Distinctive clinicopathological features and differential gene expression of cerebral venous thrombosis mimicking brain tumors

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Abstract

Cerebral venous thrombosis (CVT), a rare type of cerebrovascular disease, can mimic a brain tumor (CVT mimicking brain tumor [CVTMBT]), due to its space-occupying imaging features. We aimed to describe the clinicopathological features and identify the thrombophilia-related gene expression changes in the brain following CVT. We conducted a retrospective qualitative study of CVT patients who were misdiagnosed with brain tumors before surgery at our hospital from 2016 to 2021. We analyzed the clinicopathological characteristics of the cases from our hospital and previously published cases. Five subjects were retrospectively studied, but one refused to provide biological specimens. We performed messenger ribonucleic acid (mRNA) sequencing from eight specimens (four CVTMBT and four non-CVTMBT samples). Differentially expressed genes (DEGs) were screened using the "edge" package in R 3.6.1 software. Thrombophilia-related genes were obtained from the MalaCards human disease database and were cross-checked with DEGs. The intersection was considered to be the potential genes in the pathogenesis of CVTMBT.

The medical histories of the five patients with CVTMBT included oral non-steroidal anti-inflammatory drug use, oral contraceptive use, cesarean section, and anemia. All patients underwent craniotomy and were pathologically diagnosed with CVT. The follow-up results revealed that all patients had favorable outcomes without any recurrence. DEG analysis revealed 813 upregulated and 253 downregulated DEGs between patients with CVTMBT and controls. Nine DEGs were associated with thrombophilia, including SERPINE1, SELP, THBD, ITGB3, TFPI, F13A1, PROS1, PPBP, and PROCR, which were considered potential key genes in CVTMBT. CVTMBT presents with enhancement and mass effect on magnetic resonance imaging, accompanied by various predisposing factors, shorter disease duration, and coagulation dysfunction. The nine key genes identified as potential key genes in the pathogenesis of CVTMBT may be potential biomarkers for accurate screening and appropriate treatment.

Keywords: Cerebral venous thrombosis; Brain tumor; Gene expression; Mimicking; mRNA sequencing
1. Introduction

Cerebral venous thrombosis (CVT), a relatively rare type of cerebrovascular disease, is defined as thrombosis of the intracranial veins or sinuses. CVT accounts for 0.5% of strokes, with a bimodal age distribution: The first peak in neonates and the second in individuals in their 30s[1,2]. It is a multifactorial disease with several etiologies, and thus requires extensive preliminary screening. Moreover, CVT can cause vascular and cytotoxic edema, of which the mechanism remains unclear[2,3]. Most patients with CVT have favorable prognoses, with a mortality rate of <10%, which is better than that of arterial stroke[2,4]. However, it is difficult to predict the individual prognosis of patients with CVT[5]. Existing studies have mostly focused on arterial cerebral infarction, without much attention to CVT. Large hemorrhagic cerebral infarction accompanied by prominent vascular edema and brain tissue displacement may result in life-threatening complications when patients experience deterioration, due to delayed diagnosis and treatment[5]. An epileptic state is considered a cause of acute death in CVT[2]. Altered consciousness can occur in 15 – 19% patients with extensive venous embolism or bilateral thalamic involvement[6]. Hence, early and accurate diagnosis and treatment are often associated with better prognosis[7].

Patients with CVT can be easily misdiagnosed with various nervous system diseases due to its rarity, limited neuroimaging findings, and varying initial clinical manifestations, including isolated headache, focal neurological dysfunction, and altered consciousness[8]. These manifestations may present separately or in combination with other signs and symptoms[2]. An early diagnosis of CVT is primarily established by magnetic resonance imaging (MRI) and magnetic resonance venography. Several studies have well-characterized the imaging findings of CVT, which predominantly presents with a space-occupying effect[8,9]. However, these studies have several limitations and technical flaws[1,3,9]. Cerebral venous infarction, which is observed in approximately 60% of patients with CVT, may present with malignant vasogenic edema with minor parenchymal hemorrhage and a space-occupying mass-like enhancement in primary MRI; thus, it is often misdiagnosed as brain tumor[3,5,12]. Fewer than 10 cases of CVT mimicking brain tumor (CVTMBT) have been reported in the previous studies[7,11,12-15]. Moreover, CVT can also manifest as subarachnoid hemorrhage or a metastatic tumor[7,16,17]. In cases where establishing a pre-operative diagnosis is difficult, biopsy is performed[7].

In fact, differentiating CVTMBT from neuroglioma earlier on is necessary because the treatments and prognoses for these two diseases are different. Conventional therapies, including maximum resection, radiotherapy, and chemotherapy, play a crucial role in the treatment of brain gliomas[18]. CVT is best treated with a comprehensive therapy, emphasizing the management of pathogenic factors, antithrombotic therapy, and symptomatic treatment[5,19]. Biopsy often is the last resort for cases with difficulty in pre-operative diagnosis[9]. Invasive surgery for CVT remains controversial. Although heparin, as a first-line anticoagulant therapy, can improve the prognosis of CVT, aggressive treatment should also be considered for patients who are deteriorating[11]. So far, given the equivocal evidence of efficacy for local thrombolysis, it has not yet been considered a first-line treatment for CVT[2]. This retrospective qualitative study aimed to analyze the distinctive and clinicopathological features of patients with CVTMBT. In particular, we performed messenger ribonucleic acid (mRNA) sequencing on human lesion peripheral tissues from four CVTMBT samples and four non-CVTMBT samples from our hospital to identify the gene expression signatures in this distinctive lesion.

2. Materials and methods

2.1. Study subjects

Patients with an initial diagnosis of intracranial occupying lesion and who underwent surgical treatment at our neurosurgical center between November 2016 and October 2021 were reviewed systematically. The inclusion criteria were as follows: Patients (1) initially diagnosed with brain tumor, with their post-operative pathological results revealing CVT; (2) with available pre-operative and post-operative neuroimaging examination results, which were evaluated by multiple experienced radiologists and neurosurgeons; and (3) with consecutive medical data and sufficient follow-up information. The exclusion criteria included the following: Patients (1) pathologically diagnosed with other space-occupying lesion; (2) with insufficient consecutive neuroimaging information; (3) with incomplete medical data and follow-up information, and (4) with CVT who did not present with brain tumor-like features. Five patients with CVTMBT were included as the study subjects, but one of these patients refused to provide biological specimens. The subjects’ baseline characteristics, including demographics, pre-operative neurological dysfunction status, routine blood and coagulation function status, course of disease, seizure characteristics, detailed surgical records, and other vital records, were collected. Four subjects with CVTMBT had not received previous treatments before surgery and their specimens were obtained from the tissues surrounding the infarcts during surgery at the initial diagnosis. Another four normal brain tissues were obtained at the time of surgery from four non-CVTMBT patients, including...
one tentorial meningioma, one meningioma in the base of the anterior cranial fossa, one intracranial lymphoma, and one glioblastoma, at our hospital; these patients were assigned as the control group. The selection criteria for the control group included the following: Patients (1) without a history of stroke; (2) without liver, kidney, hematopoietic system, and cardiovascular diseases or other serious primary diseases; and (3) without predisposing factors for CVT, such as oral non-steroidal anti-inflammatory drug (NSAID) use or oral contraceptive use and pregnancy. Written and verbal informed consents for the use of the specimens were obtained before surgery.

All biopsy-confirmed patients from our hospital received anticoagulation therapy based on the definitive diagnosis of CVTMBT. Patients who presented with seizures initially received antiepileptic drugs to prevent seizure recurrence.

All procedures performed were approved by the Ethics Committee for Human Experiments of the Zhengzhou University (approval number: 2021-KY-0156-002).

2.2. mRNA library construction and sequencing
RNA sequencing was performed by GeneFund Biotechnology Co., Ltd. (Shanghai, China). The RNA was extracted from tissues surrounding the infarcts in four subjects with CVTMBT and normal brain tissues in four subjects with non-CVTMBT. mRNA extraction was performed using KAPA Stranded mRNA-Seq Kits according to the manufacturer’s instructions. The RNA fragments with polyA tail were captured by oligo(dT) beads. By heating, the captured mRNA fragments were interrupted to 200 – 300 base pairs (bp). Strand Synthesis Master Mix was added to the incubation and the mRNA was reverse transcribed to complementary deoxyribonucleic acid (cDNA). The DNA fragments were end-repaired, an adenine (A) base was added to the 3’ end, and the sequencing adaptors were ligated. Real-time polymerase chain reaction was used to synthesize cDNA with a size of 300–400 bp. The library was sequenced using the Illumina HiSeq/NextSeq platform after qualifying. The connector sequences were removed using the cutadapt program. Clean data were retained and low-quality sequences were eliminated using the Trimmomatic program[26]. Clean data volume was calculated using FastQC software (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) with q20 and q30 proportions and was aligned to the reference genome using the HISAT program[27]. Reads were spliced into transcripts using StringTie[21]. Data volume was calculated and the data were compared. The results of the comparison were annotated and the known RNAs were selected for subsequent analysis. Differential expression analysis was performed using the HISAT2 tool (select default parameters), StringTie (select default parameters), and the process-recommended downstream differential expression analysis method edgeR[22]. The P-value, Q-value (the false positive rate [FDR] error control method was used to correct P-value by multiple hypothesis testing, and the corrected P-value was the Q-value), and FC (fold change) were calculated for each gene. The genes met the differential analysis criteria: Q-value ≤ 0.05 and FC ≥ 2 or FC ≤ 0.5 were taken as differentially expressed genes (DEGs).

2.3. Screening of DEGs associated with thrombophilia
Thrombophilia-associated genes were downloaded from the MalaCards human disease database (https://www.malacards.org/) and were cross-checked with all confirmed DEGs.

3. Results
3.1. Clinicopathological features and surgical findings
Five patients (four females and one male; age, 13 – 48 years) with distinct CVTMBT in different locations and with unique clinicopathological features were included in the study. The short course of disease, which ranged from 3 to 6 days, was one of the significant clinical characteristics, with symptoms of epileptic seizure (three patients) and headache (three patients). Other significant symptoms included numbness in the right arm (one patient) and altered consciousness (one patient). The common risk factors included medication history of oral NSAIDs or analgesics (two patients), Marvelon use for hypermenorrhea (one patient), long-term anemia (one patient), and a medical history of cesarean section (one patient). All patients had remarkable routine blood and coagulation dysfunctions. The lesion was observed at a specific location (two frontal lobe, one parietal lobe, one temporal lobe, and one temporal occipital lobe) linked to a large cerebral vein on MRI. Intraoperative findings revealed that three of the five lesions were involved in remarkable occlusion of a large drainage vein and four of the five lesions presented with secondary hemorrhage surrounding the vein. Histopathological findings revealed abundant small vascular obstruction, inflammatory cell infiltration, and regional hemorrhage. The detailed data of the five patients with CVTMBT are shown in Table 1.

Representative case: A 13-year-old female patient presented with headache and epileptic seizure. The initial diagnosis was low-grade glioma, instead of vein infarction. Considering that the lesion showed atypical features on both computed tomography and MRI, the patient was misdiagnosed before surgery. T2 hyperintensity indicated
that the edema was induced by venous occlusion. The slightly increased choline (Cho) level and decreased N-acetylaspartate (NAA) level by magnetic resonance spectroscopy (MRS) analysis could have also misled the diagnosis. An infarcted inferior anastomotic vein (vein of Labbé) was confirmed during the surgery and its vascular structure was dark and swollen. The lesion was totally resected and the vein of Labbé was preserved well with sufficient decompression to relieve the symptoms of intracranial hypertension. Hematoxylin and eosin staining revealed thrombosed vein and excessive inflammatory cell infiltration (Figures 1-3).

Follow-up was continued from 1 month to 5 years. All the study subjects had favorable outcomes with intact neurological function and without symptom recurrence after surgery. Follow-up information was not available in previously published cases.

### 3.2. Identification of DEGs between CVT mimicking brain tumor (CVTMBT) and non-CVTMBT

In total, 1066 DGEs, including 813 upregulated and 253 downregulated genes, were identified based on the selection criteria. A heat map and a volcano plot of the 1066 DGEs are shown in Figure 4A and B, respectively.

### 3.3. Key genes in the pathogenesis of CVT mimicking brain tumor

In total, 38 genes were related to thrombophilia, as demonstrated by the MalaCards human disease database. According to the differential gene criteria \( Q \)-value \( \leq 0.05 \) and FC \( \geq 2 \) or FC \( \leq 0.5 \), the following nine differential genes were screened: \textit{SERPINE1}, \textit{SELP}, \textit{THBD}, \textit{ITGB3}, \textit{TFPI}, \textit{F13A1}, \textit{PROS1}, \textit{PPBP}, and \textit{PROCR}. The expression levels of nine DEGs are presented in Table 2 and in a heatmap in Figure 5. The roles of the nine DEGs are presented in Table 3.

### 4. Discussion

Glioma was the most common type of misdiagnosis in the present study, which is consistent with the results of the previous studies\(^{[7,15]}\). Misdiagnosis was observed in the present study due to non-specific primary imaging findings, including enhancement and mass effect, accompanied by intracranial hypertension and similar neurological deficits. The majority of patients had predisposing factors and coagulation dysfunction. Anticoagulation can effectively improve patients' prognosis. A flowchart for the diagnosis of CVTMBT is presented in Figure 6. In addition, we identified nine DEGs associated with thrombophilia, including:

<table>
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<tr>
<th>Case</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>History</th>
<th>Laboratory tests</th>
<th>Location</th>
<th>Misdiagnosis</th>
<th>Treatment</th>
<th>Intraoperative finding</th>
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<tr>
<td>1</td>
<td>23</td>
<td>Female</td>
<td>Headache, vomiting</td>
<td>Caesarean birth</td>
<td>High platelet count and D-dimer</td>
<td>Left frontal lobe and corpus callosum</td>
<td>Glioma</td>
<td>Anticoagulation after biopsy</td>
<td>Left superior cerebral vein to superior sagittal sinus drainage was obstructed, focal hemorrhage</td>
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<td>Oral ibuprofen</td>
<td>Low APTT and high D-dimer</td>
<td>Left parietal lobe</td>
<td>Glioma</td>
<td>Anticoagulation after biopsy</td>
<td>Large branch of Labbé vein infarction, focal hemorrhage</td>
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<td>3</td>
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<td>Female</td>
<td>Headache, epileptic seizure</td>
<td>Excessive menstruation treated by Marvelon</td>
<td>High platelet count and TT; low APTT and Fib</td>
<td>Left temporal lobe</td>
<td>Glioma</td>
<td>Anticoagulation after biopsy</td>
<td>Labbé vein infarction, regional hemorrhage</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>Male</td>
<td>Epileptic seizure</td>
<td>Oral paracetamol</td>
<td>High D-dimer</td>
<td>Right frontal lobe</td>
<td>Glioma</td>
<td>Anticoagulation after biopsy</td>
<td>Right superior cerebral vein to superior sagittal sinus drainage was obstructed, regional hemorrhage</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>Female</td>
<td>Headache, dizziness incontinence (twice)</td>
<td>Long-term moderate to severe anemia</td>
<td>Hemoglobin&lt;60 g/L</td>
<td>Left temporal-occipital lobe</td>
<td>Glioma</td>
<td>Anticoagulation after biopsy</td>
<td>The draining vein of the left temporal cortex was blue-black</td>
</tr>
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</table>

APTT: Activated partial thromboplastin time; Fib: Fibrinogen; TT: Thrombin time

Table 1. Clinicopathological features of five cerebral venous thrombosis mimicking brain tumor cases from our hospital
Cerebral venous thrombosis mimicking brain tumors

including SERPINE1, SELP, THBD, ITGB3, TFPI, F13A1, PROS1, PPBP, and PROCR, by mRNA sequencing between patients with CVTMBT and non-CVTMBT. The screening of key genes may provide valuable information for accurate diagnosis.

Figure 1. Typical pre-operative imaging images of a patient with CVTMBT from our hospital. (A) CT scan showing low-density lesion located in the left temporal lobe (red arrow). (B and C) Axial MRI demonstrating isointense on T1-weighted and hyperintense on T2-weighted lesion, respectively (red arrow). (D and E) Axial and coronal T1-weighted MRI showing no enhancement after gadolinium injection (red arrow). (F) Showing slightly increased Cho level and decreased NAA level by MRS analysis. (G) Post-operative CT showing lesion removed.

Cho: Choline; CT: Computed tomography; CVTMBT: Cerebral venous thrombosis mimicking brain tumor; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; NAA: N-acetylaspartate

Figure 2. Representative intraoperative findings of a patient with cerebral venous thrombosis mimicking brain tumor from our hospital. (A) Intraoperative photo showing obvious Labbé vein infarct (red arrow indicates the Labbe vein), with dark and swollen vascular structure. (B) Red arrow indicates the occlusion involved in the main branch of the Labbé vein. (C) Lesion totally removed and the Labbé vein preserved well. (D) Normal structure and blood flow of drainage vein as control.

Figure 3. Hematoxylin and eosin (H and E) staining of post-operative pathology of a patient with cerebral venous thrombosis mimicking brain tumor from our hospital. (A) H and E staining showing two thrombosed vein and excessive inflammatory cell infiltration scattered in the surrounding of vein (original magnification ×10). (B) H and E staining showing thrombosed vein and excessive inflammatory cell infiltration (original magnification ×40). (C) H and E staining showing regional hemorrhage. (D) Vacuolar degeneration of nerve tissue enclosed by inflammatory cell.
A previous study has demonstrated that elevated venous pressure and abnormal venous reflux as a result of venous thromboembolism could lead to brain edema and intracranial hypertension, which may present as T2 hyperintensity on MRI. Eventually, brain tissues experience anoxia when the blood-brain barrier is disrupted, which could present as tumor-like enhancement\[23\]. Although CVT may not be clearly observed on MRI, an indication to its location would still be helpful in explaining symptoms or preparing for biopsy. Moreover, a significant decrease in NAA levels may be observed in acute cerebral infarction by MRS\[24,25\], unlike in glioma.

Similar with the previous studies\[7,11,13-15\], the common thrombophilia-related risk factors of the five patients from our hospital included a medication history of oral NSAIDs or analgesics (two patients), Marvelon use for hypermenorrhea (one patient), long-term anemia (one patient), and a medical history of cesarean section (one patient). The average duration that our patients were symptomatic was <1 week. A relatively rapid progression of symptoms usually points to vascular disease, rather than invasive glioma. Our patients initially presented with generalized seizures, whereas the previous studies have reported that the most common clinical manifestation is acute hemiparesis\[7,11,13-15\]. Therefore, we conclude that the various sizes, locations, and degrees of cerebral venous occlusion are the causes of the varying initial symptoms. Our patients who presented with seizures received antiepileptics to prevent seizure recurrence. In addition to seizures, headache and vomiting caused by hypertension were also the common symptoms; a prompt depression could block the progression of cerebral infarction\[23\]. Benefited from the sensitivity to molecular diffusion of water, diffusion-weighted MRI (DW-MRI) can distinguish either the type of edema or the change of injury accompanied by the history of seizure\[3\]. Therefore, DWI can be an alternative modality to explore the pathophysiology of CVT and prospectively predict its prognosis in the future.
Table 2. Expression levels of differentially expressed genes related to thrombophilia

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All our patients had remarkable routine blood and coagulation dysfunctions. D-dimer is considered a highly sensitive and specific laboratory screening indicator, but its normal value is not an obviating standard. Five of nine patients from the previous studies have shown normal routine blood and coagulation function. However, the combination of D-dimer value and risk factors can still be helpful to predict thrombosis. Studies are now focusing on biomarkers associated with cerebral venous infarction. Serum high-sensitivity C-reactive protein level is considered an essential indicator associated with the severity of CVT in acute/subacute phase.

An early use of heparin may exert better effect, but its spontaneous agreeable change cannot be ignored. Harada et al. have reported a case of a patient with venous infarction mimicking low-grade glioma resolving spontaneously without invasive operation. In the previous reports, most patients were suspected with glioma and underwent excisional biopsy. All our patients underwent excisional biopsy and their histopathological results revealed abundant small vascular obstruction, inflammatory cell infiltration, and regional hemorrhage. We observed focal hemorrhage surrounding the vein in four of the five lesions, which is consistent with the findings of previous studies. Juxtacortical hemorrhage can thus be an important diagnostic indication.

Due to the rarity of CVT, few studies have focused on the gene expression changes in patients with CVTMBT. To identify the key genes associated with the pathogenesis of CVTMBT, mRNA sequencing was performed on specimens between patients with CVTMBT and non-CVTMBT at our hospital. Nine filtered genes were considered to be significantly related to CVT. Unexplained thrombosis is closely related to protein S deficiency induced through a new mutation Gly222Arg in PROS1. The SERPINE1 gene has shown an increased risk of arterial and venous thromboses. In general, SELP, SERPINE1, PROCR,

Table 3. Role of nine differentially expressed genes in cerebral venous thrombosis mimicking brain tumor

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Description</th>
<th>Function</th>
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<td>SELP</td>
<td>Selectin P</td>
<td>Procoagulant[32,37]</td>
</tr>
<tr>
<td>THBD</td>
<td>Thrombomodulin</td>
<td>Anticoagulant[38]</td>
</tr>
<tr>
<td>ITGB3</td>
<td>Integrin subunit beta 3</td>
<td>Procoagulant[39]</td>
</tr>
<tr>
<td>TFPI</td>
<td>Tissue factor pathway inhibitor</td>
<td>Anticoagulant[40,41]</td>
</tr>
<tr>
<td>F13A1</td>
<td>Coagulation factor XIII A chain</td>
<td>Procoagulant[37]</td>
</tr>
<tr>
<td>PROS1</td>
<td>Protein S</td>
<td>Anticoagulant[42]</td>
</tr>
<tr>
<td>PPBP</td>
<td>Pro-platelet basic protein</td>
<td>Procoagulant[43,44]</td>
</tr>
<tr>
<td>PROCR</td>
<td>Protein C receptor</td>
<td>Procoagulant[43,44]</td>
</tr>
</tbody>
</table>

https://doi.org/10.36922/bh.v1i1.188
Cerebral venous thrombosis mimicking brain tumors

**Figure 6.** A flowchart for diagnosing CVTMBT. Non-specific primary imaging findings, including enhancement and mass effect, accompanied by intracranial hypertension and similar neurological deficits, were the main reasons for clinical misdiagnosis. However, various predisposing factors of CVT, shorter disease course, and coagulation dysfunction observed in patients may aid in differentiating CVTMBT from brain tumors. In cases where establishing the initial diagnosis is difficult, biopsy is performed. The effectiveness of anticoagulation therapy confirms the diagnosis of CVTMBT.

MRI: Magnetic resonance imaging; NSAIDs: Non-steroidal anti-inflammatory drugs; CVT: Cerebral venous thrombosis; CVTMBT: Cerebral venous thrombosis mimicking brain tumor

**5. Conclusions**

CVTMBT presents with enhancement and mass effect on MRI, accompanied by various predisposing factors, shorter disease duration, and coagulation dysfunction. Obstructed vein can be found intraoperatively and thrombosed vein infiltrated by excessive inflammatory cells is the most pathogenic finding. Anticoagulation therapy is effective in treating CVTMBT. Furthermore, the nine key genes identified in the pathogenesis of CVTMBT may be potential biomarkers for accurate screening and appropriate treatment for CVT.

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**Conflict of interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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Ethics approval and consent to participate
All procedures were approved by the Ethics Committee for Human Experiments of the Zhengzhou University (approval number: 2021-KY-0156-002). Written and verbal informed consents for the use of specimens were obtained before surgery.

Consent for publication
Written and verbal informed consents for the use of the specimens were obtained before surgery.

Availability of data
Data can be obtained from the corresponding author following request.

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