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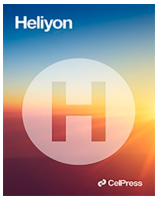

Research article

Prognostic value of PAX8 in small cell lung cancer

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ABSTRACT

Objectives: Small cell lung cancer (SCLC) shows poor prognosis since it metastasizes widely at early stage. Paired box gene (PAX) 8 is a transcriptional factor of PAX family, of which the expression in lung cancer is a controversial issue, and its prognostic value of PAX8 in SCLC is still unclear.

Materials and methods: Overall, 184 subjects who were pathologically diagnosed with SCLC were enrolled in the study. Immunohistochemical analysis of PAX8 and Ki-67 were performed. The correlations between PAX8 expression and clinical features or Ki-67 index were further analyzed. Subsequently, an analysis of the association between PAX8, stage, Ki-67 status, and overall survival (OS) were performed in 169 subjects with follow-up information.

Results: PAX8 was positive in 53.8% (99/184) SCLC specimens. The positive rate is significantly higher in extensive-stage specimens (61.0%) than in limited-stage specimens (45.24%). PAX8 expression is positively correlated with Ki-67 index ($P = 0.001$) while negatively correlated with OS (HR = 3.725, 95% CI 1.943–7.139, $P < 0.001$). In combination groups, the PAX8 negative and limited stage group had the most promising OS.

Conclusion: PAX8 expression rate in SCLC specimens is not low. It has prognostic value in small cell lung cancer.

1. Introduction

Lung cancer (LC) is the leading cause of cancer death [1,2]. Small cell lung cancer (SCLC), a neuroendocrine tumor (NET), accounts for 15% lung cancer cases [3]. SCLC grows rapidly and metastasizes widely at early stage, which correlates with the poor prognosis of SCLC patients [4]. Approximately two thirds of patients have extrathoracic metastases at the time of diagnosis, and the five-year overall survival rate is only 5–7% [1,2]. As the extent of the disease is the primary prognostic factor of SCLC, staging is a key factor in determining treatment plan. The Veterans Administration Lung Study Group classified SCLC into two stages, extensive stage and limited stage [5]. If the tumor mass is encompassed in one radiation portal, it is limited stage. Otherwise, it is classified as extensive stage [6].

Unfortunately, there is no effective treatment for SCLC for decades. Although the addition of immunotherapy to first-line chemotherapy introduced the first change in the systemic therapy for SCLC, improvements in overall response rate (ORR), progression free survival (PFS), and overall survival (OS) are quite few [7]. Therefore, there is an urgent need to further understand the

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Abbreviations

LC	lung cancer
SCLC	small cell lung cancer
NET	neuroendocrine tumor
PAX	paired box gene
ORR	overall response rate
PFS	progression free survival
OS	overall survival
NSCLC	non-small cell lung cancer
HR	hazard ratios
IHC	immunohistochemical
RTKs	receptor tyrosine kinases

pathogenesis, progression, and molecular characteristics of SCLC, to gain a deeper understanding of the disease and provide new directions for precise diagnosis and molecular targeted therapy.

PAX8, a member of paired box gene (PAX) family, is a transcription factor and essential for embryonic development of kidney, Müllerian duct and thyroid [8–10]. PAX8 is expressed in tumors such as pancreatic well-differentiated neuroendocrine tumor, rectal cancer, gastric cancer, and so forth [9,11–16]. The expression of PAX8 in lung cancer varies among reports. McHugh et al. found only 5 cases of primary lung cancer are PAX8 positive in 418 cases [17]. Asirvatham et al. [18] reported that only 1 case of poorly differentiated lung cancer was PAX8 positive in 15 cases of lung cancer. Jeong et al. [19] found that the expression rate of PAX8 in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) was 12.9% and 3.7%, respectively. Weissferdt et al. [20] demonstrated that PAX8 was not expressed in lung tumors. Toriyama et al. compared PAX8 polyclonal and monoclonal antibodies in lung tumors [16]. They found the positive rate of PAX8 using polyclonal antibody in adenocarcinoma, squamous cell carcinoma, large cell neuroendocrine carcinoma, small cell carcinoma and large cell carcinoma are 2.4%, 1.9%, 16%, 40.3% and 18.1%, respectively. However, none of them are PAX8 positive when the monoclonal antibody is used. The positive rate of PAX8 in NSCLC cells was lower than that in SCLC in the same study.

The above evidence indicates that PAX8 involves in the progression of cancer and the positive rate of PAX8 is higher in SCLC than that in NSCLC. However, the diagnostic potential of PAX8 needs to be further studied. To evaluate the significance of PAX8 in SCLC, the expression status of PAX8 in SCLC specimens were determined. Associations between clinical characteristics and PAX8 were then investigated. The association between PAX8 expression, Ki-67 index, stage status and OS is further analyzed to determine the potential of PAX8 as a prognostic factor for SCLC.

2. Materials and methods

2.1. Participants and clinical data collection

This study was approved by the Ethics Committee of Ningbo Clinical Pathology Diagnosis Center (NBPC-LL-LSP-202209). As the study is an observational anonymous study, the signed informed consent was waived. Patient inclusion criteria includes: patients with pathologically diagnosed small cell lung cancer; presence of evaluable tumor lesions; patients with complete medical records. Exclusion criteria includes: pulmonary fibrosis, bronchial asthma, chronic obstructive pulmonary disease, pulmonary infection, pulmonary tuberculosis, severe pulmonary disease, and those with tumors beyond small cell lung cancer.

The clinical data of patients with small cell lung cancer, including gender, age, smoking status, clinical stage, and imaging data, were collected by reviewing medical history and medical records. Clinical staging of patients with small cell lung cancer was determined according to the Veterans Administration Lung Study Group Staging (limited stage and extensive stage).

2.2. Immunohistochemistry staining and evaluation

The tissue samples were sliced into 3 μm-thick sections; the slices were then baked at 75 °C for 30 min or 65 °C overnight. Baked slices were processed ahead using automated Bond-III IHC stainer for immunostaining (LEICA, Germany). The samples were incubated with anti-Mouse PAX8 monoclonal antibody (1:1 dilution; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd; clone number: OTI6H8) or anti-Mouse Ki-67 monoclonal antibody (1:2500 dilution; Beijing Zhongshan Golden Bridge Biotechnology; clone number: UMAB107). Immunohistochemical (IHC) results were independently interpreted by two pathologists. PAX8 and Ki-67 are positive for cells with brownish-yellow coloration of the nucleus. Ten high-magnification fields of view in each slide were analyzed, and 200 tumor cells were counted per field of view. Judging was conducted according to the coloration and percentage of positive cells: tumor cells without coloration are negative; the tumor nucleus is colored, but the percentage of positive cells $<10\%$ is weakly positive; $\geq 10\%$ were positive for PAX8. Tumor cells without coloration are negative and the remaining positives are reported by percentage for Ki-67.

2.3. Statistical analysis

IBM SPSS Statistics version 25.0 (IBM SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Associations between PAX8 expression and clinical features were determined with the chi-square test. Survival analysis of patients was performed by Kaplan-Meier method and the significance between groups was checked by log-rank test. Cox proportional hazard model was applicated to survival data and the hazard ratios (HR) of stage, PAX8 expression and Ki-67 index were calculated. $P < 0.05$ was defined as statistical significance.

2.4. Cell culture

HEK-293T cells were cultured in DMEM with 10% FBS. Cell transfection was carried out using lipo8000 transfection reagent (Beyotime, China) according to the manufacturer's protocol.

2.5. Real-time PCR

Real-time PCR was performed by using the PerfectStart® Green qPCR SuperMix (Transgen, China) in ABI7500 PCR Systems (Applied Biosystems, USA). PAX8 was amplified with primers 5′-GTGAATACTCTGGCAATG -3′ and 5′-CTTGATGTGGAACTGTAAT-3'. GAPDH was used as control and was amplified with primers 5′-AGGTCGGAGTCAACGGATTT-3′ and 5′-TTCCCGTTCTCAGCCTTGAC-3'.

3. Results

3.1. Patient characteristics

We enrolled 184 subjects who were pathologically diagnosed with SCLC in Ningbo Clinical Pathology Diagnosis Center from January 2020 to December 2022. There were 59 specimens from never smokers and 125 specimens from smokers. The number of patients in limited stage and extensive stage was retrospectively 84 and 100 (Table 1).

3.2. PAX8 expression in small cell lung cancer specimens

The expression of PAX8 in 184 SCLC specimens was retrospectively analyzed. Overall, the positive rate of PAX8 was 53.8% (99/184). 61 cases of extensive stage (Fig. 1A) and 38 cases of limited stage (Fig. 1B) were identified as positive for PAX8. Otherwise, 39 extensive stage patients (Fig. 1C) and 46 limited stage patients (Fig. 1D) were PAX8 negative. To test the specificity of the PAX8 antibody used in this study, HEK-293T cells was transfected with PAX8 expression plasmid. The overexpression of PAX8 were confirmed by real-time PCR (Fig. 2A). There was an obvious positive staining in the nuclei compared with control cells by IHC (Fig. 2B).

PAX8 positive rate in limited stage and extensive stage is 45.24% (38/84) and 61% (61/100), respectively. The positive rate of PAX8 is significantly higher in extensive stage tumors than in limited stage tumors ($P = 0.033$) (Table 1).

3.3. PAX8 expression correlates with Ki-67 index

Association between clinical characteristics or Ki-67 index and PAX8 were further studied. The expression of PAX8 had no

Table 1
Expression of PAX8 in clinicopathological characteristics of SCLC.

Clinicopathological characteristics	n(%)	PAX8 express situation		P value
		Positive	Negative	
Sex				0.105
Men	161(87.5%)	83	78	
Women	23(12.5%)	16	7	
Age				0.507
<60	31(16.8%)	15	16	
≥60	153(83.2%)	84	69	
Smoking history				0.302
No	59(32.1%)	35	24	
Yes	125(67.9%)	64	61	
Ki-67 index[a]				0.001
≥60%	152(84.0%)	90	62	
< 60%	29(16.0%)	7	22	
Different stages of SCLC				0.033
Extensive stage	100(54.3%)	61	39	
Limited stage	84(45.7%)	38	46	

[a] There are three specimens without Ki-67 immunohistochemistry.

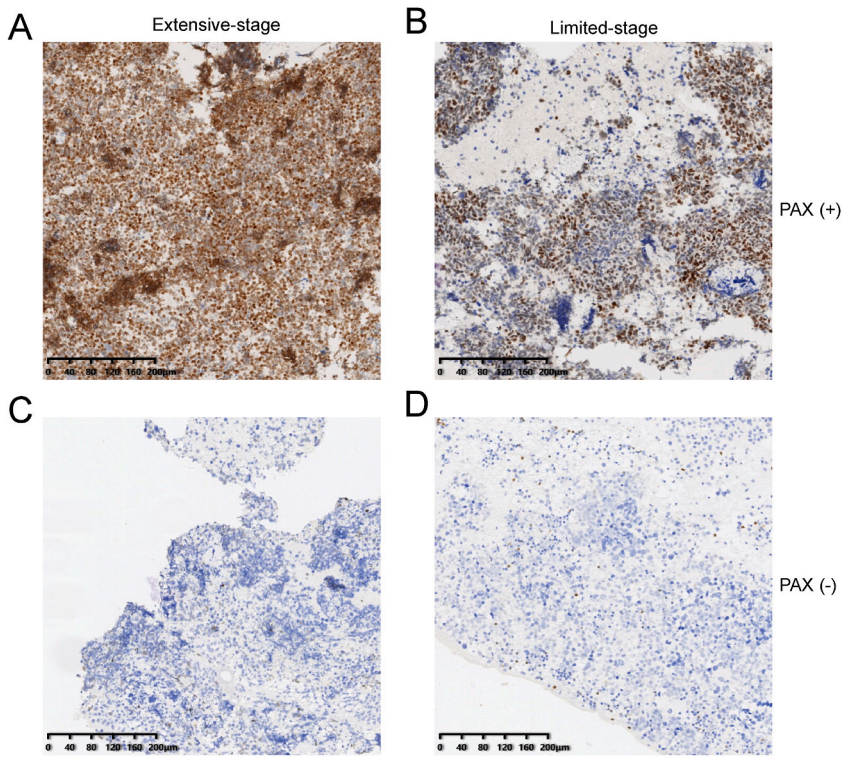

Fig. 1. Immunohistochemical expression of PAX8 in SCLC. (A) Extensive-stage SCLC PAX8 positive case. (B) Limited-stage small cell lung cancer PAX8 positive case. (C) Extensive-stage small cell lung cancer PAX8 negative case. (D) limited-stage small cell lung cancer PAX8 negative case.

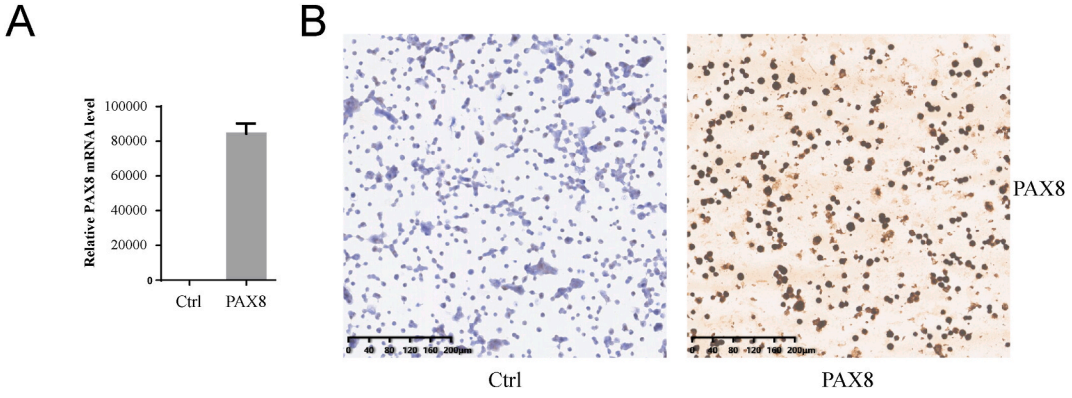

Fig. 2. Overexpression of PAX8 in HEK-293T. (A) Real-time PCR analysis of PAX8 in HEK-293T. (B) Immunohistochemical expression of PAX8 in HEK-293T.

significant correlation with sex, age and smoking history. However, in 152 high Ki-67 index (≥60%) cases and 29 low Ki-67 index (< 60%) cases, PAX8 positive rate is 59.21% (90/152) and 24.14% (7/29), respectively. High Ki-67 index subjects were at 2.45-fold greater possibility to be PAX8 positive ($P = 0.001$) (Table 1).

3.4. PAX8 expression level correlates with prognosis

To assess the prognostic value of PAX8 expression level in SCLC, the correlation between PAX8 expression level, Ki-67 index, stage status, and OS was evaluated in 169 subjects who have follow-up information. The results showed that OS in PAX8 negative group were significantly longer than those in PAX8 positive group ($P < 0.001$) (Fig. 3A). The mean OS for PAX8 positive group was 13.917 (±0.894)months, and the mean OS for PAX8 negative group was 26.085 (±1.485)months. The OS of limited stage was also significantly longer than extensive stage ($P < 0.001$) (Fig. 3C). The mean OS for limited stage and extensive stage were 26.571 (±1.546)

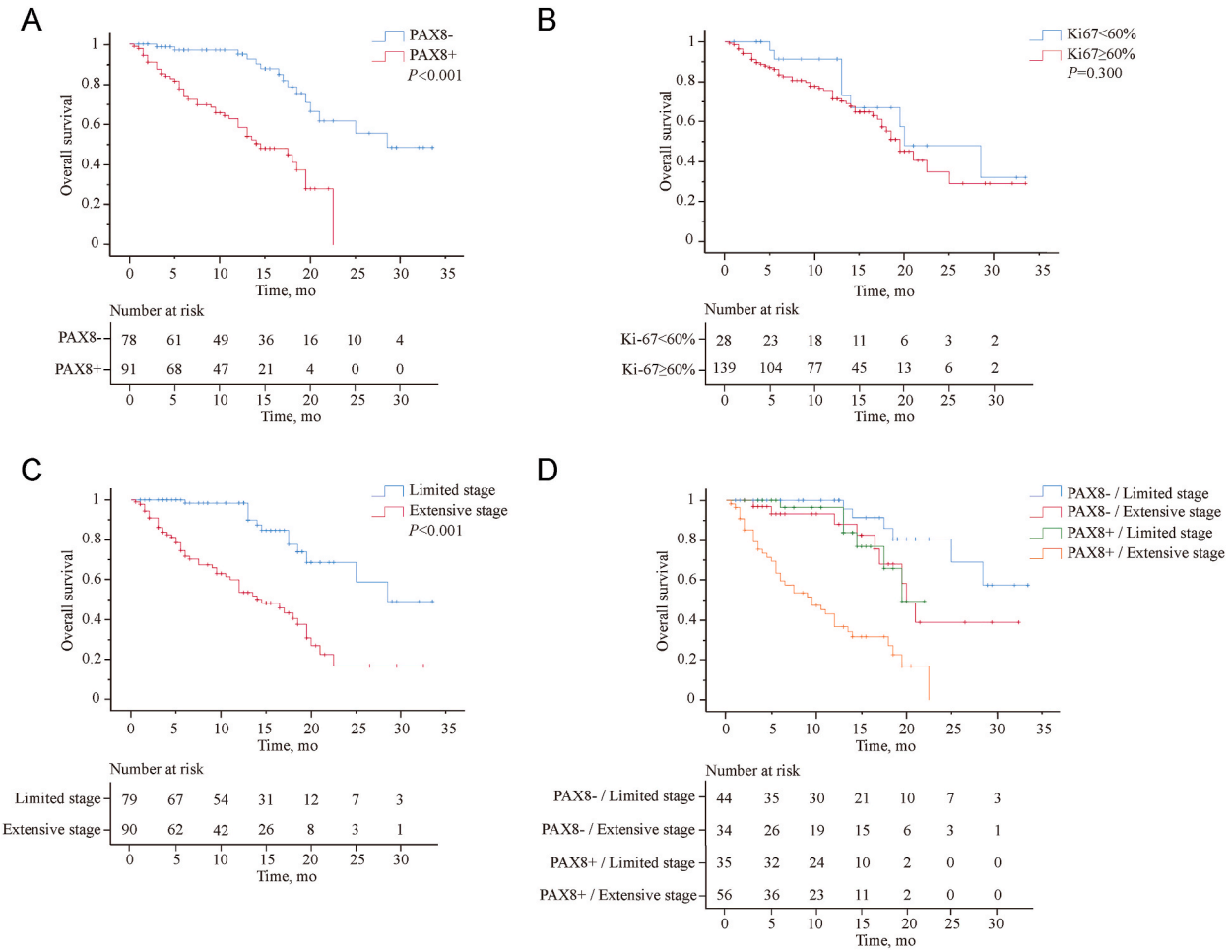

Fig. 3. Comparative survival analyses in SCLC patients. (A) Comparison of OS between PAX8 positive and PAX8 negative group. (B) Comparison of OS between Ki-67 high and Ki-67 low group. (C) Comparison of OS between Limited-stage and Extensive-stage patients. (D) Comparison of OS among PAX8 expression and stage status combination groups. The difference in OS between groups was compared by Log-rank test, with death as the outcome.

months and 15.212 (±1.367) months, respectively. Whereas, the Ki-67 index was not associated with OS ($P = 0.300$) (Fig. 3B). In multivariate Cox proportional hazard model, PAX8 positive significantly affected OS (HR = 3.725, 95% CI 1.943–7.139, $P < 0.001$). Extensive stage was significantly associated with OS as well (HR = 4.069, 95% CI 2.174–7.619, $P < 0.001$). The Ki-67 index showed no significance (HR = 0.814, 95% CI 0.384–1.725, $P = 0.591$) (Fig. 4). In combination group, the PAX8 negative and limited stage patient group has the most promising OS (Fig. 3D). It indicates that the PAX8 expression can be a prognostic factor for SCLC patients. The

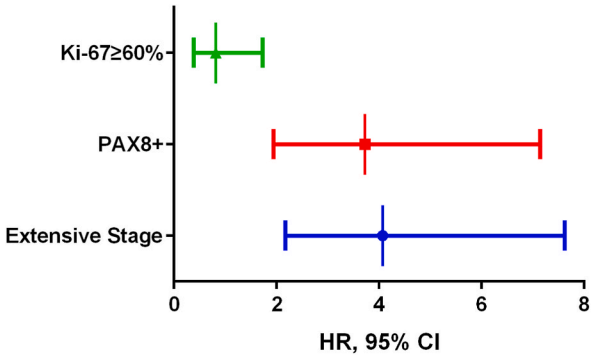

Fig. 4. The HR value of Ki-67, PAX8 and stage status for overall survival.

combination of PAX8 expression and stage statue could be a better prognostic factor for SCLC.

4. Discussion

Previous studies have shown that PAX8 is significantly expressed in a variety of tumors, exerts its biological function, and ultimately affects the development of cancer [21]. The positive rate of PAX8 varies from none to 40.3% in lung cancer, and it is higher in SCLC than NSCLC in the same study [16]. We found the positive rate of PAX8 is 53.8% (99/184) in Chinese small cell lung cancer, which is much higher than previous studies. The differences between studies could arise from the diversity of the races and ethnic groups of the specimens [22] or the application of distinct antibodies [16]. Toriyama et al. found that tests using polyclonal PAX8 antibody shows positive results while monoclonal antibody shows negative results in same specimens. It suggests that the monoclonal have a higher threshold for positive result. Detections using PAX8 monoclonal antibody have none positive sample in primary lung tumors in several studies while they have a large number of positive results in metastatic tumors [19]. The overexpression of PAX8 in metastatic tumors implies that PAX8 participates in cancer metastasis [23]. We find the PAX8 positive rate is significantly higher in extensive stage specimens than in limited stage specimens, which also indicates high PAX8 expression correlates with the metastatic ability of SCLC.

PAX8 has been found promoting tumor cell survival by inhibiting apoptosis. It can activate BCl2 transcription, and inhibit p53 transcription [24–26]. PAX8 modulats the tumor microenvironment by altering its secretome in high-grade serous ovarian cancer [27]. This study shows that PAX8 expression is significantly correlates with Ki-67 index. It suggests that PAX8 is involved in cell proliferation in SCLC.

SCLC is highly metastatic and overexpresses several RTKs, such as the receptor tyrosine kinases c-Kit and c-Met. C-Met plays an important role in cell motility and tumor metastasis [28]. Studies by Kanteti et al. have shown that PAX5 is a direct transcriptional activator of c-Met [29]. PAX8, PAX2 and PAX5 belong to the Subgroup II in PAX family according to structural similarity [24]. PAX8 and PAX5 having 70% N-terminal homology [16]. Whether PAX8 can transcriptionally activate c-Met in the same way as PAX5 does still need further research. The PAX8 has higher positive rate in extensive stage specimens than in limited stage specimens. As metastasis is the main cause of death in cancer, here we also analyzed the association between PAX8 status and overall survival (OS). PAX8 negative group have remarkable longer OS than PAX8 positive group. It indicates that PAX8 may influence patient survival through regulating cancer metastasis.

Immunohistochemical analysis of PAX8 in SCLC samples is not a routine test in clinical diagnosis. This study demonstrates the expression of PAX8 in SCLC is higher in advance SCLC. PAX8 expression is significantly correlated to the staging of SCLC and the level of Ki-67 index. PAX8 negatively correlates with a more promising overall survival. Above evidences indicate that PAX8 can a prognostic factor for SCLC patients. Whether PAX8 can be a therapeutic target in SCLC and the underlying signaling pathways still need further investigation.

Data availability statement

Data available on request from the authors.

Ethical statement

This study was approved by the Ethics Committee of Ningbo Clinical Pathology Diagnosis Center (NBPC-LL-LSP-202209). As the study is an observational anonymous study, the signed informed consent was waived.

CRediT authorship contribution statement

Fengyun Tao: Writing – original draft, Formal analysis, Conceptualization. **Hangyan Zhu:** Methodology, Formal analysis, Data curation. **Jiayun Xu:** Methodology, Formal analysis, Data curation. **Yanan Guo:** Validation, Investigation. **Xin Wang:** Methodology, Investigation. **Lei Shao:** Formal analysis. **Deng Pan:** Writing – original draft. **Guosheng Li:** Supervision, Conceptualization. **Rong Fang:** Writing – review & editing, Resources, Funding acquisition, 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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