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Research article

Efficacy and prognostic value of peripheral blood CD4$^+$ T cells and serum IL-6 and IL-8 in tuberculous meningitis

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ABSTRACT

Objective: To investigate the value of peripheral blood clusters of differentiation 4 (CD4$^+$) T-lymphocyte (T cells) count and serum interleukin-6 (IL-6) and interleukin-8 (IL-8) in the treatment and prognosis of tuberculous meningitis (TBM).

Methods: Sixty-five patients with TBM were prospectively included in the observation group. Sixty-five patients with pulmonary TB and a group of 65 healthy individuals served as the control groups. The differences in peripheral blood CD4$^+$ T-cell count, serum IL-6, and IL-8 levels were compared, and changes in these indices after anti-TB treatment in the observation group were analysed. The observation group was divided into effective and ineffective groups based on their response after 24 weeks of anti-TB treatment. The study also evaluated the influence of peripheral blood CD4$^+$ T-cell count, serum IL-6, and IL-8 levels on the adverse prognosis of TBM during anti-TB treatment.

Results: Before treatment, the CD4$^+$ T-cell count in the peripheral blood of the observation group was lower than in both the control and healthy groups, and serum IL-6 and IL-8 levels were higher than in the control group ($P < 0.001$). After 24 weeks of anti-TB treatment, the CD4$^+$ T-cell count in the peripheral blood of the observation group increased, whereas the levels of IL-6 and IL-8 decreased significantly ($P < 0.001$). The levels of CD4$^+$ T cells and IL-6 in the peripheral blood of patients before treatment were identified as independent factors influencing the efficacy of anti-TB treatment (*odds ratio [OR] = 0.989, 95 % confidence interval [CI]: 0.980–0.997; OR = 1.010, 95 % CI: 1.003–1.017*).

Conclusion: In patients with TBM, the CD4$^+$ T-cell count in the peripheral blood is decreased, whereas serum IL-6 and IL-8 are increased. The combination of CD4$^+$ T cells and IL-8 shows a degree of predictive value for the prognosis of anti-TB treatment.

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1. Introduction

Tuberculous meningitis (TBM) is a non-purulent intracranial inflammatory disease caused by *Mycobacterium tuberculosis* (*MTB*). It represents the most severe form of extrapulmonary TB, associated with high mortality and disability rates [1,2]. The pathology typically involves inflammatory exudation at the infection site, the formation of tuberculous nodules, and caseous necrosis. Immune regulation is pivotal in TB infection, with T-lymphocytes (T cells) playing a central role at the cellular level. T cells are categorised into clusters of differentiation 4 ($CD4^+$) and $CD8^+$ T cells. It is well-established that $CD4^+$ T cells are the primary immune regulatory cells in the human body's defence against *MTB*, substantially influencing the disease's outcome [3]. Upon *MTB* infection, $CD4^+$ T cells can activate macrophages, natural killer (NK) cells, and other cells to produce antibacterial components, aiding in the clearance of TB bacteria [4]. The literature has explored variations in T-cell counts in patients with TB, suggesting causes such as T-cell aggregation at the infection site, increased cellular apoptosis, and impaired thymus function [5,6].

Cytokines, bioactive substances synthesised and secreted upon stimulation by immune or specific non-immune cells, play a critical role in the immune response following *MTB* infection – interleukin-6 (IL-6) and interleukin-8 (IL-8) exhibit bidirectional immunomodulatory functions in TB [7]. Interleukin-8 can induce the infiltration of neutrophils, lymphocytes, and monocytes, fostering a localised inflammatory response that aids pathogen elimination. However, it can also disrupt the blood–brain barrier, damaging central nervous system (CNS) cells. Interleukin-6 promotes T-cell proliferation and differentiation, activates macrophages, and enhances NK cell cytotoxicity, contributing to resistance against *MTB* infection [8]. Studies have shown substantially higher levels of IL-6 in the cerebrospinal fluid (CSF) of patients with TBM than those with viral meningitis, particularly elevated during the acute phase and notably reduced following anti-TB treatment [9]. Research involving 44 paediatric patients with TBM identified a positive correlation between CSF levels of IL-6 and IL-8 and the extent of cerebral infarction [10]. Thus, the levels of IL-6 and IL-8 in the CSF are substantial for diagnosing TBM, differentiating it from other conditions, and assessing treatment efficacy. Additionally, IL-6 has been found to induce IL-8 production and promote T-cell aggregation [11]. However, the prognostic role of peripheral blood $CD4^+$ T cells and serum IL-6 and IL-8 in TBM remains unclear.

This study retrospectively collected data on peripheral blood $CD4^+$ T cells, serum IL-6, and IL-8, along with clinical data from patients with TBM, to analyse changes before and after treatment and their correlation with prognosis. The findings aim to provide valuable reference points for the clinical prognosis assessment of patients with TBM.

2. Materials and methods

2.1. Participants and grouping

This prospective study, conducted between January 2020 and December 2021, included 65 patients diagnosed with TBM. The observation group comprised 38 men (58.5 %) and 27 women (41.5 %), with a mean age of 33.5 $\pm$ 1.4 years. The control group included 56 patients with pulmonary tuberculosis (TB) but without TBM, consisting of 34 men (60.7 %) and 22 women (39.3 %), with a mean age of 33.4 $\pm$ 1.4 years. Statistical analysis confirmed no significant differences in gender distribution or age between the two groups ($P > 0.05$). Based on treatment efficacy after 24 weeks of anti-TB therapy, the observation group was subdivided into a complete/partial-response (C/PR) group with 52 patients (80.0 %) and a no-response (NR) group with 13 patients (20.0 %). The study protocol was approved by the Ethics Committee of the Third People's Hospital of Kunming, China. All participants provided informed consent.

2.2. Inclusion and exclusion criteria

The inclusion criteria for the observation group were as follows: (1) a diagnosis of TBM as per the 'Clinical Guidelines for Tuberculosis of the Central Nervous System in China' (2019) [12]; (2) age between 18 and 60 years; and (3) voluntary participation with the capability to adhere to the prescribed anti-TB regimen. For the control group, inclusion criteria were as follows: (1) diagnosis of pulmonary TB according to the 'Diagnostic Criteria for Pulmonary Tuberculosis WS288-2017 of the Health Industry Standard of the People's Republic of China' [13]; (2) no evidence of intracranial TB or other forms of extrapulmonary TB; (3) age between 18 and 60 years; and (4) voluntary participation.

The exclusion criteria for all participants included the following: (1) HIV infection; (2) previous anti-TB treatment outside the hospital for more than 1 week; (3) infants diagnosed with TB at birth, whose mothers had TB during pregnancy; (4) a history of connective tissue disease requiring corticosteroids or immunosuppressive therapy; (5) a history of malignant tumours or undergoing radiotherapy or chemotherapy within the previous year.

2.3. Tuberculous meningitis treatment protocol

The treatment protocol for TBM was structured as follows:

Anti-TB regimen [8]: The initial intensive phase involved a combination of four drugs – isoniazid, rifampicin, pyrazinamide, and ethambutol – for a minimum of 2 months. This was followed by a continuation phase with isoniazid and rifampicin lasting no less than 12 months.

Corticosteroid therapy [8,14,15]: Treatment began with dexamethasone at a daily dose of 0.3–0.4 mg/kg, which was gradually

tapered. In later stages, depending on the patient's condition, therapy could transition to oral prednisone, typically over the course of 4–8 weeks.

Intracranial pressure reduction therapy: This involved the administration of 20 % mannitol (125–250 ml intravenously) 2–3 times daily or 10 % glycerol fructose (250 ml intravenously) 2–3 times daily. Alternatives included administering high-glucose solutions and human albumin via an intravenous drip.

Symptomatic treatment: This included nutritional support, antiepileptic treatment, and neurotrophic therapies.

2.4. Tuberculous meningitis efficacy assessment criteria

The efficacy of TBM treatment was assessed using the following criteria [16]:

1) Complete response: This outcome is characterised by the complete resolution of clinical symptoms (e.g. fever, changes in consciousness, cranial nerve deficits) and signs (such as meningeal irritation indicators and pathological reflexes). Additionally, CSF test results return to normal, including routine biochemistry, a negative acid-fast bacilli smear, and no further culturing of *MTB* in the CSF. Head magnetic resonance imaging (MRI) must show nearly complete resolution or calcification of the lesions.
2) Partial response: This outcome is noted when clinical symptoms show improvement; CSF test results exhibit partial improvement, including enhancements in routine CSF biochemistry, a negative acid-fast bacilli smear, and no further culturing of *MTB*. A head MRI should indicate partial absorption of lesions.
3) No response: This outcome is characterised by no improvement or progressive worsening of clinical symptoms and/or signs (e.g. unchanged or worsening meningeal irritation signs, pathological reflexes, or the emergence of new pathological signs). CSF test results indicated no change or deterioration, and head MRI displays no absorption of lesions or a progressive increase and/or severe basal adhesions.
4) Death: This includes progressive deterioration, worsening conditions, or death during treatment.

Due to the lengthy treatment duration required for TBM, with a full course lasting no less than 12 months, and considering that 24 weeks may be insufficient for a complete treatment course, this study categorises 'complete response' and 'partial response' cases into the C/PR group. Conversely, 'no response' and 'death' cases are categorised into the NR group according to the aforementioned criteria.

2.5. Laboratory examination

For patients diagnosed with TBM, 5 ml of fasting peripheral blood was collected on the morning following admission using a heparinised tube and immediately processed for analysis. The counts of $CD4^+$ T-cells were measured using 3–5 ml of whole blood on a BD FACSVia™ flow cytometer (Beckman Coulter, USA). Levels of IL-6 and IL-8 were quantified using enzyme-linked immunosorbent assay kits provided by Jiangxi Saiji Biotechnology.

2.6. Statistical methods

Data analysis was carried out using SPSS software (version 26.0). The Shapiro–Wilk test was used to assess the normality of the

Table 1
Distribution of tuberculosis etiology, immunological tests, and extracerebral tuberculosis.

General Information	n	%
Distribution of tuberculosis outside the CNS		
Miliary Pulmonary Tuberculosis	28	43.1
Cavitary Pulmonary Tuberculosis	1	1.5
Tuberculous Pleurisy	6	9.2
Urogenital Tuberculosis	1	1.5
Tuberculous Knee Arthritis	1	1.5
Tuberculous Peritonitis	4	6.2
Tuberculous Pericarditis	1	1.5
Intestinal Tuberculosis	2	3.1
Tuberculosis Post In-Vitro Fertilization and Embryo Transfer	4	6.2
Immunological Tests		
TST (Tuberculin Skin Test)		
≥5 mm, <10 mm	5	7.7
≥10 mm, <15 mm	36	55.4
Average TST Diameter ≥15 mm	22	33.8
IGRA (Interferon-Gamma Release Assay) Positive	35	53.8
Etiological Positive		
CSF (Cerebrospinal Fluid) Smear	4	6.2
CSF Xpert MTB/RIF	8	12.3
CSF Tuberculosis Culture	27	41.5

quantitative data. Normally distributed data are presented as mean ± standard deviation and were compared between groups using the independent samples *t*-test. Skewed data are shown as median (interquartile range) (*M[Q1, Q3]*) and were analysed using the rank-sum test. Categorical data are expressed as percentages (%) and compared between groups using the χ^2 test or Fisher's exact test, as appropriate. Multifactorial logistic regression analysis was utilised to identify the risk factors affecting the efficacy of anti-TB treatment in TBM. A result indicating $P < 0.05$ was considered statistically significant.

3. Results

3.1. General information

Among the 65 patients with TBM, 37 (56.9 %) were clinically diagnosed, whereas 28 (43.1 %) received laboratory confirmation. Laboratory diagnostics included positive *MTB* cultures from CSF in 27 cases, positive acid-fast bacilli smears in 4 cases and, positive Xpert MTB/RIF assays in 8 cases. All patients were also diagnosed with pulmonary TB. After 24 weeks of treatment, the outcomes were as follows: 47 (72.3 %) patients showed a complete response, 6 (9.2 %) a partial response, 4 (6.2 %) no response, and 8 (12.3 %) died (Table 1).

3.2. Comparison of $CD4^+$ T cells, IL-6, and IL-8 levels before treatment between the observation and control groups

Initially, the observation group demonstrated substantially lower peripheral blood $CD4^+$ T-cell counts, averaging 293 (192.31, 388.11) cells/μl, compared with 837 (690.79, 986.65) cells/μl in the control group and 986 (869.18, 1084.96) cells/μl in the healthy group ($Z = 8.584$, $P < 0.001$). Serum IL-6 and IL-8 levels prior to treatment were markedly higher in the observation group at 21.16 (6.31, 64.92) pg/ml and 91.73 (38.9, 194.95) pg/ml, respectively than those in the control group (IL-6: 3.59 [1.98, 5.31] pg/ml; IL-8: 14.18 [8.15, 23.91] pg/ml) and the healthy group (IL-6: 3.01 [1.33, 4.25] pg/ml, $Z = -6.968$, $P < 0.001$; IL-8: 18.36 [8.60, 29.96] pg/ml, $Z = -8.312$, $P < 0.001$) (Table 2).

3.3. Comparison of $CD4^+$ T cells, IL-6, and IL-8 before and after treatment in the observation group

At the 24-week follow-up, the peripheral blood $CD4^+$ T-cell count in the observation group increased to 565.04 (403.21, 654.06) cells/μl; concurrently, serum IL-6 and IL-8 levels decreased to 5.29 (3.24, 9.55) pg/ml and 28.88 (15.2, 73.34) pg/ml, respectively. This represented a significant elevation in $CD4^+$ T-cell counts ($Z = 5.696$, $P < 0.001$) and a substantial reduction in IL-6 and IL-8 levels ($Z = -4.700$, $P < 0.001$; $Z = -4.962$, $P < 0.001$) compared with baseline (Table 3).

3.4. Logistic regression analysis of pre-treatment $CD4^+$ T cells, IL-6, and IL-8 with TBM prognosis

The observation group was subdivided into C/PR and NR groups to evaluate the treatment outcomes. Initial analyses revealed that the C/PR group had significantly higher peripheral blood $CD4^+$ T-cell counts at 319.75 (231.25, 418.10) cells/μl versus 161.23 (97.26, 240.80) cells/μl in the NR group ($Z = -3.624$, $P < 0.001$). Additionally, pre-treatment serum IL-6 and IL-8 levels were considerably lower in the C/PR group at 15.06 (5.27, 55.56) pg/ml and 71.52 (34.32, 176.48) pg/ml, respectively, compared with 58.16 (21.03, 165.16) pg/ml for IL-6 and 303.32 (125.89, 549.65) pg/ml for IL-8 in the NR group ($Z = -2.624$, $P = 0.009$; $Z = -3.132$, $P = 0.002$) (Table 4).

Binary logistic regression analysis indicated that a low pre-treatment level of $CD4^+$ T cells was a risk factor for poor TBM prognosis (*odds ratio [OR] = 0.989, 95 % confidence interval [CI]: 0.980–0.997*), and a high pre-treatment level of serum IL-8 was a risk factor for unfavourable treatment outcomes in TBM (*OR = 1.010, 95 % CI: 1.003–1.017*) (Table 5).

4. Discussion

Upon entering the body, *MTB* is phagocytosed by mononuclear phagocytic cells, which process and present bacterial antigens to $CD4^+$ T cells via the MHC class II pathway, thus initiating a T-cell response. Based on the cytokines they secrete, $CD4^+$ T cells are differentiated into Th1 and Th2 cells. The balance between these cell types is critical to the outcome and recovery from TB. Th1 cells, characterised by their production of interferon-gamma (IFN-γ), activation of NK cells, and promotion of cytotoxicity against cells harbouring intracellular bacteria, act as the principal effector cells against *MTB* [17,18]. Extensive *MTB* replication and infiltration can cause T-cell exhaustion. Observations indicate that even after 2 months of anti-TB drug therapy, immune activation continues, and the disrupted blood–brain barrier does not heal, highlighting the complex and sustained interaction between TB infection and the host's

Table 2
Comparison of serum CD4+T lymphocytes, IL-6, and IL-8 before treatment [median (quartile)].

	Observation Group (*n = 65*)	Control Group (*n = 65*)	Healthy Group (*n* = 65)	*Z-Value*	*P-Value*
CD4+T Lymphocytes (cells/μl)	293 (192.31, 388.11)	837 (690.79, 986.65)	986 (869.18, 1084.96)	8.584	<0.001
IL-6 (pg/ml)	21.16 (6.31, 64.92)	3.59 (1.98, 5.31)	3.01 (1.33, 4.25)	−6.968	<0.001
IL-8 (pg/ml)	91.73 (38.9, 194.95)	14.18 (8.15, 23.91)	18.36 (8.60, 29.96)	−8.312	<0.001

Table 3
Comparison of CD4+T cells, IL-6, and IL-8 before and after treatment in the observation group [median (quartile)].

	Before Treatment ($n = 65$)	After Treatment ($n = 65$)	*Z-Value*	*P-Value*
CD4+T Lymphocytes (cells/μl)	293 (192.31)	565.04 (403.21, 654.06)	5.696	<0.001
IL-6 (pg/ml)	21.16 (6.31, 64.92)	5.29 (3.24, 9.55)	−4.700	<0.001
IL-8 (pg/ml)	91.73 (38.9, 194.95)	28.88 (15.2, 73.34)	−4.962	<0.001

Table 4
Comparison of pre-treatment CD4+T cells, IL-6, and IL-8 in C/PR group and NR group [median (quartile)].

	C/PR group ($n = 52$)	NR group ($n = 13$)	*Z-Value*	*P-Value*
CD4+T Lymphocytes (cells/μl)	319.75 (231.25, 418.10)	161.23 (97.26, 240.80)	−3.624	<0.001
IL-6 (pg/ml)	15.06 (5.27, 55.56)	58.16 (21.03, 165.16)	−2.624	0.009
IL-8 (pg/ml)	71.52 (34.32, 176.48)	303.32 (125.89, 549.65)	−3.132	0.002

Table 5
Logistic regression analysis of pre-treatment CD4+T lymphocytes, IL-6, and IL-8 with TBM prognosis.

Characteristic	*β Value*	*s* Value	*Wald χ2* Value	*P-* Value	*OR* Value	95%*CI* Value
CD4+T Lymphocytes	−0.11	0.004	6.465	0.011	0.989	0.980–0.997
IL-8	0.010	0.004	7.014	0.008	1.010	1.003–1.017
Constant	0.260	1.144	0.051	0.821	1.296	

immune response [19]. The level of $CD4^+$ T-cell expression substantially influences the outcome post-*MTB* infection, as these lymphocytes interact with *MTB*-infected macrophages, playing a pivotal role in inhibiting intracellular *MTB* replication and promoting its clearance. Our study underscores the importance of $CD4^+$ T cells in assessing the host's immune status, determining the severity of the condition, and evaluating treatment effectiveness, aligning with findings reported in the literature [3,5,6].

Interleukin-6 is a multifunctional cytokine critical in regulating immune and inflammatory pathways [20]. It promotes B-cell proliferation and antibody secretion, stimulates the liver synthesis of acute-phase proteins, and plays a role in inflammatory responses, affecting both the nervous and hematopoietic systems. Following an *MTB* infection, activated macrophages release various substances, including IL-6, enhancing the body's capacity to combat *MTB* and prevent its dissemination within the host [21,22]. Initially, *MTB* infects macrophages and multiplies within these cells, prompting them to release cytokines such as IL-6, which in turn activate additional macrophages to combat the *MTB* infection [23]. It has been suggested that elevated levels of IL-6 induced by IGRA antigens in TB patients could be used to improve the diagnosis of *MTB* infection [24]. Research by Cao Xuan et al. [25] demonstrated that cytokine levels in the CSF, such as IL-6 and IL-8, are highly expressed during the early stages of TBM but gradually decrease following anti-TB treatment; these observations align with the results of our study.

Interleukin-8, a pro-inflammatory cytokine produced by monocytes in response to *MTB* stimulation, can chemotactically induce cell proliferation and participate in cellular immunity and delayed-type hypersensitivity reactions. These activities culminate in localised inflammatory responses that aid in the clearance or destruction of *MTB*. The interaction between IL-8 and *MTB* molecules may alter and enhance innate immune responses in patients with TB, intensifying localised inflammation and potentially disrupting the blood–brain barrier, leading to immune-mediated brain tissue damage [10]. Hussien et al. [26] measured CSF IL-8 levels in 90 patients with meningitis, noting substantially higher levels in bacterial meningitis and TBM compared with aseptic meningitis. Using a threshold of 121.77 pg/ml, they achieved an accuracy of 69 % in distinguishing viral from non-viral meningitis. However, IL-8 levels did not correlate with the severity or prognoses of the patients' conditions. In contrast, Sharma et al. [27] found a positive correlation between CSF IL-8 levels and the extent of brain tissue damage, as well as an association with the incidence of *MTB* invading intracranial vessels and subsequently leading to cerebral infarction. In paediatric patients with TBM, research shows that the sensitivity and specificity of diagnosing TBM through IL-8 levels in CSF are 63.2 % and 76.7 %, respectively. However, when combined with EAST-6 and IFN-γ testing, these figures increased to 91.2 % and 97.7 %, respectively [28]. Our research also identified high serum IL-8 levels as a risk factor for a poor prognosis in patients with TBM. Thus, the combined testing of IL-8 with other cytokines can support the diagnosis and assessment of therapeutic efficacy in TBM cases.

The CNS is often considered an 'immune-privileged site' due to the blood–brain barrier's usual ability to restrict the invasion of immune cells and molecules. Nevertheless, various factors can alter the permeability of this barrier, allowing adhesion molecules, antigens, and chemotactic factors to cross it and create a pathway between the CNS and the immune system, thus facilitating pathogenic microbial invasion [20]. A reduction in immune $CD4^+$ T-cell count heightens the body's susceptibility to *MTB* and can reactivate dormant *MTB* within the body. Upon *MTB* infection of the CNS, a complex series of immune responses are triggered, releasing cytokines such as IL-6 and IL-8. Although these responses bolster the body's ability to eliminate *MTB*, they exacerbate local inflammatory reactions, causing further inflammatory damage. Immunological injury to the brain parenchyma, meninges, and intracranial vessels presents substantial challenges in TBM treatment and is pivotal to outcome prognoses. Therefore, the use of $CD4^+$ T cells, IL-6, and IL-8 as indicators for analysing therapeutic efficacy and outcome prognosis in TBM can provide a more comprehensive assessment.

This study has several limitations. First, its scope is restricted by its single-centre design and relatively small sample size. Additionally, it lacks evidence from a comprehensive bacteriological examination. Notably, about 56 % of the cases were clinically diagnosed, with a smaller proportion of confirmed cases, which could potentially impact the accuracy and reliability of the findings. Second, the study did not monitor changes in IL-6 and IL-8 levels in the CSF before and after TBM treatment, nor did it assess their impact on the clinical prognosis of TBM. Furthermore, it lacked long-term follow-up results. The assessment endpoint of the study was confined to 24 weeks of anti-TB treatment, which did not allow for evaluating the prognostic efficacy of peripheral blood $CD4^+$ T cells, serum IL-6, and IL-8 throughout the entire course of therapy. Given the limited sensitivity of current bacteriological methods and the clinical criteria for diagnosing TBM, an integrated approach that combines microbiological, clinical, and radiological criteria might offer a more precise method for diagnosing TBM. Future research should focus on multi-centre prospective studies with larger patient cohorts, incorporating serial measurements and long-term follow-up at regular intervals to further validate these findings.

5. Conclusion

In summary, patients with TBM exhibited substantially lower $CD4^+$ T-cell counts and elevated levels of IL-6 and IL-8 in their serum. The combination of these blood parameters could potentially enhance the diagnostic accuracy of TBM. Following anti-TB treatment, patients with TBM experienced a substantial increase in peripheral $CD4^+$ T cells and a notable decrease in the serum levels of IL-6 and IL-8. Moreover, low pre-treatment $CD4^+$ T-cell counts and high IL-8 levels were associated with a poorer prognosis for anti-TB treatment in patients with TBM. These findings suggest that monitoring changes in $CD4^+$ T cells and IL-8 may provide early insights into the clinical efficacy of anti-TB treatment in patients with TBM, potentially enabling timely adjustments to treatment regimens and facilitating more tailored therapeutic interventions.

CRediT authorship contribution statement

Hua He: Writing – review & editing, Writing – original draft, Conceptualization. **Yan-Ling Zhang:** Writing – review & editing, Writing – original draft, Conceptualization. **Yang Li:** Writing – review & editing, Writing – original draft, Data curation. **Ying Huang:** Writing – review & editing, Writing – original draft, Data curation. **Xiang Li:** Writing – review & editing, Writing – original draft, Formal analysis. **Jun Xu:** Writing – review & editing, Writing – original draft, Conceptualization. **Ying-Rong Du:** Writing – review & editing, Writing – original draft, Conceptualization.

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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