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**Original Research Article**

# Effect of combined use of Buyang Huanwu decoction and olanzapine on clinical symptoms, neurological function, and degree of dementia in patients with vascular dementia after cerebral ischemic stroke

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## Abstract

***Purpose:*** *To determine the efficacy and safety of Buyang Huanwu Decoction (BHD) + olanzapine in the treatment of vascular dementia (VD) after cerebral ischemic stroke (CIS).*
***Methods:*** *Ninety patients with VD after CIS were assigned to 2 groups: a conventional group treated with olanzapine, and a combination group given olanzapine + BHD. Traditional Chinese medicine (TCM) symptom score was evaluated in each group. Neurological function, degree of dementia, and activities of daily living (ADL) were evaluated using National Institute of Health Stroke Scale (NIHSS), Clinical Dementia Rating (CDR) scale, and ADL scale, respectively. Levels of inflammatory factors, oxidative stress, and neurotrophic factors in peripheral blood were also determined. Middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), and vertebral artery (VA) blood flow velocity (BFV) were assessed. Therapeutic effects and adverse reactions (ARs) were recorded as well.*
***Results:*** *The TCM symptom, NHSS, and CDR scores were decreased in the combination group, while ADL scores were increased ($p < 0.05$). Levels of hs-CRP, IL-6, and malondialdehyde (MDA) also decreased, while IL-10, GPx, SOD, NT3, MCA, ACA, PVA, and VA BFV, and BDNF levels increased ($p < 0.05$). Clinical effectiveness (CE) levels in the conventional and combination groups were 73.3 and 93.3 %, while the incidence of ARs were 11.11 and 6.7 %, respectively ($p < 0.05$).*
***Conclusion:*** *Olanzapine + BHD mitigates clinical symptoms, enhances neurological function, decreases the degree of dementia, and increases ADL in patients with vascular dementia after CIS. Moreover, it improves cerebral blood flow, and it is safe to use. An increase in sample size will be needed to compare the long-term efficacy of olanzapine alone, and that of its combination with BHD in the treatment of VD after CIS.*

***Keywords:*** *Buyang Huanwu Decoction, Olanzapine, Cerebral ischemic stroke, Vascular dementia*



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## INTRODUCTION

Vascular dementia (VD) is cognitive impairment due to hemorrhagic or cerebral ischemic stroke (CIS). Amongst other factors, the etiology of VD is associated with the formation of cerebral atherosclerosis and cerebral artery occlusion [1]. The reported absolute risk of dementia after

stroke varies widely, from 7 % in population-based studies of first-ever stroke in previously non-demented individuals to over 40% in hospital-based studies of recurrent stroke with the inclusion of pre-stroke dementia, according to a systematic review and meta-analysis [2]. The disease is related to the levels of neurotransmitters, blood endothelial factors, and organic brain injury in patients [3]. Clinical symptoms may be reduced using olanzapine. Olanzapine belongs to a class of antipsychotics that inhibit the release of dopamine by binding to dopamine and serotonin receptors, thereby effectively reducing mental symptoms in patients [4]. Single-drug therapy has a significant therapeutic effect, but long-term use induces the production of antibodies and eventually affects the therapeutic effect. In Western medicine, it is believed that VD lesions are related to cerebral hemorrhage, cardiogenic cerebral embolism, small vessel lesions and hemodynamics. Ischemic white matter lesions, stroke and old age are risk factors for VD [5]. The treatment of VD using traditional Chinese medicine has also achieved excellent results. In traditional Chinese medicine (TCM), dementia belongs to a theosophical disease that is closely related to the five viscera and six organs, and the *disorder of seven emotions* is an important factor in the pathogenesis of this disease. Traditional Chinese medicine believes that the main pathogenesis of VD is *accumulation* and *positive decline* which lead to the deficiency and loss of organ function, *qi* and blood s*tasis*, as well as *vein stasis* and *qi* and mechanical obstruction [6]. Therefore, it is recommended that *goose* and blood-activating and *stasis*-removing drugs should be used in the treatment of VD. *Buyang Huanwu* Decoction (BHD) is a *qi*-promoting drug, and it enhances blood circulation [7]. This study investigated the clinical effect of combined use of BHD and olanzapine in the treatment of CIS and VD and analyzed their effects on patients' inflammation response, oxidative stress response, neurotrophic level, and cerebral blood flow state.

## METHODS

### Research subjects

Ninety patients with VD after CIS that were admitted to the Wuhan Wudong Hospital, Hubei Province, China from June 2021 to December 2022 were selected. They were enrolled in line with the following criteria: patients who met the diagnostic criteria of CIS, VD; those with at least one ischemic lesion confirmed with head computed tomography (CT) or magnetic resonance imaging (MRI); patients without cognitive dysfunction before stroke, and who had dementia 3 - 12 months after stroke, with dementia duration of at least 3 months; patients with mild or moderate dementia, as assessed using the Clinical Dementia Rating Scale (CDR), and patients whose families were aware of the study content and signed informed consent.

Patients in the following categories were excluded: those with dementia induced by other factors; those who also had severe hepatic and renal insufficiency; patients with a history of cerebral hemorrhage; those treating drug intolerance or allergy; those with malignant tumor; patients with infectious diseases; patients with other mental diseases, and those who recently received other drug treatments. This research was approved by the Ethical Committee of Wuhan Wudong Hospital (approval no. WWH021) and performed according to the declaration of Helsinki promulgated in 1964 as amended in 1996 [8].

Based on the order of admission, patients were enrolled into a conventional group and a combination group, each with 45 subjects. The conventional group comprised 25 males and 20 females with a mean age of 55.6 ± 2.8 years, and the course of disease (COD) ranged from 4 to 16 months (mean course = 12.6 ± 3.1 months). There were 26 cases of mild dementia and 19 cases of moderate dementia. 19 patients were educated up to junior high school level, 14 patients were educated up to senior high school level, and 12 patients were educated up to junior college status or above. Patients in combination group comprised 23 males and 22 females. They were 40 - 77 years old (mean age = 57.1 ± 3.0 years), and the COD ranged from 4 to 15 months (mean =13.3 ± 3.7). The numbers of patients with mild dementia and moderate dementia were 27 and 18, respectively. There were 16 patients educated up to junior high school level, 15 patients educated up to senior high school level, and 14 patients with junior college education or above. Basic data were comparable in the two groups.

### Treatments

Subjects in conventional group and combination group received routine treatment for lowering blood pressure and blood lipids and anti-platelet aggregation treatment. These included memory training, exercise physiotherapy, and diet adjustment. The memory training involved asking the patients to state their detailed home addresses, birthdays, and telephone numbers of close relatives, helping to establish a simple and feasible schedule of rest, assisting them to know the time of getting up, taking medication, eating

time, and sleeping time so as to strengthen their memory. In the conventional group, the patients were treated with olanzapine (specification: 5 mg x 14, No: H20183500, Qilu Pharmaceutical Co., Ltd.) at an initial dose of 2.5 mg/day. The dose was adjusted according to the actual condition of the patient (maximum dose was not more than 10 mg/day). The treatment lasted for one course of 6 weeks. Patients in the combination group were treated with BHD in addition to olanzapine. The decoction was composed of Astragalus (60 g), Angelica (15 g), Chuanqiang (10 g), Dilong (10 g), Honghua (10 g), red peony (15 g), and Taoren (15 g). The decoction was administered at the rate of 3 doses a day. The BHD was taken warm on an empty stomach, and the treatment course was 6 weeks.

### Indices measured

The TCM symptom score was evaluated before and after treatment. Based on the severity of the main symptoms and secondary symptoms of the patients, ADL was scored according to the *Guidelines for Clinical Research of New Chinese Medicines*. The score ranged from 0 to 3 points, and the sum of the scores was the symptom score. The higher the score, the more serious the symptoms. Neurological function was evaluated before and after treatment using National Institute of Health Stroke Scale (NIHSS). It reflects the degree of damage to neurological function in patients, and the assessment covered 11 items. The score ranged from 0 to 42 points, and the higher the score, the more serious the impairment of neurological function. The activity of daily living scale (ADL) was employed for determination of pre-and post-treatment ADL values. Assessment of ADL scale covered activities such as washing, going up and down stairs, brushing of teeth, and other contents. The score range was 0 - 56 points. The level of score was an indication of ability of subjects to perform ADL.

The CDR scale was applied to score the degree of dementia in patients before and after they were treated. The CDR scale covered memory, orientation, judgment, and problem-solving capacity; work and socialization capacity, family life, hobbies, and capacity for self-care (0 = healthy, 0.5 = suspected dementia, 1 = mild dementia, 2 = moderate dementia, and 3 = severe dementia).

Following 12-h fast pre- and post-treatment, venous blood (2 mL) was taken and centrifuged for 15 min at 3,000 rpm. Serum levels of hs-CRP, IL-6, IL-10, malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx), neurotrophic factors 3 (NT3), and brain-derived neurotrophic factors (BDNF), were measured using ELISA method. Bilateral middle cerebral artery (MCA), ACA, PCA, and VA blood flow velocity (BFV) were determined with Doppler color ultrasound. The clinical efficacy was assessed based on TCM symptom score. When TCM symptom score was decreased by more than 90 %, the patient was deemed cured. When it was decreased by 70 – 90 %, treatment was effective. When it was reduced by 30 – 70 %, treatment was effective. However, if TCM symptom score was reduced by less than 30 %, the treatment was deemed ineffective.

### Statistical analysis

Data were processed using SPSS 20.0. Count data are presented as numbers and percentages (n (%)), and $\chi^2$ test was performed for a two-group comparison. Measurement data are presented as mean ± standard deviation (SD) and were compared with *t*-test. Values of $p < 0.05$ indicated statistically significant differences.

## RESULTS

Figure 1 shows the TCM symptom scores of patients in the conventional and combination groups before and after treatment. the post-treatment primary symptoms, secondary symptoms, and tongue pulse scores of patients in the conventional group and combination group were greatly reduced, with significant differences between the combination group and the conventional group ($p < 0.05$). However, the primary symptoms, minor symptoms, and tongue pulse scores of patients in the combination group were significantly reduced after treatment, relative to the conventional group ($p < 0.05$).

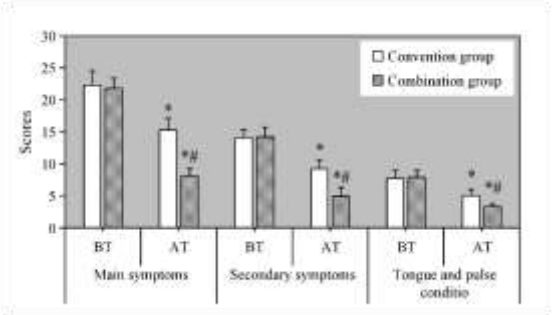


**Figure 1:** TCM symptom score of patients. BT: before treatment; AT: after treatment. *$P < 0.05$, pre-treatment score vs post-treatment score; #$p < 0.05$, combination group vs conventional groups

## Neurological function, degree of dementia, and ADL of patients

Figure 2 shows the differences in NHISS score (2 A), CDR score (2 B), and ADL score (2 C) of patients in both groups before and after they underwent different treatments. Based on the pretreatment scores, the NHISS and CDR scores of all patients were greatly reduced, while the ADL scores were increased ($p < 0.05$). Compared to the conventional group, the NHISS and CDR scores of patients treated with BHD + olanzapine were reduced, while the ADL scores were increased ($p < 0.05$).

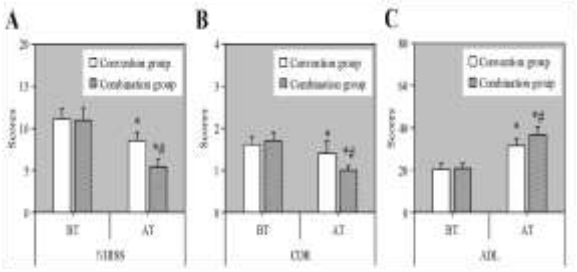


**Figure 2:** Neurological function, degree of dementia, and ADL scores of patients. BT: before treatment; AT: after treatment. *$P < 0.05$, pre-treatment score vs. post-treatment score; $^{\#}p < 0.05$, combination group vs. conventional groups

## Serum levels of inflammation-related indices

The levels of hs-CRP, IL-6, and IL-10 in patients given different treatment drugs are given in Figure 3 A - C, respectively. After treatment, hs-CRP and IL-6 levels decreased, while IL-10 levels increased significantly for all patients, with significant differences from those before treatment ($p < 0.05$). When compared to those given olanzapine only, hs-CRP and IL-6 were significantly reduced, while IL-10 was increased in patients treated with BHD + olanzapine ($p < 0.05$).

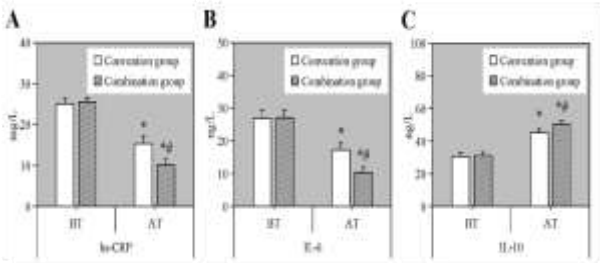


**Figure 3:** Serum levels of inflammation-related indices of patients. *$P < 0.05$, pre-treatment score vs post-treatment score; $^{\#}p < 0.05$, combination group vs conventional groups

## Oxidative stress-related indicators

Serum levels of oxidative stress indices, e.g. MDA, GPx, and SOD of patients before and after treatment with different drugs are shown in Figure 4 A - C, respectively. All patients presented decreased MDA and increased GPx and SOD levels after they were treated ($p < 0.05$). In addition, patients who received BHD + olanzapine had lower MDA levels and higher activities of GPx and SOD, when compared with the pre-treatment levels ($p < 0.05$).

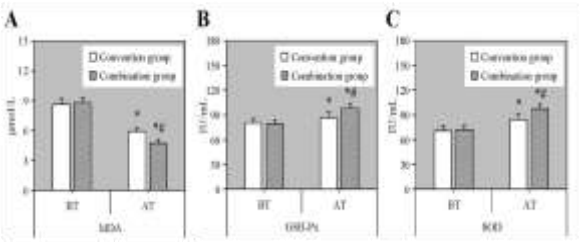


**Figure 4:** Oxidative stress-related indicators in patients. *$P < 0.05$, pre-treatment score vs post-treatment score; $^{\#}p < 0.05$, combination group vs conventional groups

## Pre-treatment and post-treatment levels of neurotrophic indices

The levels of NT3 and BDNF in patients before and after treatment are shown in Figures 5 A and B, respectively. All patients presented up-regulated levels of NT3 and BDNF after treatment, with significant differences between treated and untreated groups ($p < 0.05$). In addition, patients who received BHD + olanzapine had significantly elevated NT3 and BDNF, relative to the pre-treatment levels ($p < 0.05$).

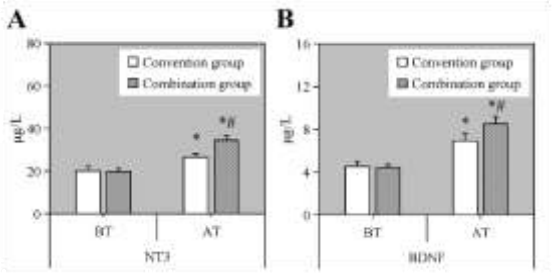


**Figure 5:** Pre-treatment and post-treatment levels of neurotrophic indices of patients. *$P < 0.05$, pre-treatment score vs post-treatment score; $^{\#}p < 0.05$, combination group vs conventional groups

## Brain BFV of patients

The levels of MCA, ACA, PCA, and VA BFV in patients before and after treatment are presented

in Figure 6 A. The levels of the indicators were increased significantly after the patients were treated ($p < 0.05$). In addition, patients who received BHD + olanzapine had higher levels of MCA, ACA, PCA, and VA BFV than untreated patients ($p < 0.05$)

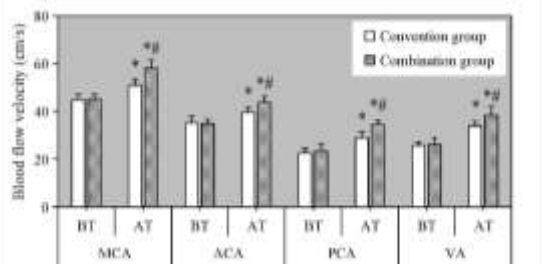


**Figure 6:** Brain levels of MCA, ACA, PCA, and VA BFV in patients before and after treatment. *$P < 0.05$, pre-treatment score vs post-treatment score; #$p < 0.05$, combination group vs conventional groups

### Clinical treatment efficacies

The clinical outcomes of patients in both groups were compared, as presented in Figure 7. In the combination group, the numbers of patients whose treatment outcomes were cured, significantly effective, effective, and ineffective were 13 (28.9 %), 22 (48.9 %), 7 (15.6 %), and 3 (6.7 %), respectively, as shown in Figure 7 A. In the conventional group, the corresponding values were 6 (13.3 %), 16 (35.6 %), 11 (24.4 %), and 12 (26.7 %), respectively (Figure 7 B). Therefore, the total treatment effectiveness was much higher in subjects given BHD + olanzapine than in those who received olanzapine only (93.3 % (42/45) vs 73.3 (33/45); $p < 0.05$).

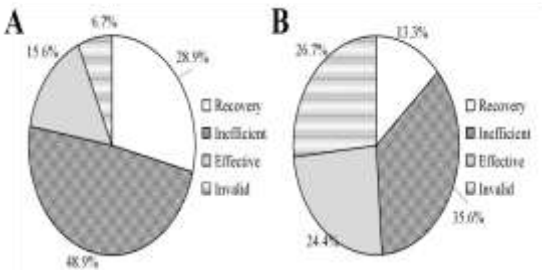


**Figure 7**: Clinical treatment efficacies in patients

### ARs of patients

In the conventional group, there were nausea (1 case), bloating (1 case), constipation (2 cases), and dizziness (1 case), accounting for 11.11 % ARs (5/45). In the combination group, there was abdominal distension (1 case), constipation (1 case) and dizziness (1 case), accounting for 6.7 % ARs (3/45). The incidence of ARs was comparable in subjects who received BHD + olanzapine and those given olanzapine only ($p > 0.05$).

## DISCUSSION

The clinical manifestations of VD patients after stroke are reduced memory and intelligence, but patients still maintain good judgment, integrity, and comprehension over a long period. The disease occurs frequently in the elderly population after stroke due to brain function excitation caused by cerebral artery occlusion, reduction in perfusion volume of brain tissue, and decrease in metabolic capacity, among other factors [9]. Early treatment may effectively reverse the development of VD in patients after stroke, and may at the same time, improve their cognitive function and promote the rehabilitation of neurological function [10]. Clinically, the principle of VD treatment is based on treating primary cerebrovascular diseases, promoting cerebral function, relieving cerebral blood flow, reducing dementia symptoms, and preventing the deterioration of the disease [11]. However, the clinical effect of symptomatic treatment of VD after stroke has certain limitations, and treatment compliance is poor. Therefore, this study was aimed at assessing the effectiveness and safety of olanzapine when used alone and in combination with BHD for treating CIS and VD. The NIHSS scale, CDR scale and ADL scale are often used in clinical assessment of neurological function, degree of dementia and ADL. In this work, after olanzapine treatment, the NIHSS and CDR scores were decreased, while the ADL scores were increased in patients with VD after CIS. Olanzapine is effective in treating positive and negative psychiatric symptoms. In addition, the NIHSS, CDR, and ADL scores of patients with VD after CIS treatment with BHD in combination with olanzapine were superior, relative to subjects who received only olanzapine. This indicated that, compared with olanzapine alone, the combined treatment with BHD improved neurological function, and reduced the degrees of dementia and ADL of patients with middle and posterior VD in the ischemic brain region. This finding is similar to that of Wang *et al* [12].

In patients, VD is often accompanied by changes in the serum levels of associated factors, thereby causing varying degrees of impact on their bodies. Due to ischemic reperfusion injury, patients with VD after CIS have impaired immune function and severe inflammatory reactions. Increased levels of Hs-CRP and IL-6 (pro-inflammatory factors) aggravate nerve cell damage [13]. This study found that olanzapine alone and its combination with BHD reduced the

serum levels of hs-CRP and IL-6 in patients with CIS and VD, but the levels of these inflammatory factors were more significantly reduced in patients with combined treatment. Oxygen free radicals damage the unsaturated fatty acids in the cell membrane of neurons through peroxidation, thereby altering the activity of $Na^+$-$K^+$-ATPase on the cell membrane surface and modifying the expression of n-methyl-D-aspartate receptor, resulting in neuronal damage [14]. It is known that SOD is the first line of defense in biological antioxidant system and the most important member of antioxidant enzyme system. In addition to the effect of delaying aging, SOD is important in anti-tumor, antiinflammation, and immunity. Moreover, GPx is an important peroxide-decomposing enzyme that is widely present in organisms. It uses reduced glutathione (GSH) to reduce toxic hydrogen peroxide ($H_2O_2$) into $H_2O$ and $O_2$, thereby reducing or eliminating the damage caused by peroxides to cells [15]. As a lipid metabolite, MDA reflects the rate and intensity of lipid peroxidation in the body and indirectly reflects the degree of tissue damage caused by free radicals. This work revealed that olanzapine as a single drug, and its combination with BHD reduced serum MDA levels of patients with VD after CIS, and increased the activities of GPx and SOD, with a more significant degree of improvement in patients given combination medication. A decrease in the level of NT3 which protects nerve cells damages neurological function [16]. Studies have shown that BDNF is mainly distributed in hippocampus, amygdala, cortex and hypothalamus, and plays the same role as traditional Chinese medicine in the growth, differentiation, proliferation and nervous system development of neurons [17]. Not only did BDNF play a protective role in neurological function, but it also participated in synaptic plasticity and learning and memory processes. This study indicated that olanzapine (a single drug) and its combination with BHD increased serum concentrations of NT3 and BDNF in subjects with VD after CIS, and the level of neurotrophic factors was increased more significantly in patients given combined drug treatment. The results showed that, when compared with olanzapine alone, the combined treatment with BHD was better at inhibiting the level of inflammation and oxidative stress in patients, and inhibiting injury to neurological function. Brain levels of MCA, ACA, PCA, and VA BFV are important indicators for evaluating cerebral hemodynamics. When the brain tissue of patients is damaged, hemodynamic levels also change. Therefore, the above indicators may be employed for evaluating the disease course and prognosis in patients. Dementia patients present with brain cell death and innervation disorders, in addition to other phenomena. Therefore, patients often have emotional irritability, body stress, and increased blood pressure in blood vessels. At this time, levels of MCA, PCA, and VA BFV are low; cerebral blood perfusion is reduced, nerve cells die, and the behavior of the patients becomes uncontrollable [18]. In this study, MCA, ACA, PCA, and VA BFV were increased in patients with VD after CIS following olanzapine treatment. Olanzapine selectively reduced the neuronal discharge of dopamine in the limbic system, thereby inhibiting dopamine-induced hyperactivity while enhancing the hyperactivity of the acetylcholine system, and ultimately improving the mood of patients. Secondly, the brain levels of MCA, ACA, PCA, and VA BFV of patients with VD after CIS who were treated with BHD in combination with olanzapine, were much higher than those of patients treated with olanzapine alone. These results suggest that BHD + olanzapine mitigated vascular disease, improved local blood circulation, increased the amount of cerebral blood perfusion, and elevated brain energy metabolism, thereby improving cerebral hemodynamics and recovery of neurological function.

### Study limitations

This study only determined the short-term effects of olanzapine single drug and its combination with BHD in treating VD after CIS, without extending the study period and monitoring changes in physical and mental states of patients after discharge.

## CONCLUSION

The use of a combination of olanzapine and BHD in the treatment of patients with VD after CIS has beneficial effect in reducing clinical symptoms and improving cerebral hemodynamics of patients. Moreover, it reduces inflammation and oxidative stress response and promotes the recovery of neurological function. The ADL of patients improves, and clinical efficacy and safety were higher. Therefore, the combination treatment is worthy of clinical application. However, an increase in sample size is needed in the future to compare the long-term efficacy of olanzapine alone, and that of its combination with BHD in the treatment of VD after CIS.

## DECLARATIONS

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***Funding***

None provided.

***Ethical approval***

None provided.

***Availability of data and materials***

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

***Conflict of Interest***

No conflict of interest associated with this work.

***Contribution of Authors***

We declare that this work was performed by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Nian Chen designed the study, supervised the data collection, and analyzed the data. Limin Zhang interpreted the data and prepared the manuscript for publication. Di Wu supervised the data collection, analyzed the data and reviewed the draft of the manuscript.

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