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CIRCULATING NERVE GROWTH FACTOR AS A NEUROIMMUNE BIOMARKER IN FIRST-EPISODE MAJOR DEPRESSIVE DISORDER: INTEGRATIVE ANALYSIS OF SERUM LEVELS AND NGF ALA273VAL (RS6330) POLYMORPHISM

FAKTOR RASTA CIRKULIŠUĆIH NERAVA KAO NEUROIMUNI BIOMARKER U PRVOJ EPIZODI VELIKOG DEPRESIVNOG POREMEĆAJA: INTEGRATIVNA ANALIZA NIVOA U SERUMU I POLIMORFIZMA NGF ALA273VAL (RS6330)

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Summary

Background: Major depressive disorder (MDD) has been increasingly recognized as a systemic disorder involving neuroimmune and biochemical dysregulation. Circulating neurotrophic factors, particularly nerve growth factor (NGF), may serve as potential laboratory biomarkers reflecting neurobiological alterations.
Methods: This case–control study enrolled 47 drug-naïve patients with first-episode MDD and 40 age- and sex-matched healthy controls. Serum NGF concentrations were quantified using enzyme-linked immunosorbent assay (ELISA). The NGF Ala273Val (rs6330) polymorphism was genotyped via polymerase chain reaction and direct sequencing. Statistical analyses included group comparisons, correlation analysis, and genotype–phenotype association evaluation.
Results: Serum NGF levels were significantly elevated in patients with MDD compared with controls (36.81 ± 7.11 vs. 29.74 ± 5.69 pg/mL, $P < 0.001$). However, no significant correlation was observed between NGF concentrations and HAMD-17 scores ($r = 0.12$, $P = 0.42$). Genotype and allele distributions of the NGF Ala273Val polymorphism did not differ significantly between groups ($P > 0.05$), and no genotype-dependent differences in serum NGF levels were detected.

Kratak sadržaj

Uvod: Veliki depresivni poremećaj (VDP) se sve više prepoznaje kao sistemski poremećaj koji uključuje neuroimunu i biohemijsku disregulaciju. Cirkulišući neurotrofični faktori, posebno faktor rasta nerava (NGF), mogu poslužiti kao potencijalni laboratorijski biomarkeri koji odražavaju neurobiološke promene.
Metode: Ova studija slučaj-kontrola obuhvatila je 47 pacijenata sa prvom epizodom velikog depresivnog poremećaja koji nisu primali lekove i 40 zdravih kontrola usklađenih po starosti i polu. Koncentracije serumskog NGF-a kvantifikovane su korišćenjem imunosorbentnog testa (ELISA). Polimorfizam NGF Ala273Val (rs6330) genotipiziran je pomoću lančane reakcije polimeraze i direktnog sekvenciranja. Statističke analize su obuhvatale poređenje grupa, analizu korelacije i procenu povezanosti genotipa i fenotipa.
Rezultati: Nivoi serumskog NGF-a bili su značajno povišeni kod pacijenata sa velikim depresivnim poremećajem (MDD) u poređenju sa kontrolnom grupom (36,81 ± 7,11 naspram 29,74 ± 5,69 pg/mL, $P < 0,001$). Međutim, nije primećena značajna korelacija između koncentracija NGF-a i HAMD-17 rezultata ($r = 0,12$, $P = 0,42$). Distribucija genotipa i alela polimorfizma NGF Ala273Val nije se značajno razlikovala između grupa ($P > 0,05$), i nisu otkrivene razlike u nivoima serumskog NGF-a zavisne od genotipa.

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Conclusion: Circulating NGF is significantly altered in first-episode MDD, supporting its role as a neuroimmune-related biochemical marker associated with disease presence rather than symptom severity. The NGF Ala273Val polymorphism does not appear to influence susceptibility or peripheral NGF expression. These findings highlight the potential utility of serum NGF as a laboratory biomarker in the biochemical characterization of MDD.

Keywords: major depressive disorder, nerve growth factor, gene polymorphism, Ala273Val, first-episode

Zaključak: Cirkulišući NGF je značajno izmenjen kod prve epizode velikog depresivnog poremećaja (MDD), što potvrđuje njegovu ulogu kao neuroimunološki povezanog biohemijskog markera povezanog sa prisustvom bolesti, a ne sa težinom simptoma. Polimorfizam NGF Ala273Val ne utiče na osetljivost ili perifernu ekspresiju NGF. Ovi nalazi ističu potencijalnu korisnost serumskog NGF-a kao laboratorijskog biomarkera u biohemijskoj karakterizaciji MDD.

Ključne reči: veliki depresivni poremećaj, faktor rasta nerava, genski polimorfizam, Ala273Val, prva epizoda

Introduction

Major depressive disorder (MDD) represents a widespread and severely disabling psychiatric condition, defined clinically by sustained emotional depression, the inability to experience pleasure (anhedonia), alongside diverse deficits spanning cognitive function, somatic health, and behavioral regulation (1). As reported by the World Health Organization, depression afflicts over 350 million individuals globally; notably, China exhibits a prevalence rate of 3.02%, thereby contributing 10.3% to the worldwide burden of disease (2). Despite its high prevalence, the exact pathophysiological mechanisms of MDD remain incompletely elucidated, which is recognized to result from the interaction of biological, genetic and psychosocial factors.

The neurotrophic hypothesis posits that the etiology of major depressive disorder (MDD) stems not only from dysregulation of classical neurotransmitter systems but also, importantly, from impaired neural plasticity (3). Within this framework, neurotrophic factors, a family of proteins that regulate neuronal survival, proliferation, differentiation, and synaptic plasticity, have emerged as potential peripheral biomarkers for MDD. While Brain-Derived Neurotrophic Factor (BDNF), the most thoroughly characterized member, is robustly associated with disease susceptibility, symptom severity, and therapeutic outcomes, the specific contribution of Nerve Growth Factor (NGF) remains ambiguous (4). Despite its established neuroprotective functions, the role of NGF in MDD pathophysiology is currently ill-defined and marked by conflicting evidence.

NGF is predominantly expressed in the central nervous system (CNS), including the hippocampus, cerebral cortex and hypothalamus, and plays a vital role in promoting neuronal growth and survival, as well as regulating synaptic and morphological plasticity (5). It also participates in the modulation of the neuroendocrine-immune system in response to stress (6). Peripheral NGF is detectable in human serum, potentially deriving from CNS sources via blood-brain barrier translocation or through direct secretion by immune cells (7). Preclinical investigations indicate that elevated peripheral NGF concentrations correlate with adaptive stress mechanisms, implying a neuroprotective function for NGF in maintaining cerebral integrity (8). Nevertheless, clinical assessments of serum NGF levels in patients with MDD have produced conflicting findings: whereas most Western cohorts report reduced serum NGF concentrations among elderly and adolescent MDD populations (9, 10), studies conducted in China observe increased plasma or serum NGF levels in MDD subjects presenting with comorbid anxiety or experiencing their first depressive episode (11–13). Such inconsistencies likely stem from variations in demographic characteristics, disease progression stages, and ethnic compositions across study populations.

Gene polymorphisms are important genetic factors that affect the expression and function of neurotrophic factors. The Ala273Val polymorphism (rs6330) in the NGF gene, a common single nucleotide polymorphism (SNP), has been reported to be associated with the expression of NGF and the susceptibility to various neuropsychiatric disorders. However, the potential link between the NGF Ala273Val polymorphism and MDD remains insufficiently characterized; indeed, existing literature is sparse, with the limited studies conducted thus far failing to demonstrate any statistically significant correlation (14).

To elucidate the involvement of NGF in the etiology of first-episode MDD and to investigate its potential genetic modulation, we designed a case-control investigation. This study compared circulating NGF concentrations between drug-naïve individuals experiencing their initial MDD episode and matched healthy controls. Furthermore, we examined whether the Ala273Val polymorphism within the NGF gene correlates with MDD susceptibility and influences serum NGF levels among Han Chinese participants recruited from central and southwestern regions of China.

Materials and Methods

Study Participants

A total of 47 drug-naive outpatients and inpatients with first-episode MDD were recruited from Wuhan Mental Health Centre and the Affiliated Hospitals of Kunming Medical University. All patients met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for a single episode of MDD, with a HAMD-17 score ≥17 and a score of ≥2 on the depressed mood item (item 1). The exclusion criteria included: 1) comorbid brain organic diseases, somatic diseases or immune system diseases; 2) a history of substance abuse or allergy; 3) comorbid other psychiatric disorders such as schizophrenia and bipolar disorder.

A cohort of forty healthy individuals, meticulously matched for age and sex, was enrolled from the surrounding community to serve as controls. The exclusion criteria for controls were: 1) a HAMD-17 score ≥7; 2) abnormal blood routine, liver or kidney function; 3) a personal or family history of psychiatric disorders; 4) a history of substance abuse or severe somatic diseases. The same exclusion criteria for somatic diseases and allergies were applied to controls as to patients.

Prior to participant enrollment, this investigation secured formal approval from the Institutional Ethics Review Committees, alongside the acquisition of written informed consent from every individual involved.

Clinical Assessment

Demographic characteristics (including name, sex, age, occupation, marital status, and educational attainment) alongside clinical parameters (specifically age at onset, duration of illness, and familial history of psychiatric disorders) for all enrolled subjects were gathered utilizing a custom-developed general information questionnaire. The severity of depressive symptoms was assessed by two trained psychiatrists with a Kappa coefficient of 0.93 using the 17-item Hamilton Depression Rating Scale (HAMD-17) before treatment.

Sample Collection

Fasting elbow venous blood (5 mL) was collected from each participant in two vacuum tubes: one without anticoagulant for serum separation, and one with EDTA for genomic DNA extraction. To prepare serum specimens, whole blood was incubated at ambient temperature for 30 minutes to facilitate clotting, followed by centrifugation at 3,000 revolutions per minute (rpm) for a duration of 10 minutes. The upper serum layer was collected, added with 10 μL of protease inhibitor, aliquoted and stored at -20 °C until NGF detection. EDTA-anticoagulated blood samples were directly stored at -20 °C for DNA extraction.

Measurement of Serum NGF Levels

Serum levels of NGF were quantified via a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA), employing a commercial human NGF detection kit manufactured by Senxiong Technology Co., Ltd. (Shanghai, China). All operations were performed strictly according to the kit instructions and laboratory standard operating procedures. Each serum sample was tested in duplicate, and the average value was used for statistical analysis. The detection range of the kit was 5–200 pg/mL.

Intra-assay and inter-assay precision: In the present study, the intra-assay coefficient of variation (CV) of NGF detection was less than 5%, and the inter-assay CV was less than 10%, indicating satisfactory intra-assay precision.

Calibration procedure: Calibration was performed using gradient dilution of the recombinant NGF standard provided by the kit. A standard curve ($R^2 > 0.99$) was plotted for each plate to calculate sample concentrations.

Sample stability: All serum samples were stored at −80 °C and avoided repeated freeze-thaw cycles. Previous validation studies have confirmed that NGF levels remain stable for at least 6 months under this storage condition, which is consistent with the sample processing protocol in this study.

Genotyping of NGF Gene Ala273Val Polymorphism

Genomic DNA was isolated from EDTA-anticoagulated peripheral blood utilizing a commercial rapid extraction kit specifically optimized for whole blood samples. Subsequently, the specific genomic region of the nerve growth factor (NGF) gene harboring the Ala273Val (rs6330) single-nucleotide polymorphism was enriched via polymerase chain reaction (PCR). Primer sequences were adopted from established literature (15) and verified by the UCSC Genome Bioinformatics database (16), with the sequences as follows: forward primer 5′-GATTCCAGGTGCATAGCGTAAT-3′, reverse primer 5′-AGATCCTGAGTGTCTGCAGCTT-3′.

The polymerase chain reaction (PCR) was conducted in a final volume of 25 μL, comprising 12.5 μL of 2× Taq Master Mix, 0.5 μL each of forward and reverse primers (10 μmol/L), 1 μL of genomic DNA template, and 10.5 μL of sterile deionized water. Thermal cycling parameters included an initial

denaturation step at 94°C for 5 min, followed by 30 cycles consisting of denaturation at 94°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s. A final extension phase was performed at 72°C for 7 min. Subsequently, the amplified products were purified and directly sequenced to characterize the genotypic variants associated with the Ala273Val polymorphism.

Statistical Analysis

Statistical computations were executed utilizing Statistic Package for Social Science (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are reported as mean ± standard deviation (mean ± SD), with distributional normality assessed through the Shapiro-Wilk procedure. Continuous variables between the MDD and control groups were compared using independent-samples t-tests, and categorical variables as well as Hardy-Weinberg equilibrium (HWE) were analyzed with chi-square tests. One-way ANOVA was used to compare serum NGF levels across different genotypes, and Spearman correlation analysis to examine the association between serum NGF levels and HAMD-17 scores. A two-tailed $P < 0.05$ was deemed statistically significant.

Results

Demographic and Clinical Characteristics

The study cohort comprised 87 individuals, stratified into two groups: 47 patients diagnosed with major depressive disorder (MDD), consisting of 20 males and 27 females, and 40 healthy controls, including 19 males and 21 females. There was no significant difference in gender distribution (χ^2=0.214, P=0.644) or age (35.4±11.4 years vs. 38.3±9.4 years, t=1.235, P=0.220) between the MDD group and the control group (*Table I*). The average disease duration of MDD patients was 6.26±3.59 months, and the average HAMD-17 score was 24.3±4.1 points.

Comparison of Serum NGF Levels Between Groups

As presented in *Table II*, patients diagnosed with MDD exhibited markedly elevated serum NGF concentrations (36.81 ± 7.11 pg/mL) relative to healthy controls (29.74 ± 5.69 pg/mL). This intergroup disparity reached statistical significance, as evidenced by a t-value of 5.06 and a P-value less than 0.001. The serum NGF levels ranged from 24.71 to 50.68 pg/mL in the MDD group and from 22.28 to 44.66 pg/mL in the control group. Spearman correlation analysis showed no significant correlation between serum NGF levels and HAMD-17 scores in MDD patients (r=0.12, P=0.42) (*Table III*).

Hardy-Weinberg Equilibrium Test

Genotyping analysis of the overall cohort (n=87) showed the frequencies of the Ala/Ala, Ala/Val and Val/Val genotypes were 63.22% (55 participants), 31.03% (27 participants) and 5.76% (5 participants), respectively. Subsequent Chi-square assessments confirmed that the distribution of the NGF Ala273Val polymorphism adhered to Hardy-Weinberg equilibrium expectations across the total population, as well as within both the MDD and control subgroups (all $P > 0.05$). These findings underscore the robust genetic representativeness of the study sample (*Table IV*).

Table I Baseline demographic profile of the study cohort.

Variables	Total (n=87)	MDD group (n=47)	Control group (n=40)	t/χ^2	P
Gender (n, %)				0.214	0.644
Male	39 (44.8)	20 (42.6)	19 (47.5)		
Female	48 (55.2)	27 (57.4)	21 (52.5)		
Age (years, $\bar{x}$±s)	36.7±10.6	35.4±11.4	38.3±9.4	1.235	0.22

MDD: Major Depressive Disorder

Table II Comparison of serum NGF levels between the MDD group and the control group (pg/mL, $\bar{x}$±s).

Groups	n	Minimum	Maximum	Mean±SD	t	P
Total	87	22.28	50.68	33.56±7.37	-	-
MDD group	47	24.71	50.68	36.81±7.11	5.06	<0.001
Control group	40	22.28	44.66	29.74±5.69	-	-

MDD: Major Depressive Disorder; NGF: Nerve Growth Factor

Comparison of Genotype and Allele Frequencies Between Groups

In the cohort of patients with MDD, the observed genotype frequencies for Ala/Ala, Ala/Val, and Val/Val were 63.83% (30/47), 29.79% (14/47), and 6.38% (3/47), respectively. Corresponding values in the healthy control group were 62.50% (25/40), 32.50% (13/40), and 5.00% (2/40). Statistical analysis revealed no significant disparity in genotype distribution between the two cohorts ($\chi^2 = 0.13$, P = 0.94; *Table IV*). Regarding allele frequencies, the C (Ala) and T (Val) variants appeared at rates of 78.72% (74/94) and 21.28% (20/94) within the MDD group, compared to 78.75% (63/80) and 21.25% (17/80) in controls. Notably, the minor allele frequency (MAF) for the T variant remained consistent at 0.21 across both populations. Consequently, no statistically significant difference was detected in allele distribution between the groups ($\chi^2 = 0.00$, P = 0.997; *Table V*).

Table III Association between circulating NGF concentrations and HAMD-17 ratings among individuals diagnosed with Major Depressive Disorder.

Variables	NGF (pg/mL)	HAMD-17 score
NGF (pg/mL)	1	0.12
P	-	0.42
HAMD-17 score	0.12	1
P	0.42	-

NGF: Nerve Growth Factor; HAMD-17: 17-item Hamilton Depression Rating Scale; MDD: Major Depressive Disorder

Association of NGF Genotypes with Serum NGF Levels

One-way ANOVA showed no significant difference in serum NGF levels among the three Ala273Val genotypes (Ala/Ala, Ala/Val, Val/Val). Specifically, mean levels were recorded as 33.35 ± 7.01 pg/mL for Ala/Ala, 34.41 ± 8.06 pg/mL for Ala/Val, and 31.39 ± 8.46 pg/mL for Val/Val, yielding an F-statistic of 0.41 with a corresponding P-value of 0.67. Furthermore, stratified examinations confirmed that these null findings persisted within both the MDD subgroup (F = 0.33, *P* = 0.72) and the healthy control group (F = 0.48, *P* = 0.62), indicating a lack of genotype-dependent influence on serum NGF profiles regardless of disease status (*Table VI*).

Table IV Distribution of NGF gene Ala273Val genotypes in the MDD group and the control group (n, %).

Genotypes	Total (n=87)	MDD group (n=47)	Control group (n=40)	χ^2	P
Ala/Ala	55 (63.22)	30 (63.83)	25 (62.50)	0.13	0.94
Ala/Val	27 (31.03)	14 (29.79)	13 (32.50)		
Val/Val	5 (5.76)	3 (6.38)	2 (5.00)		

NGF: Nerve Growth Factor; MDD: Major Depressive Disorder

Table V Distribution of NGF gene Ala273Val alleles in the MDD group and the control group (n, %).

Alleles	Total (n=174)	MDD group (n=94)	Control group (n=80)	χ^2	P
C (Ala)	137 (78.74)	74 (78.72)	63 (78.75)	0	0.997
T (Val)	37 (21.26)	20 (21.28)	17 (21.25)		

NGF: Nerve Growth Factor; MDD: Major Depressive Disorder

Table VI Serum NGF levels among different NGF gene Ala273Val genotypes (pg/mL, $\bar{x}\pm s$).

	Ala/Ala	Ala/Val	Val/Val	F	P
Total (n=87)	55: 33.35±7.01	27: 34.41±8.06	5: 31.39±8.46	0.41	0.67
MDD group (n=47)	30: 36.50±7.02	14: 37.94±7.13	3: 34.60±10.14	0.33	0.72
Control group (n=40)	25: 29.56±4.85	13: 30.50±7.44	2: 26.46±0.07	0.48	0.62

NGF: Nerve Growth Factor; MDD: Major Depressive Disorder (n: number of participants)

Discussion

MDD is a multifactorial psychiatric disorder with intricate pathogenesis, and the neurotrophic hypothesis serves as a core framework for elucidating its onset and progression. NGF (17), a key member of the neurotrophic factor family with important neuroprotective and plasticity-regulating functions, has attracted increasing attention for its role in MDD (18), but clinical research results remain controversial across ethnic groups and study populations. In this case-control investigation involving drug-naïve individuals of Han descent from central and southwestern China experiencing their first episode of MDD, we observed a marked elevation in serum NGF concentrations among patients relative to healthy controls matched for age and sex. Conversely, no statistically significant association was detected between circulating NGF levels and the severity of depressive symptoms, as quantified by the 17-item Hamilton Depression Rating Scale (HAMD-17). Additionally, the NGF gene Ala273Val (rs6330) polymorphism was not associated with MDD susceptibility or peripheral serum NGF expression in the studied population.

Our finding of elevated serum NGF levels in first-episode MDD patients is consistent with the results of previous Chinese studies (11–13), but contrary to most Western studies that reported decreased serum NGF levels in MDD patients (9, 10, 19). This cross-ethnic difference may stem from genetic, environmental, and population-related differences (e.g., age, disease stage, comorbidities). Most Western studies focused on elderly or adolescent MDD patients, whereas ours and other Chinese studies enrolled primarily first-episode, drug-naive adult MDD individuals, potentially accounting for inconsistent findings. Furthermore, higher rates of comorbid anxiety in Chinese MDD patients may also contribute to elevated NGF levels (11), as anxiety is a strong stressor that can activate the neuroendocrine-immune system and induce the secretion of NGF.

The elevated serum NGF in first-episode MDD suggests a compensatory neuroprotective mechanism in disease pathophysiology. According to the neurotrophic hypothesis, depressive symptoms are associated with neuronal injury and impaired neural plasticity caused by chronic stress (3). NGF, as a key neurotrophic factor, can promote the survival of neuronal soma, accelerate the directional growth of axons, and participate in the repair and regeneration of damaged neurons (20–22). Elevated serum NGF in MDD patients may reflect an endogenous feedback mechanism against depression-related neuronal damage, consistent with preclinical evidence that NGF mediates stress adaptive responses (8). Furthermore, our analysis revealed no statistically significant association between circulating NGF concentrations and HAMD-17 scores. This observation implies that NGF likely contributes to the pathogenesis of MDD rather than modulating the intensity of depressive manifestations. Consequently, serum NGF appears to serve as a promising diagnostic biomarker for identifying MDD, whereas its utility in assessing clinical severity remains limited.

The NGF gene Ala273Val polymorphism is a common coding-region SNP that may alter NGF protein structure, function, expression and biological activity. However, no significant differences in genotype distribution or allele frequency of this variant were found between MDD patients and healthy controls. The minor allele frequency of Val was 0.21, consistent with reported data in the Han Chinese population. These findings collectively suggest that this specific genetic variation does not confer susceptibility to first-episode MDD in our cohort. Furthermore, our data corroborate the work of Yeh et al., who similarly reported an absence of association between NGF gene polymorphisms and MDD risk among individuals of Taiwanese Han ancestry (14). In addition, we found no significant difference in serum NGF levels across genotypes, indicating that the Ala273Val polymorphism does not regulate peripheral NGF expression. As a synonymous SNP, it does not alter the amino acid sequence or structure of NGF, and thus has no effect on its expression or function.

This study has several strengths: first, all MDD patients were drug-naive with first-episode MDD, which excluded the interference of antidepressant drugs on serum NGF levels and genotype detection, making the results more reliable; second, the study strictly matched age and gender between the MDD group and the control group, and excluded participants with severe somatic diseases and other psychiatric disorders, reducing the confounding factors; third, the genotype detection used PCR combined with direct DNA sequencing, which has high accuracy and reliability.

However, this investigation is subject to certain constraints. Primarily, the modest cohort size may compromise statistical power, thereby limiting the detection of subtle genetic associations; consequently, subsequent research employing expanded populations is requisite to validate these findings; second, the study only included Han patients from central and southwest China, and the results cannot be generalized to other ethnic groups or regions; third, the study only detected the Ala273Val polymorphism of the NGF gene, and did not explore other SNPs of the NGF gene or gene-gene interactions, which may be involved in the pathogenesis of MDD; fourth, this investigation was confined to the quantification of NGF concentrations in peripheral serum, precluding direct assessment within the central nervous system; consequently, the precise rela-

tionship between circulating and central NGF pools warrants further elucidation.

Conclusion

Serum NGF levels were significantly elevated in drug-naive first-episode MDD patients but showed no correlation with symptom severity. The NGF Ala273Val (rs6330) polymorphism was not associated with MDD risk or serum NGF levels. Circulating NGF may serve as a peripheral diagnostic biomarker for first-episode MDD, likely reflecting compensatory neuroprotection. This polymorphism does not contribute to MDD susceptibility in Han Chinese individuals. Larger multicenter studies are needed to confirm these findings.

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Author Contributions

Yong Zeng: Conceptualization, Supervision, Funding acquisition, Writing – Review and Editing. Liu Lian: Methodology, Investigation, Formal analysis, Writing – Original Draft. Xiong Peng: Resources, Data curation, Validation.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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