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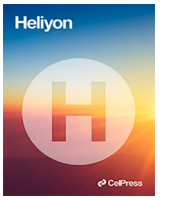

Research article

Time association study on a sub-acute mouse model of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a severe neurodegenerative disease that disturbs human health. In the laboratory researches about PD, the mice model induced by intraperitoneal injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was widely used. However, there has been controversy about the model effectiveness to simulate PD symptoms and pathology, and the time-varying development of behavioral and pathological characteristic after MPTP treatment remains unclear. In order to solve these problems, we designed a series of experiments to evaluate this PD model at different time points. We constructed the subacute PD mouse model by intraperitoneal injection of MPTP for 5 consecutive days. The rotarod test, open field test and the immunohistochemical staining of tyrosine hydroxylase were conducted at −5, 1, 5, 7, 14, 21 and 28 days after the last injection of MPTP. The results showed that 5 days after the last MPTP administration, typical motor disorders with significant balance function damage in rotarod test began to appear and remained stable throughout the entire experiment. Simultaneously, we also observed the loss of tyrosine hydroxylase (TH) positive cells in the substantia nigra compacta and reduction of TH content in the striatum but this pathological change in the substantia nigra compacta reversed 21 days after injection. Besides, the spontaneous movement of mice in open field test remained unchanged by MPTP. This research indicated the time-dependence of MPTP neurotoxicity that impair the motor function and histological features and confirmed the

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symptom occurrence time after MPTP injection, which provides a reference for the future research about MPTP-induced PD.

1. Introduction

Parkinson's disease (PD) is the second neurodegenerative disease characterized by both motor dysfunction including tremors, posture and gait disorders and nonmotor dysfunction such as depression, constipation and dysphagia [1]. Recent data shows that there are over 3.6 million PD patients in China [2]. The pathological feature of PD is mainly the loss of dopaminergic neurons in the substantia nigra compacta (SNc) [3]. And the striatum, which is the main axonal target of the SNc, also undergoes changes of neuron morphology and function [4].

Currently, the pathogenesis of PD is known to be related with the gene mutation and some environmental toxins, but the specific cause remains still unclear [5]. So, abundant researches are in progress with the rodent animal models. The routine animal models in the study of PD include brain stereotaxic injection of 6-hydroxydopamine [6], intraperitoneal injection of MPTP [7], subcutaneous injection of rotenone [8], some transgenic animals [9] and so on. Among these methods, intraperitoneal injection of MPTP with mice is widely used due to its simple operation and high modeling rate. The MPTP-induced PD mice models can be divided into three types of the acute [10] subacute [11] and chronic [12]. And the subacute protocol to establish a PD mouse model is suitable for researchers and the most common dosage of MPTP is 30 mg/kg/d for five consecutive days [3]. Until now, the MPTP-induced animal model of PD has had a significant impact on PD physiopathology and the new drug development, and it has become one of the most often used rodent models for PD to investigate the underlying disease mechanism.

Although many researchers chose the method, there are problems need to be solved and ensured in the application process [13]. First, there has been controversy about the effectiveness of this disease model to accurately simulate PD symptoms and pathology. Moreover, the development of behavioral and pathological characteristic at different timepoint after MPTP treatment remains unclear, which restricts the application in researches of disease mechanisms and especially the intervention therapeutics. Thus, it is necessary to evaluate this model systematically from both behavioral and pathological prospects. With this aim, this study designed two experiments to explore changes at different time points after MPTP subacute treatment.

2. Materials and methods

2.1. Animals

37 SPF male healthy C57BL/6 J mice (8-week age) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. After entering the laboratory, the mice adapted to the environment for a week Animals were housed in standard SPF environment in

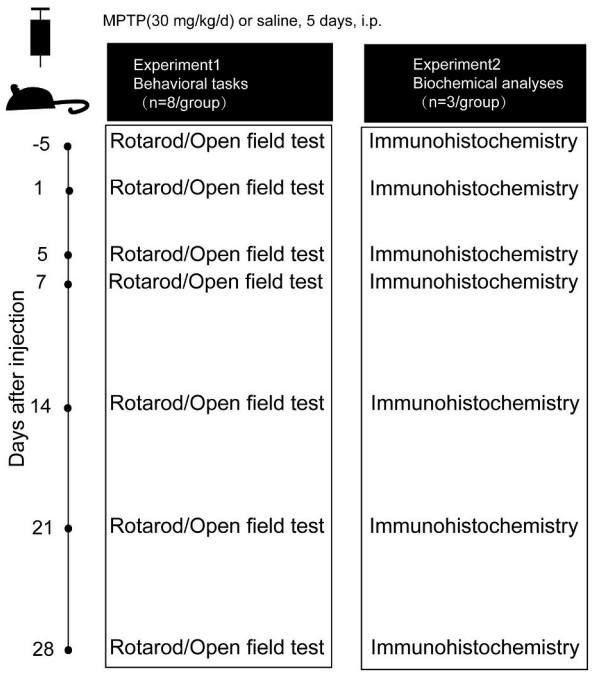

Fig. 1. Experimental procedure.

Laboratory Animal Center of Shandong University of Traditional Chinese Medicine with the temperature of 21 ± 1 °C and 12 h light and dark cycle (light on at 20:00 and light off at 8:00). Grasp parallel was operated daily to eliminate the impact of human operations. All animal experimental operations complied with the "Guidelines for the Care and Use of Experimental Animals" issued by NIH in the United States, and were approved by the Experimental Animal Ethics Committee of Shandong University of Traditional Chinese Medicine (approval number: SDUTCM2023033001).

2.2. Experimental design

The experiment was divided in two batches (Fig. 1). In Experiment 1, 16 mice were divided into two groups (control group and model group) randomly for behavioral tests. Rotarod and open field were tested at −5, 1, 5, 7, 14, 21 and 28 days after the last injection of MPTP. In Experiment 2, 21 mice were used for histological examination: at each time point, 3 mice were sacrificed and brain samples were obtained for immunohistochemical analysis.

2.3. MPTP treatment

The animals in model group in Experiment 1 and all in Experiment 2 were administered intraperitoneal injection with a dosage of 1 ml/100 g body weight MPTP (30 mg/kg/d, M0896, sigma) for 5 consecutive days (Jackson-Lewis and Przedborski, 2007b). MPTP is dissolved in normal saline. The administration time was 14:30 daily and the control group in Experiment 1 was given the corresponding volume of saline.

2.4. Behavioral tests

2.4.1. Rotarod test

The rotarod test was performed using rotating rod tester (Ugo Basile) including a 4-channel rotating rod (diameter 3.5 cm), a trip box, a touch screen, and driving devices. Three days before the test, the mice were trained and placed on a rotating rod at a constant speed (12 r/min) for 60 s once a day for 3 days. During the test, the rotarod was set at acceleration mode (4r/min to 40r/min, lasting for 10min) and was used to record the duration of animals. Each animal was tested three times with an interval of 10 min, and the average value was taken for statistical analysis.

2.4.2. Open field test (OFT)

The open field box (L × W × H = 100 cm × 100 cm × 50 cm) and high-sampling rate camera (15 frames/second) were used in experience. And the XR-Super Maze animal behavior system was used to track and analysis animal's behavior. Each mouse was placed in the center of the box and observed for 6 min, and the activity of the animals was recorded. The movement trajectory of the mice was analyzed by a computer, and the total movement distance was compared between control and model animals.

2.5. Immunohistochemical examination

Mice were anesthetized with isoflurane and cardiac perfusion surgery was performed. After flushing out the whole blood with pre cooled phosphate buffer, 4 % paraformaldehyde (PFA) was infused and the brain tissue was cut off and placed in a 15 ml EP tube containing 4 % PFA. After 48 h fixation, it was transferred to a 15 ml EP tube containing 30 % sucrose for dehydration. Then, the tissue was stored at −80 °C.

Consecutive coronal sections were performed in tissue containing the SNc and striatum. The sections were blocked with goat serum for 2 h, then incubated with anti-tyrosine hydroxylase (TH) primary antibody (1:1000) overnight (E2L6M, Cell Signaling Technology). And the TH^+ signals were revealed using Rabbit Specific HRP/DAB (ABC) Detection IHC Kit (ab64621, Abcam).

Six brain slices containing SNc or STR from each animal were used with 80 μm iinterval. The number of TH positive cells in SNc and the light intensity of the striatum area under the 20× objective were counted with Image J Software and the mean value of these 6 slices were used in statistics. The last number shown is the number of TH^+ cells in the unilateral substantia nigra compact. The intensity of the striatum was statistically statistic of the dorsolateral striatum.

2.6. Statistical analysis

The statistics were performed with GraphPad Prism 9 (GraphPad Software, USA). In terms of behavioral data, we performed the Kolmogorov–Smirnov test for normality followed by the unpaired *t*-test (two-tailed) in data with normal distribution. If the normality assumption failed, we used nonparametric test. In terms of pathological findings, we chose one-way ANOVA. All data were expressed as the mean ± standard error of the mean.

3. Results

3.1. The MPTP-induced obvious motor disorder of mice in rotarod test occurred 5 days after the injection

In the results of the rotarod experiment, the duration of mice in model group was significantly decreased by MPTP compared to the

control group on the 5, 7, 14, 21, 28 days after injection ($P < 0.05$, Fig. 2B). On the 14, 21, 28 days after injection, the speed of the rotarod when mice dropped showed significant differences ($P < 0.05$, Fig. 2C). However, from analysis of the total distance in OFT, we did not observe any changes of animals in the model group compared with the control animals (Fig. 2E). Besides, the body weight of model mice decreased significantly after 1 week of the MPTP intervention ($P < 0.01$), and quickly returned to normal level (Fig. 2F).

3.2. MPTP induced significant pathological changes in SNc and STR and the decrease of TH $^{+}$ cells in SNc reversed

The results of immunohistochemical staining are shown in Fig. 3 and the statistical results are in Fig. 4. From the results, we can conclude that 5 days after the last intraperitoneal injection of MPTP, the TH^{+} cell number in the SNc of mice decreased compared to tissues without MPTP intervention (the day before the intraperitoneal injection) ($P < 0.05$) and the difference remained until the 21 day ($P < 0.05$) with the largest difference on day 14 ($P < 0.01$). Subsequently, the number of TH^{+} cells in the SNc gradually recovered. On the 28th day, there was no significant difference (Fig. 4A).

Similar to the expression of tyrosine hydroxylase in SNc, the expression of striatal tyrosine hydroxylase also reduced. Unlike the substantia nigra, the striatal tyrosine hydroxylase content showed a significant difference on the first day after modeling ($P < 0.0001$). The difference persisted until 28 days after molding (Fig. 4B).

4. Discussion

This research is a time association study on a sub-acute mouse model of PD induced by MPTP. Our data showed that 5 days after last MPTP administration, typical motor disorders began to appear and remained stable throughout the entire experiment. Simultaneously, we also observed the significant pathological characteristics like the loss of TH^{+} positive cells in the SNc and reduction of TH content in the striatum. Besides, it is worth noting that the pathological change in SNc reversed 21 days after MPTP injection.

Although MPTP has been commonly utilized to create the subacute mouse model of PD, there has recently been much controversy regarding how successfully MPTP can induce the PD phenotype [14]. One of the controversial issues is whether MPTP-intoxicated mice can mimic the motor or pathological impairments of PD. In our research, behavioral data suggest that MPTP-induced subacute model of PD showed significant movement disorder in rotarod test while there was no significant difference in the open field experiment. This implies that, despite the presence of a behavioral impairment, the motor deficits in mice in this model may exhibit behavioral uniqueness. Unlike our conclusion, a recent report showed that MPTP-treated mice with subacute regimen failed to display significant motor deficits in open field, rotarod, and gait analysis tests at different time points (1, 7, 14, and 21 days) after modeling [13]. This previous research also detected the histological changes but only on 21 days after modeling, and results indicated MPTP induced a significant dopaminergic neuron reduction in the midbrain. However, this study did not dynamically observe the pathological features at each time point to correspond to the behavioral changes. Besides, we reviewed other recent researches about behavioral changes in subacute MPTP-induced mice model. Inconsistent to our results, some articles reported the decreased spontaneous activity in OFT [15–17] but some reported similar tendency to our OFT results [18–20]. We suppose the reasons to account for these discrepant findings may be related to the differences of MPTP dosage regimen and the test time point. However, most of the above researches reported the disorders in rotarod test with decreased balance and motor coordination, which is consistent with our report. So, some compensatory work should be done to reveal the mechanisms underlying the different presentations of MPTP-induced PD mice in OFT (mainly reflect the spontaneous activity) and rotarod tests (mainly reflect the balance and motor coordination) and we need further research to clarify the effect of specific factors, such as age, sex, or behavioral protocols on the conclusion aberrations.

Meanwhile, the pathological results in this research showed that the TH^{+} cells in SNc and the TH content in STR were significantly

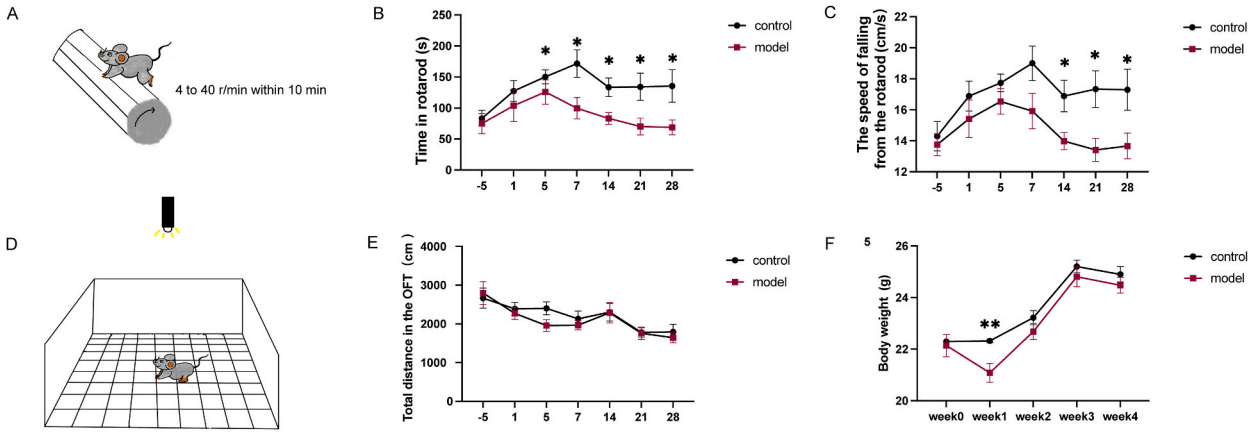

Fig. 2. The time-dependent toxicity of MPTP on the behavior and body weight of mice. A: Schematic diagram of the rotarod; B: Time on rotarod; C: Speed of the rotarod during the fall; D: Schematic diagram of the open field test (OFT); E: Total distance in the OFT; F: Body weight of the mouse. (n = 8 mice/group) *P < 0.05, **P < 0.01 vs. control group (two-tailed unpaired *t*-test).

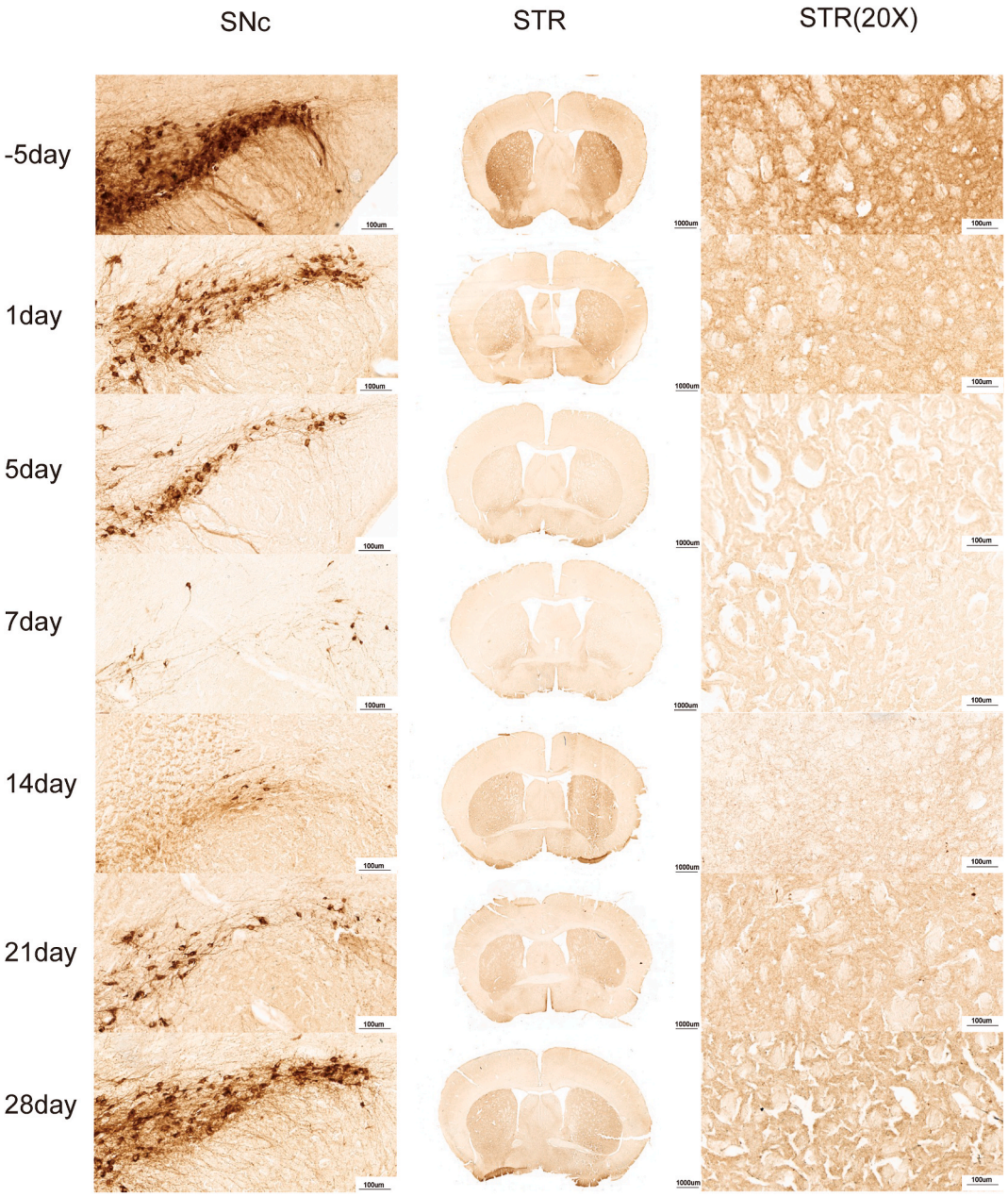

Fig. 3. Example of tyrosine hydroxylase immunohistochemical staining with mice brain on different day after MPTP injection. SNc: substantia nigra compacta; STR: striatum.

reduced after modeling. Besides, we surprisingly found that the pathological changes in the SNc mice gradually developed after modeling, and then began to reverse in 21 days after modeling. This suggests that the damage in SNc from MPTP toxicity is seemingly reversible. In researches in this field, there has been a unified understanding that MPTP could significantly result in the PD-like pathological features and abundant researches confirmed this and use the MPTP toxin to cause a dopamine depletion in the nigrostriatal region [21–24]. However, few studies focused on pathological processes at different time points after MPTP model construction. A similar previous study reported the pathological changes in 1, 2, 8, 16 days after acute MPTP injection and observed a small but gradually significant recovery of dopamine signaling in the STR [18]. Differently, in our results, we can find the recovery of TH^+ cells in SNc without the TH content in STR, which indicated the behavioral dysfunction is roughly consistent with the trend of striatal lesions instead of the SNc. In previous studies, it has been reported that the fragmentation and loss of dopaminergic neurons in the substantia nigra density is retrograde from the striatum to the substantia nigra [25,26]. Therefore, the role of the striatum in PD may be more important than that of the substantia nigra, and the exploration of STR or its associated upstream brain regions has become more

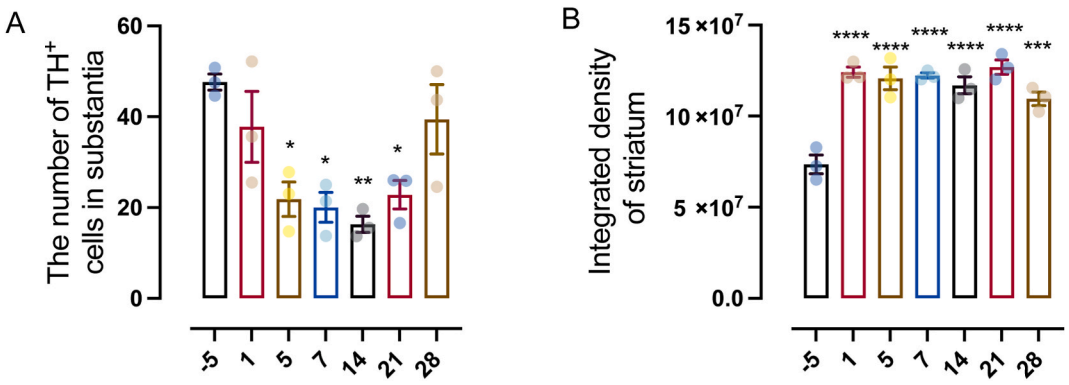

Fig. 4. Statistical results of immunohistochemical staining. A: Number of tyrosine hydroxylase positive (TH^+) cells in substantia nigra compacta. B: Light intensity in sections of striatum with TH immunohistochemical staining. (n = 3 mice/group) *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, vs. the day before the intraperitoneal injection of MPTP (−5 day) (one-way ANOVA).

important. Moreover, further studies are warranted to identify the mechanisms possibly involved in the recovery of SNc dopamine deficiency, such as the improved inflammation by astrocytes or microglia [27].

Furthermore, our experiment innovatively identified the behavioral and corresponding pathological features of the subacute MPTP-induced PD model at −5, 1, 5, 7, 14, 21 and 28 days after the last injection. We can conclude that the lesions of behavior and histology are time-dependent. The classic motor dysfunction and TH loss caused by MPTP occurred on the 5th day after modeling and achieve the most obvious level on the 7th day. Therefore, we believe that the subacute model of PD induced by MPTP exhibits the most significant behavioral and pathological changes 7 days after the modeling, which may be an important reference for future researches using this model. There has been a review trying to find the time-dependent pattern of this model and concluded that symptoms began from the 7th day after MPTP treatment, which is demonstrated by our experiment [27]. There was also research assessed this subacute MPTP-treated mouse at different time points but they did not observe the pathological feature at each point [13].

The limitation of this research is that we did not reveal the possible mechanisms underlying these behavioral or pathological changes caused by subacute MPTP treatment. Besides, we failed to answer the question that MPTP induced different presentations in different behavior test paradigm and we need more comprehensive behavioral analysis in the future.

5. Conclusion

In this paper, we established a PD mouse model with subacute injection of MPTP. The most commonly used time nodes after MPTP administration in previous researches were selected for evaluation of their behavioral and pathological features. The results indicated the time-dependence of MPTP neurotoxicity that impair the motor function and histological features and confirmed the symptom occurrence time after MPTP injection, which provides a reference for the future research about MPTP-induced PD.

Ethics statement

All animal experimental operations complied with the “Guidelines for the Care and Use of Experimental Animals” issued by NIH in the United States, and were approved by the Experimental Animal Ethics Committee of Shandong University of Traditional Chinese Medicine (approval number: SDUTCM2023033001).

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Jinfeng Ren: Writing – original draft, Visualization, Investigation. **Tongzheng Liu:** Writing – original draft, Visualization,

Investigation, Data curation. **Luyan You:** Writing – review & editing, Visualization, Investigation. **Minghui Hu:** Writing – original draft, Investigation, Data curation. **Jianping Zhu:** Writing – review & editing, Visualization. **Xinyu Wang:** Writing – review & editing, Visualization. **Hao Zhang:** Writing – review & editing. **Jiayu Zhang:** Writing – review & editing, Investigation. **Zifa Li:** Validation, Supervision, Conceptualization. **Sheng Wei:** Writing – review & editing, Resources, Conceptualization. **Xiwen Geng:** Writing – review & editing, Visualization, Methodology, Data curation.

Declaration of competing interest

All authors declared there were no conflict of interest.

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