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Comparison of ^{18}F-FDG PET/CT and conventional methods in diagnosing extranodal natural killer/T-cell lymphoma

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ABSTRACT

Background: The utility of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in natural killer (NK)/T-cell lymphoma patients is yet to be established. The aim of this study was to investigate the role of PET/CT scanning in detecting NK/T-cell lymphoma.

Methods: We analyzed the PET/CT imaging characteristics of 38 patients with a primary diagnosis of NK/T-cell lymphoma and also compared the ability of PET/CT to detect tumor lesions with conventional methods (CMs) (physical examination, computed tomography (CT) with intravenous contrast, magnetic resonance imaging (MRI), biopsies from primary sites, and bone marrow examinations)and their impact on staging and treatment options. Biopsy and clinical follow-up (including imaging) are the gold standard for diagnosis.

Results: We analyzed PET/CT images of NK/T-cell lymphomas. We found that most of the primary lesions were located in the nasal cavity, with the sinuses and the posterior pharyngeal wall being the most common sites of adjacent invasion. The majority of cases involved cervical lymph nodes, and the distribution of affected lymph nodes between the cervical and extra-cervical regions was random. There was no discernible pattern to the locations of affected tissues and organs across the body. In total, 219 lesions (including 81 nodal lesions and 138 extranodal lesions) tested positive for malignancy. The number of positive lymph node lesions detected by PET/CT and CMs was 79 (97.5 %) and 62 (76.5 %), respectively ($P = 0.004$). There were 53 (96.4 %) and 46 (83.6 %) cervical lymph nodes detected ($P = 0.008$), 26 (100 %) and 16 (61.5 %) other lymph nodes detected ($P = 0.041$)), respectively. The number of positive extranodal lesions detected by PET/CT and CMs was 137 (99.3 %) and 98 (71.0 %), respectively ($P = 0.01$), and there were no discernible differences in the upper respiratory tract. PET/CT outperformed CMs in the detection of malignant lesions by a significant margin, detecting 79 (98.8 %) extranodal lesions compared to 45 (56.3 %) by CMs ($P = 0.034$). PET/CT results changed the initial staging in 15.8 % of cases and the treatment plan in 10.5 % of patients.

Conclusion: Our findings indicate that ^{18}F-FDG PET/CT scanning is crucial in identifying tumor lesions, determining staging, and devising treatment strategies for individuals diagnosed with NK/T-cell lymphoma.

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1. Introduction

Extranodal natural killer (NK)/T-cell lymphoma originates from mature T cells and NK cells [1–7]. The disease has a low incidence, high malignancy, rapid progression, and poor prognosis, and is a distinct type of lymphatic and hematopoietic tissue tumor [8]. Extranodal NK/T-cell lymphoma often involves extranodal sites, such as the respiratory systems , the digestive tract, the testis, the skin, and the kidney. Due to its tendency to affect extranodal sites, evaluating the lesion before treatment is crucial to achieving precise staging and effective treatment [9].

Currently, The utilization of ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is crucial in determining the staging, response assessment, and prognostic evaluation of diffuse large B-cell lymphoma, Hodgkin's lymphoma, and follicular lymphoma [10,11]. Conventional methods (CMs) currently used as a standard to stage the disease include physical examination, computed tomography (CT) with intravenous (IV) contrast, magnetic resonance imaging (MRI), biopsies from primary sites, and bone marrow examinations. However, due to the low incidence of NK/T-cell lymphomas, there are relatively few studies available on the clinical significance of using PET-CT for detecting NK/T-cell lymphomas. Therefore, this study aimed to analyze the imaging manifestations of NK/T-cell lymphomas detected on PET/CT scans and to further explore the practical value of PET/CT imaging in diagnosing and staging this type of cancer compared to conventional staging techniques.

2. Materials and methods

2.1. Study participants

For this retrospective study, we collected relevant details of 38 patients with newly diagnosed NK/T-cell lymphomas from June 2016 to October 2022, in Shanxi Bethune Hospital. This study was conducted with the approval from the Ethics Committee of Shanxi Bethune Hospital (No.YXLL-2022-146). The pathologic diagnosis was determined based on the World Health Organization lymphoma classification criteria [12]. Patients with NK/T-cell lymphoma underwent whole body ^{18}F-FDG PET/CT and CMs examination before treatment, including physical examination, CT venography, bone marrow biopsy, and primary lesion biopsy. There was one patient who underwent an additional cranial MRI due to brain invasion. The disease stage was determined using the Ann Arbor staging system [13] based on the results of CMs and PET/CT scans. Each patient's clinical stage was reevaluated following PET-CT, and the ensuing restaging was used to determine the best course of treatment. The gold standard for diagnosing all lesions was a surgical biopsy or follow-up results including imaging studies. There was at least a 6-month follow-up for all patients.

2.2. PET/CT scan

Data for this study were obtained using a Discovery VCT combined PET/CT hybrid system manufactured by GE Healthcare in Milwaukee, Wisconsin,USA. All patients fasted for at least 6 h during the examination, and their blood glucose levels were below 200 mg/dL before the 18F-FDG injection.^{18}F-FDG was injected intravenously at 4.44 MBq/kg; Patients were advised to take a 50 to 60-min break in silence, and the bladder was emptied before examination.

Image acquisition and reconstruction: the CT scan was first conducted from the head to the thigh with the following parameters: 30–170 mA in automatic mA mode, 140 keV, and 3.75 mm in section width; PET images were acquired within the same range, 3 min/bed for the head and 2.5 min/bed for the body, for a total of 6–8 beds. PET reconstructed images based on CT attenuation correction and ordered subset expectation maximum (OSEM) algorithm.

2.3. PET/CT image analysis

Two experienced nuclear medicine physicians analyzed all fused PET/CT images by using visual analysis and the standardized

Table 1
Patient characteristics.

Characteristic	n	%
Age (y)		
≤60	27	77.1
>60	8	22.9
Sex		
Male	17	48.6
Female	18	51.4
Stage		
I	17	48.6
II	11	31.4
III	1	2.9
IV	6	17.1
Bone marrow involvement		
Positive	1	2.9
Negative	34	97.1

uptake value (SUV) semi-quantitative method. A consensus was reached to resolve any divergent viewpoints. The region of interest (ROI) was outlined by selecting the site of increased uptake, and the workstation automatically produces the maximum standardized uptake value (SUVmax). The lesion was considered positive if its value was greater than the SUVmax of the surrounding background.

2.4. Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences Version 23.0 software (SPSS Inc., Chicago, IL, USA). Comparison of the detection rate of malignant lesions by ^{18}F-FDG PET/CT versus CMs using the Wilcoxon signed rank test. $P < 0.05$ was considered statistically significant.

3. Results

Table 1 displays a summary of the general characteristics of patients with extranodal NK/T-cell lymphomas. Thirty-eight patients (18 men and 20 women) participated in the study. Their median age was 50 years (range: 23–75 years), and their median follow-up period was 40.2 months (range: 6–72 months). PET/CT identified 216 positive lesions in 38 patients, and the SUVmax of all lesions was 5.6–41.9, with a mean of 15.2 ± 6.5.

Of the 38 patients, 36 patients had upper respiratory tract involvement, one patient had a primary lesion located in the bilateral adrenal glands, and one patient had extra-nasal multisystem involvement (skin, muscle, lung, liver, bone).

All of the patients had a biopsy of their iliac bone marrow. Eight patients had discordant results between ^{18}F-FDG PET/CT and CMs and underwent additional biopsies to confirm the lesion. Additional biopsy sites included skin, bone, liver, and neck.

3.1. Lesion site and PET/CT imaging features

In 16 cases, the upper respiratory tract involvement was limited to the nasal cavity. PET/CT scans showed thickening of the nasal mucosa with metabolic hyperplasia and changes along the unilateral or bilateral nasal cavity with metabolic hyperplasia and significant narrowing to occlusion of the nasal cavity in the most severe cases. There were 20 cases of superficial nasal cavity (superficial cavity) lesions, which showed invasion and spread of hypermetabolic soft tissue masses to adjacent areas and partial worm-like destruction of bone, with common sites of involvement including paranasal sinuses in 12 cases (31.6 %, combined with soft tissue invasion of the face in 2 cases and orbit in 1 case), posterior pharyngeal wall in 6 cases (15.8 %, including 1 case with simultaneous invasion of the hard palate), and both in 2 cases (5.3 %). In addition, mucosal thickening of the maxillary sinus was seen on CT in 3 patients, but no metabolic increase was seen on PET/CT, so the diagnosis of combined obstructive paranasal sinusitis was made.

Lymph node invasion in extranodal NK/T-cell lymphoma: Lymph node invasion was seen in 50 % (19/38 cases) of the patients, and among these, 28.9 % of patients (11/38 cases) had invasion of cervical lymph nodes, in 18.4 % of patients (7/38 cases) invasion involved both cervical and lateral cervical lymph nodes, and only 1 patient had external cervical lymph node (right axilla) invasion, with simultaneous involvement of cervical and lateral cervical lymph nodes showing a random distribution.

Extranodal lesions outside the upper respiratory tract were found in 8 patients, and these included 1 case of primary adrenal gland, 1 case of extra-nasal multi-system (skin, muscle, lung, liver, bone) involvement, 1 case of simultaneous lung, spleen, and liver involvement, 1 case of simultaneous bone and brain involvement, 1 case of bone involvement, and 3 cases of skin of the extremities. The lesions of bilateral adrenal involvement showed nodule-like hypermetabolism in PET/CT; the density of some liver and spleen lesions did not show significant abnormalities in CT; morphological changes of skin-involved lesions were not obvious; some bone involvement showed slightly reduced bone density; and some bone density did not show any significant abnormalities. All the above lesions showed abnormal hypermetabolic foci in PET/CT. There was no discernible pattern to the distribution of affected tissues and organs across the body.

3.2. Detection rate of PET/CT versus CMs

There were 219 lesions in total in the 38 patients that were detected by CMs and confirmed by biopsy, imaging and clinical follow-up. Compared to CMs, PET/CT scans detected more anatomical areas of malignancy (98.6 % vs 73.1 %, $P = 0.001$). The detection rate of lymph node regions was significantly higher in PET/CT scans compared to CMs ((97.5 % vs 76.5 %, $P = 0.004$), cervical lymph nodes (96.4 % vs 83.1 %, $P = 0.008$), and other lymph nodes (100 % vs 61.5 %, $P = 0.041$)).For the detection of extranodal regions, the detection rates of PET/CT and CMs were 99.3 % and 71.0 %, respectively ($P = 0.01$). There was no difference in the detection rate of upper respiratory tract lesions, but the detection rate of other extranodal lesions by PET/CT was higher than that of CMs (98.8 % vs 56.3 %, P = 0.034) (Table 2). The lesions that were missed in PET/CT included 1 bone marrow infiltration and 2 cervical lymph nodes

Table 2
Comparison between PET/CT and CSMs in detecting malignant lesions.

Site	All lesions	PET/CT (%)	Cms (%)	*P*
Lymph nodes	70	68 (97.1)	56 (82.4)	0.004
Extranodal	123	122 (99.2)	85 (69.1)	<0.001
In total	193	190 (98.4)	141 (73.1)	<0.001

that were misdiagnosed as inflammatory lymph nodes due to the coexisting gingivitis in the patient, and the involvement was confirmed by lymph node puncture. PET/CT false positive lesions included a skin lesion due to inflammation caused by a mosquito bite and a duodenal lesion confirmed to be inflammatory by endoscopy.

3.3. Impact of PET/CT on staging and treatment

The results of PET/CT altered the clinical stage of 15.8 % of patients (6/38 cases) by varying degrees, compared to CMs. PET/CT findings resulted in the upgrade of two cases from Stage I to Stage II due to the detection of neck or chest lymph node involvement (Fig. 1 A-D, Small mediastinal lymph nodes involvement were detected by PET/CT and the stage was changed). One case was upgraded from Stage II to Stage IV, with lung, liver, and spleen involvement (Fig. 2 A-D, PET/CT showed multiple organ involvement and staging changes), another case was upgraded from Stage II to Stage IV, with bone, brain, and skin involvement, one case from Stage III to Stage IV, with cervical, inguinal lymph node, and skin involvement, and one case from Stage II to Stage III, with retroperitoneal lymph node involvement.

Our findings showed that PET/CT was superior to CMs in determining the clinical staging of NK/T-cell lymphomas. In one patient, the PET staging differed from the final staging, and the PET/CT scan resulted in incorrectly downgrading the staging of a patient with Stage IV disease due to a missed detection of bone marrow infiltration.

^{18}F-FDG PET/CT results changed the clinical treatment plan in 10.5 % (4/38) of patients. Treatment in 2 cases was changed from only radiotherapy to radiotherapy combined with chemotherapy, and in 2 cases, it was changed from radiotherapy combined with chemotherapy to only chemotherapy due to upstaging. The PET/CT results also altered the radiotherapy target area in 3 patients: 1 patient had the radiotherapy field enlarged to include a lesion not detected in CMS, while 2 patients had their radiotherapy field reduced to exclude paranasal sinus involvement.

4. Discussion

Extranodal NK/T-cell lymphoma is a low incidence sub-type of peripheral T-cell lymphoma that mainly affects middle-aged and elderly men. The lesions usually occur in the upper respiratory and digestive tract and are more common in the nasopharynx and nasal cavity, but other extranodal sites are often involved [14–22]. Stage I and II patients typically receive local radiotherapy and chemotherapy, whereas stage III and IV patients often receive a more intensive degree of chemotherapy with or without stem cell transplantation [23]. The prognosis for nasopharyngeal extranodal NK/T-cell lymphoma in stages I-II is significantly better than for nasal extranodal NK/T-cell lymphoma in stages III-IV [24]. Hence, accurate and early diagnosis, along with proper staging are essential for effective clinical treatment and determining the prognosis of extranodal NK/T-cell lymphoma.

^{18}F-FDG PET/CT combines both structural imaging and functional metabolic information to provide a comprehensive and non-

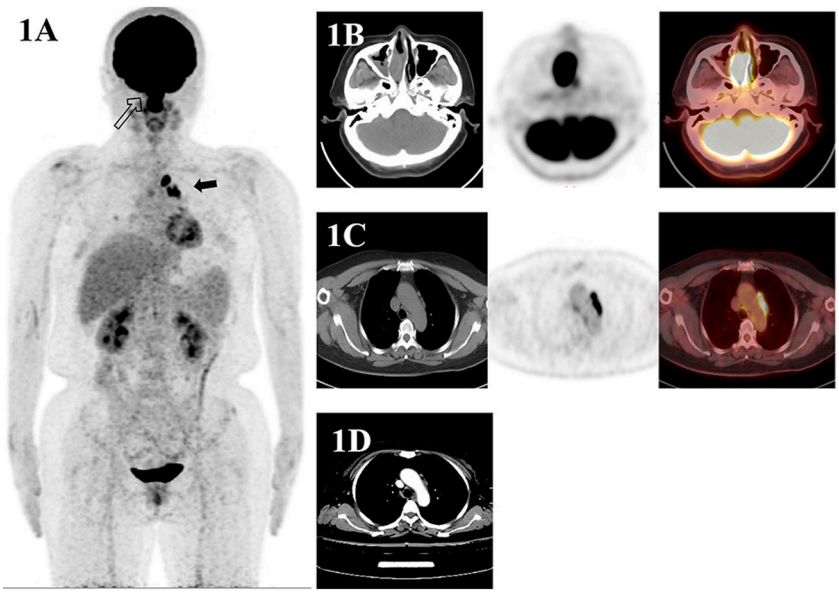

Fig. 1. A 54-year-old woman with newly diagnosed nasal-type NK/T-cell lymphoma underwent ^{18}F-FDG PET/CT scan (A–C) and enhanced CT scan (D) for initial staging. Maximum-intensity-projection image (A) shows hypermetabolic lesions in right ethmoid sinus (empty arrow), mediastinal lymph nodes (arrow). Transaxial images of ^{18}F-FDG PET/CT scan shows ^{18}F-FDG-avid mass in right ethmoid sinus (B). ^{18}F-FDG PET/CT scan shows intense ^{18}F-FDG uptake in mediastinal lymph nodes, suggesting malignancy (C). However, enhanced CT scan shows only small lymph nodes with less than 1 cm of short-axis diameter in mediastinal , which is not consistent with malignancy (D). Finally, after PET/CT scan is obtained, staging is changed from I to II. After 4 cycles of chemotherapy, follow-up ^{18}F-FDG PET/CT scan shows normalized ^{18}F-FDG uptake mediastinal lymph nodes.

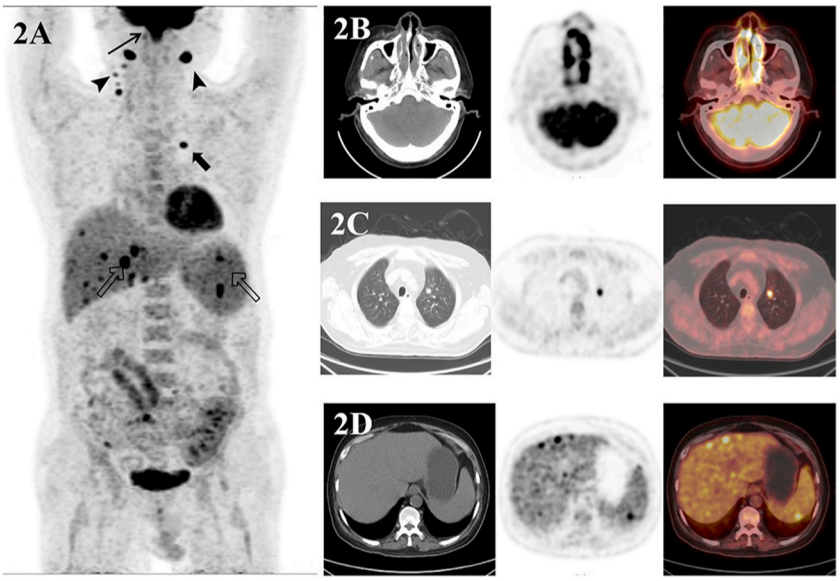

Fig. 2. A 50-year-old man with recently diagnosed nasal-type NK/T-cell lymphoma underwent ^{18}F-FDG PET/CT scan (A–D) for initial staging. Maximum-intensity-projection image (A) shows hypermetabolic lesions in both ethmoid sinus (thin arrow), both cervical lymphatic chains (arrowhead), left upper lung (thick arrow), liver, and spleen. Transaxial images of ^{18}F-FDG PET/CT scan show ^{18}F-FDG-avid mass in both ethmoid sinus (B). ^{18}F-FDG PET/CT scan shows intense ^{18}F-FDG uptake in left upper lung and multiple ^{18}F-FDG uptake in the liver and spleen (CT showed no lesions), suggesting malignancy (C–D). Finally, after PET/CT scan is done, staging is changed from II to IV.

invasive evaluation of systemic involvement in a single examination. This imaging modality displays the morphology, location, and invasion of lesions, and compensates for the limitations of conventional examinations enabling comprehensive pre-treatment evaluation and more accurate staging. Despite its utility, PET/CT for mature NK-cell and T-cell tumors, particularly extranodal NK/T-cell lymphomas, has not been extensively studied due to its low prevalence and limited available data.The findings of our study on NK/T-cell lymphomas highlight the significance of PET/CT in lesion detection and initial staging.

This study's maximum standardized uptake value of ^{18}F-FDG in NK/T-cell lymphoma was 15.2 $\pm$ 6.5. Due to its high metabolic characteristics, it is easier to detect lesions and reduce missed diagnosis, which is consistent with previous reports [19–21,25]. PET/CT imaging characteristics pointed to the upper respiratory tract as the primary site of the lesion. Extranasal invasion in NK/T-cell lymphoma was extremely rare, occurring in only 2 cases. In 13 cases, the disease was confined to the nasal cavity, manifesting primarily as nasal casts with increased metabolism; in the remaining 20 cases, the disease spread beyond the nasal cavity, with adjacent tissue invasion, with invasion of the paranasal sinuses and posterior nasopharyngeal wall, being the primary manifestation in many cases. We found that the lymph node invasion followed a random distribution, with cervical lymph node involvement being the most common. Our findings are consistent with those of previous studies on identifying extranodal lesions [19,25–27], which indicated that NK/T-cell lymphoma involved the liver, spleen, lung, bone, brain, skin, muscle, and adrenal glands, amongst others. The distribution of the involved tissues and organs throughout the body had no obvious pattern.

In terms of correctly detecting malignant lesions, ^{18}F-FDG PET/CT scans had a better detection rate for NK/T-cell lymphoma than CMs. This result is consistent with previous studies [19,26]. Fujiwara et al. proposed that there was no significant difference between ^{18}F-FDGPET/CT and CMs in the detection of lymph node lesions [19]. In contrast, PET/CT was found to be significantly more effective than CMs in this study at identifying lymph node and extranodal lesions (97.5 % and 99.3 % vs. 76.5 % and 71.0 %, respectively). We also compared the detection rates of PET/CT and CMs for nodal and extranodal regions, including the cervical lymph nodes, other lymph nodes, the upper respiratory tract, and other extranodal lesions, and found that the detection rate of PET/CT was higher than that of CMs except in the case of the upper respiratory tract.

Clinical staging of lymphomas is critical for developing treatment strategies and improving prognosis, and PET/CT scans have accurately altered the clinical staging of some patients.There are few studies on PET/CT staging of NK/T-cell lymphoma [26,28,29]. According to Wu et al. PET/CT scans can be helpful in staging [29]. Their study of 15 patients with NK/T-cell lymphoma found that PET/CT scans could correctly localize undetected lesions in CMs and readjust lymphoma staging in CMs.

Our results suggest that PET/CT has a significant advantage over CMs for lesion detection and staging of extranodal NK/T-cell lymphomas.The clinical staging of 15.7 % of patients (6/38 cases) was restaged to varying degrees after PET/CT findings, and PET/CT results helped in changing the treatment plan for 10.5 % (4/38) of patients. This is primarily because PET/CT overcomes the limitations of CMs. By relying on the manifestations of radioactive concentrations, it is possible to increase the detection rate of small and early-stage lesions, such as normal-sized hypermetabolic lymph nodes or occult lesions involving lymphoma. However, there are limitations to PET/CT. One case of bone marrow involvement was missed by PET/CT, two false negatives were misdiagnosed as inflammatory lymph nodes, and two false positives were due to inflammation of the duodenum and skin. Therefore, other examinations

such as biopsy and endoscopy should be used as supplements.

This study found that ^{18}F-FDG PET/CT imaging results significantly impacted the treatment plan for some patients. As NK/T-cell lymphoma is responsive to radiotherapy [30–35], it is crucial to accurately locate the target volume before the initiation of treatment. Too small or too large a target volume is detrimental to treatment and can potentially increase the risk of recurrence or adverse reactions after treatment. We found that the radiotherapy target volume was altered after PET/CT in three patients, with the radiation field being expanded in one patient as PET/CT results detected positivity where findings of CMs were negative, and the radiation field was reduced in two patients due to PET/CT results indicating negativity where CMs findings were positive, thereby excluding paranasal sinus involvement.

The present study has some limitations: The study lacks a large sample size because of the low prevalence of NK/T-cell lymphoma. Also, the positive lesions detected by PET/CT were only partially validated through biopsy or surgical pathology, and the use of clinical follow-up and other imaging modalities as reference standards could have resulted in misclassification of lesions. However, in routine clinical practice, biopsy of every lesion is neither ethical nor practical, and this limitation is consistent with those of previously published studies [19,26,27].

5. Conclusion

In this study, we examined ^{18}F-FDG PET/CT imaging characteristics in patients with extranodal NK/T-cell lymphoma and found that PET/CT has a higher detection rate of lymph node and extranodal involvement than CMs, making it more precise in staging and guiding clinical treatment. Additionally, it proved critical for accurately defining target areas and planning radiotherapy prior to treatment.

Ethics approval and consent to participate

I confirm that I have read the Editorial Policy pages. This study was conducted with approval from the Ethics Committee of Shanxi Bethune Hospital (No.YXLL-2022-146). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Availability of data and material

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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CRediT authorship contribution statement

Huixia Geng: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Jinhao Li:** Data curation, Formal analysis, Resources, Software. **Wanchun Zhang:** Conceptualization, Project administration, Writing – review & editing.

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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