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ORIGINAL RESEARCH

# Relationship between Serum Neurotransmitters and Cognitive Impairment in Adults with Obstructive Sleep Apnea

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**Introduction:** The primary aim of this study was to investigate the serum levels of acetylcholine (Ach), norepinephrine (NE), dopamine (DA), and 5-hydroxytryptamine (5-HT) in two groups: those with obstructive sleep apnea (OSA) and cognitive impairment (CI) and those with OSA but no cognitive impairment (NCI).

**Methods:** A total of 30 adults (CI) and 75 adults (NCI) who completed polysomnography examinations between December 2023 and September 2024 were enrolled in the study. Enzyme-linked immunosorbent assays were used to measure serum levels of Ach, NE, DA, and 5-HT. Correlation and pooled analyses were conducted to assess the relationship between cognitive scores and four serological indicators. Logistic regression was performed to identify risk factors for cognitive impairment.

**Results:** Serum DA levels were higher in the CI group (275.10, 216.73–426.91, pg/mL) than in the NCI group (219.69, 138.46–261.97, pg/mL) ($P < 0.001$). No significant differences were found in serum NE, 5-HT, and Ach levels between the two groups ($P = 0.582$, $P = 0.287$, and $P = 0.715$, respectively). Moreover, the correlation analysis showed a correlation between DA and body mass index, Montreal Cognitive Assessment, average saturated oxygen ($SaO_2$), minimum $SaO_2$, the percentage of oxygen saturation less than 90% (all $P < 0.05$). The area under the receiver operating characteristic curve of DA was 0.732 (95% confidence interval: 0.628–0.836) ($P < 0.001$). Logistic regression analysis revealed a correlation between tonsil size, hypertension, DA, stuffy nose, and cognitive impairment.

**Conclusion:** Serum DA levels were associated with the severity of cognitive impairment in adults diagnosed with OSA and might serve as a potential, objective biomarker for identifying cognitive dysfunction in this population.

**Keywords:** neurotransmitter, acetylcholine, norepinephrine, dopamine, 5-hydroxytryptamine, cognitive dysfunction, obstructive sleep apnea

## Introduction

Obstructive sleep apnea (OSA) is a highly prevalent medical condition, affecting nearly 1 billion people worldwide, with rates exceeding 50% in some countries.[1,2] The disease involves repetitive pharyngeal collapse during sleep. This pharyngeal collapse can be complete (causing apnea) or partial (causing hypopnea). Repeated intermittent hypoxia, hypercapnia and sleep fragmentation in patients with OSA can cause cognitive impairment, cardiovascular and cerebrovascular diseases, metabolic abnormalities and other complications, among which cognitive impairment caused by OSA has been a research hotspot in recent years.[3–5]

The effects of OSA on cognitive functioning, include decreased attention, impaired memory, decreased executive functioning, language deficits, irritability, anxiety or depression, and reduced psychomotor functioning.[3,6,7] Cognitive dysfunction in OSA patients may be related to regional hippocampal volume changes; an increase in the volume suggests inflammation and glial activation and a decrease in volume may be a result of long-term neuronal damage. Intermittent

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hypoxia may play a central role in causing attention, memory and executive function impairment in OSA patients.[8–11] The clinical manifestations of cognitive impairment in patients with OSA are diverse and complex and can be assessed using a wide variety of methods. The commonly used cognitive impairment assessment methods can be categorized into subjective and objective assessments. The former mainly consists of comprehensive cognitive assessment scales, including the Mini-Mental State Examination and the Montreal Cognitive Assessment (MoCA). The latter mainly includes biological markers, quantitative electroencephalogram, magnetic resonance imaging and other neurophysiological tests. Presently, cognitive assessment scales remain the mainstream method used to assess cognitive function. However, individual differences in patient compliance and examiners using these scales can cause subjective errors. Furthermore, completing these scales is time-consuming and labor-intensive and requires assistance from professionals. Consequently, a more objective and convenient measure of neurocognitive function is needed to enable risk and vulnerability stratification during the initial evaluation of snoring and assess cognitive dysfunction in patients with OSA.

Neurotransmitters are endogenously synthesized signaling molecules,[12] which are stored in vesicles at the presynaptic terminal and released into the synaptic gap after an action potential or reaching a gradient potential threshold. Once released, they can elicit physiological responses in postsynaptic or nearby cells.[13] Acetylcholine (Ach) is a neurotransmitter that significantly influences attention, which is essential for working memory because it increases the level of attention required to sustain activity in the presence of distractions.[14–17] Norepinephrine (NE) regulates sleep patterns, attention, and vigilance.[18] Dopamine (DA) plays an important role in the regulation of motor neurons,[19] such as spatial memory functions,[20] motivation, arousal, reward, and pleasure.[21–23] 5-Hydroxytryptamine (5-HT or serotonin) plays a crucial role in regulating the essential elements of our daily lives (eg mood, sleep, social behavior, learning, and appetite).[24,25] To the best of our knowledge, although these four neurotransmitters play an important role in physiological and pathological processes, neurotransmitter levels (Ach, NE, DA, 5-HT) in adults with OSA have not been reported yet.

Therefore, the aim of this study was to investigate serum Ach, NE, DA, and 5-HT levels in adults with OSA and explore their relationship with cognitive dysfunction caused by OSA. The results of this study may provide objective diagnostic blood biomarkers for cognitive dysfunction in adults with OSA.

# Methods

## Study Design and Participants

The study included patients diagnosed with OSA at the Department of Otolaryngology-Head and Neck Surgery of the Second Affiliated Hospital of Xi'an Jiaotong University from December 2023 to September 2024. Written informed consent was obtained from all study participants after a detailed explanation of the study procedures was provided. This study was conducted under the tenets of Declaration of Helsinki. The Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University approved the study (Approval No. 2021001).

The inclusion criteria were as follows: 1. age from 18 to 65 years; 2. diagnosed with OSA established by a polysomnographic study according to the criteria of the American Academy of Sleep Medicine;[26] 3. underwent MoCA and blood examinations; and 4. the presence of complete records. The exclusion criteria were as follows: 1. any genetic syndromes associated with cognitive impairment, or any chronic disease or psychiatric condition; 2. the use of psychotropic or sedative drugs that affect memory or sleep; 3. history, radiological examination or electroencephalogram showing neurological abnormalities; 4. history of vision or hearing impairment; 5. life-threatening sleep apnea; 6. accompanying nasal or throat tumors; 7. other sleep problems, such as insomnia, parasomnia, difficulties with bedtime behavior, restless legs syndrome, or abnormal movements during sleep; and 8. any previous treatment for OSA.

## Data Collection and Definitions

The following data were recorded: sex, age, the duration of snoring, whether apnea was witnessed, nasal congestion, daytime sleepiness, Friedman stage, body mass index (BMI), smoking, drinking, accompanying hypertension, Epworth Sleepiness Scale (ESS) value (All assessments were conducted by board-certified otolaryngologists using a validated Mandarin version. The simplified Chinese version of the scale was validated through standardized translation, and released it publicly by Professor Li Jinrang's team).,[27,28] and tonsil size. Tonsil size was graded from 0 to 4. Tonsil size 0

indicated that the tonsils were restricted to the tonsil fossae. Tonsil size 1 indicated that the tonsils were hidden within the pillars. Tonsil size 2, indicated that the tonsils extended to the pillars. Tonsil size 3 meant that the tonsils were situated beyond the pillars but did not reach the midline, and tonsil size 4, indicated that the tonsils extended to the midline.[29–31] The data were assessed by two attending otolaryngologists with over 3 years of work experience.

## Polysomnography

All patients underwent full-overnight in-laboratory (or in-home) polysomnography (PSG). 35 patients completed PSG at home, while 70 patients completed it in the hospital. The PSG results were collected, including the apnea-hypopnea index (AHI), average oxygen saturation ($SaO_2$) at night, minimum $SaO_2$ at night, and the percentage of oxygen saturation less than 90%. The AHI was defined as the number of apneas and hypopneas per hour of total sleeping time. The obtained PSG data were scored according to the American Academy of Sleep Medicine guidelines.[26] OSA was diagnosed as an AHI of $\geq 5$ events per hour obtained by PSG.[2] PSG was assessed by two sleep specialists.

## Cognitive Function

MoCA (Chinese version)[32,33] was used to assess the participants' cognitive functions, including visuospatial and executive functions, naming, attention, language, abstraction, memory, and orientation.[34] The maximum score was 30, and with higher scores indicating better cognitive function. A total MoCA score of $< 26$ indicated cognitive impairment.[35] The assessment was conducted face-to-face by an experienced psychiatrist following the guidelines and protocols and took approximately 30 minutes.

## Serum Sample Preparation

Venous blood samples were collected between 6:00 and 7:00 am after a 12-h overnight fast, and then added to a sterile, enzyme-free test tube. After blood collection, allow the sample to stand at room temperature for 1 hour. The serum was then extracted by centrifuging for 15 min at 3000 rpm at 4°C. Serum was used to determine neurotransmitter levels. The samples were stored at –80°C until further use. Serum Ach (E-EL-0081, Elabscience), DA (JL13292, Jonln), NE (E-EL-0047, Elabscience) and 5-HT (E-EL-0033, Elabscience) concentrations were quantified using enzyme-linked immunosorbent assay kits. Each reaction was performed in triplicate.

## Statistical Data Analysis

An Excel database was established and imported into IBM SPSS Statistics 25 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Software Inc, San Diego, CA, USA) for data analysis. The distribution of the continuous data was tested using the Kolmogorov–Smirnov test. Quantitative data with normal distribution are expressed as the mean ± standard deviation, and comparisons between groups were performed using the Student's *t*-test. Quantitative data with non-normal distribution are presented as M (P25, P75) and analyzed using non-parametric tests between groups. Correlation analysis was performed using the Spearman method. Categorical variables are presented as n (%) and analyzed using the Chi-squared test or Fisher' s exact test. Receiver operating characteristic (ROC) were used to evaluate the diagnostic value of DA. A logistic regression model was used to assess the factors affecting cognitive impairment.

# Results

## Patient Characteristics

A total of 150 adult patients were diagnosed with OSA at our center from December 2023 to September 2024. Thirty-eight patients were excluded from the study for various reasons, as shown in the detailed patient flowchart in Figure 1. Following the review of the available serum samples, a total of 105 patients were included in the final analysis.

Table 1 summarizes the demographic and clinical characteristics of the group. The proportions of hypertensive patients with OSA and cognitive impairment group (CI) and OSA without cognitive impairment (NCI) were significantly different ($P < 0.05$). No significant differences were found in age, sex, BMI, snoring course, obstructive apnea, stuffy

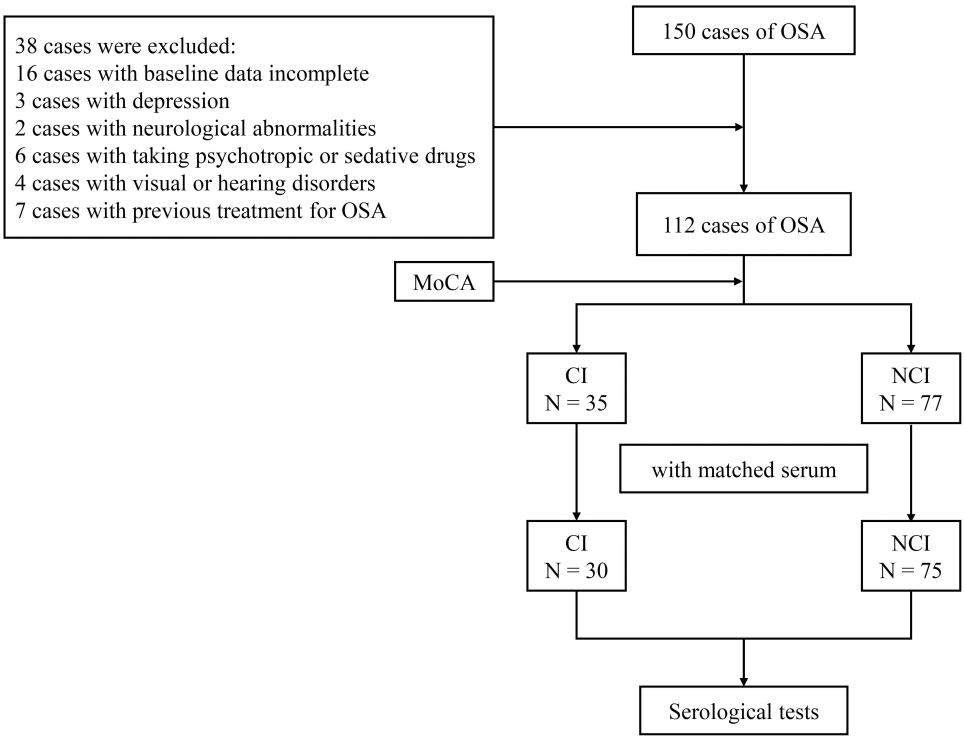


**Figure 1** Summary of patient and exclusion.
**Abbreviations**: OSA, Obstructive sleep apnea; CI, OSA with cognitive impairment; NCI, OSA without cognitive impairment.

nose, excessive daytime sleepiness, tonsil size, Friedman clinical stage, Epworth sleepiness scale, smoking, and drinking between the two groups. Table 2 shows a retrospective analysis of the included patients with OSA and hypertension. Thirty-three hypertensive patients were included in this study: 15 in the CI group and 18 in the NCI group. The data review revealed that 13 of 15 patients in the CI group and 12 of 18 in the NCI group received regular antihypertensive therapy, and long-term monitoring showed that blood pressure was well controlled. A total of 25 patients also had a history of hypertension shorter than their OSA history (CI (11/15); NCI (14/18)). Table 3 shows the PSG results. No

**Table 1** Demographic Characteristics of the Different Groups

| Characteristics | CI n=30 | NCI n=75 | *P* value |
|---|---|---|---|
| Age (Year)[a] | 41.03±8.72 | 37.65±8.31 | 0.066 |
| Sex (Male/female, n)[b] | 30 (24/6) | 75(69/6) | 0.160 |
| BMI (Kg/m$^2$)[a] | 28.51±3.89 | 27.62±3.62 | 0.267 |
| Snoring course (Years)[c] | 5(3–10) | 7(3–10) | 0.874 |
| Obstructive apnea (n)[b] | 27 | 62 | 0.520 |
| Stuffy nose (n)[b] | 8 | 10 | 0.101 |
| Excessive daytime sleepiness (n)[b] | 19 | 40 | 0.351 |
| Tonsil size (n)[b] | | | 0.095 |
| 0 | 3 | 1 | |
| 1 | 8 | 12 | |
| 2 | 8 | 26 | |
| 3 | 11 | 36 | |
| 4 | 0 | 0 | |

(*Continued*)

**Table 1** (Continued).

| Characteristics | CI n=30 | NCI n=75 | *P* value |
|---|---|---|---|
| Friedman Clinical Stage (n)[b] | | | 0.563 |
| 1 | 4 | 14 | |
| 2 | 9 | 27 | |
| 3 | 17 | 34 | |
| ESS[a] | 12.03±6.27 | 11.49±5.58 | 0.666 |
| Smoking (n)[b] | 14 | 41 | 0.458 |
| Drinking (n)[b] | 12 | 41 | 0.174 |
| Hypertension (n)[b] | 15 | 18 | < 0.05 |

**Notes**: [a]The Student's *t*-test. [b]The Chi-squared test or Fisher' s exact test. [c]Non-parametric tests.
**Abbreviations**: OSA, Obstructive sleep apnea; CI, OSA with cognitive impairment; NCI, OSA without cognitive impairment; BMI, Body mass index; ESS, Epworth sleepiness scale.

**Table 2** Retrospective Analysis of the Patients Combined Hypertension in CI and NCI

| Characteristics | CI n=15 | NCI n=18 |
|---|---|---|
| Antihypertensive therapy | 13 | 12 |
| Shorter history of hypertension | 11 | 14 |

**Abbreviations**: CI, OSA with cognitive impairment; NCI, OSA without cognitive impairment.

**Table 3** Comparisons of PSG Characteristics of the CI and NCI Patients

| Characteristics | CI n=30 | NCI n=75 | *P* value |
|---|---|---|---|
| AHI[a] | 68.80(51.88–77.47) | 69.16(48–77.20) | 0.771 |
| Average $SaO_2$[a] | 89(86–93) | 91(88–93) | 0.431 |
| Minimum $SaO_2$[b] | 68.10±10 | 67.61±8.90 | 0.808 |
| The percentage of oxygen saturation less than 90%[a] | 28.95(5.20–50.40) | 30.8(11.70–49.80) | 0.544 |

**Notes**: [a]Non-parametric tests. [b]The Student's *t*-test.
**Abbreviations**: OSA, Obstructive sleep apnea; CI, OSA with cognitive impairment; NCI, OSA without cognitive impairment; $SaO_2$, Oxygen saturation; AHI, Apnea-hypopnea index; Average $SaO_2$, mean oxygen saturation during sleep; Minimum $SaO_2$, minimum oxygen saturation during sleep.

significant differences were found in PSG characteristics. Table 4 shows the cognitive test scores. Apart from total MoCA scores, cognitive scores were lower in the CI group than in the NCI group across all tested fields.

## Serum Ach, 5-HT, DA, and NE Levels

Serum DA levels were higher in the CI group (275.10, 216.73–426.91, pg/mL) than in the NCI group (219.69, 138.46–261.97, pg/mL) ($P < 0.001$) (Figure 2). No significant differences were found in serum NE,5-HT, and Ach levels between the two groups ($P = 0.582$, $P = 0.287$, and $P = 0.715$, respectively).

## Correlations between Ach, 5-HT, DA, NE and Clinical Parameters

The correlation analysis showed a correlation between DA and BMI, MoCA, average $SaO_2$, minimum $SaO_2$, and the percentage of oxygen saturation less than 90% (r = 0.250, $P < 0.01$; r = –0.297, $P < 0.01$; r = –0.265, $P < 0.01$;


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**Table 4** Cognitive and Behavioral Function Tests Between Groups

| Characteristics | CI n=30 | NCI n=75 | *P* value |
|---|---|---|---|
| MoCA[a] | 23.5(21–25) | 28(27–28) | < 0.001 |
| VEF[a] | 4(3–4) | 5(5–5) | < 0.001 |
| Naming[a] | 3(2.24–3) | 3(3–3) | < 0.001 |
| Attention[a] | 6(5–6) | 6(6–6) | < 0.05 |
| Language[a] | 2(1–2) | 2(2–3) | < 0.001 |
| Memory[a] | 2(1–3) | 4(3–5) | < 0.001 |
| Abstraction[a] | 1(1–2) | 2(2–2) | < 0.001 |
| Orientation[a] | 6(5.87–6) | 6(6–6) | < 0.05 |

**Note**: [a]Non-parametric tests.
**Abbreviations**: OSA, Obstructive sleep apnea; CI, OSA with cognitive impairment; NCI, OSA without cognitive impairment; MoCA, Montreal Cognitive Assessment; VEF, Visuospatial and executive functions.

r = –0.216, $P < 0.05$; and r = 0.223, $P < 0.05$, respectively). Serum DA levels were negatively correlated with visuospatial and executive functions and memory (r = –0.340, $P < 0.001$; r = –0.322, $P < 0.01$, respectively) (Figure 3 and Table 5). It also revealed that serum NE levels were correlated with a stuffy nose and excessive daytime sleepiness (r = –0.214, $P < 0.05$; r = –0.220, $P < 0.05$, respectively). A correlation was also between 5-HT and excessive daytime sleepiness (r = –0.214, $P < 0.05$). Furthermore, a negative correlation was observed between Ach and hypertension (r = –0.222, $P < 0.023$).

## Diagnostic Performance of DA Levels

Serum DA levels could discriminate between CI and NCI patients with an area under the curve (AUC) of 0.732 (95% confidence interval: 0.628–0.836) ($P < 0.001$) and a maximal Youden index value of 0.347 (Figure 4). Using a DA cutoff value of 196.935 pg/mL resulted in 93.3% sensitivity and 58.7% specificity (Table 6). We utilized tonsil size, combined hypertension, serum DA levels, age, BMI, stuffy nose, excessive daytime sleepiness, and snoring course, to establish a logistic regression model. Probability of cognitive impairment for each patient were calculated using the following model formula: logit(P) = −3.0039 + 0.0588 × Age (years) - 0.1079 × BMI (kg/m²) + 0.055 × Snoring course (years) + 1.3233 × stuffy nose (0 = absent; 1 = present) + 0.3817 × excessive daytime sleepiness (0 = absent; 1 = present) - 0.6631 × Tonsil size (grade 0–4) + 1.5663 × Hypertension (0 = normotensive; 1 = hypertensive) + 0.01 × serum DA level (pg/mL). The AUC of this model is 0.845 with 60% sensitivity and 94.7% specificity, which is higher than that of DA alone (Figure 4) (Table 6).

## Analysis of Factors Influencing Cognitive Impairment in Participants

Logistic regression analysis was performed to analyze the factors influencing participants' cognitive impairment (Table 7). The results showed an association between tonsil size, hypertension, DA and cognitive impairment tonsil size was recognized as a protective factor against cognitive impairment (odds ratio (OR) = 0.515, 95% confidence interval: 0.271–0.924). Patients with high blood pressure had a higher risk of cognitive impairment than those without hypertension (OR = 4.789, 95% confidence interval: 1.440–17.610). Additionally, participants with high DA levels had significantly higher odds of developing cognitive impairment (OR = 1.01, 95% confidence interval: 1.005–1.016).

# Discussion

Many studies have shown that OSA causes cognitive impairment. In this study, we looked for an easily available objective marker to accurately assess the cognitive status of patients with OSA. Studies have shown that abnormal neurotransmitter levels are associated with various neuropsychiatric disorders, such as schizophrenia and depression,[36,37]

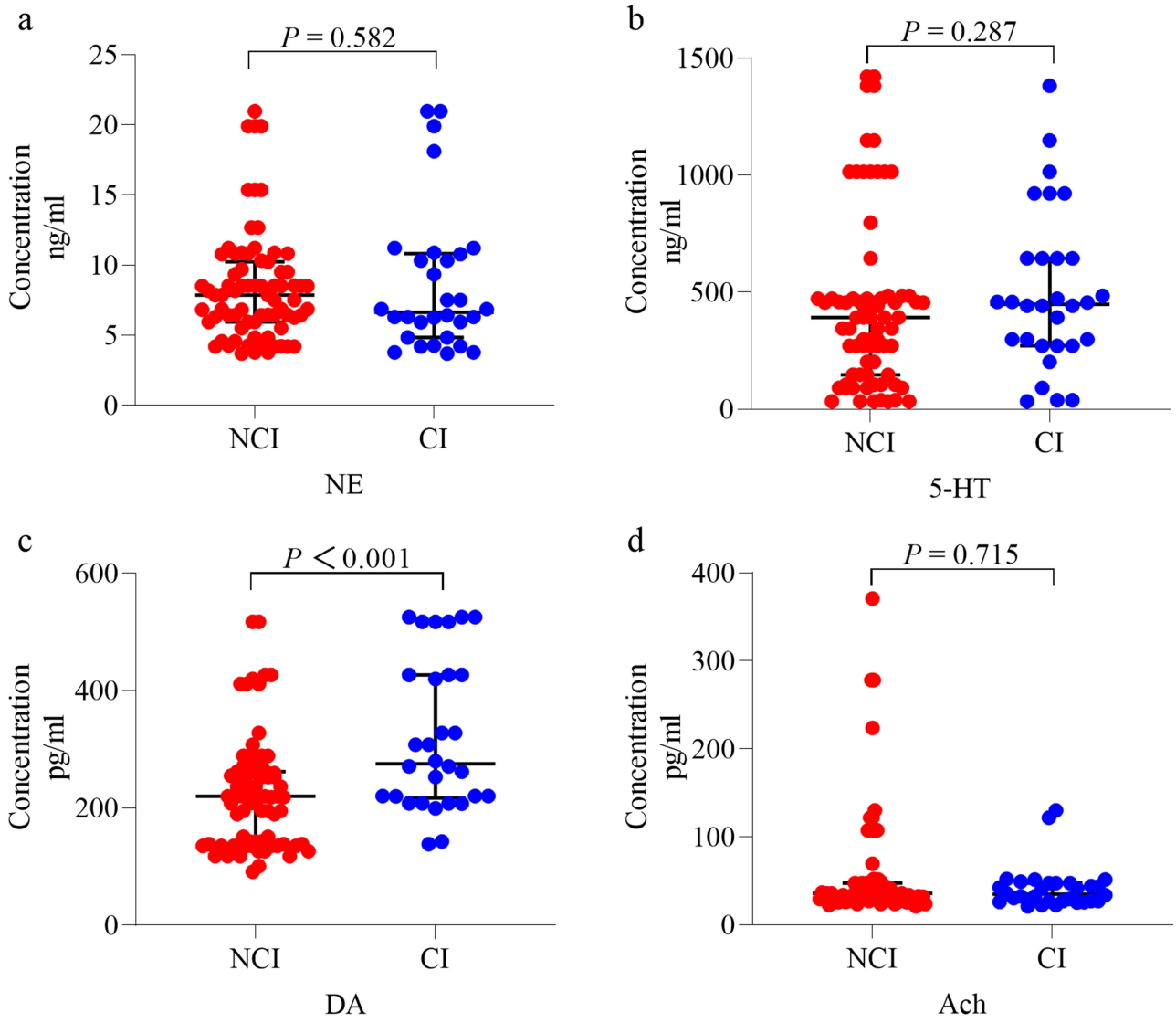


**Figure 2** Comparison of serum Acetylcholine (Ach), Norepinephrine (NE), Dopamine (DA) and 5-Hydroxytryptamine (5-HT) levels between the OSA with cognitive impairment group (CI) and OSA without cognitive impairment (NCI). (**a**) There were no significant differences in serum NE levels between the two groups ($P = 0.582$). (**b**) There were no significant differences in serum 5-HT levels between the two groups ($P = 0.287$). (**c**) The serum DA levels were higher in the CI group (275.10, 216.73–426.91, pg/mL) compared with the NCI group (219.69, 138.46–261.97, pg/mL) ($P < 0.001$). (**d**) There were no significant differences in serum Ach levels between the two groups ($P = 0.715$).
**Abbreviations**: DA, Dopamine; NE, Norepinephrine; 5-HT, 5-Hydroxytryptamine; Ach, Acetylcholine. CI, OSA with cognitive impairment; NCI, OSA without cognitive impairment.

however, neurotransmitters for OSA have not been reported. Therefore, this study aimed to investigate the serum levels of Ach, 5-HT, DA, and NE in patients with OSA with or without cognitive impairment and explore their relationship with cognitive dysfunction potentially caused by OSA to find potentially objective and convenient biomarkers for cognitive impairment related to OSA.

The demographic and clinical characteristics of the groups showed that the percentage of patients with hypertension was higher in the CI group than in the NCI group. First, chronic hypertension continually challenges the structural and functional integrity of the cerebrovascular system, leading to microvascular rarefaction and dysfunction, as well as neurovascular uncoupling, which typically decreases cerebral blood supply.[38,39] Second, hemodynamic cerebral blood flow dysregulation and blood-brain barrier damage disrupt homeostasis in the brain microenvironment. However, its progression and mechanistic association with cognitive decline remain to be determined.[40–42] Several observational studies reported that antihypertensive medication use was associated with less cognitive decline.[43,44] Therefore, we

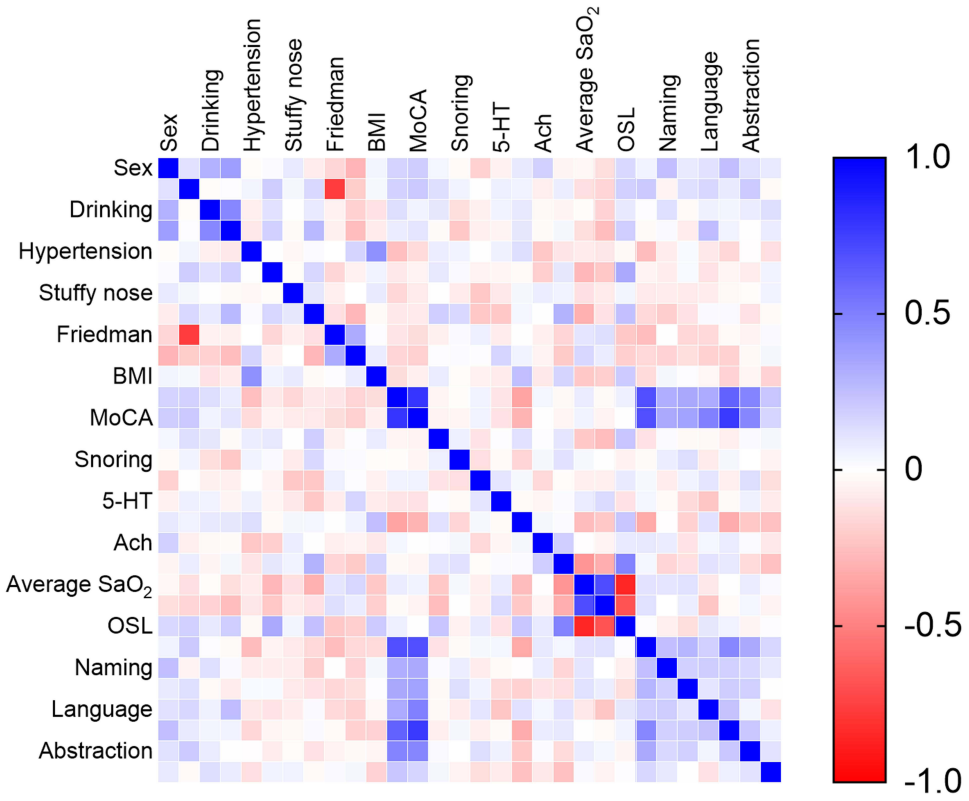


**Figure 3** Multivariate correlations between baseline characteristics and neurotransmitters. The numerical value of each cell is the Spearman correlation coefficient. The baseline (r) value (white) is 0, the maximum value (blue) is 1, the minimum value (red) is –1.
**Abbreviations**: BMI, Body mass index; 5-HT, 5-Hydroxytryptamine; Ach, Acetylcholine; Average $SaO_2$, mean oxygen saturation during sleep; OSL, the percentage of oxygen saturation less than 90%.

suspect that both hypertension and OSA may affect the cognitive status of the study participants. Thirty-three hypertensive patients were included in this study, of whom 25 received antihypertensive treatment, and blood pressure was well controlled through long-term monitoring. Additionally, 25 patients had a history of hypertension shorter than their OSA history, so we could exclude the influence of hypertension. Therefore, we considered that the most likely etiology of cognitive impairment was OSA.

In the present study, no significant differences were seen in PSG characteristics between the two groups. All participants were diagnosed with OSA, so no difference in PSG results between the two groups was expected. However, except for differences in total MoCA scores between the two groups, the cognitive scores of the CI group

**Table 5** Correlation Analysis Between Serum DA Levels and Other Parameters

| **Variables** | **DA levels** | |
|---|---|---|
| | **Spearman Correlation** | ***P* value** |
| BMI | 0.250 | < 0.05 |
| Average $SaO_2$ | –0.265 | < 0.01 |
| Minimum $SaO_2$ | –0.216 | < 0.05 |
| The percentage of oxygen saturation less than 90% | 0.223 | < 0.05 |
| MoCA | –0.297 | < 0.01 |
| VEF | –0.340 | < 0.001 |
| Memory | –0.322 | < 0.01 |

**Abbreviations**: DA, Dopamine; BMI, Body mass index; MoCA, Montreal Cognitive Assessment; $SaO_2$, Oxygen saturation; Average $SaO_2$, Mean oxygen saturation during sleep; Minimum $SaO_2$, Minimum oxygen saturation during sleep; VEF, Visuospatial and executive functions.

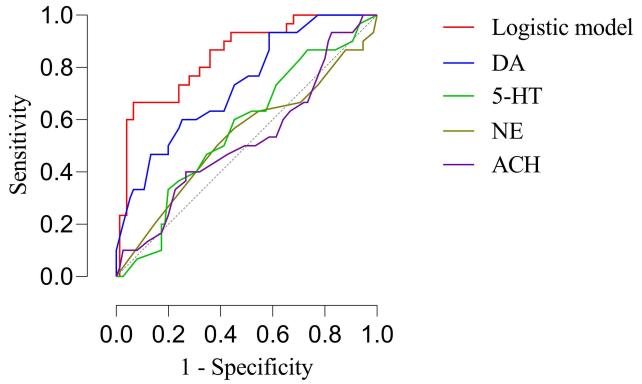


**Figure 4** Diagnostic performance of Dopamine (DA). Area under the curve (AUC) = 0.732 (95% confidence interval: 0.628–0.836), *P* < 0.001. Diagnostic performance of logistic regression model. Area under the curve (AUC) = 0.845 (95% confidence interval: 0.763–0.927), *P* < 0.001.
**Abbreviations**: DA, Dopamine; NE, Norepinephrine; 5-HT, 5-Hydroxytryptamine; Ach, Acetylcholine.

were lower than those of the NCI group across all tested fields, which is consistent with the general trend reported in published studies; however, some details were different. Numerous studies have shown that neurocognitive impairment is a common complication in patients with OSA, including declines in executive function, attention, verbal/visual long-term memory, visuospatial/constructive abilities, and information processing. In contrast, language, psychomotor function, and short-term memory are less likely to be affected.[45–49] However, our findings showed that scores for naming, language, memory, abstraction, and orientation were significantly lower in the CI group than in the NCI group. We speculated that

**Table 6** Diagnostic Performance of Dopamine (DA)

| Variables | Cutoff (pg/mL) | AUC | *P* value | Sensitivity | Specificity | Youden Index |
|---|---|---|---|---|---|---|
| DA | 196.935 | 0.732 | < 0.001 | 0.933 | 0.587 | 0.347 |
| NE | – | 0.466 | 0.583 | – | – | – |
| 5-HT | – | 0.567 | 0.287 | – | – | – |
| Ach | – | 0.477 | 0.715 | – | – | – |
| Logistic model | – | 0.845 | < 0.001 | 0.6000 | 0.947 | 0.547 |

**Abbreviations**: DA, Dopamine; NE, Norepinephrine; 5-HT, 5-Hydroxytryptamine; Ach, Acetylcholine.

**Table 7** Univariate and Multivariate Logistic Regression Analysis for the Risk Factors of Cognitive Impairment

| Variables | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| Age (older vs younger) | 1.048 (0.997–1.105) | 0.070 | 1.061 (0.991–1.139) | 0.092 |
| Sex (male vs female) | 0.348 (0.099–1.209) | 0.091 | | |
| BMI (higher vs lower) | 1.067 (0.952–1.201) | 0.267 | 0.898 (0.756–1.053) | 0.196 |
| Snoring course (longer vs shorter) | 1.010 (0.927–1.098) | 0.817 | 1.057 (0.950–1.176) | 0.307 |
| Obstructive apnea (yes vs No) | 1.887 (0.553–8.711) | 0.351 | | |
| Stuffy nose (yes vs No) | 2.364 (0.811–6.763) | 0.108 | 3.756 (0.950–15.930) | 0.062 |
| Excessive daytime sleepiness (yes vs No) | 1.511 (0.640–3.695) | 0.352 | 1.465 (0.484–4.507) | 0.498 |
| Tonsil size (larger vs smaller) | 0.603 (0.367–0.974) | 0.041 | 0.515 (0.271–0.924) | 0.032 |
| Friedman Clinical Stage (later vs earlier) | 1.363 (0.767–2.529) | 0.304 | | |
| ESS (higher vs lower) | 1.017 (0.944–1.096) | 0.663 | | |
| Smoking (yes vs No) | 0.726 (0.307–1.696) | 0.459 | | |
| Drinking (yes vs No) | 0.553 (0.229–1.296) | 0.177 | | |

(*Continued*)


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**Table 7** (Continued).

| Variables | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| Hypertension (yes vs No) | 3.167 (1.304–7.820) | 0.011 | 4.789 (1.440–17.610) | 0.013 |
| AHI (higher vs lower) | 1.002 (0.984–1.022) | 0.818 | | |
| Average $SaO_2$ (higher vs lower) | 0.958 (0.870–1.056) | 0.376 | | |
| Minimum $SaO_2$ (higher vs lower) | 1.006 (0.960–1.054) | 0.805 | | |
| Percentage of $SaO_2$ less than 90% (higher vs lower) | 0.995 (0.976–1.014) | 0.633 | | |
| DA (higher vs lower) | 1.007 (1.004–1.012) | < 0.001 | 1.010 (1.005–1.016) | < 0.001 |
| NE (higher vs lower) | 1.008 (0.909–1.109) | 0.879 | | |
| 5-HT (higher vs lower) | 1.000 (0.999–1.002) | 0.478 | | |
| Ach (higher vs lower) | 0.993 (0.977–1.002) | 0.240 | | |

**Abbreviations**: BMI, Body mass index; ESS, Epworth sleepiness scale; $SaO_2$, Oxygen saturation; AHI, Apnea-hypopnea index; Average $SaO_2$, mean oxygen saturation during sleep; Minimum $SaO_2$, minimum oxygen saturation during sleep; DA, Dopamine; NE, Norepinephrine; 5-HT, 5-Hydroxytryptamine; Ach, Acetylcholine.

this might be because the participants included in this study were hospitalized and scheduled for surgical treatment due to tonsil hypertrophy, pharyngeal stenosis, or other organic conditions. These patients had more severe OSA symptoms than outpatients, indicating selection bias.

Various clinical studies have shown abnormal levels of 5-HT, DA, Ach and NE in patients with psychiatric[36,50,51] and neurodegenerative disorders.[52,53] However, no studies have shown a correlation between 5-HT, DA, Ach, NE, OSA, and cognitive impairment. Our results showed that serum DA levels were higher in the CI group than in the NCI group, while there were no differences in the other three indicators between the two groups. Speranza et al[54] showed that DA is a key neurotransmitter involved in multiple physiological functions, including motor control, the modulation of affective and emotional states, reward mechanisms, the reinforcement of behavior, and selected higher cognitive functions. Our research findings, showed different DA levels in the CI group compared with the NCI group, leading us to consider that OSA could influence serum DA levels. Currently, dopamine theory is a major focus of research regarding the pathogenesis of schizophrenia. It is believed that abnormal dopamine release and dysfunctional dopamine receptor activity may underpin the neurobiological basis of schizophrenia symptoms. However, significant manifestations of schizophrenia include dysfunction in cognitive, emotional, behavioral, and thought processes.[55,56] We are curious about whether we might be able to connect this to our study. Existing research shows that the dopamine 3 (D3) receptor is linked to mood, exercise, reward-seeking and cognitive function.[57–59] Many scholars have proposed that excessive activation of D3 receptor by dopamine increase or abnormal activity of D3 receptor may cause cognitive impairment. However, they were all indirectly verified by animal experiments or D3 receptor antagonists. For example, Glickstein et al showed that D3 receptor knockout mice exhibited better levels of cognition than wild-type mice, including selective attention, aversion/correlation learning, spatial memory, and executive function.[60] Therefore, we speculated that the increase in dopamine secretion caused by OSA and excessive activation of the D3 receptor leads to cognitive dysfunction. Thus, we propose that a D3 receptor antagonist can be used to treat cognitive impairment in OSA patients. However, this must be verified by subsequent animal modeling experiments with large sample sizes.

In this study, a negative correlation was found between DA and MoCA, mainly the score of visuospatial and executive functions and memory scores, indicating that the higher the serum DA level, the lower the cognitive assessment score, suggesting that DA levels represent the cognitive status evaluated by the MoCA. DA levels might reflect the severity of cognitive dysfunction in adults with OSA. At the same time, the correlation analysis showed a positive correlation between DA and BMI. The patients were diagnosed as having obesity according to their BMI. Together with previous reports, obesity is the most important risk factor for OSA, and at least 70% of patients are obese.[61–63] Ling-Yi Wang et al[64] investigated the effect of obesity on neurocognitive dysfunction, significantly delayed reaction times in the psychomotor vigilance task, and a decrease in working memory in patients with OSA. Their findings are consistent with ours, where higher serum DA levels and higher BMIs were associated with more severe cognitive

impairment. The results also showed that DA levels were negatively correlated with PSG parameters, including average $SaO_2$ and minimum $SaO_2$, and were positively correlated with the percentage of oxygen saturation less than 90%. These results indicate that the higher serum DA level, the more severe the hypoxia. Hypoxia has been investigated as a cause of brain injury, and chronic intermittent hypoxia is one of the main pathophysiological mechanisms of OSA.[65–69] Our research findings showed that DA levels may correlate with the severity of hypoxia in adults with OSA. This relationship could further indicate the extent of craniocerebral injury, thereby providing a more accurate assessment of cognitive impairment.

Serological tests are relatively inexpensive, fast, and accessible, and the development of new serological biomarkers is very meaningful for distinguishing patients with OSA and cognitive dysfunction from those with OSA but no cognitive impairment. The results of this study showed that the AUC of DA was 0.732 (0.628–0.836). To further enhance the predictive ability for cognitive impairment in OSA patients, we utilized the three independent factors mentioned above (tonsil size, combined hypertension, and serum DA levels) along with five important clinical symptoms or signs that are easily accessible: age, BMI, stuffy nose, excessive daytime sleepiness, and snoring course, to establish a logistic regression model. The AUC of this model is 0.845, which is higher than that of DA alone.

The logistic regression analysis results showed an association between tonsil size, hypertension, DA, and intellectual status. Smaller tonsil size increased the risk of cognitive impairment. However, our findings conflict with current research. Jara et al found that tonsil size was strongly associated with AHI.[70] At the same time, evidence from multiple population-based cohorts indicated that the severity of OSA was associated with the degree of cognitive function.[71] We have not yet identified the reasons for the discrepancies in the results, and further validation with a larger sample size is required. Chronic hypertension typically decreases cerebral blood supply, so this may explain why hypertension increases the risk of cognitive impairment.

Numerous clinical studies have demonstrated that abnormal levels of neurotransmitters are associated with psychiatric and neurodegenerative disorders. Patients with all of these diseases show varying degrees of cognitive function decline. Cognitive dysfunction in patients with OSA has caused widespread anxiety and attracted extensive research. However, no studies have yet examined their correlation. To our knowledge, the current study is the first to assess the relationship between cognitive status and serum DA, NE, 5-HT, and Ach levels in adults with OSA. In the future, we aim to assess serum DA levels in OSA patients to help screen for those who may have cognitive impairment. Based on clinical symptoms and signs, including tonsil size, presence of hypertension, age, BMI, stuffy nose, excessive daytime sleepiness, and snoring course, we have constructed a formula to calculate a score. A threshold is obtained according to numerous experimental studies to evaluate whether a patient has cognitive impairment and to assess the severity of that impairment. In addition, we have also proposed the use of a D3 receptor antagonist to treat cognitive impairment in patients with OSA for the first time. This suggestion requires thorough validation using extensive animal modeling experiments. Nonetheless, the present study has some limitations. First, the sample size was relatively small, especially the number of women, and we did not include children. Future prospective large-scale, multicenter, hospital-community studies are needed to assess whether DA levels can reflect the degree of cognitive dysfunction and whether they can be used as a reliable predictor of cognitive dysfunction in adults with OSA. At the same time, the sample sizes of the CI and NCI groups are not well balanced, differences in group sizes may have influenced the results. The proportion of patients with cognitive impairment needs to be increased further. To better analyze neurotransmitter levels and determine whether the observed changes are specific to patients with OSA and associated cognitive impairment or are general features of OSA, it is essential to include a healthy control group without OSA in a follow-up study. Second, in this study, we included only patients who were hospitalized and scheduled for surgical treatment, and whether our results could be used for patients who accepted other treatments, such as continuous positive airway pressure, positional therapy and weight loss remains to be determined. Third, only the MoCA assessment scale was used to assess cognitive function, and future studies are necessary to explore the relationships between serum DA levels and specific areas of cognitive impairment in adults diagnosed with OSA by using a more comprehensive cognitive assessment system. Fourth, 35 patients completed PSG at home, while 70 patients completed it in the hospital. Changes in the environment can impact sleep state; therefore, it is essential to standardize the PSG completion site and eliminate any influencing factors in future large-scale experiments.

## Conclusions

Serum DA levels were elevated in adults with cognitive impairment and OSA compared with adults with OSA but no cognitive impairment. Serum levels of DA were correlated with total MoCA scores, visuospatial and executive functions and memory. Thus, DA levels might reflect the severity of cognitive dysfunction in adults with OSA and have the potential to become a new noninvasive, objective marker to identify cognitive dysfunction in patients with OSA.

## Data Sharing Statement

Research data are not publicly available but can be obtained from the corresponding author on request after approval from the institutional review boards of all participating institutions.

## Consent Statement and Ethics Approval

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (approval no.2021001). The procedures used in this study adhered to the tenets of the Declaration of Helsinki.

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## Author Contributions

Xiaoyong Ren and Yewen Shi: Conceptualization, Resources, Supervision, Funding acquisition, Project administration and Writing – review & editing. Fangli Yang: Software, Data curation, Formal analysis, Validation, Investigation, Methodology, and Writing – original draft. Simin Zhu: Software, Data curation, Visualization and Writing – original draft. Xinru Lv, Yanuo Zhou, Zitong Wang, Chendi Lu and Zihan Xia: Data curation, Investigation and Writing – original draft. Jin Hou and Jingguo Chen: Methodology and Writing – review & editing. Haiqin Liu, Jing Yan and Hui Lv: Investigation, Visualization, Project administration and Writing – review & editing. All authors drafted or written, or substantially revised or critically reviewed the article, agreed on the journal to which the article will be submitted, agreed to take responsibility and be accountable for the contents of the article.

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## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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