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The prevalence of hereditary angioedema in a Chinese cohort with decreased complement 4 levels

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ABSTRACT

Objective: Hereditary angioedema (HAE) is a rare, life-threatening autosomal dominant disorder. We aimed to investigate the prevalence of HAE in a Chinese population with a decreased Complement 4 (C4) level.

Methods: All the patients present in Tongji Hospital with C4 below lower normal range were included from January 2019 to June 2020. The individual data were extracted from the database and categorized by diagnosis. Patients suspected of HAE were further evaluated by C1 inhibitor level and function test to confirm the HAE diagnosis.

Results: A total of 8226 patients were enrolled in our study, among whom 18 had symptoms similar to HAE and received C1 inhibitor level and function tests. Two (1 male and 1 female) of the 18 patients were identified as HAE patients. This means the prevalence of HAE was 2.43/10 000 among the C4-decreased population and 10.1/10 000 in the C4-decreased population with etiology undetermined. The 2 HAE patients had experienced skin and oropharynx edema attack and received tracheotomy. The female patient had a family history. Laboratory tests showed significant decrease of C4 and C1 inhibitor levels in the 2 patients, both of whom were diagnosed as type 1 HAE.

Conclusion: The prevalence of HAE is low in C4-decreased patients. In a large cohort, C4 level can serve as a practical indicator to screen the HAE patients, but further testing of C1 inhibitor activity and levels is needed to confirm the diagnosis of HAE.

Keywords: Hereditary angioedema, Complement 4, Prevalence, Chinese cohort, Etiology

INTRODUCTION

Hereditary angioedema (HAE) is a rare life-threatening autosomal dominant disorder characterized by recurrent attacks of non-pruritic, non-pitting subcutaneous, and/or submucosal angioe-dema that can affect the face, extremities, genitalia, oropharynx, larynx, and digestive system.[1] The prevalence of HAE is estimated at 1:50 000 in the global population with

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no major ethnic or gender differences.[2] So far, several forms of HAE have been defined: type 1 HAE (HAE-1) (85% of the HAE patients), which results from C1 inhibitor (C1–INH) deficiency and is characterized by low C1–INH level and function, type 2 HAE (HAE-2) (15% of the HAE patients), which is caused by C1–INH dysfunction and is characterized by normal or slightly higher levels of C1–INH but functional damage; and HAE with normal C1 inhibitor level and function (HAE-nC1-INH). With HAE-1 and HAE-2, the mutation lie within the SERPING1 gene; with HAE-nC1-INH which has very relatively fewer cases reported, the mutation lies in the FXII gene (HAE-FXII), the angiopoietin-1 gene (HAEANGPT1), in the plasminogen gene (HAE-PLG), the kininogen 1 gene (HAE-KNG1), the myoferlin gene (HAE-Myoferlin), the heparan sulfate-glucosamine 3-O-sulfotransferase 6 gene (HAE-HS3ST6) and unknown genes (HAE-UNK, including mutation in TNFAIP3 or SYTL2).[3-5] It is known that the genetic mutations of HAE-1 and HAE-2 lead to overproduction of bradykinin and subsequent leakage of plasma from postcapillary venules, and cause angioedema in target organ and tissues.[6,7] However, the pathogenesis of HAE with normal C1–INH remains unclear.

In most epidemiological reports, type 1 and type 2 HAE, characterized by deficiency in C1–INH quantity and/or quality, account for the majority of the patients.[8,9] One study involving 137 Chinese HAE patients with C1–INH deficiency showed that type 1 HAE accounts for the majority (98.73%) of HAE patients and a minority (1.27%) of Chinese patients developed type 2 HAE.[10] Several SERPING1 gene mutations have been reported in Chinese HAE-C1INH patients.[11,12] Other types of HAE with the defects in factor XII (HAE-FXII), plasminogen (HAE-PLG) or angiopoietin-1 (HAE-ANGPT1), kininogen-1 (HAE-KNG1), myoferlin (HAE-Myoferlin), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HAE-HS3ST6) and HAE-UNK have not been reported in China, so far. For type 1 and type 2 HAE, the deficiency of C1–INH leads to activation of the complement system, causing a decrease in C4. It is worth noting that consumption of C4 happens even when patients do not have exposure to angioedema attacks.[8] Approximately 95% of HAE-C1INH patients show a reduced C4 level during remission and virtually 100% during an attack.[13]

As HAE is a rare disease and the symptoms in the involved organ (for example, gastrointestinal tract) may resemble those of more common diseases (such as irritable bowel syndrome, small bowel obstruction, pancreatitis, or appendicitis), many patients with HAE may be underdiagnosed or misdiagnosed. For the HAE-suspected patients, lab tests including quantitative and functional C1INH tests, are crucial to establishing a confirmatory diagnosis.[6] However, these lab tests are available in very few centers in China, which poses an obstacle to an accurate and timely diagnosis of HAE. In fact, only about 400 HAE patients from 120 different families have been identified in China.[11]

Given that the decreased level of C4 is present during HAE attacks in both HAE type 1 and type 2, and these 2 types account for the majority of HAE patients, we hypothesize that C4 level could be a practical screening tool for HAE-suspected patients. In this study, we investigated the prevalence of HAE in a cohort with C4 below normal lower range and identified the clinical characteristics of the HAE patients in this population.

METHODS

This was a single-center, non-interventional study. All the patients admitted to Tongji Hospital with decreased C4 levels between January 2019 and July 2020 were enrolled in this study. C4 decrease was defined as the serum C4 level lower than 0.16 g/L (normal range 0.16 g/L to 0.38 g/L). Patients with incomplete clinical data were excluded from the study. This study had been approved by the Independent Ethic Committee of Tongji Hospital.

Data extract procedure

The electronic medical record of each patient was reviewed (Fig. 1). Patients with underlying diseases which could lead to C4 decrease were regarded as etiologically clear. These underlying diseases included but were not limited to rheumatic and immune diseases, infectious diseases, kidney diseases, hepatic insufficiency, hematological systemic diseases, and allergic purpura.

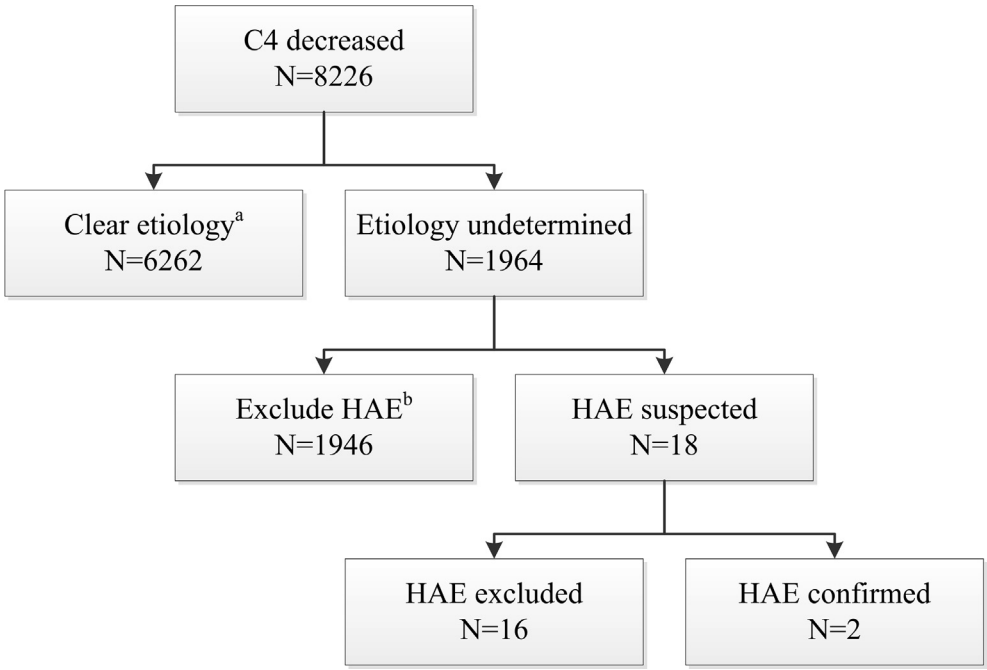

Fig. 1 The flowchart of HAE screening process in a C4-decreased Chinese cohort. a) Data include infectious diseases n = 1836, rheumatic and immune diseases n = 1689, kidney diseases n = 1201, hepatic insufficiency n = 932, hematological systemic diseases n = 413, skin diseases n = 190. b) Data include nerve system diseases n = 657, digestive system diseases n = 373, hematological system diseases n = 155, malignant tumor n = 117, cardiovascular diseases n = 130, skin diseases n = 95, respiratory system diseases n = 94, otolaryngological diseases n = 70, endocrine diseases n = 63, obstetrical and gynecological diseases n = 33, ophthalmic diseases n = 18, urinary system disease n = 16, poisoning n = 17, others n = 108.

Patients with C4 decrease which could not be explained by their underlying diseases were defined as etiologically undetermined. For these patients, their medical records were checked respectively by 2 doctors to figure out if the patients met at least 1 of the following criteria: (1) a history of recurrent angioedema without urticaria; and/or (2) a history of recurrent attacks of abdominal pain or vomiting; and/or (3) a history of recurrent laryngeal edema.[14] If the answer was "No", the patient would be marked as "not HAE patient"; if the answer was "Yes", the patient would be put into "HAE suspected" group.

For the HAE suspected patients, information about the family history of HAE, onset of symptom, and responses to antihistamines, glucocorticoids, or epinephrine were collected. The patient would also be asked to take C1 inhibitor level and function tests to confirm the diagnosis of HAE. If the test result was below normal range, the patient would retake the test within 1 month.

Statistical analysis

All data were presented as means and standard deviations (SDs) for normally distributed continuous data, frequencies for categorical data, medians, and 25%–75% interquartile ranges (IQRs) for abnormal distribution data.

RESULTS

A total of 8226 subjects with low plasma level of C4 were included in our study with 4600 (55.92%) being female. The average age was 33.79 years old. Among these patients, 6262 were categorized as etiologically clear, including 1836 (29.32%) with infectious diseases (C4 level: 0.13 g/L, IQR: 0.11–0.14 g/L), such as pneumonia, sepsis, urinary infection; 1689 (26.97%) with rheumatic and immune diseases (C4 level: 0.12 g/L, IQR:0.09–0.14 g/L), such as systemic lupus erythematosus, connective tissue disorders, Sjogren's syndrome; 1201 (19.17%) with kidney diseases (C4 level: 0.13 g/L, IQR: 0.11–0.14 g/L), such as nephrotic syndrome, IgA nephropathy, renal insufficiency; 932 (14.88%) with hepatic insufficiency (C4 level: 0.12 g/L, IQR: 0.09–0.13 g/L), such as hepatitis, cirrhosis, hepatic encephalopathy; 413 (6.59%) with hematological systemic diseases (C4 level: 0.13 g/L, IQR: 0.10–0.14 g/L), such as multiple myeloma, myelodysplastic syndromes, lymphadenoma and 191

(3.05%) with skin diseases (C4 level: 0.13 g/L, IQR: 0.12–0.14 g/L), such as Henoch-Schonlein purpura, leukoderma, psoriasis.

Patients with etiology undetermined

There were 1964 (23.87%) patients categorized as etiologically undetermined. Among them, 657 (33.45%) suffer from nervous system disease; 373 (18.99%), digestive system diseases, such as gastrointestinal hemorrhage, gastroenteritis, gastrointestinal polyps; 155 (7.89%), hematological system diseases; 130 (6.62%), cardiovascular diseases; and 117 (5.96%), malignant tumor (Table 1). After reviewing the electronic medical records of these patients, 18 of them were categorized as HAE suspected, and received further serum C1 inhibitor quantitative and function tests. Two of the 18 suspected patients were confirmed as HAE.

Prevalence of HAE in C4 decreased cohort

The prevalence of HAE was 2.43/10 000 in the C4 decreased cohort and 10.1/10 000 in C4 decreased patients with etiology undetermined. In clinically HAE-suspected patients with C4 below normal lower range, the prevalence of HAE was 11.1%.

Clinical characteristics of HAE patients

Patient 1, 51-year-old male. The first HAE attack happened when he was 20 and his symptoms were recurrent edema of the extremities without urticaria or abdominal pain. The frequency of attacks was less than 10 times per year, and most of the attacks were caused by trauma. However, the patient did not have a family history. The patient experienced a severe attack and underwent tracheotomy due to laryngeal edema induced by gingival bleeding in 2016. The blood level of C4 was 0.05 g/L, C1 inhibitor level was 0.04 g/L (normal range: 0.21–0.39 g/L). He was diagnosed type 1 HAE at 45.

Patient 2, 35-year-old female. She had experienced skin edema for 18 years. The symptoms were usually relieved in 3–4 days and she had no responses to antihistamines. She underwent tracheotomy for laryngeal edema in March 2019 and was misdiagnosed as anaphylaxis. On June 8, 2019, she was hit on the head by a small ball, and then developed head edema and dyspnea. She was admitted to our hospital on June 9, 2019 and experienced loss of consciousness quickly. She received tracheal intubation and tracheotomy in the emergency room. The blood level of C4 was 0.05 g/L. The activity of C1–INH was 0.01 IU/ml (normal range: 0.7–1.3 IU/ml). Her sister had similar symptoms but did not receive C1 inhibitor test. The patient was finally diagnosed as type 1 HAE. She died on July 18, 2019 due to systemic organ failure following hypoxic ischemic encephalopathy and pulmonary infection.

DISCUSSION

HAE is a rare disease in the global population. Our study firstly investigated the prevalence of HAE in a serum C4 decreased cohort. We found the prevalence of HAE was 2.43/10 000 in this population. However, in the patients whose C4 decreased without clear etiology, the prevalence increased to 10.1/10 000. When we combined the decreased C4 level and clinical manifestation of angioedema (recurrent skin edema or abdominal pain or larynx edema) as a screening criterion, 11.1% of the patients were finally diagnosed as HAE. Therefore, our study suggests C4 level test as a practical screening tool in clinics to identify HAE patients based on the following findings.

First, a comparison between the prevalence of HAE in the global population and that of China suggests the possibility of many misdiagnoses or underdiagnoses in China. In previous reports, HAE prevalence ranged from 1/50 000 to 4/50 000 in Caucasians, and about 5000 people (1/60 000) were affected by HAE in the United States.[15–18] According to the Spanish HAE patient registry, the minimum prevalence rate of HAE was 1 case in 100,000 inhabitants.[18,19] Although the exact prevalence of HAE in Asia was unclear, limited numbers of studies had indicated that the prevalence was very low. It was estimated that the prevalence of HAE in Japan was 4.1/10 000 000.[20] According to some reports, the minimum prevalence of HAE in Korea was estimated to be 1.3/1 000 000.[16] The prevalence of HAE in the general Chinese population is not clear. But since the documented prevalence of HAE in Asian countries was lower than western countries and data show the prevalence of HAE is about

Diseases No. of Patients C4 level (g/L)	Group									
	1	2	3	4	5	6	7	8	9	10
Nervous system N = 657 0.14 (0.12-0.15)	Cerebrovascular disease N = 188	Twitch and Limb weakness N = 107	Dizziness headache N = 91	Neuropathy N = 76	Abnormal function N = 55	Encephalo-myelopathy N = 40	Epilepsy N = 34	Mental illness N = 20	Parkinson N = 17	Others N = 29
Digestive system N = 373 0.13 (0.11-0.14)	Gastrointestinal bleeding N = 128	Gastrointestinal symptoms N = 51	Gastrointestinal polyposis N = 41	Jaundice N = 13	Ulcer N = 11	Ascites N = 9	Biliary disease N = 6	Intestinal obstruction N = 7	Reflux esophagitis N = 3	Others N = 25
Hematological system N = 155 0.13 (0.12-0.14)	Anemia N = 46	Coagulation abnormalities N = 37	Lymphadenopathy N = 22	Leucocyte abnormality N = 18	Post bone marrow transplantation N = 12	Blood hematopoietic stem cell donor N = 13	Others N = 7	-	-	-
Cardiovascular disease N = 130 0.13 (0.12-0.14)	Coronary heart disease N = 27	Heart failure N = 25	Arrhythmia N = 16	Blood clots N = 13	Hypertension N = 11	Cardiom-yopathy N = 9	Hydroperi-cardium N = 8	Aortic dissection N = 5	Congenital heart disease N = 5	Others N = 11
Skin disease N = 95 0.13 (0.12-0.14)	Skin rash N = 24	Urticaria N = 23	Dermatitis N = 18	Seborrheic alopecia N = 6	Psoriasis N = 5	White hair N = 4	Erythroderma N = 3	Skin lumps N = 3	Nevus N = 3	Others N = 6
Respiratory system N = 94 0.13 (0.12-0.15)	Asthma N = 25	Respiratory failure N = 18	Hydrothorax N = 16	Cough hemoptysis N = 11	Pulmonary embolism N = 9	Lung nodule N = 7	Others N = 2	-	-	-
otolaryngological diseases N = 70 0.14 (0.12-0.15)	Sudden deaf N = 27	Deviation of nasal septum N = 19	Nasopharyngeal lumps N = 11	Nasal polyp N = 7	Nasal bone fracture N = 2	Adenoid hypertrophy N = 2	Others N = 2	-	-	-
Endocrine disease N = 63 0.13 (0.11-0.15)	Thyroid dysfunction N = 15	Diabetes N = 13	Electrolyte disturbance N = 7	Pituitary adrenal dysfunction N = 6	Diabetes insipidus N = 4	Malnutrition N = 6	Others N = 11	-	-	-
Obstetrical and gynecological N = 33 0.14 (0.11-0.15)	Gestation N = 11	Abortion premature N = 6	Uterine disease N = 6	Eclampsia N = 2	Menstrual disturbance N = 2	Others N = 6	-	-	-	-
Ophthalmic disease N = 18 0.14 (0.10-0.15)	Uveitis N = 8	Corneal ulcer N = 5	Glaucoma N = 2	Retinopathy N = 2	Others N = 1	-	-	-	-	-

(continued)

Diseases No. of Patients C4 level (g/L)	Group									
	1	2	3	4	5	6	7	8	9	10
Urinary system N = 16 0.13 (0.12–0.15)	Urinary lithiasis N = 4	Rhabdomyolysis N = 3	Urinary incontinence N = 4	Others N = 5	-	-	-	-	-	-
Malignant tumor N = 117 0.13 (0.11–0.15)	-	-	-	-	-	-	-	-	-	-
Poisoning N = 17 0.12 (0.11–0.14)	-	-	-	-	-	-	-	-	-	-
0thers N = 108 0.13 (0.11–0.14)	-	-	-	-	-	-	-	-	-	-

Table 1. (Continued) C4-decreased patients with etiology undetermined (N = 1946)

1:50 000 in the global population, we estimate there are around 28 000 HAE patients in China. However, only about 400 HAE patients from different regions in China were identified, which implied the majority of the HAE patients may be misdiagnosed or underdiagnosed.[11]

Second, our study suggests it may be a better way to find out the HAE patients in a subpopulation (such as C4 decreased with etiology undetermined) rather than from a general population. For one thing, we found the prevalence of HAE in C4 decreased population was 2.43/10 000, much higher than the reports from many other countries. When we excluded the patients with clear etiology in the cohort, the prevalence of HAE in this population increased to 10.1/10 000. For another, the huge gap between the estimated and identified patients may be attributed to the very low prevalence and nonspecific symptoms of HAE (the symptoms resemble those of acquired angioedema and acute abdominal diseases). Consequently, HAE patients often received inappropriate treatment (such as corticosteroids and antihistamine) and unnecessary procedures, which increases the mortality risk. Multiple studies from different countries have shown that the patients will be in a life-threatening condition if they are never properly diagnosed because of not receiving appropriate and timely treatment.[21-24]

Indeed, delayed diagnosis of HAE is a global challenge. In previous studies, there was a diagnostic delay of 8–10 years for HAE in Europe and the United States.[25] The mean delay in diagnosis of HAE for Chinese patients could be even longer (12.64 years).[26] A study showed the Chinese HAE patients usually needed to consult 6 doctors before getting a confirmed diagnosis; their most frequently visited departments included emergency (90.6%), dermatology (71.9%), allergy (61.5%), gastroenterology (52.1%), rheumatology (34.4%), and otolaryngology (34.4%).[27] For the 2 HAE patients identified in our cohort, they both had received systemic corticosteroids for many times and had delayed diagnosis up to 25 years. Therefore, all clinicians, especially emergency physicians and dermatologists, should be aware of the clinical symptoms of HAE and its treatment approaches. It would be very crucial and helpful to establish an early diagnosis and subsequently reduce potential risks of fatal HAE attack.[14]

Apart from addressing the urgent need to give a proper and timely diagnosis of HAE, our study also showed that serum C4 level was a feasible screening tool for identifying HAE patients. Given that the type 1 and type 2 HAE accounted for nearly all the HAE patients and there were no other types of HAE reported in China, it's reasonable to include the decreased C4 level as a diagnostic criterion for HAE. One study reported the sensitivity of low C4 level in diagnosing HAE was 81%.[28] In our study, we found among the 18 patients with angioedema-related manifestation, 2 of them were confirmed HAE when they had a low C4 level, which also implied C4 was a sensitive indicator to diagnose HAE patients, especially in the context of the extremely low prevalence of HAE in the general population. Moreover, C4 tests are easily available in China whereas the C1 inhibitor concentration and function tests are only available in very few clinical centers, making the former very practical in clinics.

Emphasizing the practicality of this screening tool does not mean that we are not aware of possible doubts about the effectiveness of this proposal. For example, given that the 2 confirmed cases in our study presented relatively low C4 levels, should we consider a more stringent *cut-off* C4 value for more effective screening? If we take C4 level below 50% of the lower normal range as the screening criterion in our study, the prevalence of HAE will increase to 2.5/1000 in the subpopulation and 100% in HAE-suspected patients. That might mean quicker diagnosis. But it may also risk possible missed diagnoses by excluding potential HAE patients because C4 level fluctuates and may be restored to normal in intermittent period of HAE. In other words, if we set too strict a cut-off value of C4 level, some HAE patients may fail to be identified, which is at odds with our hope to reduce possible missed diagnoses by proposing this screening tool.

There are some limitations in the study. Firstly, we only included C4 decreased subjects in our study. However, some HAE patients may have normal C4 level during the remission period, and non-type 1/type 2 HAE patients might also be excluded due to the study design. Secondly, the HAE related symptoms may not have been fully documented in the electronic medical records. Some HAE patients may be wrongly excluded from further C1 inhibitor tests. Finally, there are reports of C4 allotype deficiency in 1/60 up to 1/250 individuals in the population.[29] The HAE-suspected patients might include people of C4 allotype deficiency as we didn't perform C4 allotype evaluation in our study. These limitations may lead to an underestimate of the prevalence of HAE in our cohort.

In conclusion, when we analyzed the prevalence of HAE in a C4 decreased Chinese cohort, we found the prevalence of HAE was low in the cohort but relatively high in C4 decreased patients with etiology undetermined. Our findings highlight the C4 level test is a good screening tool for diagnosing HAE in suspected patients. We strongly suggest doctor perform a C4 test when HAE is suspected. In addition, HAE should be considered if a decreased C4 level cannot be explained by the underlying diseases. It is noteworthy that the diagnosis of C1–INH-HAE should be identified by measurement of serum level of C1–INH protein and C1–INH activity. In short, raising awareness of this rare disease among doctors is essential for early diagnosis, effective treatment and long-term prophylaxis of the HAE patients.

Abbreviation

HAE, Hereditary angioedema; C4, Complement 4; C1, Complement 1; C1–INH, Complement 1 Inhibitor; HAE-1, type 1 Hereditary angioedema; HAE-2, type 2 Hereditary angioedema; HAE-nC1-INH, HAE with normal C1–INH; FXII, factor XII; ANGPT1, angiopoietin-1; PLG, plasminogen; KNG1, kininogen-1; TNFAIP3, tumor necrosis factor alpha-induced protein 3; SYTL2, synaptotagmin like 2; HS3ST6, heparan sulfate-glucosamine 3-O-sulfotransferase 6; UNK, unknown; SDs, standard deviations; IQRs, interquartile ranges; IgA, immunoglobulin A.

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Consent for publication

All authors provided consent for publication.

Contribution of each author

Cui Qi, perform laboratory test, data collection, statistical analysis, paper writing; Xu Qingxiu, data collection, statistical analysis; Yang Yaqi, statistical analysis, data collection; Li Wenjing, data collection; Huang Nan, data collection; Chen Hao, data collection; Ma Dongxia, data

collection; Zhang Shuchen, data collection; Yang Lin, perform laboratory test, data collection; Rongfei Zhu, data collection, paper writing and revising.

Availability of data and materials
All data supporting the findings of this study are available within the article and its Supplementary Information files or are available from the corresponding author upon request.

Ethics approval
The study was approved by the Independent Ethic Committee of Tongji Hospital as it is part of a routine procedure in which no additional consent is required.

Confirmation of unpublished work
We confirm our manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Declaration of competing interest
The authors declare that they have no conflict of interest.

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