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Clinical study of the effect of 5 kinds of antiepileptic drugs on the postictal state

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ABSTRACT

Objective: To compare the effects of levetiracetam (LEV) , lamotrigine(LTG), oxcarbazepine(OXC), topiramate (TPM) and valproate (VPA) on postictal state (PIS).
Methods: A total of 187 epilepsy patients undergoing monotherapy were enrolled in a long-term follow-up study at the Affiliated Hospital of Yangzhou College. This included 30 patients on levetiracetam, 41 on valproate, 30 on oxcarbazepine, 28 on topiramate, and 31 on lamotrigine. A control group of 28 newly diagnosed or previously untreated epilepsy patients was also included. The Liverpool Seizure Severity Scale 2.0 (LSSS2.0) and the Seizure Severity Questionnaire (SSQ) were utilized to evaluate the patients' condition, with comparison based on the results of the postictal status items. EEG during PIS termination was assessed using the Grand Total EEG score (GTE) as an objective tool to measure the impact of Antiseizure medications (ASMs) on the post-seizure state.
Results: The LSSS2.0 score indicated a statistically significant difference in post-seizure status score among the 5 groups ($p < 0.05$). The difference between the 5 groups and the control group was statistically significant ($p < 0.05$). Results of the SSQ demonstrated that all 5 drugs significantly reduced the post-seizure status score compared to the control group ($p < 0.05$). The GTE score revealed that, in the later stage of the seizure, the GTE score of the levetiracetam group, valproate group, oxcarbazepine group, and lamotrigine group significantly decreased compared to the control group ($P < 0.05$). There was no significant decrease in the GTE score in the topiramate group ($P < 0.05$).
Conclusion: Levetiracetam, lamotrigine, oxcarbazepine, topiramate, and valproate demonstrate favorable efficacy in ameliorating the severity of post-seizure condition. Further investigations are warranted to assess the potential of other widely employed anti-seizure medications in enhancing post-seizure status.

1. Introduction

Epilepsy represents a prevalent neurological condition, with seizures being categorized as preictal, ictal, postictal, and interictal. The postictal state (PIS) encompasses alterations in behavior, motor function, and neuropsychological manifestations that occur during the latter stages of a seizure and persist until these variables return to their typical state. This period can endure for just a few seconds, extend to hours, or even span days [1]. The severity and duration of postictal status significantly impact the patient's quality of life and are closely linked to the perceived severity of the seizure by the patient, but they tend to receive limited attention in epilepsy treatment [2]. Antiseizure medications (ASMs) are capable of addressing postictal events in various ways. Ideally, ASMs can prevent seizure-related events entirely, leading to a seizure-free state for the patient. Even in cases where seizures persist, ASMs have the potential to shorten the postictal duration. If the post-seizure period is reduced, allowing the patient to swiftly resume normal activities, the treatment can be considered successful despite the seizures not ceasing entirely [3]. Therefore, the evaluation of the efficacy of ASMs on PIS is of great clinical importance. Consequently, evaluating the effectiveness of ASMs on PIS holds significant clinical importance. There is limited research on the impact of antiepileptic drugs on postictal states. Furthermore, the influence of different antiepileptic drugs on PIS following the treatment of epilepsy with a similar seizure frequency and

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duration remains unclear. This study serves as an initial exploration into the effects of five commonly used ASMs on PIS.

2. Methods

2.1. Patients

From 2018 to 2023, a total of 297 cases of outpatients and inpatients with epilepsy at Yangzhou College Hospital were gathered, of which 198 cases were included in the research. Inclusion criteria: [1] age > 18 years; [2] patients underwent EEG/video-EEG, cranial MR, and met the diagnostic criteria of ILAE2017 [4] or epilepsy for definitive diagnosis and staging; [3] patients and their family members signed an informed consent form; [4] at least one seizure in the 3 months prior to enrollment in the study; and [5] the medication group had been taking one type of ASMs for ≥ 3 months and the medications had been titrated to effective doses. Exclusion criteria: (1) non-epileptic seizures with clear treatable etiology, such as acid-base balance and electrolyte disturbances, poisoning, infection, and intracranial space-occupying lesions; (2) other conditions that interfere with the assessment of post-seizure status, such as psychiatric disorders and mental disorders. (3) pregnant or breast-feeding patients. Each participant completed the Liverpool Seizure Severity Scale 2.0 (LSSS2.0) during the study and the Seizure Severity Questionnaire (SSQ) during the interictal period, with 88 patients completing the EEG during the PIS period. All participating neurologists were trained to assist participants in completing the questionnaire.

2.2. Measures

In this research, LSSS 2.0 [5], SSQ and the Grand Total EEG Score (GTE) were utilized for patient assessment. The LSSS 2.0 is sensitive to clinical changes in epilepsy patients, comprising 12 items describing the severity of seizures, with 7 indicators for evaluating seizures during the seizure and 5 indicators for evaluating the post-seizure condition. Every item receives a score on a Likert-type scale ranging from 4 to 6. The patient's assessment of the seizure's severity, the length of time they were disoriented or lost consciousness, any lip-smacking, agitation, or unusual behavior, the presence of moist skin during the seizure, a fall that occurred at the height of the seizure, a tongue bite that occurred during the seizure, and any other injuries sustained during the seizure are the seven evaluation indicators. ② Five evaluation signs (the length of panic after a seizure, headache after a seizure, tiredness after a seizure, and duration of the seizure state). Indicators of post-ictal state evaluation: Five items: post-ictal drowsiness, post-ictal headache, post-ictal panic, duration of panic, and post-ictal state duration. The PIS-related LSSS 2.0 items were separately evaluated, and total scores were calculated. The SSQ consists of four sections: Before seizure (BS), During seizure (DS), After seizure (AS), and Overall severity and bothersomeness (SB), Higher scores indicated more severity, with the exception of warning items. In this study, each portion of the SSQ was assessed independently, and total scores were computed. Scores ranged from 1 to 7 for BS, DS, and SB, and 0–7 for AS. while the GTE score quantifies abnormal changes in the EEG, ranging from 1 to 31. The study assessed each component of the SSQ and calculated the total score, with higher scores indicating higher severity, except for the warning items. [6]. The GTE score measures and standardizes unusual EEG changes, allowing for comparisons and reflecting the extent and nature of cortical damage [7]. The scale ranges from 1 (normal EEG) to 31 (most severe EEG). Two EEG specialists independently rated the EEGs blinded to all clinical information. If there was a difference of more than three points in the GTE, the EEGs were discussed with one additional rater and consensus was reached. The weighted kappa before the consensus meeting was 0.81.

2.3. Statistical analyses

In this research, the measurement data were presented as mean ± standard deviation (mean ± SD) and the count data as frequency (%), which aligned with the normal distribution. The data underwent analysis using the independent samples *t*-test and chi-square test to assess disparities between two groups. Variations among multiple groups were compared using analysis of variance (ANOVA), with statistical significance set at $P < 0.05$.

3. Results

As depicted in Table 1, a total of 297 cases of epilepsy outpatients and inpatients were gathered at Yangzhou College Hospital from 2018 to 2023. Out of these, 198 cases satisfied the inclusion and exclusion criteria to be included as study participants, with 93 cases (46.97 %) being female and 105 cases (53.03 %) being male. The age ranged from 18 to 86 years (mean 41.85 ± 18.61), and the duration of the disease ranged from 0.17 to 62 years (mean 8.28 ± 10.82). There were 4 cases (2.02 %) with a family history of epilepsy, while 194 cases (97.98 %) did not have a family history of the condition. In terms of educational level, 35 cases (17.68 %) had an elementary school education, 55 cases (27.78 %) had a junior high school or secondary school education, 67 cases (33.84 %) had a high school or junior college education, and 41 cases (20.71 %) had a college education or higher. The types of seizures observed were focal in 85 cases (42.93 %), generalized in 109 cases (55.05 %), and other seizure types in 4 cases (2.02 %), with 88 patients (44.44 %) experiencing status epilepticus. The use of antiepileptic drugs included levetiracetam (LEV) in 30 cases (15.15 %), valproate (VPA) in 41 cases (20.71 %), oxcarbazepine (OXC) in 30 cases (15.15 %),

Table 1
Baseline demographic data.

Program		Case(n = 198)
Age (year) (Mean ± SD)		41.85 ± 18.61
Duration of epilepsy, year (Mean ± SD)		8.28 ± 10.82
Sex (n , %)	Female	93(46.97)
	Male	105(53.03)
Family history (n , %)	No	194(97.98)
	Yes	4(2.02)
Education level (n , %)	primary school	35(17.68)
	Middle school	55(27.78)
	Senior high scool	67(33.84)
	Undergraduate and above	41(20.71)
Seizure type (n , %)	Focal	85(42.93)
	Generalized	109(55.05)
	unknown	4(2.02)
Seizure frequency (n , %)	> 1/week	23(11.62)
	> 1/month	40(20.20)
	> 1/3 months	45(22.73)
	> 1/6 months	38(19.19)
	> 1/year	25(12.63)
	1/1-2years	13(6.57)
	> 1/1-2years	14(7.07)
SE (n , %)	No	110(55.56)
	Yes	88 (44.44)
ASMs (n , %)	LEV	30(15.15)
	VPA	41(20.71)
	OXC	30(15.15)
	TPM	27 (13.64)
	LTG	31 (15.67)
	Other drugs	11 (5.05)
	Not taking medication	28 (14.14)
LSSS2.0 (Mean±SD)		66.52±10.13(37.5~92.5)
GTE (Mean±SD) (n)		12.76±5.45 (3~27) (88)
SSQ (Mean±SD)		2.9±1.19 (0.75~8)

topiramate (TPM) in 27 cases (13.64 %), and lamotrigine (LTG) in 31 cases (15.67 %). Other drugs such as carbamazepine, phenytoin sodium, and pirempanel were used in 11 cases (5.56 %). Additionally, 28 cases (14.14 %) did not take any medication. The LSSS2.0 scores ranged from 37.5 to 92.5 (mean 66.52 ± 10.13), and the GTE scores of the 88 EEGs performed during the PIS period ranged from 3 to 27 (mean 12.76 ± 5.45), with SSQ scores ranging from 0.75 to 8 (mean 2.9 ± 1.19).

There were 30 instances in the LEV group, 41 instances in the VPA group, 30 instances in the OXC group, 27 instances in the TPM group, 31 instances in the LTG group, and 28 instances in the control group. There was no statistically significant difference in the general clinical data (sex, age, timing of drug administration, drug dosage, and number of episodes in the 2 months prior to enrollment in the group) (Table 2).

Comparison of PIS-related LSSS2.0 item scores in the 6 patient groups (Table 3): the overall difference between the five total scores of the patients in the six groups was statistically significant ($p < 0.001$). Compared with the control group, the LEV group, the VPA group, the TPM group, the OXC group, and the LTG group could reduce the five total scores ($p < 0.05$). Each of the relevant LSSS2.0 items was analyzed individually (Fig. 1.). Compared to the control group, the LEV group showed a significant decrease in postictal panic, postictal panic duration scores decreased significantly ($p < 0.05$). The VPA group caused a significant decrease in postictal panic and postictal panic duration scores ($P < 0.05$). The OXC group caused a significant decrease in postictal panic duration and postictal sleepiness scores ($P < 0.05$). The TPM group caused a significant decrease in postictal panic and postictal headache scores ($P < 0.05$). And the LTG group caused a significant decrease in postictal sleepiness and postictal state duration scores ($P < 0.05$).

The comparison of SSQ scale scores among 6 patient groups (Table 4) showed a statistically significant overall difference in SSQ total scores between the 6 groups ($P < 0.05$). All 5 drugs led to a significant decrease in SSQ total scores, DS scores, AS scores, and SB scores compared to the control group ($P < 0.05$), while the difference in BS scores was not statistically significant ($P < 0.05$).

The GTE scores of the 6 patient groups were compared (Table 5). Statistically significant differences in GTE scores were observed at the PIS stage for all 6 groups ($p < 0.05$). Compared to the control group, the LEV, VPA, OXC, and LTG groups all resulted in a significant decrease in GTE scores during the later stages of the seizure ($p < 0.05$).Table 5 Comparison of 6 groups of patients on GTE scores.

4. Discussion

PIS's mechanisms are still not completely understood. Using cerebral angiography, single photon emission computed tomography, and functional magnetic resonance imaging, some researchers [8] have discovered that intracranial blood flow and metabolism gradually decrease after a seizure ends in patients with focal epilepsy who experience hyperperfusion or hypermetabolism during the seizure period. Changes in blood flow and brain metabolism following a seizure are thought to have a significant role in PIS development. According to some academics, PIS might be connected to changes in the brain's neurotransmitter release patterns and receptor affinities. The threshold for seizure recurrence is raised by increased brain release of opioid peptide transmitters and elevated affinities for opioid receptors, which have endogenous antiepileptic effects, according to Burtscher and Schwarzer's study [9] of PIS in temporal lobe epilepsy. This allows patients to exhibit a postictal state of inhibition of brain function. Moreover, it has been proposed that PIS may potentially be linked to neurovascular uncoupling, active neuronal inhibition, and immunoinflammatory reactions [10–12].

PIS has no established treatment guidelines; nevertheless, prior research suggests that pharmacologic and nonpharmacologic interventions are both part of the management of PIS. While pharmacologic treatments for PIS have not been thoroughly explored, some experts [13,14] think that vagus nerve stimulation, low-frequency repetitive transcranial magnetic stimulation, and electroconvulsive shock may be useful in improving PIS.

The study involved 170 patients in the treatment group who had been using one of the ASMs for ≥ 3 months and had their medication adjusted to an effective dosage, and 28 patients in the control group who had received a new epilepsy diagnosis and had not previously taken medication. The LSSS2.0 and SSQ were the primary tools used to evaluate PIS, and the findings demonstrated that the treatment group was able to reduce the scores associated with PIS in both the LSSS2.0 and the SSQ, in comparison to the control group.

Table 3
Comparison of PIS-related LSSS2.0 scores in 6 groups of patients (X ± s) .

Group	Q4	Q5	Q7	Q8	Q12	Total score
LEV	1.57 ± 0.82	2.10 ± 0.71	1.83 ± 0.70	2.07 ± 1.05	2.70 ± 0.95	10.33 ± 1.37
VPA	1.61 ± 0.80	2.05 ± 0.74	2.02 ± 0.82	2.10 ± 1.00	2.12 ± 1.05	9.90 ± 1.32
OXC	1.94 ± 0.77	2.26 ± 1.09	2.19 ± 0.79	1.58 ± 1.23	2.97 ± 0.98	10.94 ± 2.05
TPM	1.82 ± 0.68	2.67 ± 1.11	1.78 ± 0.75	1.93 ± 1.11	2.15 ± 1.13	10.63 ± 1.60
LTG	1.90 ± 0.76	2.70 ± 1.37	1.56 ± 0.90	1.83 ± 1.15	1.93 ± 1.08	10.07 ± 2.07
Control group	2.25 ± 0.59	2.96 ± 1.26	2.32 ± 0.72	2.46 ± 0.69	2.61 ± 1.13	12.64 ± 1.64
P	0.006	0.002	0.003	0.043	0.001	<0.001

Abbreviations: Q4 = the scores of confusing after the most seizures;Q5 = the duration of the confusion after the most seizures;Q7 = the scores of postictal headache;Q8 = the scores of Post-ictal sleepiness;Q12 = the duration of PIS.

Table 2
Comparison of core data of 6 groups of patients (X ± s) .

Group	n	Female	Male	Age(year)	timing of drug administration (year)	Dosage administration (m/mg)	Attack frequency	Seizure type (n)	
								Generalized	Focal
LEV	30	14	16	38.40 ± 17.77	6.35 ± 4.15	500 ~ 2000	2.01 ± 0.46	16	14
VPA	41	17	24	43.61 ± 18.16	7.46 ± 3.53	750 ~ 2000	3.73 ± 0.96	23	18
OXC	30	16	17	42.81 ± 17.59	6.73 ± 4.32	300 ~ 1050	3.65 ± 0.75	13	17
TPM	27	12	15	43.15 ± 16.21	5.79 ± 2.93	5000 ~ 2000	2.85 ± 1.14	14	13
LTG	31	18	13	49.63 ± 19.57	6.39 ± 3.65	500 ~ 1000	2.81 ± 0.68	18	13
Control group	28	13	15	50.64 ± 21.94	–	–	1.93 ± 0.51	10	18
P	–	0.51		0.43	0.27	1.18	0.39	0.33	0.29

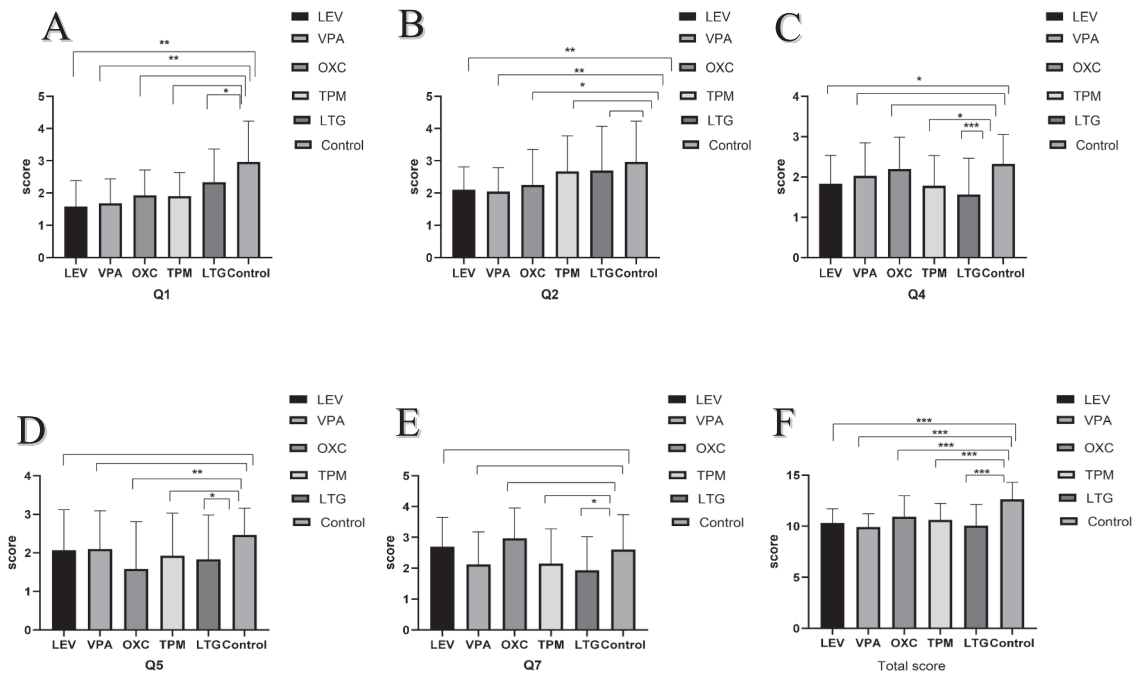

Fig. 1. Abbreviations: Q4 = the scores of confusing after the most seizures;Q5 = the duration of the confusion after the most seizures;Q7 = the scores of postictal headache;Q8 = the scores of Post-ictal sleepiness;Q12 = the duration of PIS.

Table 4
Comparison of SSQ scores in 6 groups of patients (X ± s) .

Group	BS	DS	AS	SB	Total
LEV	1.54 ± 0.74	2.29 ± 0.85	2.61 ± 1.73	2.18 ± 1.28	3.58 ± 1.66
VPA	2.05 ± 1.20	3.63 ± 1.22	1.86 ± 1.30	3.07 ± 1.08	1.96 ± 0.89
OXC	2.06 ± 1.06	3.52 ± 1.34	3.19 ± 1.01	3.61 ± 1.20	3.10 ± 0.84
TPM	1.70 ± 0.87	3.41 ± 1.69	2.81 ± 1.47	2.70 ± 1.79	2.66 ± 1.10
LTG	1.83 ± 0.95	2.60 ± 1.13	2.60 ± 1.13	2.77 ± 1.36	2.45 ± 0.89
Control group	2.10 ± 1.13	3.73 ± 1.72	3.33 ± 1.40	4.13 ± 1.66	4.12 ± 5.88
P	0.190	<0.001	0.001	<0.001	0.039

Table 5
Comparison of GTE scores in 6 groups of patients (X ± s) .

Group	LEV	VPA	OXC	TPM	LTG	Control group	P
GTE	6.83 ± 3.15	7.35 ± 3.22	7.95 ± 3.56	9.57 ± 3.83	8.68 ± 3.74	11.32 ± 4.15	0.003

In a research study [15] examining the impact of LEV on EEG activity during and after seizures, it was observed that LEV led to a quicker recovery of EEG background activity. As EEG background activity recovered, the patients also exhibited improvements in their level of consciousness and behavioral states. However, there was no correlation with the patients' subjective experiences. Out of the eighty-eight patients who underwent EEG during PIS, thirteen were taking LEV. While there was a statistically significant decrease in GTE scores among patients in the LEV group compared to the control group, the sample size was limited, and the findings may not be entirely convincing. A study [16] demonstrated that the only medication found to improve PIS in first-generation ASMs was VPA. The results of this study also indicated that VPA led to a significant decrease in postictal panic scores and postictal panic duration scores on the LSSS 2.0. It was concluded by Chen [17] et al. that OXC can significantly enhance the quality of life of epileptic patients and improve their mood. [18]. In this study, the SSQ and LSSS 2.0 were utilized to evaluate PIS in epilepsy patients, and it was found that OXC could result in a reduction in anxiety and significant decreases in post-seizure panic duration scores and post-seizure sleepiness scores on the LSSS 2.0. Another recent study [19] utilized the SSQ scale to assess changes in seizure severity in patients taking eslicarbazepine acetate, and it was found that the scores were significantly lower than those of patients treated with placebo. However, there are limited studies on whether OXC improves PIS in epilepsy patients. This study offers an initial evaluation of this and presents a new rationale for the clinical use of OXC, but the sample size is limited, and more samples are necessary for further investigation. TPM is widely used to treat primary generalized tonic-clonic seizures or focal seizures in both adults and children (2–16 years) [20]. Studies carried out by KERR [21] and BAKER [22] et al. with epileptic patients taking TPM using the LSSS scale showed significantly decreased scores in these patients, but the post-seizure subscales were not reported in the above-mentioned studies. The present study was conducted to assess the postictal subscale, and it showed that TPM can lead to a decrease in postictal panic and postictal headache item scores, which may be attributed to the fact that TPM itself is used as a treatment option for migraine headache [23–25]; Lamotrigine is a broad-spectrum antiepileptic drug used for partial seizures in adults and generalized seizures in children with Lennox-Gastaut syndrome older than 2 years, as well as in the adult population. [26], It is also considered a first-line treatment for patients with focal epilepsy [27], A 16-week prospective, non-randomized clinical trial [28] conducted by Bryant et al. showed that patients completing a 16-week observational study of lamotrigine treatment had significantly lower LSSS scores and scores related to the time to recovery from seizures, as reported by physicians, but separate scores for PIS were not reported. The results of this study indicate that lamotrigine improves PIS in epileptic patients.

Over time, new ASMs continue to enter the market with efficacy and tolerability at least equivalent to or better than older anti-seizure medications [29]. Lancman [30] et al. utilized the LSSS in patients with refractory partial epilepsy who were taking lacosamide to assess seizure

severity at baseline and at the end of the study (28 weeks). There was no significant difference in LSSS, but another study [31] also discovered that lacosamide led to postictal EEG improvement in 40.9 % of patients. Glauser [32] et al. incorporated seizure severity as one of the secondary efficacy parameters in a study of lufenamide in patients with Lennox-Gastaut syndrome, and at the end of the study, there was a notable reduction in seizure severity scores. Similar to many drug trials of ASMs, there was no distinct measurement of postictal seizure.

This study has several shortcomings. First, as a single study, sample collection was regionally limited, and second, a controlled trial was not conducted for the 3rd generation ASMs, such as lufenamide and lacosamide, because there are fewer studies and some of the drugs have not yet been introduced in the country, making it difficult to collect information in the clinic.

5. Conclusion

Levetiracetam, lamotrigine, oxcarbazepine, topiramate, and valproate demonstrate favorable efficacy in ameliorating the severity of post-seizure condition. Further investigations are warranted to assess the potential of other widely employed anti-seizure medications in enhancing post-seizure status.

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CRediT authorship contribution statement

Lanlan Cao: Writing – original draft, Validation, Investigation, Conceptualization. **Yue Chen:** Investigation, Data curation. **Ning Lv:** Investigation, Data curation. **Yanchi Xu:** Software, Formal analysis. **Honghua Chen:** Investigation, Formal analysis. **Lihong Tao:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

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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