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Epidemiological and initial clinical characteristics of patients with family aggregation of COVID-19

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ABSTRACT

Background: Since December 2019, a new outbreak of the coronavirus disease 2019 (COVID-19) in Wuhan (Hubei, China) and rapidly spread throughout China, however, confirmed cases are still increasing worldwide. **Objectives:** To investigate the epidemiological history and initial clinical characteristics of 10 patients with family aggregation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Western Chongqing, China.

Study design: Ten patients positive for SARS-CoV-2 nucleic acid detection by real time Reverse Transcription-Polymerase Chain Reaction (RT-PCR), were collected from The People's Hospital of Dazu District, Chongqing. Epidemiological data and laboratory and imaging results were collected on the first day of admission, and analyzed based on *the Diagnosis and Treatment Guideline for COVID-19 (5th edition, China)*.

Results: Of the 10 cases, case A had a history of a temporary stay in Wuhan and transmitted the virus to the others through family gathering, living together, and sharing vehicles. The average age was 56.5 years (± 11.16), six patients were males, and the incubation period was 2–14 days. Dry cough was the main symptom, followed by fever and fatigue. Most patients were clinically classified as ordinary-type, with three cases being severe-type. Chest computed tomography results were nonspecific, mainly with ground-glass attenuation and/or shadow images. Extensive lesion distribution was seen in severe cases. CD4+ lymphocyte counts were 61, 180, and 348 cells/uL in severe-type patients, respectively. Notably, viral nucleic acid values in nasopharyngeal swabs were lower (19, 25, and 26) than those of ordinary-type patients, suggesting a higher viral load. Neutrophil-lymphocyte ratio (NLR) was also higher in severe-type patients.

Conclusions: Initial examination results of lower CD4+ lymphocyte counts and RT-PCR-CT values coupled with higher NLR may indicate the severity of COVID-19 infection for these family clusters.

1. Background

The outbreak of the new emerging disease COVID-19 coincided with the Chinese Lunar New Year holiday, and the large movement of people has expanded and spread this outbreak rapidly, from Hubei province to the other areas of China. The continuous rising number of infected people is causing a serious threat to public health and a great loss to the social economy. As of February 18, 2020, a cumulative report confirmed that the number of cases had risen to 74185 [1], based on 31 provinces (autonomous regions and municipalities directly under the central government) and Xinjiang Production and Construction Corps, confirmed cases are still increasing worldwide.

2. Objectives

To provide the information for public health strategies for rapid and appropriate assessment and corresponding initial management, we investigated the epidemiological and clinical features of these SARS-CoV-2-infected family clustering patients between January 23 and February 18, 2020.

3. Study design

3.1. Patients

Our hospital serves as one of the designated hospitals for the initial

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diagnosis and assessment of suspected SARS-CoV-2-infected patients in Western Chongqing, China. Diagnoses were made with reference to *The Diagnosis and Treatment Guideline for COVID-19 (5th edition, China)* from The National Health Commission of China [2]. Suspected cases were isolated using air borne precautions in the designated hospital. Patients positive for nasopharyngeal-swabs SARS-CoV-2 nucleic acid detection by real time RT-PCR were identified as confirmed cases. Of the 80 suspected cases were admitted into our hospital, 14 patients were confirmed to be infected with SARS-CoV2 among which 10 patients with family aggregation of COVID-19 were identified. This study was approved by the Ethics Commission of The People's Hospital of Dazu District. Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

3.2. Information collection

3.2.1. Epidemiological data

Patient data were acquired in detail regarding any travel history in Wuhan and its surrounding areas, contact with local community confirmed cases within 14 days before disease onset, contact with febrile patients with respiratory syndrome from Wuhan and its surrounding areas, any possible contact with pathogenic nucleic acid-positive patients within 14 days before onset, or any chance of family aggregation, among others. The criteria used for determination of close contacts was from the *Reference to Prevention and Control Guideline for COVID-19 (4th edition, China)* from The National Health Commission of China [3]. The number of close contacts of the first confirmed case was provided by the Center of Disease Prevention and Control (CDC) of Dazu District, Chongqing.

3.2.2. Clinical data

Clinical data of the 10 patients positive for nasopharyngeal-swab SARS-CoV-2 nucleic acid detection by RT-PCR, were collected from The People's Hospital of Dazu District. SARS-CoV2 open reading frame 1ab (ORF1ab) and nucleocapsid protein (N) gene were detected with the use of real-time quantitative fluorescence quantitative. Cycling threshold (CT) values of both ORF 1ab and N gene that both less than 35 were considered positive cases, values ranging between 35–38 were considered suspicious cases, and those greater than 38 were considered negative cases. White blood cell (WBC) counts, lymphocyte absolute values (Lymph#), NLR, platelet count, renal function, liver function, CD4 + T lymphocytes, myocardial enzymes, blood gas analysis, coagulation function, procalcitonin (PCT), C-reactive protein (CRP), diverse respiratory virus antigen assay, influenza A/B virus antigen, and chest CT were assessed on the first day of admission.

3.3. Data collection

We reviewed electronic medical records, nursing records, laboratory results, and chest CT for 10 patients with positive SARS-CoV-2 detection from The People's Hospital of Dazu District. Epidemiological, clinical manifestations, laboratory, and radiological characteristics data were collected from the electronic medical record system. To ascertain epidemiological data, two researchers directly communicated with patients or their families, and independently reviewed all of the data to double-checked the data collected.

4. Results

4.1. Close contacts

According to the investigation of Dazu District CDC, case A had a total of 75 close contacts, including 15 relatives and 60 non-relatives. Among the relatives, 9 patients were positive for SARS-CoV-2 nucleic acid detection except for his wife, daughter, son, sister, sister-in-law and niece. Family relationships are shown in Fig. 1.

4.2. Epidemiology

Case A was born in Dazu District, and lived in Foshan, Guangdong, China for a long time. On December 18, 2020, he returned to Chongqing West railway station by high-speed rail, and then to Dazu District by coach. On January 1, 2020, he went to Hunan province for a commercial meeting, returned home 4 days later via high-speed rail, went to Guangzhou thereafter via the same vehicle on January 15, and returned to Dazu by car on January 17 (passing through Wuhan). He had dinner with his father (case B), younger aunt (case C), younger brother (case D), cousin (case E), uncle (case F), and older aunt (case G) several times between January 19, 2020 and January 24, 2020. Since January 24, case F lived in case G's house, and case G lived with her husband (case H) and son (case J). On January 28, case A had dinner with case I, the mother of case E, and they stayed together. On January 19, case A had a cough and felt fatigue, then consulted the doctor that day; a chest CT scan showed scattered multiple ground-glass shadows in the bilateral lung periphery, and final confirmation was verified by positive novel coronavirus nucleic acid detection based on two nasopharyngeal swabs. Cases B, C, D, E, F, G, H, I and J were confirmed by contact-tracing and screening with typical symptoms of fever, cough, and fatigue, and the incubation period was 2–14 days, the average incubation period was 7 (SD 2.59) days. The chronology of symptom onset and identification of positive SARS-CoV-2 findings on RT-PCR and CT among the family cluster are shown in Fig. 2.

4.3. Demographics and Clinical manifestations

The 10 individuals infected with SARS-CoV-2 were of clustering onset; the average age was 56.5 years (SD 11.16), including six men and four women; two of the patients had underlying diseases. Patients showed clinical manifestations of dry cough (70%, 7/10), fever (70, 7/10), fatigue (30%, 3/10), diarrhea (10%, 1/10), shortness of breath, nausea, itchy throat, and chills. According to the clinical classification criteria, one patient was mild-type (10, 1/10), six were ordinary-type (60%, 6/10), and three were severe type (30%, 3/10) infection (Table 1).

4.4. Laboratory examinations

Only one case had reduced WBC and platelet counts owing to complications of liver cirrhosis, whereas the rest had normal counts for both. Except for one case with normal absolute value of lymphocytes, the rest had lower values. Eight cases had increased CRP values up to varied extents. Four patients had reduced partial pressure of oxygen (PO₂), out of which, three were severe cases; The CT values of nasopharyngeal-swab RT-PCR for the three severe cases were lower than those of other patients, and CD4+ lymphocyte counts were reduced to different extents, with a minimum of 61 cells/uL (reference value: 355–1213 cells/ uL). NLR was higher than 10 in these three severe cases, the others being between 1.29 and 6.14. All cases had normal PCT, creatinine, coagulation function, influenza A/B virus antigen, and respiratory virus antigen (Table 2).

4.5. Chest CT

Chest CT showed ground-glass shadow, fuzzy shadow, or nodular shadows, mainly in the lung periphery. Eight cases (80%, 8/10) involved the bilateral lungs and two cases involved the unilateral lung; subpleural lesions were seen in two cases and interstitial pulmonary diseases were involved in 2 cases. The severe cases of A, G, and I had extensive lesion distribution, as shown in Fig. 3.

5. Discussion

According to previous investigations [4], the initial confirmed cases

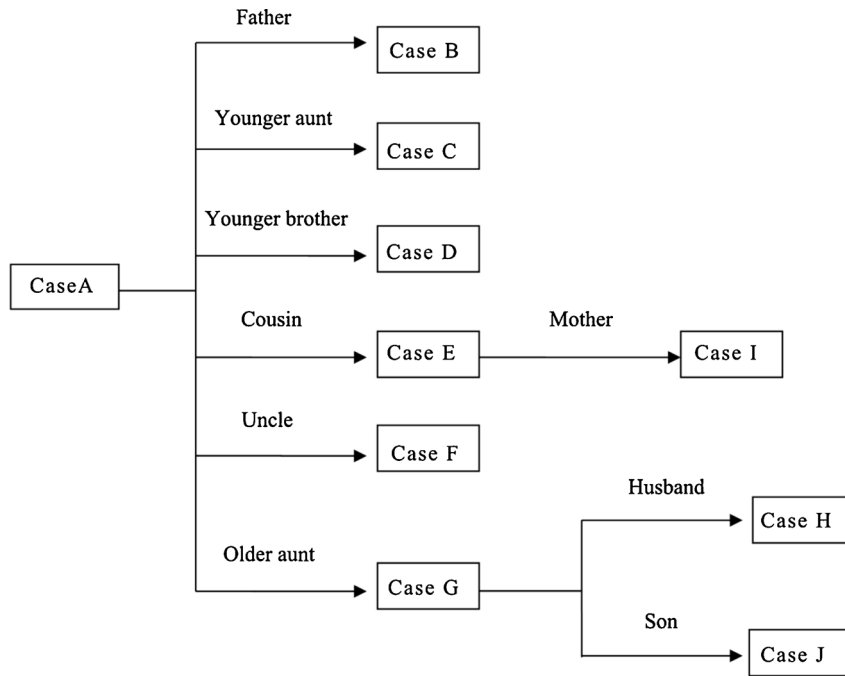


Fig. 1. The family relationship of the 10 COVID-19 cases.

of COVID-19 shared a history of exposure to seafood markets in Wuhan. However, with the development of the epidemic, studies in several provinces and cities in China have identified the phenomenon of family aggregation in this outbreak, which accounts for 50 to 80% of all

confirmed cases [5]. In this area, 14 cases were confirmed with 10 of whom sharing the same family relationship. Characteristics of the 10 familial clusters were as follows: the initial case, Case A, had a history of Wuhan stay; Case B, C, D, E, F, G, and I were infected during family

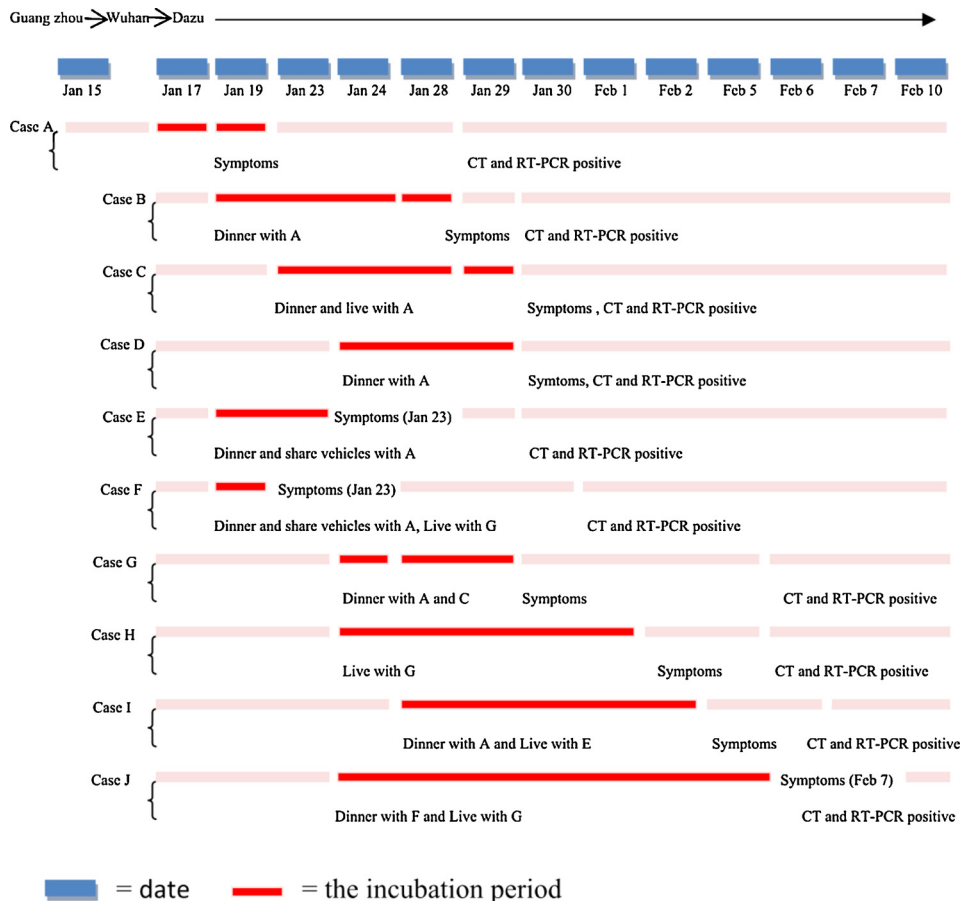


Fig. 2. Chronology of symptom onset and identification of positive SARS-CoV-2 findings on RT-PCR and CT of the 10 COVID-19 cases.

Table 1
Baseline characteristics and clinical manifestations of the 10 COVID-19 cases.

Case	Gender	Age	Underlying diseases	First symptom	Concomitant symptom	Clinical classification
Case A	male	48 y	no	cough and fever	fatigue	severe
Case B	male	70 y	no	fever	no	ordinary
Case C	female	51 y	no	fever	no	ordinary
Case D	male	43 y	no	diarrhea	no	ordinary
Case E	female	47 y	no	fatigue	chill and dry cough	ordinary
Case F	male	54 y	no	dry cough and fever	itchy throat	ordinary
Case G	female	66 y	no	cough and fever	fatigue, nausea, and shortness of breath	severe
Case H	male	71 y	Liver cirrhosis	cough	fever	mild
Case I	female	71 y	no	cough	fever	severe
Case J	male	44 y	hypertension	cough	no	ordinary

meals, among which, Case E and F took the same transportation means along with Case A before the onset; Case H and J were infected while living together with Case G; except for Case A, none of the other cases had ever been to the epidemic area, which confirmed that interpersonal transmission does occur with this disease. Droplets containing the virus can deposit on any surface and can be spread by touching, which would contaminate the hands; moreover, the virus might enter the oral cavity, nasal cavity, and eyes when infected hands come in contact with areas containing mucous membranes. The novel coronavirus has been detected on the surfaces of doorknobs, mobile phones, and other objects in the surroundings of confirmed patients in Guangzhou and Shandong provinces, China, thus assuring that the virus can be transmitted by contact [5]. The fifth edition of the Diagnosis and Treatment guideline for SARS-CoV-2 infection published by the National Health Commission has clearly indicated that people are generally susceptible to this virus, and the incubation period is 3–7 days, which is consistent with the average 7-day incubation period for the familial cluster cases in our district.

Two epidemiological studies [6,7] of familial aggregation cases infected with SARS-CoV showed that the spread of SARS-CoV does not occur during the incubation period, but rather in the diseased period, mostly in the population with a history of living together or having close contact with confirmed patients. Meanwhile, retrospective studies [5] from various provinces and cities found very strong transmissibility in the incubation period for SARS-CoV-2, which is in line with the results of our study. Here, only case C and A had been living together; the rest were all exposed to SARS-CoV-2-infected patients through dinner parties or via transportation, which also proved the strong infectivity and communicability of this virus during the incubation period.

An analysis [8] of 1099 confirmed SARS-CoV-2-infected patients (up to January 29) revealed the most ordinary symptoms to be fever (87.9%), cough (67.7%), and rarely diarrhea (3.7%); further, 25.2% patients had at least one co-morbidity (such as hypertension and chronic obstructive pulmonary disease), and 82.1% had decreased lymphocyte counts. One study [4] on 41 patients from the early stage of this epidemic outbreak (until January 2) found that 63% patients had

lymphocytopenia, whereas all had pneumonia. Zhao [9] et al analyzed the clinical characteristics of 28 patients with novel coronavirus pneumonia (from diagnosis date up to February 5) and found the ordinary starting symptoms to be fever and cough (mainly dry cough) as well, in addition to other symptoms like chill, throat irritation, and fatigue. Radiographic tests showed that the lesions occurred in each part of the bilateral lungs; chest CT showed ground-glass shadow, edge fuzzy shadow, and spot or patchy shadow. The aforementioned results were consistent with the clinical manifestations, laboratory examinations, and chest images of the cluster cases in our district. Further, an analysis [10] of 4021 confirmed patients in China suggested that the proportion of mild, severe, and ordinary patients is 4.5%, 25.5%, and 69.9%, respectively. The same trend could be seen among the 10 patients in our district. It is possible that the majority of patients with COVID-19 are ordinary-type cases [11].

One patient was characterized by diarrhea, with no fever or respiratory symptom, and another case had nausea caused by SARS-CoV-2 involvement in the gastrointestinal tract, which was observed with other coronavirus infections such as SARS in 2003. Cheng [12] reported that 10.6% (15/142) of patients with SARS present with symptoms of diarrhea at admission, whereas this occurs in 48.6% (69/142) of patients within 7.6 ± 2.6 days after this; the mechanism might be related to viral replication in the gut. Additionally, one study [13] on 298 young children with febrile urinary tract infection revealed NLR as a practical biomarker capable of predicting acute pyelonephritis; there is also an important association between NLR and bacterial infection such as pneumonia, sepsis, and systemic inflammatory response. Increased NLR outperforms conventional markers, such as WBCs, neutrophil counts, and CRP, as a useful biomarker to detect bacteremia. In this study, the NLR in severe cases was significantly higher than that in ordinary-type cases, indicating that NLR might be related to the severity of COVID-19. NLR is a simple, cheap, and easy parameter of inflammation, because it can be measured in almost all laboratories. This indicator can be used for routine analysis to further explore the role of NLR in predicting the severity of COVID-19. Notably, it can be seen that CRP increased in most patients here, but PCT values were normal for all

Table 2
Laboratory indicators of the 10 COVID-19 cases.

Case	WBC $10^9/L$	Lymph# $10^9/L$	CRP mg/L	NLR	CD4 cells/uL	RT-PCR-CT values 1ab	N gene	PO ₂ mmHg	PCT ng/mL
Case A	7.62	0.59	55.76	10.47	61	19.19	19.85	63.20	0.35
Case B	6.12	0.43	7.01	4.58	452	27.62	27.60	83.40	0.32
Case C	5.50	0.78	48.54	5.45	418	32.19	32.75	100	0.23
Case D	6.44	0.77	12.75	6.14	618	33.42	32.04	88	0.44
Case E	4.22	0.65	13.51	4.82	399	33.58	34.54	89.20	0.23
Case F	4.26	0.96	48.51	2.93	402	27.60	27.73	78	0.14
Case G	4.49	0.46	33.47	10.13	180	25.01	25.61	70	0.11
Case H	2.77	0.99	1.66	1.29	425	27.02	27.60	96	0.18
Case I	7.96	0.60	35.84	11.35	348	26.29	26.73	72	0.05
Case J	6.44	1.48	2.67	2.80	688	27.93	27.90	125	0.27

WBC = white blood cells, Lymph# = lymphocyte absolute values; CRP = C-reactive protein; NLR = neutrophil-lymphocyte ratio; CT = cycling threshold; ORF1ab = open reading frame 1ab; N gene = nucleocapsid protein; PO₂ = partial pressure of oxygen; PCT = procalcitonin;

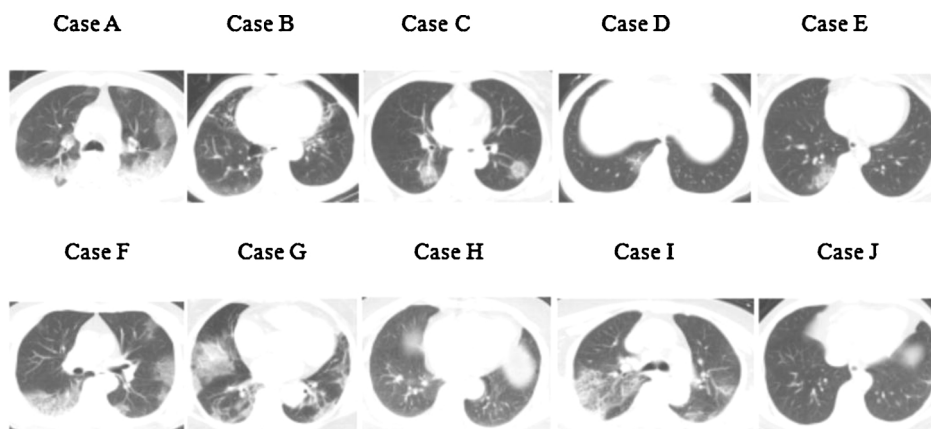


Fig. 3. Chest CT images of the 10 COVID-19 cases.

of these cases. Previous studies [14,15] showed that PCT is normal during virus infection and that the specificity of predicting bacterial infection is higher than that of CRP. Therefore, the routine use of antibacterials is not recommended for COVID-19 patients in the absence of PCT elevation.

As is well known, viral infection is closely related to the human immune system [16,17]; good immune function can help the body to eliminate foreign microorganisms, control infection, and eventually restore health. Wang [17] analyzed the correlation between changes in lymphocytes in 252 SARS cases and the disease itself and reported that CD3, CD4, and CD8 T cells are significantly diminished in the first week of the disease. The patients' conditions improved as CD4 T lymphocytes became normal; in contrast, it indicates the deterioration of diseases related to cellular immunity damage. Recently, Guo et al [18] analyzed the clinical data of patients with viral pneumonia and found that the absolute counts of CD3 + T cells, CD3 + CD4 + T cells, and CD3 + CD8 + T cells in the group that died was significantly lower than those in the surviving group, indicating the impairment of cellular immunity as well. In the severe-type in our study, the CD4 count for Case A was 61 cells/uL, for Case G was 180 cells/uL, and for Case I was 348 cells/uL, whereas the CD4 counts were all above 399 cells/uL for other patients, with both ordinary-and mild-types, suggesting decreased cellular immunity at the onset of disease in severe patients.

Currently, the fluorescence-based real-time RT-PCR method is widely used to detect SARS-CoV-2 nucleic acids [19–22]. Although at present the nucleic acids of SARS-CoV-2 cannot be quantified, it is known that the lower the RT-PCR-CT value during amplification, the higher the virus load in the specimen being examined [23] and vice versa. With recovery of the patient's condition, the CT values can change from low to high, and therefore, the communicability of the patient as an infectious source also decreases [24]. In this study, the RT-PCR-CT values in three patients with severe-type infection were lower than those in the rest; specifically, in case A, the RT-PCR-CT was 19.19, implicating a high viral load and the strong infectivity of this patient.

Based on these data, we consider a higher NLR, lower CD4 counts, and lower RT-PCR-CT values likely to predict severity of the disease at the early stage. Lower RT-PCR-CT values also indicate the infectivity of the patient. Therefore, the three parameters can be used to predict the prognoses of patients. Certainly, the clinical significance of NLR, CD4 counts, and RT-PCR-CT values need to be verified further using larger sample sets.

Ethical Approval

This study was approved by the Ethics Commission of The People's Hospital of Dazu District. Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

Authors' contributions

XYX conceived the study. XYX, JW and HLL collected the data. XYX and HLL analyzed the data. XYX and JW wrote this article. BJ and WXH revised it. HX supervised study conduct. All the authors have read and approved the final version of this manuscript.

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Declaration of Competing Interest

The authors declare that there are no competing interests.

CRediT authorship contribution statement

Xiao-ying Xia: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft. **Jing Wu:** Investigation, Writing - original draft. **He-lei Liu:** Investigation, Formal analysis. **Hong Xia:** Supervision, Funding acquisition. **Bei Jia:** Writing - review & editing, Supervision, Funding acquisition. **Wen-xiang Huang:** Writing - review & editing.

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