, 1 study reported lower levels. This discrepancy may have resulted from differences in the biological specimens, laboratory techniques, or the time of assessment used in the studies.

The role of serum 8-OHdG in the pathophysiology of PSD remains unknown. Many behavioral factors, such as smoking and alcohol use are related to increased exposure to ROS. 8-OHdG has been reported to be positively associated with a range of sociodemographic and lifestyle determinants, such as age and cigarette exposure. Dysregulations of the hypothalamic–pituitary–adrenal axis have been reported in depression, and these could be contributing factors to increased oxidative stress. It is already known that ischemic stroke activates the inflammatory pathway, and

### Table 2 Adjusted OR of depression for 8-OHdG levels in stroke patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.006 (0.965–1.048)</td>
<td>0.779</td>
</tr>
<tr>
<td>Sex</td>
<td>0.728 (0.292–2.181)</td>
<td>0.497</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>1.288 (1.099–1.511)</td>
<td>0.002***</td>
</tr>
<tr>
<td>MMSE score</td>
<td>0.931 (0.870–0.996)</td>
<td>0.038*</td>
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<tr>
<td>BI score</td>
<td>1.002 (0.985–1.020)</td>
<td>0.795</td>
</tr>
<tr>
<td>Smokers</td>
<td>1.379 (0.568–3.350)</td>
<td>0.477</td>
</tr>
<tr>
<td>Alcohol consumers</td>
<td>0.745 (0.332–1.673)</td>
<td>0.476</td>
</tr>
<tr>
<td>CAT</td>
<td>1.007 (0.991–1.024)</td>
<td>0.383</td>
</tr>
<tr>
<td>FBG</td>
<td>1.198 (1.020–1.407)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.385 (0.642–2.991)</td>
<td>0.406</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.566 (0.205–1.559)</td>
<td>0.271</td>
</tr>
<tr>
<td>Statins at admission</td>
<td>1.979 (0.139–28.158)</td>
<td>0.614</td>
</tr>
<tr>
<td>Vitamin C at admission</td>
<td>0.722 (0.160–3.255)</td>
<td>0.745</td>
</tr>
<tr>
<td>8-OHdG level at admission</td>
<td>1.019 (1.012–1.027)</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>8-OHdG level at admission</td>
<td>7.477 (3.432–16.289)</td>
<td>&lt;0.001***</td>
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<tr>
<td>&gt;200.0 ng/L</td>
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</table>

Note: *P<0.05, **P<0.01, ***P<0.001.

Abbreviations: 8-OHdG, 8-hydroxy-2’-deoxyguanosine; BI, Barthel index; CAT, catalase; FBG, fasting blood glucose; MMSE, mini-mental state examination; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

### Figure 1

Serum levels of 8-OHdG and CAT in patients with PSD and those without depression.

Notes: (A) 8-OHdG levels, (B) CAT levels. In the box-and-whisker plots, the horizontal line in the middle of each box indicates the median value; the lower and upper ends of the box represent the 25th and 75th percentiles, respectively, and the peripheral lines extending to the outer fences represent 10th and 90th percentiles. *P<0.05; ***P<0.001 compared with the non-PSD group via Mann–Whitney U test.

Abbreviations: 8-OHdG, 8-hydroxy-2’-deoxyguanosine; CAT, catalase; PSD, post-stroke depression.
pro-inflammatory cytokines, in turn, amplify the oxidative stress response. Moreover, recent studies have revealed that exogenous 8-OHdG could be a functional molecule in the regulation of oxidative stress-induced gastritis through binding or blocking the related signals responsible for the gastric inflammatory cascade. The brain, characterized by high oxygen consumption and low antioxidant defenses, is particularly vulnerable to oxidative damage. Oxidative DNA damage has been identified as an important contributor to neurodegeneration associated with acute central nervous system injuries and neurological diseases. In particular, unchecked oxidative DNA damage has been found to be associated with the activation of a series of signaling events, such as p53 and poly(ADP-ribose) polymerase-1, which have been shown to promote neuronal loss following ischemic stroke. There is some evidence from post-mortem studies that has suggested that 8-OHdG levels increased in depressed patients.

Another important finding of our study was that serum 8-OHdG levels were positively correlated with serum CAT levels. In our study, serum CAT levels increased in depressed patients. The increased CAT levels might be a compensatory mechanism for the excessive production of ROS in depressed patients during the acute phase. Galecki et al also found that major depressive disorder (MDD) patients had significantly higher red blood cell CAT activities than healthy controls during acute depressive episodes. Our results were in line with the recent evidence supporting that increased serum CAT levels might be indicators of acute depressive episodes in MDD patients.

There were several limitations to our study. First, we excluded patients with severe comprehension deficits or a history of stroke, which may have added some bias to the results. Second, the serum 8-OHdG levels were evaluated only once at the time of admission. It is worth investigating whether there are longitudinal changes in serum 8-OHdG levels and the relationship between these results and PSD. Third, we did not compare the 8-OHdG levels in serum with those in the urine. Fourth, the study subjects came from only 1 clinic; thus, it would be inappropriate to generalize the findings.

**Conclusion**

In summary, in spite of these limitations, our study demonstrated an important association between serum 8-OHdG levels at admission and the development of PSD 1 month after stroke. Stroke patients should be monitored for high 8-OHdG levels and followed up for appropriate interventions. Additional studies are needed to confirm this association, which may provide new proposals for the development of PSD.
Acknowledgments
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Author contributions
JH designed the study and wrote the protocol. ZL and YC conducted literature searches and provided summaries of previous research studies. ZL conducted the statistical analysis and wrote the first draft of the manuscript. JH took responsibility for the integrity of the data. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. All authors reviewed and approved the final version of the manuscript.

Disclosure
The authors report no conflicts of interest in this work.

References


8. Tsai MC, Huang TL. Increased activities of both superoxide dismutase and catalase were indicators of acute depressive episodes in patients with major depressive disorder. Psychiatry Res. 2016;235:38–42.


Supplementary materials

Figure S1 Study flow chart.
Abbreviation: PSD, post-stroke depression.

Table S1 Prescribed drugs employed of the studied subjects at admission

<table>
<thead>
<tr>
<th>Drugs</th>
<th>PSD patients</th>
<th>Non-PSD patients</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Statins use, n (%)</td>
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<tr>
<td>Non-PSD patients</td>
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<tr>
<td>Alprostadil injection, cinepazide maleate injection, or vinpocetine injection</td>
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<tr>
<td>Aspirin or clopidogrel use, n (%)</td>
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<tr>
<td>Hypertension medicine use, n (%)</td>
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<tr>
<td>Diabetes medicine use, n (%)</td>
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<tr>
<td>Butylphthalide use, n (%)</td>
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<tr>
<td>Vitamin C injection use, n (%)</td>
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<tr>
<td>Mannitol use, n (%)</td>
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<tr>
<td>Ginkgo leaf extract and dipyridamole injection use, n (%)</td>
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<tr>
<td>Urinary kallidinogenase use, n (%)</td>
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<tr>
<td>Folic acid use, n (%)</td>
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</table>

Notes:
Patients were divided into 4 groups according to the severity of stroke and depression. A group: minor stroke (NIHSS ≤3) + depression (-); B group: minor stroke (NIHSS ≤3) + depression (+); C group: moderate-to-severe stroke (NIHSS >4) + depression (-); D group: moderate-to-severe stroke (NIHSS >4) + depression (+). The P-values reflect comparisons of serum 8-OHdG and CAT levels in the 4 groups. ***P<0.001 compared to A group by univariate analysis; ****P<0.001 compared to B group by univariate analysis; P=0.001 compared to C group by univariate analysis.

Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; CAT, catalase; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

Table S2 Serum 8-OHdG and CAT levels according to the severity of stroke and depression

<table>
<thead>
<tr>
<th>Laboratory variables</th>
<th>A (n=130)</th>
<th>B (n=34)</th>
<th>C (n=41)</th>
<th>D (n=36)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-OHdG (ng/L), median (IQR)</td>
<td>163.9 (124.8–211.1)</td>
<td>223.1*** (185.4–258.8)</td>
<td>164.9*** (106.7–200.7)</td>
<td>212.9*** (166.4–239.2)</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>CAT (U/L), median (IQR)</td>
<td>57.1 (42.9–70.7)</td>
<td>64.6 (45.1–77.6)</td>
<td>56.8 (43.1–69.1)</td>
<td>63.4 (51.2–80.4)</td>
<td>0.150</td>
</tr>
</tbody>
</table>
Table S3 Comparisons of serum 8-OHdG and CAT levels in patients with minor stroke and those with moderate-to-severe stroke

<table>
<thead>
<tr>
<th>Laboratory variables</th>
<th>NIHSS ≤3 (n=164)</th>
<th>NIHSS &gt;3 (n=77)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-OHdG (ng/L), mean ± SD</td>
<td>182.5±60.6</td>
<td>184.1±58.4</td>
<td>0.841</td>
</tr>
<tr>
<td>CAT (U/L), mean ± SD</td>
<td>58.8±21.9</td>
<td>60.2±20.4</td>
<td>0.638</td>
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</tbody>
</table>

Abbreviations: 8-OHdG, 8-Hydroxy-2′-deoxyguanosine; CAT, catalase; NIHSS, National Institutes of Health Stroke Scale.

Table S4 Correlations between oxidative stress markers and NIHSS scores

<table>
<thead>
<tr>
<th>NIHSS scores</th>
<th>8-OHdG</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS1</td>
<td>r=-0.03, P=0.642</td>
<td>r=0.041, P=0.523</td>
</tr>
<tr>
<td>NIHSS2</td>
<td>r=-0.219, P=0.068</td>
<td>r=0.090, P=0.458</td>
</tr>
<tr>
<td>NIHSS3</td>
<td>r=-0.086, P=0.265</td>
<td>r=-0.030, P=0.700</td>
</tr>
</tbody>
</table>

Notes: NIHSS1: stroke group. NIHSS2: post-stroke depression group. NIHSS3: non-PSD group.
Abbreviations: 8-OHdG, 8-Hydroxy-2′-deoxyguanosine; CAT, catalase; NIHSS, National Institutes of Health Stroke Scale.