Long-term Outcomes of Patients with Anti-Leucine-Rich Glioma-Inactivated 1 Encephalitis

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Abstract

Background: This report aims to provide a detailed description of the clinical manifestation, immunotherapy, and long-term outcomes of 117 Chinese patients with anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis.

Methods: We retrospectively selected 117 patients diagnosed with anti-LGI1 encephalitis from the databases of multiple clinical centers from September 2014 to December 2019. The clinical features, ancillary test results, and details of long-term outcomes were analyzed.

Results: Among the 117 anti-LGI1 encephalitis patients, 81 (69%) were male and 36 (31%) were female; the median onset age was 51 years (range: 30-77 years). The median time from symptom onset until diagnosis was 8.7 weeks (range: 2-49 weeks). The main features evaluated in our cohort were seizures, cognitive impairment, and mental and behavioral abnormalities. One hundred and nine patients were treated with immunotherapy. After 3-5 days of treatment, the clinical symptoms were somewhat alleviated in all the patients, and their memory, mental ability, and behavior improved. The median follow-up time was 33 months (range: 6-59 months). A total of 19 (16%) patients experienced a relapse; the median duration from onset to the first relapse was 5 (0.3-27) months. There were no mortalities during the follow-up period.

Conclusions: The outcome of patients with anti-LGI1 encephalitis is mostly favorable, although some patients continue to suffer from cognitive dysfunction. Early recognition is of great significance for the treatment of anti-LGI1 encephalitis. Prompt adequate immunotherapy has positive implications for the improvement of clinical symptoms of anti-LGI1 encephalitis. Long-term follow-up is important for the assessment of LGI1 antibody-mediated encephalitis.

1. Background

Autoimmune encephalitis (AE) refers to a group of inflammatory diseases caused by the immune system to the central nervous system. With the increased research in autoimmunity, the spectrum of AE subtypes has broadened.\(^1\)\(^-\)\(^3\) Different subtypes of AE have shown complex clinical manifestations, resulting in diagnosing difficulties. Leucine-rich glioma inactivated 1 (LGI1) is one of the antigenic targets of voltage-gated potassium channel (VGKC) complex antibodies associated with AE.\(^4\)\(^,\)\(^5\) Since its first report in 2010,\(^6\)\(^,\)\(^7\) increasing numbers of anti-LGI1 encephalitis cases have been identified and reported.

According to previous reports, there are differences between countries in clinical features and treatment strategies of anti-LGI1 encephalitis.\(^4\)\(^,\)\(^5\)\(^,\)\(^8\)\(^,\)\(^9\) China proposed a consensus for the management of AE in 2017 to better identify and manage this disease in Chinese patients.\(^10\) Due to the lack of reports with relatively large sample sizes and since an AE-related antibody analysis is not routinely performed, the data of clinical characteristics and long-term prognoses of Chinese patients with anti-LGI1 encephalitis is limited.
To improve the clinical refinement of this disease and provide experiential knowledge for clinical diagnosis and treatment, in this retrospective study we describe the clinical characteristics, treatment regimen, and long-term outcomes of 117 patients diagnosed with anti-LGI1 encephalitis in China.

2. Methods

A total of 117 patients, who were diagnosed with anti-LGI1 encephalitis according to the diagnostic criteria suggested by previous studies, were retrospectively selected from the database of 5 clinical centers (Qilu Hospital of Shandong University, Shandong Provincial Hospital Affiliated to Shandong University, The First Affiliated Hospital of Shandong First Medical University, Affiliated Hospital of Binzhou Medical College, Liaocheng People’s Hospital) from September 2014 to December 2019. Inclusion criteria were as follows: (1) acute or subacute onset of 1 or more of major groups of manifestations: psychosis, seizures, memory deficit, speech disturbance, (2) CSF tested positive for NMDAR antibodies, (3) reasonable exclusion of other disorders. The exclusion criteria were as follows: (1) incomplete clinical data; (2) central nervous system infection caused by intracranial pathogens; (3) loss to follow-up. This study was approved by the Ethics Committee of Qilu Hospital of Shandong University. Informed consent was obtained from the patients or their family.

Clinical features, cognitive testing, laboratory findings (cerebrospinal fluid [CSF] and serum analyses), video electroencephalograms (VEEGs), cranial magnetic resonance images (MRIs), tumor screenings, and details of therapy were recorded. The autoantibodies of N-methyl-D-aspartate receptor (NMDAR), LGI1, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA1, AMPA2), contactin-associated protein-like 2 (CASPR2), and γ-aminobutyric acid receptor-B (GABABR) from 49 patients were assessed by indirect immunofluorescence tests in serum or CSF. The protocol for indirect immunofluorescence was followed according to the instructions provided by the manufacturer (Euroimmun, Germany). Bound antibodies were visualized with a fluorescence microscope (Olympus, Japan). Tumor screenings consisted of tumor marker tests, chest computed tomography (CT) scans, and abdominal and pelvic ultrasounds. After treatment completion, patients underwent follow-up every 3 months during the first year, then every 6 months thereafter. Clinical outcomes were evaluated using the modified Rankin Scale (mRS).

Statistical analyses were performed using GraphPad Prism Software 8.0 (GraphPad Software, Inc., California, USA). The classification variables were described as percentages. Quantitative data with normal distributions were presented as mean ± SD, otherwise represented by the median. Student’s t-test was used to compare the mRS score at onset and 6 months after immunosuppressive therapy. Results with P < 0.05 were considered statistically significant.

3. Results

3.1 Clinical characteristics
Eighty patients (68%) were positive for anti-LGI1 antibodies in both CSF and serum. Twenty-eight (24%) patients were positive in serum but negative in CSF, while 9 (8%) patients were only positive in CSF. With the development of diagnostic methods, the annual number of confirmed cases trended upward in our study, as shown in Fig. 1A. Among the 117 anti-LGI1 encephalitis patients, 81 (69%) were male and 36 (31%) were female; the median onset age was 51 years (range: 30–77 years). The majority of patients were 40 to 70 years old (79%). The distribution of gender and age of anti-LGI1 encephalitis patients is showed in Fig. 1B. The most common clinical manifestations of anti-LGI1 encephalitis were seizures (102, 88%), cognitive impairments (82, 70%) and insomnia (61, 52%). Table 1 describes details of the clinical characteristics of anti-LGI1 antibody-positive patients. Details of the common initial symptoms in these 117 patients are shown in Fig. 2A. The median time from symptom onset until diagnosis was 8.7 weeks (range: 2–49 weeks).
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>81/36</td>
</tr>
<tr>
<td>Age at onset, y, median, range</td>
<td>57(5–77)</td>
</tr>
<tr>
<td>Time from symptom onset until diagnosis, week, median, range</td>
<td>8.7(2–49)</td>
</tr>
<tr>
<td>Followed up time, month, median, range</td>
<td>33(6–59)</td>
</tr>
<tr>
<td>Clinical syndrome, n (%)</td>
<td>102(88)</td>
</tr>
<tr>
<td>Seizures, n (%)</td>
<td>82(70)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td></td>
</tr>
<tr>
<td>Insomnia, n (%)</td>
<td>61(52)</td>
</tr>
<tr>
<td>Disorder of behavior, n (%)</td>
<td>37(32)</td>
</tr>
<tr>
<td>Autonomic dysfunction, n (%)</td>
<td>36(31)</td>
</tr>
<tr>
<td>Involuntary movements</td>
<td>5(4)</td>
</tr>
<tr>
<td>Pain, n (%)</td>
<td>5(4)</td>
</tr>
<tr>
<td>Peripheral nervous system symptoms, n (%)</td>
<td>3(3)</td>
</tr>
<tr>
<td>Number of patients with available data</td>
<td></td>
</tr>
<tr>
<td>Serum, n (%)</td>
<td>117(100)</td>
</tr>
<tr>
<td>CSF, n (%)</td>
<td>117(100)</td>
</tr>
<tr>
<td>EEG, VEEG, n (%)</td>
<td>99(85), 25(21)</td>
</tr>
<tr>
<td>MRI, n (%)</td>
<td>92(79)</td>
</tr>
<tr>
<td>PET, n (%)</td>
<td>2(2)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>First-line immunotherapy (high-dose corticosteroids and/or immunoglobulins), n (%)</td>
<td>112(96)</td>
</tr>
<tr>
<td>Second-line immunotherapy (cyclophosphamide or Mycophenolate mofetil), n (%)</td>
<td>7(6)</td>
</tr>
</tbody>
</table>

CSF, Cerebrospinal fluid; EEG, electroencephalography; VEEG, video electroencephalography; MRI, magnetic resonance imaging; PET, photon emission tomography

Seizures occurred in 102 of the 117 patients. Most patients (42/102) presented with faciobrachial dystonic seizures (FBDSs); among them, 27 patients started with FBDSs. Faciobrachial dystonic seizures always involved the arm and involvement of the ipsilateral hemiface was common (29/42). Patients with
FBDSs had sudden, short, and mainly tonic contractions of the upper limbs accompanied by an ipsilateral hemifacial grimacing and dystonic posture that lasted for 0.3-5 seconds and occurred 5–80 times per day. Prodromal symptoms were not found, nor was there a loss of consciousness. In some patients, the hemi-trunk (8/42) and a lower limb (6/42) were engaged. Sixty patients also developed other seizure types. The characteristics of 102 patients are shown in Supplement 1.

Cognitive impairments were diagnosed in 82 of the 117 patients based on a neurological examination at admission. Sixty-six patients had memory deficits, and anterograde memory deficits were frequent (51/82). Five patients presented with recent memory loss; 16 patients showed a decrease in response capacity. In 42 patients median Mini-Mental State Examination (MMSE) score was 20 (range: 10–29) and these patients were also evaluated by the Montreal Cognitive Assessment Scale (MOCA), the median score of which was 15 (range: 4–28) (Fig. 2B). Immunosuppressive therapy improved the decline in cognitive function. In addition, 11 of the 82 patients developed language dysfunction.

Other common symptoms were sleep disturbances (61%), mental and behavioral abnormalities (37%) and autonomic dysfunction (36%, mostly hyperhidrosis, 3 cases of central hypoventilation syndrome). Patients with sleep disorders were usually characterized as having shortened sleep time and more dreams. Five patients presented with involuntary movements (4%, chorea). Five cases started with chronic headaches. Three patients suffered from peripheral nervous system dysfunction. One patient’s electromyogram showed extensive peripheral neuropathy, mainly involving axons. Another 2 patients showed peripheral neuropathy in both lower limbs, and motor and sensory fibers were involved (Table 1). Three patients had peripheral neuropathy, with the electromyograms showing bilateral peripheral neuropathy. There was 1 patient with psoriasis and 1 patient with Hashimoto's thyroiditis. During the follow-up period, none of the 117 patients were found to have neoplastic disease.

### 3.2 Ancillary test results

Of the 117 patients with positive anti-LGI1 antibodies, antibody titers in the cohort ranged from 1:1 to 1:100 in serum and from 1:1 to 1:320 in CSF. Five patients had slightly increased cerebrospinal fluid pressure (205–220 mmH$_2$O). White blood cell counts were predominantly normal or slightly elevated. Seventeen patients had mildly elevated white blood cells, mainly lymphocytes (the lymphocyte ratio ranged from 56 to 90%, median, 80%). The protein levels of 43 patients were increased (49–900 mg/L, median 590 mg/L, normal value 150–450 mg/L), mainly IgG and IgA. Glucose and chloride levels and oligoclonal band measurements were normal or negative. There were 76 cases of hyponatremia and 25 cases of hypokalemia, while there were 23 cases of both hyponatremia and hypokalemia; hyponatremia can be corrected by oral sodium supplementation. Thyroid function indexes of 37 patients were abnormal, and 8 of these 37 patients showed elevated serum thyroid peroxidase antibody (TPO Ab). In 32 cases the serum tumor markers were mildly abnormal. Rubella virus/cytomegalovirus and herpes simplex virus IgG were detected in the serum of 11 patients.

Brain MRIs were performed in 92 of the 117 patients. Thirty-eight patients had an abnormal MRI (20 patients had abnormal bilateral hippocampal signals, 14 showed an abnormal signal in the left
hippocampus, 2 showed an abnormal signal in the left basal ganglia, 2 had abnormal signals in the right occipital lobe and corpus callosum). Two patients underwent PET examinations of the brain with 18F-fluorodeoxyglucose (18F-FDG) (one patient had PET-CT results from outside the hospital, showing hypermetabolism in the right medial temporal lobe but not a brain MRI at the same stage). A PET examination of another patient revealed bilateral hypermetabolism in the basal ganglia and medial temporal lobe (Fig. 3E-H). During the same period, a craniocerebral MRI showed abnormal bilateral signals in the hippocampus and occipital lobe (Fig. 3A-D).

An electroencephalogram (EEG) was conducted for 99 of the 117 patients. Video-electroencephalograms (VEEGs) were performed for 25 patients, and the monitoring time ranged from 8 h to 36 h. EEG abnormalities were detected in 61 of 99 patients, most showing generalized slow waves, sometimes accompanied by paroxysmal sharp waves. Sharp waves were commonly detected in the frontal and temporal lobes, which were considered epileptiform discharges (Fig. 4). In 10 patients who had a VEEG, 42 FBDSs were recorded (median 3 per patient, range 1–12), no significant abnormal discharge was detected during the corresponding EEG. Thirty-two FBDSs involved the ipsilateral hemiface and an arm, of which 6 involved the legs. Four events involved only the face, 4 involved only an arm, and 2 events exclusively involved the legs. Faciobrachial dystonic seizures occurred during wakefulness (n = 21), from drowsiness (n = 5), and sleep (n = 18), which lasted 0.3–5 s (median = 1.8 s).

3.3 Treatment outcomes

Of the 117 patients, 109 patients were treated with immunotherapy. Thirty-four patients received both intravenous immunoglobulin (IVIG); 0.4 g/kg/d, 5 days) and steroids, including intravenous methylprednisolone (500–1000 mg (15–30 mg/kg/d) daily for 3–5 days), dexamethasone (intravenous infusion; 10 mg/d, for 7–14 days) or oral prednisone (1 mg/kg/d). Seven patients received the second-line (mycophenolate, cyclophosphamide, azathioprine) treatment because of a relapse. Except for patients with a relapse, steroids were maintained for 6 months. Details of immunotherapy and strategy are shown in Table 2 and Supplement 2. After 3–5 days of immunotherapy, the clinical manifestations were somewhat alleviated in all the patients who demonstrated improvements in memory, mental ability, and behavior. The neurological mRS score of the patients changed from 3.19 ± 0.13 before immunotherapy (range: 1–5) to 1.71 ± 0.09 after 6 months of immunotherapy (range: 1–3) (Fig. 2C). The 112 patients with seizures received single or a combination of 2 or 3 antiepileptic drugs (AED), including levetiracetam (1000–1500 mg/day), valproate acid (600–1000 mg/day), carbamazepine (300–600 mg/day), and oxcarbazepine (600–1200 mg/day). Details are shown in Supplement 3. Antiepileptic drugs were maintained for at least 1 year after the patients were seizure-free and had a normal EEG.
Table 2
Treatment and follow-up

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>Cases</th>
<th>Relapse</th>
<th>Second-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPD 1000 mg 3–5 d; 500 mg 3–5 d; Prednisone 1 mg/kg/d</td>
<td>13</td>
<td>3</td>
<td>3, Mycophenolate,1 g/d,7d</td>
</tr>
<tr>
<td>MPD 1000 mg 3–5 d; 500 mg 3–5 d; Prednisone 1 mg/kg/d + IVIG</td>
<td>10</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>MPD 500 mg 3–5 d; 240 mg 3–5 d; Prednisone 1 mg/kg/d</td>
<td>15</td>
<td>0</td>
<td>1, Cyclophosphamide,0.8 g qw</td>
</tr>
<tr>
<td>MPD 500 mg 3–5 d; 240 mg 3–5 d; Prednisone 1 mg/kg/d + IVIG</td>
<td>38</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DXM 10 mg/d 7–14 d; Prednisone 1 mg/kg/d</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>DXM 10 mg/d 7–14 d; Prednisone 1 mg/kg/d + IVIG</td>
<td>12</td>
<td>3</td>
<td>1, Azathioprine,150 mg/d,30d</td>
</tr>
<tr>
<td>Prednisone 1 mg/kg/d</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Prednisone 1 mg/kg/d + IVIG</td>
<td>9</td>
<td>1</td>
<td>1, Azathioprine,150 mg/d,30d</td>
</tr>
<tr>
<td>IVIG</td>
<td>9</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

MPD, intravenous methylprednisolone; IVIG, intravenous immunoglobulins (0.4 g/kg daily for 5 days); DXM, intravenous dexamethasone;

3.4 Relapse

The median follow-up duration was 33 months (range 22–47 months). There were no mortalities during the follow-up. A total of 19 (16%) patients experienced a relapse. The median period from onset to the first relapse was 5 (0.3–27) months. Of the relapsed patients (6 (32%) females, 13 (84%) males), 16 patients had received immunotherapy, 3 patients came from the group of 5 patients who had never received immunotherapy, 9 patients were positive for anti-LGI1 antibodies in both CSF and serum, 4 patients were positive in serum but negative in CSF, and 3 patients were only positive in CSF (Supplement 4). The most common symptoms of recurrence manifested as impaired cognitive function, epilepsy, and increased sleep. Of the 19 relapsed patients, 12 had EEG slow wave delivery at the time of onset, and 5 of them had sharp waves. The brain MRIs of only 3 patients revealed an abnormal signal of hippocampus T2-Flair at the onset, and the remaining 16 patients showed no obvious abnormalities in brain MRIs.

4. Discussion

Anti-LGI1 encephalitis is a rare neuroinflammatory brain condition. Since the disease was first reported in 2010, an increasing number of anti-LGI1 antibody-positive cases have recently been described.11-15
However, there has been few large-scale epidemiological surveys of anti-LGI1 encephalitis in China. In this study, we provide detailed clinical information of 117 Chinese patients from 5 clinical centers who had positive LGI1 antibodies and report important incidence rates and long-term outcomes.

In the analysis of age distribution, we observed that the majority of patients were 40 to 70 years old (79%). Male patients were more common and this result is consistent with reported data on other autoimmune diseases. A total of 19 (16%) patients experienced a relapse in our cohort, indicating that the overall prognosis of anti-LGI1 encephalitis is good, and this finding is consistent with previous studies.\textsuperscript{1,8,11} A report from the United States on clinical syndrome and long-term follow-up of anti-LGI1 encephalitis stated that 67% of 21 patients who were followed up for more than 2 years had a favorable outcomes.\textsuperscript{4} These data are consistent with a good prognosis for anti-LGI1 encephalitis, although some differences may be related to race, region, and number of cases. Currently, research on the relationship between anti-LGI1 antibody titer and disease is still lacking, and research conducted with a large sample size is still needed for further exploration. From our perspective, the detection of anti-LGI1 antibody seems to be higher in serum.

In the last few decades, the field of autoimmune epilepsy has received increasing attention with the discovery of different subtypes of neural autoantibodies.\textsuperscript{5,16-19} In the latest 2017 epilepsy classification, autoimmune epilepsy has been recognized as a distinct entity by the International League Against Epilepsy.\textsuperscript{20} Most patients with autoimmune epilepsy present with seizures, cognitive decline, and behavioral or psychiatric dysfunction. At present, the diagnosis of autoimmune epilepsy is based on clinical characteristics, MRI results, EEG and CSF analyses. Faciobrachial dystonic seizures is considered to be the characteristic clinical symptom of anti-LGI1 encephalitis epilepsy.\textsuperscript{4,13,21} Faciobrachial dystonic seizures usually manifest as involuntary movements involving posturing of the arm and the ipsilateral hemiface or leg, occur very briefly and frequently, and respond well to immunotherapy. The treatment for patients with autoimmune epilepsy is comprised of immunotherapy and symptomatic therapy including antiseizure medications. According to multiple previous studies, the favorable effects of immunotherapy has been demonstrated to be an early initiation on seizure frequency and cognition. Immunotherapy is classically divided into first-line and second-line therapies. First-line therapies include methylprednisolone, IVIG, or plasma exchange. Second-line therapies (rituximab, mycophenolate, cyclophosphamide, azathioprine) are used in refractory cases or as a maintenance therapy to prevent relapses. The treatment of autoimmune epilepsy should be based on the severity of the clinical course. Immunotherapy plays a key role in the treatment of autoimmune epilepsy.\textsuperscript{3,5,16,22-24} A study of 29 patients with anti-LGI1 encephalitis by Sarosh et al. found that immunotherapies showed a remarkable reduction in FBDS frequency\textsuperscript{21}. Among 27 patients receiving immunotherapy, 14 patients (52%) showed a > 50% reduction in seizure frequency.\textsuperscript{4} Our current research partly confirms the above findings. In our series, after 3-5 days of immunotherapy, seizures were alleviated in all the patients. This suggests the importance of immunotherapy in LGI1-related seizures. Immunotherapy should be applied in the early stage after the diagnosis of anti-LGI1 encephalitis. However, the timing of the withdrawal of immunosuppressive drugs and antiepileptic drugs in patients with different types of autoimmune encephalitis remains controversial.
In our study, except for patients with relapse, steroids were maintained for 6 months. Fifteen out of 109 patients undergoing immunotherapy experienced a relapse in long-term follow-up. The reason for a relapse in some patients was irregular medication. Our report provides detailed long-term follow-up data of patients to provide useful insights for improving understanding of the disease experience of patients with anti-LGI1 encephalitis, and to better inform clinical management.

Relapses were not common in our cohort. The definition of relapse in our study was based on observations of clinical symptoms. When monitoring and evaluating the relapses, the MRI findings were not remarkable. According to previously research, the serum or CSF antibody titer did not correlate with the clinical severity perfectly. Furthermore, AE-related antibody monitoring is not routinely performed during follow-up, and better indicators should be identified in future studies. In our cohort, the brain MRIs of only 3 (3/19) patients showed abnormal signals at the onset. This is consistent with previous reports. Interestingly, we observed that a large number of EEG slow waves or intermittent spikes were detected at onset in 12 (12/19) relapsed patients. This may suggest the importance of EEG monitoring for disease recurrence. In our research, the follow-up duration was ranged from 22 to 47 months. Although, most patients experienced a first relapse within 24 months in our research, other studies have also suggested that AE relapse could occur years after the initial episode. As a result, extended follow-up may be essential.

5. Conclusion

We describe the clinical characteristics, immunotherapy, and long-term outcomes of patients with anti-LGI1 encephalitis in China. Early adequate immunotherapy has positive implications for the improvement of clinical symptoms of anti-LGI1 encephalitis. The outcome for patients with anti-LGI1 encephalitis is mostly favorable, although some patients continue to suffer from cognitive dysfunction. The treatment of severe, refractory, and recurrent anti-LGI1 encephalitis has yet to be explored. Long-term follow-up is important for the assessment of the disease. Recurrence not uncommon, and doctors should be aware that relapses may occur years after the onset of the initial disease. Further research with advanced study designs and more extended follow-up period are still required.

Abbreviations

AE: Autoimmune encephalitis

LGI1: Leucine-rich glioma-inactivated 1

VGKC : voltage-gated potassium channel

AMPA: 5 α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

NMDA: N-methyl-D-aspartate
Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Qilu Hospital of Shandong University. All patients gave written informed consent.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.
Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
SQ and HW Wu performed the study, wrote the manuscript. LL and KZ collected the data and perform the follow-up. XL designed the research and performed the manuscript revision. All authors read and approved the final version of the manuscript.

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References


