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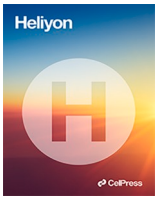

Research article

Prognostic factors for postoperative papillary thyroid cancer with unexplained elevated Tg: A retrospective study

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ABSTRACT

Objective: This study aimed to investigate the underlying reasons for unexplained elevated thyroglobulin (Tg) in postoperative papillary thyroid cancer (PTC) patients according to follow-up results post RAT and to explore the long-term clinical outcomes and prognostic factors associated with these patients.

Methods: From April 2016 to June 2019, a retrospective study was conducted on postoperative PTC patients who underwent RAT at our institution. Patients with preablative stimulated thyroglobulin (psTg) > 10 ng/mL but no structurally evident disease were enrolled. The causal categorization for elevated Tg was analyzed 6 months post RAT and the long-term therapeutic responses were assessed at the end of follow-up. To identify risk factors influencing recurrence-free survival (RFS), both univariate and multivariate Cox regression analysis were employed. Kaplan-Meier method was utilized for plotting survival curves.

Results: A cohort of 165 subjects was enrolled for the analyses. Based on the results of a six-month follow-up, the postoperative unexplained elevated Tg among 165 patients could be ultimately attributed to thyroid remnant in 13.94% (23/165), biochemical disease in 60.00% (99/165), and structural disease in 26.06% (43/165). With a median follow-up of 58 months, 51 (30.91%), 34 (20.60%), 21 (12.73%), and 59 (35.76%) of the 165 patients achieved ER, IDR, BIR and SIR, respectively. Univariate analysis showed that N stage, TNM stage and suppressed Tg 6 months post RAT may be prognostic factors affecting RFS. Multivariate analysis showed that N1b stage [HR:2.749, P = 0.003] and II/III stage [HR:2.910, P = 0.001] were independent risk factors for RFS.

Conclusion: The proportion of 165 postoperative PTC patients with unexplained elevated Tg developing structural disease within nearly 5 years was over 30%. Patients with N1b stage and higher TNM stage were more likely to develop structural disease.

1. Introduction

Patients with papillary thyroid cancer (PTC) typically have a favorable prognosis, despite the common occurrence of recurrence. Predicting both recurrence and prognosis is crucial for determining appropriate subsequent treatment strategies [1]. In detecting

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disease persistence or thyroid remnant and predicting potential recurrence, preablative stimulated thyroglobulin (psTg) is a valuable tool. A patient with psTg levels exceeding 10 ng/mL may require further evaluation and potential complementary treatments as the 2015 American Thyroid Association (ATA) guidelines recommend [2]. However, a subgroup of PTC patients who exhibit psTg levels greater than 10 ng/mL but lack structural evidence of disease, known as those with unexplained elevated Tg, remained controversial in terms of clinical treatment options. Some scholars [3–5] have advocated that thyroidectomized differentiated thyroid cancer (DTC) patients with unexplained elevated Tg may benefit from radioiodine (^{131}I) adjuvant therapy (RAT). Cheng et al. [4] conducted a study on 254 postoperative DTC patients with unexplained elevated Tg, assessing their responses to RAT over a 6-12-month period. They found that over 80% of patients achieved a non-structural incomplete response with a median follow-up of 10.6 months. Other studies [6–10] have investigated the long-term outcomes of DTC patients with unexplained elevated Tg 1–2 years following total thyroidectomy and initial ^{131}I treatment. These studies revealed that a substantial proportion of these patients (41–66%) were reclassified as developing structural disease during a median follow-up of 10–12 years. Despite this, the long-term outcomes and prognostic factors of PTC patients with unexplained elevated Tg within three months of total thyroidectomy remain largely unexplored. Therefore, we undertook this retrospective study to analyze the underlying reasons for unexplained elevated Tg in postoperative PTC patients. Furthermore, we explored the long-term clinical outcomes and prognostic factors of these patients, aiming to assist clinicians in making timely and optimal clinical decisions.

2. Materials and methods

2.1. Study populations

We conducted a retrospective analysis of medical records from patients with PTC who were treated and monitored at the Affiliated Hospital of Qingdao University between April 2016 and June 2019. Inclusion criteria: (1) Total thyroidectomy and cervical lymph node dissection were performed, and the postoperative pathological diagnosis confirmed the presence of PTC; (2) Patients were required to undergo RAT within three months following total thyroidectomy. This therapy was preceded by withdrawal of thyroid hormone to maintain TSH levels above 30mU/L, and patients were instructed to adhere to a low-iodine diet for 3–4 weeks. Given that RAT is not routinely recommended for low-risk patients, the study cohort exclusively comprised intermediate- and high-risk PTC patients; (3) PsTg $>$10 ng/mL and TgAb $<$115 IU/mL measured at the same time; (4) No persistence/recurrence and residual thyroid tissue was detected by ultrasound or CT before RAT; (5) $^{99m}TcO^{4-}$ static thyroid imaging showed no apparent visible remnant before RAT; (6) Follow-up time$\geq$2 years, complete medical records. Exclusion criteria: (1) Evidence of local recurrence or distant metastasis was found before RAT; (2) Residual thyroid tissue was visible on ultrasound and/or static thyroid imaging; (3) Loss of follow-up or incomplete medical records.

Patients received orally administered radioiodine with an activity ranging from 3.70 to 5.55 GBq (100–150 mCi) for the purpose of RAT. All patients underwent ^{131}I whole-body scintigraphy 4 days post RAT. After RAT, all patients took levothyroxine for TSH suppression and underwent regular follow-up. During follow-up, some patients who developed structural disease underwent reoperation or radiofrequency ablation or ^{125}I seed implantation or observation under TSH suppression therapy, while some patients performed repeated ^{131}I treatment on the premise of ^{131}I-avid lesions.

2.2. Evaluation of the therapeutic response

Clinical outcomes were determined based on all clinical data collected during the final follow-up. Diagnostic ^{131}I scintigraphy was used in patients with abnormal uptake of ^{131}I outside of the thyroid bed or persistent elevated Tg after RAT, as well as routine examinations including neck ultrasound and stimulated or suppressed Tg and TgAb. Additional imaging studies (CT, MR or positron emission tomography/CT) were performed at the clinicians' discretion. The therapeutic responses include excellent response (ER), biochemical incomplete response (BIR), indeterminate response (IDR), and structural incomplete response (SIR) (Table S1). In instances where structural evidence of the disease emerged, the presence of lymph node metastasis was verified through fine-needle aspiration biopsy with positive cytology, while distant metastasis was confirmed via biopsy and/or imaging modalities. The long-term outcomes at the end of follow-up were evaluated.

2.3. Causal categorization for elevated Tg

The underlying reasons for unexplained postoperative elevation of Tg levels were elucidated through a combination of methods, including ^{131}I whole-body scan post RAT, serial serum Tg tests, medical imaging, ultrasound-guided fine needle aspiration, and clinical follow-up within six months post RAT. The criteria for classification are outlined below [4]: (1) **Thyroid remnant** was identified through the presence of visible uptake in the normal thyroid bed or ectopia on post-RAT scanning, absence of persistent/recurrent/metastatic disease, and a suppressed Tg level of less than 0.2 ng/mL (2) **Biochemical disease** was confirmed in the absence of structural disease but with a Tg level of 0.2 ng/mL or higher. (3) **Structural disease** was defined as the identification of structural or functional evidence of disease through post-RAT scanning and/or other imaging examinations conducted during surveillance.

2.4. Sample analysis

The determination of TSH levels was carried out using an electrochemiluminescence immunoassay provided by Roche (Mannheim, Germany), with a detectable laboratory range spanning from 0.004 to 100 μIU/mL. The Tg level was assayed using the Elecsys® Tg II kit(Roche Diagnostics, Basilea, Switzerland), with a detection range of 0.04–500.00 ng/mL. The TgAb level was measured using the Elecsys® TgAb kit from Roche Diagnostics, and TgAb levels less than 115 IU/mL were considered negative. Tg was measured with the Elecsys® Tg II kit(Roche Diagnostics, Basilea, Switzerland), with a detection range of 0.04–500.00 ng/mL. Additionally, the TgAb level was assayed using the Elecsys® TgAb kit(Roche Diagnostics, Basilea, Switzerland). TgAb levels falling below 115 IU/mL were deemed negative. Genomic DNA was extracted from the primary tumors and subjected to traditional Sanger sequencing for the identification of $BRAF^{V600E}$ mutations.The $BRAF^{V600E}$ mutation status of primary PTC tumors was determined after surgery.

2.5. Study variables and definitions

Variables of interest included sex, age at diagnosed, tumor size, T stage, N stage, TNM stage, risk stratification of recurrence, $BRAF^{V600E}$ mutation, psTg, suppressed Tg (sup-Tg) 6 months post RAT. The primary endpoint of the study was recurrence-free survival (RFS).

Definitions: (1) PsTg was measured within 3 days prior to the initial RAT on the premise that TSH 30mU/L after thyroid hormone withdrawal and followed a low-iodine diet for 3–4 weeks. (2) The TNM stage followed the AJCC TNM staging 8th edition (Table S2) [11] and risk stratification of recurrence followed 2015 ATA guidelines (Table S3) [2]. (3) The observed end event was disease relapse, defined as developing SIR. RFS defined as duration from the first ^{131}I treatment to relapse. If the patient did not relapse(including ER, IDR, BIR), the RFS was defined as duration from the first ^{131}I treatment to the last follow-up.

2.6. Statistical analysis

The IBM SPSS 23.0 software (IBM Corp, NY, USA) was employed to carry out statistical analyses. Parameters that were not normally distributed were expressed as the median with the interquartile range (IQR). To investigate the risk factors affecting RFS, both univariate and multivariate Cox regression analyses were performed. The calculation of hazard ratios (HRs) and their associated 95%

Table 1
Baseline characteristics of postoperative papillary thyroid cancer with unexplained elevated Tg prior^{131}I therapy.

Variable	Number(%)
Sex	60(36.4)
Male	105(63.6)
Female	139(84.2)
Age(years)	26(15.8)
< 55	61(37.0)
≥55	15(9.1)
T stage	43(26.0)
T1	46(27.9)
T2	4(2.4)
T3	47(28.5)
T4	114(69.1)
N stage	139(84.2)
N0	14(8.5)
N1a	12(7.3)
N1b	90(54.5)
TNM stage	75(45.5)
I	19(11.5)
II	64(38.8)
III	82(49.7)
Risk Stratification	1.50(1.00,2.50)
Intermediate-risk	20.98(13.99,36.16)
High-risk	0.67(0.22,1.99)
$BRAF^{V600E}$ mutation	
Negative	
Positive	
Unknown	
Primary tumor size (cm) [median (IQR)]	
PsTg(ng/ml)[median (IQR)]	
Sup-Tg(ng/ml)[median (IQR)]	

Continuous variables are presented as median [interquartile range].
Categorical variables are presented as number.
PsTg, preablative stimulated thyroglobulin; Sup-Tg, suppressed thyroglobulin 6 months post radioiodine adjuvant therapy.

confidence intervals (CIs) was performed. Kaplan-Meier methodology was utilized to plot survival curves, and the cumulative recurrence-free survival (RFS) rates were compared among different N stages and TNM stages using the log-rank test. The reported probabilities were two-tailed, and statistical significance was established at a P value less than 0.05.

3. Results

3.1. Baseline characteristics

From April 2016 and June 2019, a cohort of 218 postoperative patients with PTC was enrolled, among whom 163 patients exhibited a psTg level exceeding 10 ng/mL. Following the exclusion of 53 patients(4 patients with TgAb≥115 IU/mL, 23 patients with apparent visible remnant, 18 patients with suspicious loco-regional disease, and 8 patients with possible distant metastases), 165 patients were deemed eligible for further analysis. The baseline characteristics of these 165 patients were summarized in Table 1.

3.2. Causal categorization for elevated Tg

According to the findings of 6 months follow-up, the postoperative unexplained elevated Tg could be ultimately attributed to thyroid remnant in 13.94% (23/165), biochemical disease in 60.00% (99/165), and structural disease in 26.06% (43/165) of the 165 patients (Fig. 1A).

3.3. The long-term responses in postoperative PTC patients with unexplained elevated Tg

Before additional treatment (reoperation, radiofrequency ablation, ^{125}I seed implantation) in addition to ^{131}I treatment, with a median follow-up of 58 (IQR, 52–60) months, 51 (30.91%), 34 (20.60%), 21 (12.73%), and 59 (35.76%) of the 165 patients achieved ER, IDR, BIR and SIR, respectively (Fig. 1B).

3.4. Analysis of prognostic factors

With a median follow-up of 58 (IQR, 52–60) months, 106 (64.24%) patients achieved recurrence-free (including 51 ER, 34 IDR and 21 BIR) while 59 (35.76%) developed structural disease (59 SIR). Univariate Cox regression analysis showed that age, N stage, TNM stage and sup-Tg 6 months post RAT significantly affected RFS of postoperative PTC patients with unexplained Tg. However, RFS was not significantly affected by sex, tumor size, T stage, *BRAF*^{V600E} mutation and psTg (Table 2).

To further investigate the independent factors associated with RFS, we employed a multivariate Cox proportional hazards model, incorporating the four statistically significant factors identified. Finally, N1b and II/III were deemed as independent risk factors for RFS in postoperative PTC patients with unexplained elevated Tg (Table 3).

The 1-, 3- and 5-year RFS rates of 165 patients were 81.8%, 69.0% and 58.3%, respectively, and the median RFS was not achieved. Kaplan-Meier survival curves for different N stages and TNM stages were shown in Fig. 2. The RFS rate in the N1b group was significantly lower than that in the N0/N1a group ($P = 0.007$) (Fig. 2A), and the RFS rate in the II/III stage group was significantly lower than that in the I stage group ($P = 0.002$) (Fig. 2B). The RFS rate observed in the N1b group exhibited a statistically significant

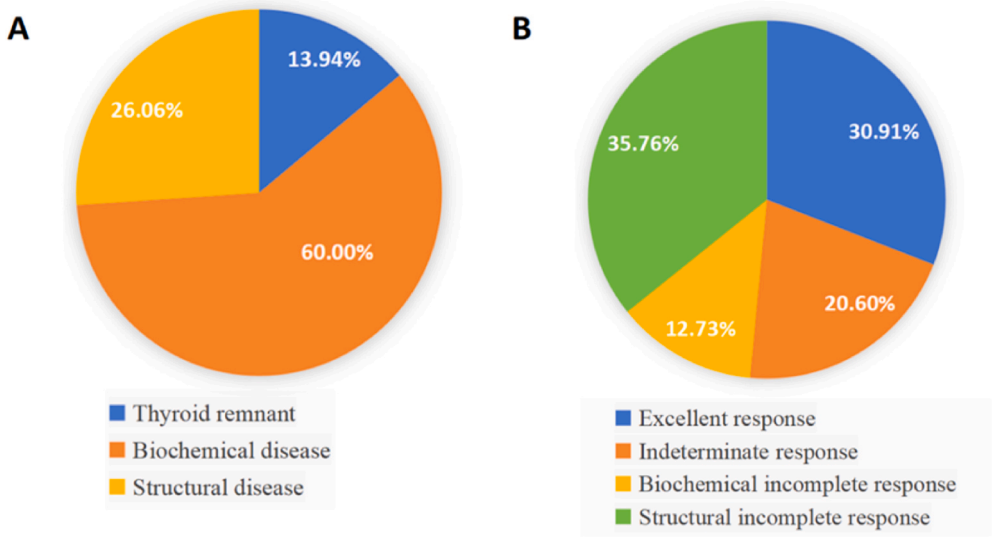

Fig. 1. The causal distribution of unexplained elevated Tg in postoperative papillary thyroid cancer (PTC) patients (A) and long-term response (B).

Table 2
Univariate analysis of 165 postoperative papillary thyroid cancer with unexplained elevated Tg.

	β	Wald	*P* value	HR(95%CI)
Sex	0.243	0.749	0.387	1.00(reference)
Female				1.275(0.736–2.210)
Male				
Age	0.898	8.736	**0.003**	1.00(reference)
< 55y				2.455(1.353–4.545)
≥55y				
Tumor size	0.161	1.937	0.164	1.175(0.936–1.740)
BRAF^{V600E} mutation	0.614	1.285	0.257	1.00(reference)
Negative				1.849(0.639–5.348)
Positive				
T stage	0.117	0.194	0.659	1.00(reference)
T1+T2				1.124(0.669–1.886)
T3+T4				
N stage	0.876	6.756	**0.009**	1.00(reference)
N0+N1a				2.401(1.240–4.648)
N1b				
TNM stage	0.898	8.736	**0.003**	1.00(reference)
I				2.455(1.353–4.545)
II + III				
Risk Stratification	0.198	0.565	0.452	1.00(reference)
Intermediate				1.219(0.728–2.040)
High				
PsTg	0.002	0.311	0.577	1.002(0.996–1.007)
Sup-Tg	0.074	4.859	**0.028**	1.076(1.008–1.149)

Table 3
Multivariate analysis of 165 postoperative papillary thyroid cancer with unexplained elevated Tg.

	β	Wald	*P* value	HR(95%CI)
N1b/N0+N1a	1.011	8.816	0.003	2.749(1.410–5.359)
II + III/I	1.068	11.966	0.001	2.910(1.589–5.329)

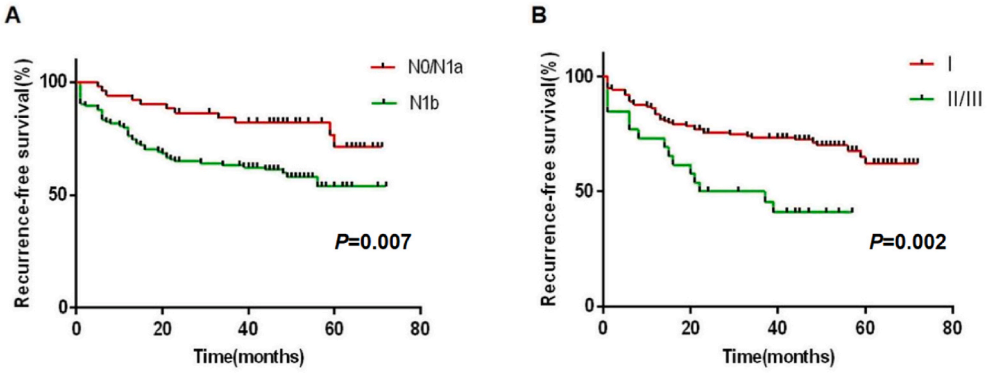

Fig. 2. Recurrence-free survival (RFS) curves of postoperative papillary thyroid cancer (PTC) patients with unexplained elevated Tg: **A** different N stage, **B** different TNM stage.

decrease compared to the N0/N1a group ($P = 0.007$) (Fig. 2A). And the RFS rate in the II/III stage group was notably lower than that in the I stage group ($P = 0.002$) (Fig. 2B).

4. Discussion

In this retrospective study, we thoroughly examined the underlying reasons of unexplained elevated Tg in a cohort of 165 postoperative PTC patients and pointed out factors capable of predicting their long-term outcomes. The findings could potentially have a crucial impact on improving nuclear medicine practices and promoting cross-disciplinary collaboration.

We first analyzed the causes of unexplained elevated Tg in a cohort of 165 postoperative PTC patients. According to the findings of a 6-month clinical follow-up, unexplained elevated Tg could be attributed to thyroid remnant in 13.94%, biochemical disease in 60.00%,

and structural disease in 26.06% of the 165 patients. These findings were similar to the results reported by Cheng et al. [4] of 17.3%, 54.3%, and 28.4%. Given the limitations of medical imaging before RAT, the elevation of the Tg level cannot be fully explained. For $^{99m}TcO^{4-}$ thyroid static imaging, the affinity of the residual thyroid tissue for technetium is significantly lower than that for iodine, which means some residual cannot be detected by $^{99m}TcO^{4-}$ imaging and ultrasound. However, these can be revealed by ^{131}I scan post RAT. Additionally, some lymph node metastases may be missed by ultrasound and some functional metastases may be missed by CT, both of which can be detected by ^{131}I scan. On one hand, ultrasound has limitations in the detection of metastatic lymph nodes. Distinguishing small lymph node lesions can be challenging due to postoperative scar formation and neck edema, which can obscure the lesions and make them difficult to identify. Furthermore, the restricted ability of ultrasound to detect mediastinal lesions may result in misdiagnosis [12,13]. On the other hand, ^{131}I scan offers superior detection of functional lesions compared to CT. To some extent, this demonstrates the value of RAT.

Subsequently, we assessed the long-term outcomes with a median follow-up duration of 58 months. Before additional intervention, 35.75% of 165 patients developed SIR at the end of follow up. And the proportion was higher than 8–17% reported in previous studies [3,8,9], which may be related to different inclusion criteria of subjects. The enrolled cases in this study were intermediate- and high-risk postoperative PTC patients who were evaluated as BIR before RAT with clinical follow up of nearly 5 years. While in previous studies, BIR was assessed after total thyroidectomy and initial ^{131}I treatment in low-, intermediate- and high-risk patients with follow-up of 5–10 years. Of the 59 patients with structural lesions, 57 presented with lymph node metastases and only 2 developed lung metastases. It followed that even if biochemical disease developed into structural disease, most was local recurrence or metastasis. In addition, some of these lesions can be improved by ^{131}I therapy under the premise of ^{131}I-avid lesions, surgery or radiofrequency ablation, and some are stable for a long time and can be under observation. Therefore, early identification of these patients who may develop structural lesions is conducive to timely adjustment of clinical management. Next, we further analyzed the factors affecting the long-term prognosis.

In this study, variables such as sex, age, tumor size, T stage, N stage, TNM stage, risk stratification, $BRAF^{V600E}$ mutation, psTg and sup-Tg 6 months post RAT were enrolled in a Cox proportional regression model affecting RFS. Univariate analysis showed that age, N stage, TNM stage and sup-Tg 6 months post RAT were significant indicators affecting RFS in postoperative PTC patients with unexplained elevated Tg. After adjusting for confounding factors, multivariate analysis demonstrated that only N stage and TNM stage were independent risk factors for RFS. Given that it has been reported that N1b increased the risk of recurrence and death in DTC patients [14–17] and N1b was independently identified as a predictor of an unfavorable response to ^{131}I therapy [18]. Our study also showed that the RFS rate in the N1b group was significantly lower than that in the N0/N1a group, with a hazard ratio of 2.749. Consequently, for patients with unexplained elevated Tg and N1b, the level of TSH suppression must be adjusted accordingly to ensure optimal therapeutic effectiveness and intensive follow-up should be conducted to detect recurrence and metastasis as early as possible. Steinschneider et al. [10] demonstrated that patients experiencing a BIR shift to SIR exhibited a significantly elevated TNM stage and ATA risk category in comparison to BIR patients who did not transition to SIR. Similarly, our findings revealed a statistically significant decrease in the RFS rate for patients in the II/III stage compared to those in the I stage, with a hazard ratio of 2.910. It is suggested that TNM stage is of great significance for the long-term prognosis of patients.

Certain limitations inherent in this study must be taken into account. First, this was a single-center retrospective study, which inevitably had selective bias. Second, due to the limited sample size, some groups with multiple classification variables, such as TNM stage, had relatively small numbers of cases. Consequently, these smaller groups were combined for the purposes of analysis using COX regression and survival curves. Third, the prognosis of PTC is generally excellent, and the 5-year survival rate is more than 95.0% [19,20]. Future studies would benefit from a longer follow-up period of 5–10 years to further assess outcomes.

5. Conclusion

In summary, over 30% of postoperative PTC patients with unexplained elevated Tg developed structural lesions within 5 years. Patients with N1b stage and advanced TNM stage had an increased likelihood of developing structural disease during long-term follow-up. Our findings offer valuable insights for assessing treatment response among postoperative PTC patients exhibiting unexplained elevated Tg, thereby guiding clinical decision-making and patient management.

Ethic declaration

This study was approved by Ethics Committee of the Affiliated Hospital of Qingdao University (QYFYWZLL27846. The study was conducted according to established ethical guidelines and written informed consent obtained from all patients.

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Data availability

The data associated with our study has not been deposited into a publicly available repository and will be made available from the

corresponding author upon request.

CRediT authorship contribution statement

Chenghui Lu: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Na Han:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Jiao Li:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Guoqiang Wang:** Visualization, Validation, Data curation. **Congcong Wang:** Validation, Supervision, Funding acquisition. **Qiang Jia:** Validation, Supervision. **Jian Tan:** Visualization, Validation, Supervision. **Xufu Wang:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Conceptualization. **Zhaowei Meng:** Writing – review & editing, Visualization, Validation, Funding acquisition.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27736.

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