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Malignant Transformation and Treatment Recommendations of Chronic Hyperplastic Candidiasis—A Six-year Retrospective Cohort Study

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Abstract

Background: Oral chronic hyperplastic candidiasis (CHC) is the most uncommon type of oral candidiasis with diverse manifestations. Up to date the diagnosis, long-term management and prognosis of this oral potentially malignant disorder remain obscure.

Objectives: The aim of this study was to provide the recommendations guiding the diagnostic procedure, clinical management and prognosis assessment of CHC.

Methods: A retrospective cohort study was performed during January 2015 to April 2021 involving patients with a definite diagnosis of CHC in the Department of Oral Medicine of Peking University School and Hospital of Stomatology. Demographic features, clinical and histopathological features, treatment protocols and follow-ups including malignancy transformation were analysed.

Results: Fourty eight CHC patients were collected and reviewed, with a male-to-female ratio of 2.69:1. The average age at diagnosis was 54.92 ± 9.79 (36–80) years old. Clinically, the multiform oral lesions were diverse and frequently presented as white plaque and erythematous lesions. As a result, the initial diagnostic accordance rate was only 54.17%, and the most common presumptive initial diagnoses were oral lichen planus (22.92%), oral leukoplakia (20.83%) and traumatic lesion (2.08%). Histopathologically, ten (20.83%) patients had varying degrees of epithelial dysplasia, and two (4.17%) patients had malignant transformation with a mean transformation time of 6.5 ± 6.36 months. Among the 28 patients who underwent fungal culture, 24 patients were exclusively infected by *Candida albicans*, with two patients each mixed infected by *C glabrata* and *C tropicalis*, respectively. Notably, treatment with fluconazole had the lower recurrence rate compared with topical nystatin.

Conclusions: The diagnosis and management of CHC remain a challenge due to its polymorphic clinical presentations, chronic progression and potential of malignant transformation.

KEYWORDS
candida, chronic hyperplastic candidiasis, malignant transformation, oral mucosa, retrospective cohort study

1 | INTRODUCTION

Oral candidiasis or oral candidosis (OC) is the most common fungal infectious disease of oral mucosa, mainly caused by the opportunistic pathogen of *Candida* spp. According to the different clinical manifestations, OC can be classified into pseudomembranous candidiasis, erythematous candidiasis and chronic hyperplastic candidiasis (CHC).[1] Among these types, CHC is a rare type of OC, with an incidence of about 1.61% in OC patients, mainly affecting middle-aged smoking men.[2] The prevalence of chronic hyperplastic candidiasis is around 0.5% in Chinese patients with oral candidiasis.[3] Up to date, there are no large sample size studies due to the rarity of CHC.

Chronic hyperplastic candidiasis is of particular significance due to the difficulties of differential diagnose and more importantly, the potential of malignant transformation. It is clinically diversely manifested as thick white plaques, erythematous lesions or mixed red and heterogeneous white plaques, mimicking and commonly misdiagnosed as the diseases presented as white lesions such as lichen planus and leukoplakia.[4] As a result, the diagnosis of CHC is often difficult and time-consuming. To establish the diagnosis, besides the clinical manifestations, the sensitivity of laboratory tests such as exfoliative cytology and fungal culture is rather low. In order to rule out dysplasia or malignant conditions, the diagnosis must be based on histopathology.[5]

It has been previously reported that the incidence of epithelial dysplasia in CHC can be as high as 15%.[6] If CHC patients are not treated promptly and effectively, some of lesions may progress to various degrees of epithelial dysplasia and even malignant transformation to oral squamous cell carcinoma (OSCC). The incidence of malignant transformation in untreated CHC patients has been estimated to be as high as 10%.[7] Although it is generally accepted that fungal infectious diseases do not undergo malignant transformation, CHC is considered as oral potentially malignant disorder and is associated with OSCC.

Up to date the diagnosis, long-term management and prognosis of CHC remain challenging. There are few studies about CHC in recent years, and the clinical and histological features, treatment effectiveness and long-term follow-up of CHC are still worth exploration. Therefore, this retrospective cohort study aimed to provide the recommendations guiding the diagnostic procedure, clinical management and prognosis assessment of this uncommon and severe type of oral candidiasis.

2 | MATERIALS AND METHODS

2.1 | Study design and ethics approval

This retrospective cohort study was conducted at the Department of Oral Medicine of Peking University School and Hospital of Stomatology. The Ethics Committee of Peking University Health Science Center reviewed and approved this study (PKUSSIRB-202059163).

2.2 | Study population

The researchers reviewed the hospital records of the patients (from January 2015 to April 2021) at the Department of Oral Medicine of the Peking University School and Hospital of Stomatology. Patients with a definite diagnosis of CHC were collected and analysed. The diagnosis of CHC should follow both of the criteria[8,9]: (1) Clinical manifestations are consistent with CHC; (2) Oral biopsy is indispensable, and special staining procedures such as periodic acid-Schiff (PAS) and Grocott's methenamine silver (GMS) assist in the definitive diagnosis, and mycological culture and *candida* spp. identification assist in the antifungal applications. Although some researchers proposed CHC was a delayed onset of chronic mucocutaneous candidiasis (CMC),[6] patients with CMC were excluded in this study considering the identified genetic defects.

2.3 | Data collection and follow-up

Demographic data of the patients (gender, age, smoking habit, alcohol consumption, removal denture, comorbidities and initial diagnoses), mycological information including aetiological organisms, characteristics of lesions (site, type, size and histopathological features) and follow-ups (treatment course of antifungal therapy, recurrence rate and meantime of malignant transformation) were collected.

2.4 | Statistical analysis

Statistical analyses were performed using the SPSS (version 22.0 s). Percentages were calculated for categorical variables, and means and standard deviations were calculated for continuous variables.

3 | RESULTS

3.1 | Demographic features and mycological information

A total of 48 cases with 35 (72.92%) males and 13 (27.08%) females, with a definitive diagnosis of CHC were reviewed, and the demographic characteristics and mycological information of those patients were presented in Table 1. The ages of these patients ranged from 36 to 80 years (mean, 54.92 $\pm$ 9.79), and the ratio of male to female was 2.69:1. A total of 22 patients had a history of smoking, eight had alcohol consumption, and all were male patients. Five male and three female patients wore removable dentures. As to the comorbidities, ten patients had hypertension, five had diabetes, one had hepatitis C, and one had anaemia.

Among the 28 patients who underwent fungal culture, 24 patients (85.71%) were simply caused by *C albicans*, while other patients were caused by *C albicans* combined with *C glabrata* ($n = 2$, 7.14%), and *C albicans* combined with *C tropicalis* ($n = 2$, 7.14%).

TABLE 1 Demographic and mycological characteristics of the cohort of individuals with CHC

Characteristic	Male	Female	Total
Cases (*n*)	35	13	48
Age (year)			
Mean ±SD	55.23 ± 9.15	54.08 ± 11.69	54.92 ± 9.79
Range	36-75	42-80	36-80
<40	0	1	1
40-49	9	5	14
50-59	15	5	20
≥60	10	3	13
Smoking			
Yes	22	0	22
No	13	13	26
Alcohol consumption			
Yes	8	0	8
No	27	13	40
Removal Denture			
Yes	5	3	8
No	30	10	40
Comorbidities			
Hypertension	10	0	10
Diabetes mellitus	4	1	5
HCV	1	0	1
Anaemia	1	0	1
Initial diagnosis			
Oral lichen planus	7	4	11
Oral leukoplakia	9	1	10
Traumatic lesion	1	0	1
Fungal culture			
C albicans	17	7	24
C albicans and *C glabrata*	0	2	2
C albicans and *C tropicalis*	2	0	2

3.2 | Clinical and histopathological characteristics

Most patients ($n = 30$, 62.5%) had oral lesions at multiple sites, while 18 (37.5%) at single site, wherein the dorsum of tongue and commissure were the most affected sites, followed by the lateral border of tongue, the buccal mucosa and palate. Regarding the clinical characteristics, the lesions frequently presented as white plaque ($n = 36$, 75%), erythematous lesion ($n = 30$, 62.5%), atrophy ($n = 28$, 58.33%), granular hyperplasia ($n = 10$, 20.83%), nodule ($n = 9$, 18.75%) and ulcer ($n = 3$, 6.25%) (Table 2). Oral manifestations of CHC are shown in Figure 1. Surprisingly, the initial diagnoses of 22 out of 48 patients were oral lichen planus ($n = 11$, 22.92%), oral leukoplakia ($n = 10$, 20.83%) and even traumatic lesion ($n = 1$, 2.08%).

With regard to histopathological characteristics, CHC usually manifested as hyperkeratosis or hypokeratosis of the epithelium, with inflammatory cell infiltration and exudation, and significant proliferation of the spinous layer. Special staining procedures such as PAS and GMS can reveal hyphae extending vertically into the epithelial layer and micro-abscesses in the superficial epithelium. Notably, ten (20.83%) patients presented with dysplasia (10.42% with mild dysplasia, 8.33% with moderate dysplasia and 2.08% with severe dysplasia). In the patients with dysplasia, the male-to-female ratio is 7:3, and four male patients have history of smoking. The histopathological features of CHC lesions are shown in Figure 2.

3.3 | Antifungal therapy

In this study, 45 (93.75%) patients received≧one course of antifungal therapy. For the efficiency of antifungal therapy, both clinical and etiological aspects were comprehensively considered. Under the premise of the resolution of clinical symptoms, the medication could only be terminated when the mycological examination turned negative as well. In 26 patients that follow the entire course of treatment taking clinical resolution and mycological negative as the endpoint of antifungal therapy, 11 patients were treated with fluconazole with the mean course of 4.45 ± 1.21 weeks, 11 patients were treated with nystatin with the mean course of 4 weeks, and four patients treated with the combination of fluconazole and nystatin with the mean course of 4.4 ± 0.89 weeks. Through the analysis, recurrences were observed in three patients treated with nystatin group, while none in the other groups.

3.4 | Malignant transformation

Malignant transformation occurred in two male patients out of the 48 CHC patients with a transformation rate of 4.17% during the observation period. Both the two patients had multiple sites lesions. In the initial visit, the two patients underwent incisional biopsy in the most severely and significantly affected tissues. The initial biopsy of the two patients revealed mild and severe epithelial dysplasia, respectively, and the lesions of patients were clinically and pathologically progressive and eventually developed malignant transformation with an average time of 6.5 ± 6.36 months.

To summarised, based on the findings of this retrospective cohort study and the literature review, the diagnosis, treatment and follow-up of CHC were illustrated in the flow chart (**Figure 3**).

4 | DISCUSSION

CHC is a rare and refractory type of OC, with a potential for malignant transformation. However, there is a paucity of information

TABLE 2 Histopathologic and clinical features of the lesions

Site of lesions	Type of lesions (n)					Dysplasia (n)			Size of lesion (n)	
	Granular hyperplasia	Nodule	White plaque	Ulcer	Atrophy	Erythematous lesion	Mild	Moderate	Severe	<2 cm^2	≥2 cm^2
Commissure	4	0	11	0	1	10	3	1	/	1	4
Buccal mucosa	6	1	15	4	0	8	/	/	/	5	5
Dorsum of tongue	8	10	12	0	27	12	/	2	/	9	12
Lateral border of tongue	6	2	7	3	0	3	2	1	/	4	2
Palate	2	3	2	0	0	2	/	/	1	1	1
Lips	1	0	1	0	0	2	/	/	/	1	0
Total	27	12	41	3	24	31	5	4	1	16	22

and no overall clinical consensus about the diagnosis, treatment and prognosis of this disease. Based on the significance and necessity of recognition of CHC, a retrospective study was conducted. In this study, CHC was more susceptible to middle-aged smoking men, although OC is common in women.[2] Smoking may be the reason of this phenomenon. It is proposed that smoking may play a role in the pathogenesis for certain components in tobacco such as nicotine are considered to be a nutrient for *Candida*, which can promote its colonisation. Furthermore, nicotine can affect the local immune system by impairing oral neutrophil function, changing the levels of cytokines and reducing the production of saliva IgA.[6,10]

The diagnosis of CHC remains a challenge due to its polymorphic and diverse clinical presentations. It was found out in this study that the initial diagnostic accordance rate was not satisfying. Clinically, 45.83% of CHC cases need to be carefully differentiated from oral lichen planus (OLP), oral leukoplakia (OLK) and even traumatic lesions. Therefore, the clinical manifestations as the alarm sign should be recognised, and the diagnosis should be based on biopsy with special staining. Histopathology is necessary for the diagnosis of CHC, since CHC has special histopathological features, and the use of special staining can assist the diagnosis of previously unsuspected fungal infections with high specificity.[6,8] Moreover, as a potential malignant disorder, histopathological examination can also help assess the degree of progression of the lesions.[11]

It is worth mentioning that 20.83% of CHC patients in this study had varying degrees of epithelial dysplasia, and 4.17% had malignant transformation. Currently, the risk factors for CHC related to the development of malignancy have not been fully elucidated. It has been suggested that long-term *C albicans* infection may increase the risk of malignant transformation of the oral mucosa. Current studies have summarised that the possible carcinogenic mechanism of *C albicans* involves the production of carcinogens (including nitrosamines and acetaldehyde), the destruction of the epithelial barrier, triggering inflammation and the Th17 response of the immune system.[12,13] Moreover, the malignant transformation of CHC seems to be not only the result of long-term effect of *C albicans*, but may also be promoted by a variety of factors, including the genotype of the strain, smoking, epithelial dysplasia and the increase of P53.[6,14] Based on the preliminary findings, the average conversion time of patients with malignant transformation in this study was two months and 11 months, respectively. So it is recommended that the follow-up interval for patients without dysplasia is every 3–6 months and that for patients with dysplasia is every 1–3 months.

Although in the WHO classification of head and neck tumours, 'chronic candidiasis' is included in oral potentially malignant disorders (OPMDs),[15] there is a debate about whether CHC is included in OPMDs. OPMDs refer to a group of diseases that affect the oral mucosa with an increased risk of malignancy. Up to date WHO working group for oral cancer did not include CHC for inclusion within the OPMDs due to its insufficient evidence for malignant potential.[16] Compared with typical OPMDs such as OLK and OLP (canceration incidence of 0.7% ~ 2.9% and 1% ~ 2%, respectively), the malignant transformation rate of CHC in our study is 4.17%,

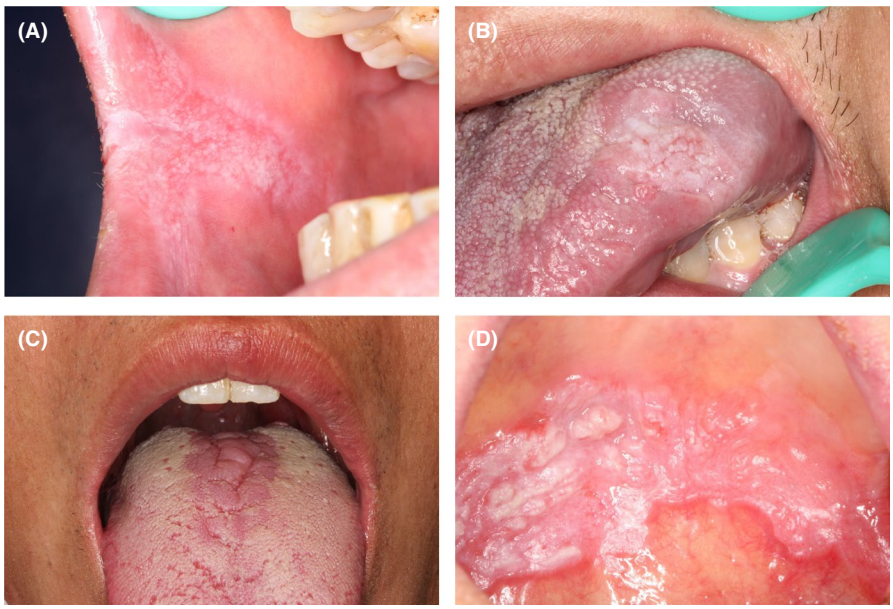

FIGURE 1 Clinical features of CHC in different sites: (a)White stripes like lesion with granular hyperplasia in the right commissure should be differentiated with heterogeneous oral leukoplakia; (b)white cornification with granular hyperplasia in the left lateral border of tongue should be differentiated with traumatic lesion; (c) atrophy with nodule in the posterior dorsum of tongue should be differentiated with erythematous candidosis; (d) white plaque with nodular lesion in the palate should be differentiated with oral leukoplakia

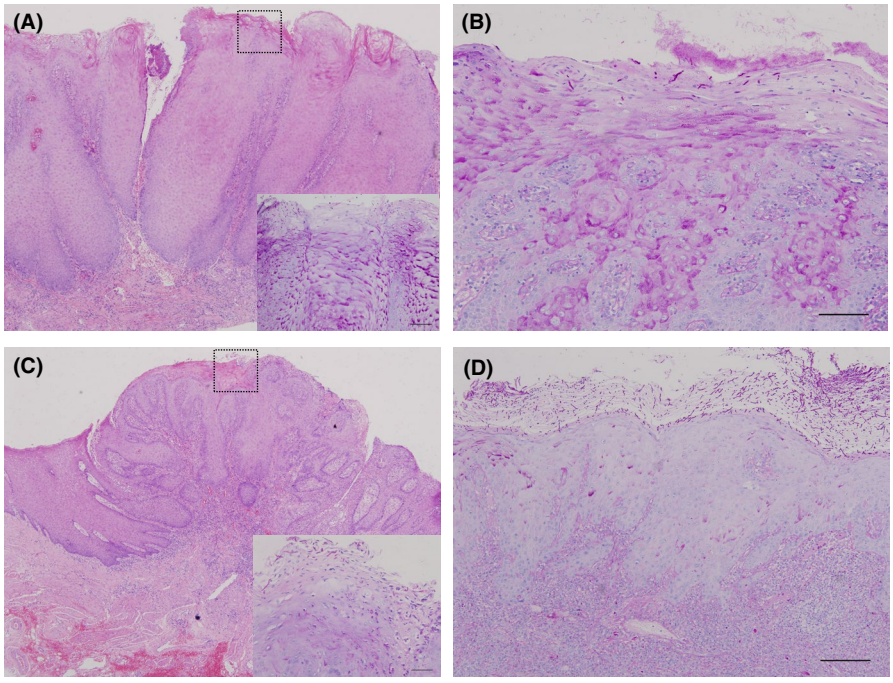

FIGURE 2 Histopathology features of CHC at different stages: (a) Histopathologic manifestations of a biopsy from the lateral border of tongue showing no epithelial dysplasia (H&E, ×25 magnification) (inset- the dotted box points to hyphae perpendicular to the stratum corneum) (PAS, ×100 magnification); (b) biopsy specimen from the commissure where mild epithelial dysplasia was identified (PAS, ×100 magnification); (c) histopathologic manifestations of a biopsy from the lateral border of tongue showing moderate epithelial dysplasia (H&E, ×100 magnification) (inset- the dotted box points to numerous hyphae perpendicular to the stratum corneum) (PAS, ×400 magnification); (d) biopsy specimen from the buccal mucosa where early carcinomatous change was identified (PAS, ×100 magnification)

which is even higher.[17] Moreover, an animal study showed that *C albicans* can cause severe epithelial dysplasia of the oral mucosa in mice, and may promote the carcinogenic progress of carcinogenic compounds.[18] Warnakulasuriya has previously proposed including CHC into OPMDs,[19] and here, we also highly recommend a unified consensus based on rather solid clinical evidence of high epithelial dysplasia rate and potential of malignant transformation.

There is currently no evidence-based guideline for the management of CHC, and the recommendations in the previous publications are based on limited clinical experience, including antifungal therapy, isotretinoin and surgical management.[4,6] Local factors such as smoking and trauma, and systemic factors such as diabetes and immunological defects should also be actively removed.[6] In 2016, the Infectious Diseases Society of America (IDSA) updated

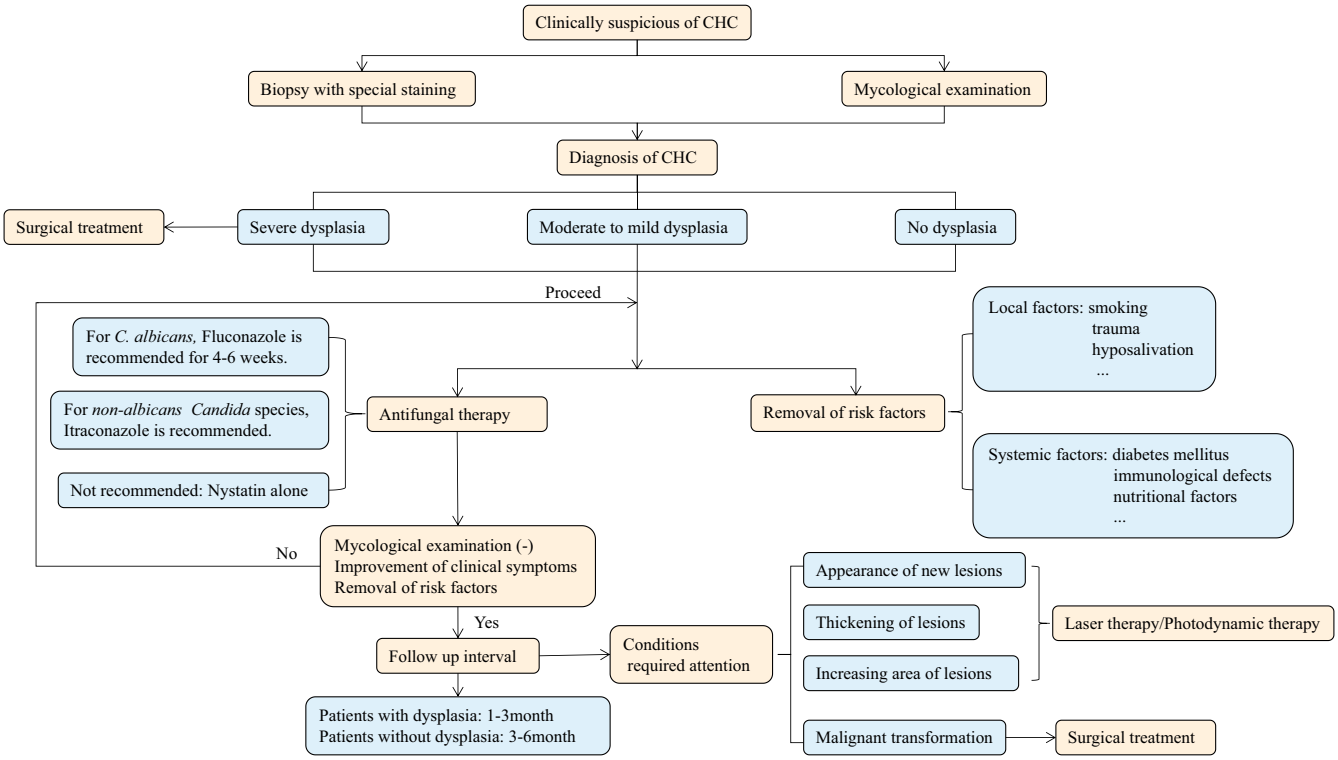

FIGURE 3 Flow chart of diagnosis, treatment and follow-up recommendations of CHC

its clinical practice guidelines for the management of candidiasis, including oropharyngeal candidiasis. The guidelines recommend topical antifungal agents such as nystatin for mild candidiasis, while systemic antifungal agents such as fluconazole for moderate to severe candidiasis.[20] It is worth noting that CHC are not specified in this guideline, so antifungal management strategies for CHC need to be further explored. In this study, the management recommendations illustrated in the flow chat is based on longitudinal follow-up of CHC patients treated with different antifungal regimens.

This study is a retrospective cohort study on the uncommon type of oral candidiasis, oral chronic hyperplastic candidiasis, with a comparatively large sample size. However, it has some limitations that merit discussion. First, the integrity of the clinical data is not satisfying due to the retrospective nature of the study. Second, not all patients underwent fungal cultures, which makes the analysis of results less informative. Third, the evaluation of malignant transformation of CHC cases still need consistent and long-term follow-up.

In conclusion, a six-year retrospective cohort study including 48 CHC patients was conducted. In addition to the comprehensively analysis of demographic data, clinical and histopathological manifestations, the prognosis of CHC such as treatment efficiency and malignant transformation were also prospectively observed. The diagnosis and management of CHC remain a challenge due to its polymorphic clinical presentation and chronic progression or even malignant transformation. Fluconazole with 4–6 weeks application is recommended for the treatment, and the follow-up interval should be individualised according to the elimination of risk factors, presence of epithelial dysplasia and appropriate management.

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CONFLICT OF INTEREST

No conflict of interest to declare.

AUTHOR CONTRIBUTION

Wenqing Zhang: Data curation (equal); Writing-original draft (lead). **Shuangshuang Wu:** Data curation (equal). **Xu Wang:** Resources (equal). **Yan Gao:** Resources (equal). **Zhimin Yan:** Methodology (lead); Supervision (lead); Writing-review & editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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